Novel Semisynthetic Oxo and Alkyl Macrolide Antibacterials and Related Derivatives

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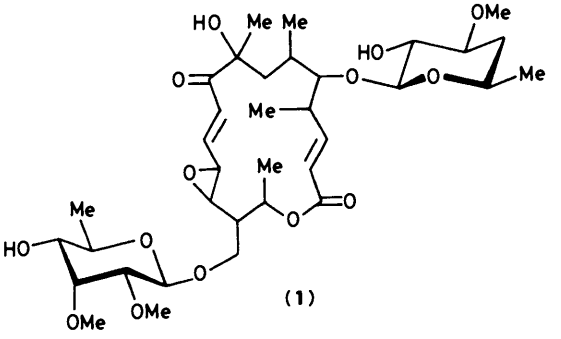
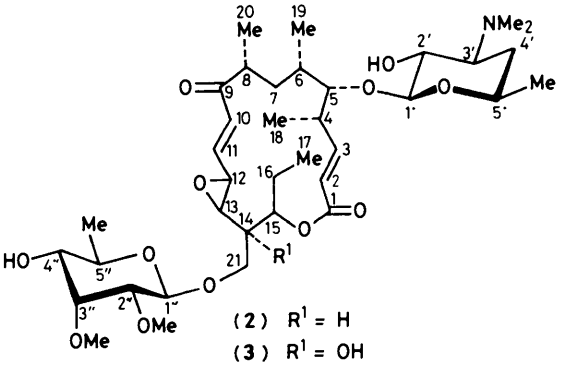
An efficient method of protecting the 10,11-double bond in dienone and epoxy enone 16-membered macrolides has been developed. This involves Michael addition of thioacetic *S*-acid to the 10,11-ene to give exclusively the 11-acetylthio derivatives, which can be smoothly deprotected by treatment with fluoride ion. The protected intermediates have been used to prepare a novel class of macrolide antibacterials in which the aldehyde group has been converted into an alkyl ketone by reaction with the appropriate diazoalkane. Thus 20-oxo analogues of rosaramicin, 12,13-de-epoxy-12,13-dehydrorosaramicin, tylosin, and desmycosin have been prepared. The reaction of diazomethane with unprotected macrolides has also been studied including the synthesis of 18-*C*-methyl-3″-*O*-propionylleucomycin A_5. Derivatives in which the 20-formyl group has been replaced by methyl and by halogeno groups, as well as derivatives having a 2,3-ene are described. A number of base-catalyzed rearrangement products including desmycosin 8β,20α-aldol and desmycoin 8α,20β-aldol are also described.

The structures of chalcomycin (**1**)[1] and the recently isolated 16-membered macrolide antibiotics mycinamicin I (antibiotic AR-5 1) (**2**), II (AR-5 2) (**3**), III (**4**), IV (de-epoxy AR-5 1) (**5**), and V (de-epoxy AR-5 2) (**6**)[2-9] revealed two unusual structural features to be present in these macrolides. One of these was the presence of a methyl substituent at C-6 in place of the usual formylmethyl group. The other was the absence of a 3-substituent and the presence of a 2,3-ene group in the molecule. The mycinamicins exhibited high antibacterial potency against sensitive Gram-positive strains, erythromycin-resistant *Streptococcus* strains and *Streptoccus pneumoniae* strains.[10] They were much less active against group B and D *Streptoccus* strains and showed little Gram-negative activity. They were also inactive against macrolide-resistant strains of *Staphylococcus*.[10] The mycinamicins, however, exhibited good serum levels following oral administration in mice and also showed long half-lives.[10] This prompted us to incorporate some of the structural features of the mycinamicins, into rosaramicin (**7**),[11,12] 12,13-de-epoxy-12,13-dehydrorosaramicin (**15**),[13] tylosin (**26**),[14-16] desmycosin (**32**),[14-16] and 3″-*O*-propionyl-leucomycin A_5 (**45**)[17,18] in the hopes of obtaining compounds having a broader antibacterial spectrum than the mycinamicins, while retaining the superior absorption characteristics of the mycinamicins. We therefore envisaged preparing a series of novel 20-oxo macrolides as well as a series of 20-deoxo-20-dihydro macrolides.

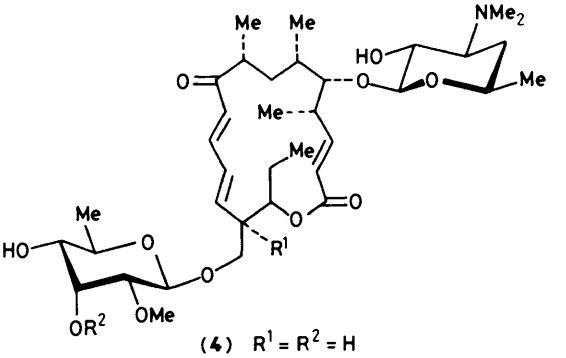
In order to prepare the 20-oxo macrolides it was necessary first to develop a suitable method of protecting the unsaturated oxo group found in most of these 16-membered macrolides. The addition of ammonia to the 10,11-double bond in mycinamicin II (**3**) to give the 11-amino derivative (**47**) was first observed in these laboratories.[19] A number of 11-thio and 11-amino derivatives of the mycinamicins were subsequently prepared,[20,21] as well as 11-ethylthiorosaramicin (**48**).[20] The facile nature of the above Michael addition of alkane thiols to epoxy enone macrolides, encouraged us to explore the use of thioacetic *S*-acid to form the Michael adduct at the 10,11-double bond in both epoxy enone and dienone macrolides. The Michael addition reactions of the latter had not been studied at the time although a subsequent report[22] has appeared describing the addition of thiols to the 10,11-double bond of *O*-(β-D-mycaminosyl)-(1→5)-tylonolide. This would afford us a new series of 11-acetylthio-10,11-dihydro protected macrolides that could be used to prepare a novel series of 20-



(**1**)



(**2**) R^1 = H
(**3**) R^1 = OH

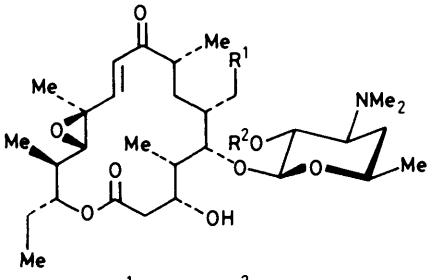


(**4**) $R^1 = R^2$ = H
(**5**) R^1 = H, R^2 = Me
(**6**) R^1 = OH, R^2 = Me

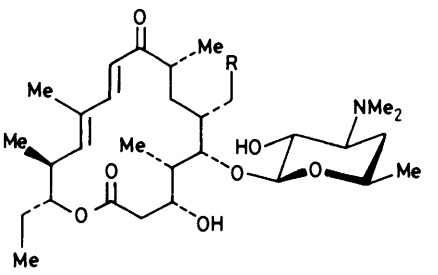
oxo macrolides by reaction with the appropriate diazoalkane.[23] Subsequent deprotection with a suitable base such as fluoride ion would be expected to regenerate the enone moiety.

Thus, rosaramicin (**7**) on treatment with thioacetic *S*-acid (2 equiv.) at 25 °C for 21 h, afforded a single diastereoisomer, namely (11*R*)-11-acetylthio-10,11-dihydrorosaramicin (**49**) in high yield.* Under similar conditions de-epoxyrosaramicin (**15**) hardly reacted at all, necessitating the use of more vigorous reaction conditions. Thus (**15**) reacted with 20 equivalents of thioacetic *S*-acid in a concentrated solution in dichloromethane to give (11*R*)-11-acetylthio-12,13-de-epoxy-12,13-dehydrorosaramicin (**56**)* in 26% yield, together with the 11*S*-diastereoisomer (**57**)* in 15% yield, after 40 h at 25 °C. Under the forcing conditions used, the 2′-hydroxy group was also acetylated and it was necessary to subject the crude reaction mixture to methanolysis to remove the acetyl group before isolating (**56**) and (**57**). When the reaction was carried out in neat thioacetic *S*-acid, somewhat lower yields of (**56**) and (**57**) were obtained, together with (11*R*)-11-acetylthio-12,13-de-epoxy-12,13-dehydro-10,11-dihydrorosaramicin-9,19-aldol (**62**). The reaction products again had to be methanolized to remove the acetyl group. In both of the above reactions some unchanged (**15**) was recovered. The ^{1}H n.m.r. of (**62**) revealed a signal at δ_H 9.61 due to the 20-aldehyde. The ^{13}C n.m.r. (Table 1) contained signals at δ_C 201.5 for C-20, at δ_C 61.3 for the 19-methine group, and at δ_C 95.2 for the 9-hemiacetal carbon.

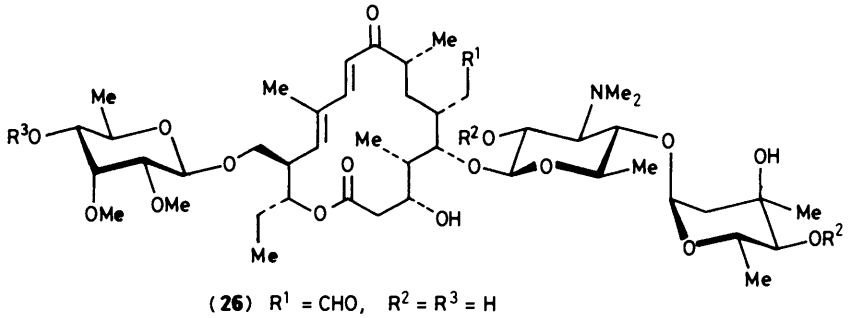
Tylosin (**26**) on treatment with thioacetic *S*-acid afforded both the 11*R*- and 11*S*-acetylthio adducts, (**63**) and (**64**)



(**7**) R^1 = CHO, R^2 = H
(**8**) R^1 = Ac, R^2 = H
(**9**) R^1 = –C(Me)=N–N(SO$_2$), R^2 = H
(**10**) R^1 = $CO(CH_2)_3Me$, R^2 = H
(**11**) R^1 = $CH(SPh)_2$, R^2 = H
(**12**) R^1 = CH=N–N(SO$_2$), R^2 = H
(**13**) R^1 = CH_3, R^2 = H
(**14**) R^1 = CH_3, R^2 = Ac

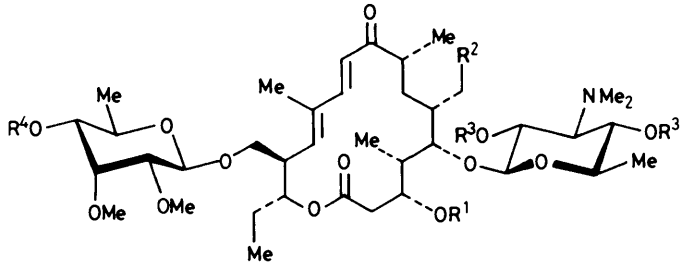


(**15**) R = CHO
(**16**) R = Ac
(**17**) R = $CH(SPh)_2$
(**18**) R = CH_2OAc
(**19**) R = C(Me)=N–N(SO$_2$)
(**20**) R = COBu
(**21**) R = C(Bu)=N–N(SO$_2$)
(**22**) R = CH=N–N(SO$_2$)
(**23**) R = Me
(**24**) R = CH_2OH
(**25**) R = CH_2Cl

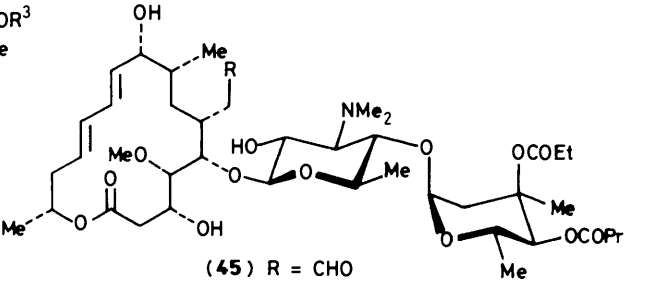


(**26**) R^1 = CHO, R^2 = R^3 = H
(**27**) R^1 = $CH(SPh)_2$, R^2 = R^3 = H
(**28**) R^1 = Ac, R^2 = R^3 = H
(**29**) R^1 = CHO, R^2 = R^3 = Ac
(**30**) R^1 = Me, R^2 = R^3 = H
(**31**) R^1 = CH(N=N–N=)(OSi(Me$_2$)CMe$_3$), R^2 = H, R^3 = $OSi(Me_2)CMe_3$

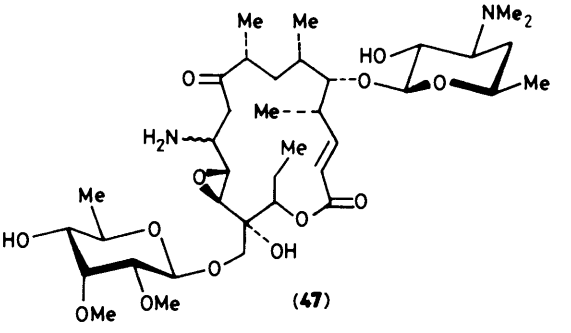
* The assignment of the absolute stereochemistry at C-11 will be discussed later.



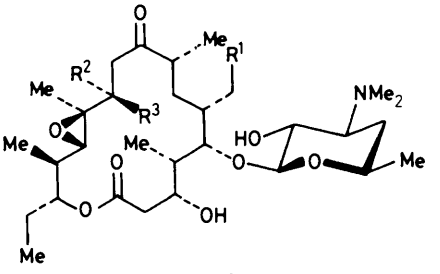
(32) $R^1 = R^3 = R^4 = H$, $R^2 = CHO$
(33) $R^1 = R^3 = R^4 = H$, $R^2 = Ac$
(34) $R^1 = R^3 = R^4 = H$, $R^2 = COEt$
(35) $R^1 = R^3 = R^4 = H$, $R^2 = COPr$
(36) $R^1 = R^3 = R^4 = H$, $R^2 = COBu$
(37) $R^1 = R^3 = R^4 = H$, $R^2 = CH_2OH$
(38) $R^1 = R^3 = R^4 = H$, $R^2 = CH_2Cl$
(39) $R^1 = R^3 = R^4 = H$, $R^2 = CH_2Br$
(40) $R^1 = R^3 = R^4 = H$ $R^2 = CH_2I$
(41) $R^1 = R^3 = R^4 = H$ $R^2 = Me$
(42) $R^1 = H$, $R^2 = CHO$, $R^3 = R^4 = Ac$
(43) $R^1 = R^3 = R^4 = H$, $R^2 = CH(OMe)_2$
(44) $R^1 = H$, $R^2 = CH(OMe)_2$, $R^3 = R^4 = Ac$



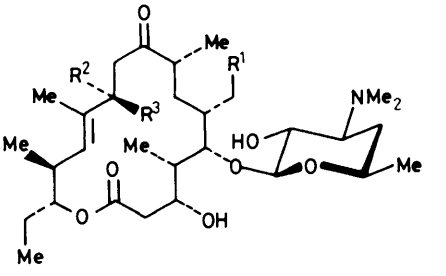
(45) R = CHO
(46) R = Ac



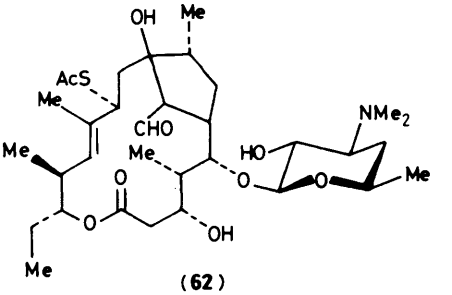
(47)



(48) R^1 = CHO, R^2 R^3 = SCH_2Me/H
(49) R^1 = CHO, R^2 = SAc, R^3 = H
(50) R^1 = CHO, R^2 = SPh, R^3 = H
(51) R^1 = CHO, R^2 = H, R^3 = SPh
(52) R^1 = Ac, R^2 = SAc, R^3 = H
(53) R^1 = COBu, R^2 = SAc, R^3 = H
(54) $R^1 = CH(SPh)_2$, R^2 = SPh R^3 = H
(55) Structure unassigned

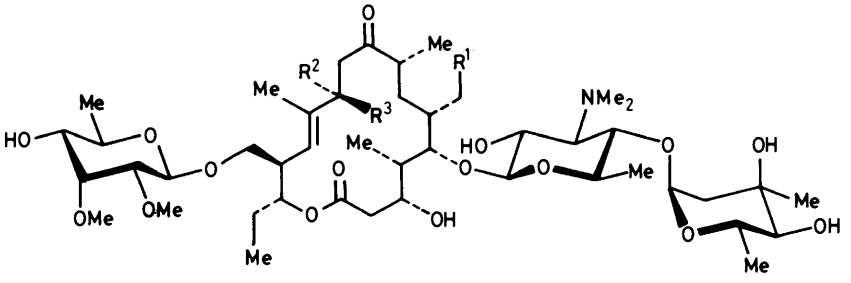


(56) R^1 = CHO, R^2 = SAc, R^3 = H
(57) R^1 = CHO, R^2 = H, R^3 = SAc
(58) R^1 = CHO, R^2 = SPh, R^3 = H
(59) R^1 = CHO, R^2 = H, R^3 = SPh
(60) R^1 = Ac, R^2 = SAc, R^3 = H
(61) R^1 = Ac, R^2 = H, R^3 = SAc

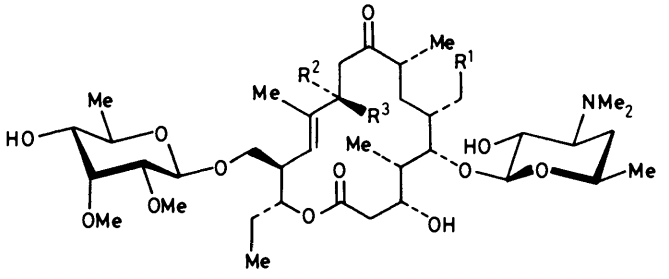


(62)

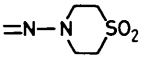
respectively. Treatment of the adduct (**63**) with tetrabutylammonium fluoride resulted in the predicted β-elimination to regenerate tylosin (**26**). Desmycosin (**32**) also reacted with thioacetic *S*-acid to give the 11*R*- and 11*S*-acetylthio derivatives, (**67**) and (**68**) respectively, the latter being the major product in this case. The adduct (**68**) was converted into the hydrazone derivative (**69**). In the case of tylosin (**26**) and desmycosin (**32**), the intermediate 2′,4′-diacetates were also formed and were methanolized prior to isolation of the desired adducts. In none of the above dienone macrolides, was any



(**63**) R^1 = CHO, R^2 = SAc, R^3 = H
(**64**) R^1 = CHO, R^2 = H, R^3 = SAc
(**65**) R^1 = $CH(SPh)_2$, R^2 = SPh, R^3 = H
(**66**) R^1 = Ac, R^2 = H, R^3 = SAc



(**67**) R^1 = CHO, R^2 = SAc, R^3 = H
(**68**) R^1 = CHO, R^2 = H, R^3 = SAc

(**69**) R^1 = CH=N—  , R^2 = H, R^3 = SAc

(**70**) R^1 = CHO, R^2 = SPh, R^3 = H
(**71**) R^1 = CHO, R^2 = H, R^3 = SPh
(**72**) R^1 = Ac, R^2 = H, R^3 = SAc
(**73**) R^1 = COEt, R^2 = H, R^3 = SAc
(**74**) R^1 = COPr, R^2 = H, R^3 = SAc
(**75**) R^1 = COBu, R^2 = H, R^3 = SAc

addition to the terminal position of the dienone observed. The ^{1}H n.m.r. and ^{13}C n.m.r. (Table 1)* data in all instances indicated that the addition had occurred to the 10,11-double bond. 2D-N.m.r. studies carried out on (**67**) and (**68**) using δ_H/J and δ_H/δ_C correlations, confirmed the location of the 11-acetylthio group.

Having demonstrated that the enone chromophore of both epoxy enone and dienone macrolides could be successfully protected as the 11-acetylthio adducts, we next turned our attention to the determination of the absolute stereochemistry of these adducts. In order to study the shielding effects of the 11-substituent on neighbouring groups, we felt that it would be advantageous to prepare the 11-phenylthio derivatives in view of the larger anisotropic effect of the phenyl ring. The desired 11-phenylthio derivatives were prepared by the direct Michael addition of thiophenol to rosaramicin (**7**) to give the 11*R*- and 11-*S*-phenylthio adducts (**50**) and (**51**) respectively; to de-epoxyrosaramicin (**15**) to give the 11*R*- and 11-*S*-phenylthio adducts (**58**) and (**59**) respectively; and to desmycosin (**32**) to give the 11*R*- and 11*S*-phenylthio adducts (**70**) and (**71**) respectively. In none of the above reactions was any aldol product produced and the 20-formyl groups were unaffected by the reaction conditions used. After completion of this work, Omura[25] reported that tylosin failed to undergo a Michael addition reaction with thiophenol in the presence of triethylamine, but gave instead the 8,19-aldol product. No addition of thiophenol was observed under his conditions. He therefore protected the 20-formyl group as the 20-diphenylthio acetal, or as the 20-dimethyl acetal derivative and succeeded in preparing the 11-phenylthio derivatives by adding thiophenol in the presence of triethylamine. Subsequent deprotection of the acetals afforded an 11-phenylthio adduct of tylosin and an 11-phenylthio adduct of desmycosin, but no absolute stereochemistry was assigned to either product. It was evident from our own work that no protection of the aldehyde was needed and that no aldol products were formed under our reaction conditions. The ^{1}H n.m.r. and ^{13}C n.m.r. data (Table 1) once again clearly confirmed the location of the 11-phenylthio group. Key ^{1}H n.m.r. and c.d. data for both the 11-acetylthio and 11-phenylthio derivatives are summarized in Table 2, along with relevant data for the parent macrolide in each instance. The less polar diastereoisomers (**49**), (**50**), (**56**), (**58**), (**63**), (**67**), and (**70**) all exhibited shielding of the 12-methyl group relative to the parent macrolide. On the other hand the more polar diastereoisomers (**57**), (**64**), and (**68**) showed almost no shift of the 12-methyl group relative to the parent macrolides. The more

* Tables 1 and 3 have been treated as a Supplementary publication: see footnote on p. 12. Table 1 contains reference 24.

Table 2. ^{1}H N.m.r. and c.d. data for key 11-*SR* adducts

Parent compd.	11*R*-Diastereoisomer (less polar)	11*S*-Diastereoisomer (more polar)
Rosaramicin (**7**)	11-SAc (**49**)	—
12-Me, δ_H 1.51	12-Me, δ_H 1.32	
14-Me, δ_H 1.10	14-Me, δ_H 1.06	
$[\theta]_{242}$ −107 817	$[\theta]_{230}$ +50 086	
$[\theta]_{277}$ +15 646	$[\theta]_{293}$ +23 850	
	11-SPh (**50**)	11-SPh (**51**)
	12-Me, δ_H 1.40	12-Me, δ_H 1.58
	14-Me, δ_H 1.05	14-Me, δ_H 0.86
	$[\theta]_{298}$ +86 877	$[\theta]_{296}$ −15 042
De-epoxyrosaramicin (**15**)	11-SAc (**56**)	11-SAc (**57**)
12-Me, δ_H 1.78	12-Me, δ_H 1.63	12-Me, δ_H 1.76
14-Me, δ_H 1.08	14-Me, δ_H 0.96	14-Me, δ_H 0.90
13-H, δ_H 5.68	13-H, δ_H 5.33	13-H, δ_H 5.08
$[\theta]_{247}$ −7 072	$[\theta]_{232}$ +213 967	$[\theta]_{249}$ −38 827
$[\theta]_{290}$ −70 720	$[\theta]_{296}$ +51 963	$[\theta]_{268}$ −51 665
	11-SPh (**58**)	11-SPh (**59**)
	12-Me, δ_H 1.64	12-Me, δ_H 1.87
	14-Me, δ_H 0.56	14-Me, δ_H 0.80
	13-H, δ_H 4.76	13-H, δ_H 4.89
	$[\theta]_{286}$ +81 112	$[\theta]_{286}$ +26 378
Tylosin (**26**)	11-SAc (**63**)	11-SAc (**64**)
12-Me, δ_H 1.79	12-Me, δ_H 1.68	12-Me, δ_H 1.79
13-H, δ_H 5.91	13-H, δ_H 5.28	13-H, δ_H 5.02
$[\theta]_{230}$ −19 720	$[\theta]_{232}$ +230 811	$[\theta]_{250}$ −54 546
$[\theta]_{270}$ +39 440	$[\theta]_{290}$ +97 559	$[\theta]_{300}$ +24 794
Desmycosin (**32**)	11-SAc (**67**)	11-SAc (**68**)
12-Me, δ_H 1.80	12-Me, δ_H 1.67	12-Me, δ_H 1.80
13-H, δ_H 5.93	13-H, δ_H 5.30	13-H, δ_H 5.04
$[\theta]_{225}$ −28 433	$[\theta]_{233}$ +184 690	$[\theta]_{250}$ −51 224
$[\theta]_{270}$ +22 036	$[\theta]_{290}$ +86 691	$[\theta]_{300}$ +22 271
	11-SPh (**70**)	11-SPh (**71**)
	12-Me, δ_H 1.70	12-Me, δ_H 1.93
	13-H, δ_H 4.95	13-H, δ_H 4.90
	$[\theta]_{289}$ +193 231	$[\theta]_{290}$ +28 228

polar 11-phenylthio diastereoisomers (**51**), (**59**), and (**71**) exhibited some deshielding of the 12-methyl group relative to the parent macrolides. The olefinic proton 13-H was strongly shielded in both the less polar and more polar diastereoisomers, but it was more pronounced in the former case.

The chemical shifts of the 14-methyl group in the de-epoxyrosaramicin adducts were particularly informative. Both the less polar and the more polar 11-acetylthio adducts (**56**) and (**57**), showed modest shielding of the 14-methyl group relative to (**15**). In the less polar 11-phenylthio adduct (**58**) the shielding of the 14-methyl was very great (δ_H 0.56). In the more polar 11-phenylthio adduct (**59**) the shielding was still pronounced (δ_H 0.80), but much less so than in the case of (**58**). From space-filling models it is evident that the 11*R*-diastereoisomer would be predicted to have the 14-methyl group in the closest proximity to the face of the phenyl ring, thus producing the greatest shielding of that methyl group. The 11*S*-diastereoisomer would be predicted to show less pronounced shielding as was observed. The presence of the 12,13-epoxide group in the corresponding 11-phenylthiorosaramicin adducts (**50**) and (**51**), resulted in rotation of the phenyl ring away from the 14-methyl group in the less polar diastereoisomer (**50**), so that the 14-methyl group was hardly shielded at all (δ_H 1.05). The more polar diastereoisomer (**51**) on the other hand, again showed similar shielding of the 14-methyl group (δ_H 0.86) to that observed with (**59**). In this diastereoisomer the 12,13-epoxide group would be expected to have little effect on the orientation of the 11-phenylthio group. The ^{1}H n.m.r. data therefore suggests that the less polar diastereoisomers have the 11*R* configuration, while the more polar diastereoisomers have the 11*S* configuration.

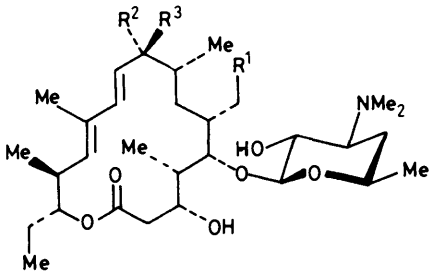
Further support for the above assignments was obtained from the c.d. data (Table 2). The less polar 11-acetylthio adducts (**49**), (**56**), (**63**), and (**67**) all exhibited positive extrema at 290—296 nm due to the ketone chromophore. Assuming that the Octant Rule for ketones is valid, one would predict that the 11*R*-acetylthio derivatives would have a positive contribution as was observed. On the other hand the 11*S*-acetylthio derivatives would contribute in a negative sense to the extremum due to the ketone chromophore and this was observed to be the case. The 11*R*-acetylthio derivatives would also be expected to make a positive contribution to the extremum at *ca.* 230 nm due to the olefinic chromophore in (**56**), (**63**), and (**67**), and this was observed. On the other hand the 11*S*-acetylthio derivatives (**57**), (**64**), and (**68**) would exhibit a negative contribution to the extremum due to the olefinic chromophore and this was indeed observed. The 11*R*-phenylthio derivatives all showed positive maxima at 286—298 nm, while the 11*S*-diastereoisomers exhibited negative maxima. Both the ketone and phenyl chromophores would be expected to contribute to the observed maxima.

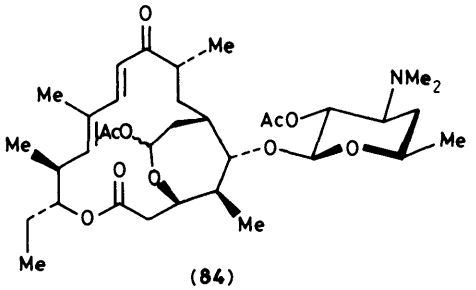
The 11-acetylthio macrolides could now be used to prepare a novel series of oxo derivatives. The 11*R*-acetylthio derivative of rosaramicin (**49**) reacted smoothly with diazomethane to give the 20-ketone (**52**) in high yield. The latter on treatment with tetrabutylammonium fluoride afforded 20-*C*-methylrosaramicin (**8**). The latter was converted into the hydrazone derivative (**9**) by treatment with 4-aminothiomorpholine *S,S*-dioxide in the presence of toluene-*p*-sulphonic acid. The 11*R*-acetylthio derivative (**49**) was also allowed to react with diazobutane[26-28] to give the butyl ketone (**53**), which on deprotection gave 20-*C*-butylrosaramicin (**10**).

Both the 11*R*-acetylthio and 11*S*-acetylthio derivatives of de-epoxyrosaramicin (**56**) and (**57**) respectively, reacted with diazomethane to give the corresponding 20-ketones (**60**) and (**61**) respectively. A mixture of (**60**) and (**61**) was deprotected to give 20-*C*-methylrosaramicin (**8**) by reduction of the epoxide with chromous ions under acidic conditions.[29]

An alternative synthesis of the 20-*C*-alkyl derivatives was also investigated. This involved protection of the dienone system by reduction of the 9-oxo group. In order to do this it was necessary first to protect the 20-formyl group with an acetal that could be removed under neutral conditions. We therefore investigated the use of diphenyl disulphide and tributylphosphine[30] to form the 20-diphenylthioacetals of the macrolide substrates which interested us. Rosaramicin (**7**) on treatment with diphenyl disulphide and tributylphosphine afforded the desired 20-deoxorosaramicin-20-diphenylthioacetal (**11**) in low yield, together with (11*R*)-20-deoxo-10,11-dihydro-11-phenylthiorosaramicin 20-diphenylthioacetal (**54**), an unknown (**55**), (11*R*)-10,11-dihydro-11-phenylthiorosaramicin (**50**), and unchanged (**7**). Tylosin (**26**) under similar conditions gave (11*R*)-20-deoxo-10,11-dihydro-11-phenylthiotylosin 20-diphenylthioacetal (**65**)* in modest yield together with unchanged tylosin (**26**) as the principal product of the reaction. By using less of the reactants, de-epoxyrosaramicin (**15**) afforded the 20-diphenylthioacetal (**17**) as the principal product of the reaction. Reduction of (**17**) with sodium borohydride

* After completion of this work Omura[25] reported the preparation of 20-deoxotylosin 20-diphenylthioacetal (**27**) using similar techniques with a shorter reaction time; and also on its Michael reaction with thiophenol and triethylamine to give (**65**).



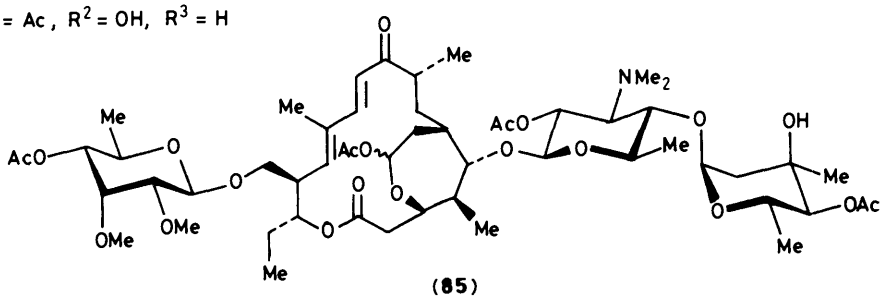


(84)

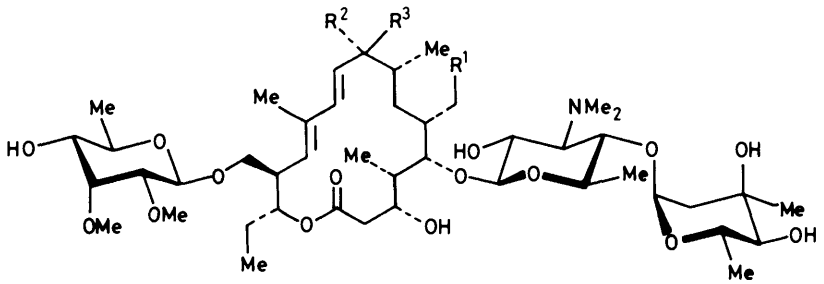
(76) R^1 = CH(SPh)$_2$, R^2 = OH, R^3 = H
(77) R^1 = CH(SPh)$_2$, R^2 = H, R^3 = OH
(78) R^1 = CHO, R^2 = OH, R^3 = H
(79) R^1 = CHO, R^2 = H R^3 = OH

(80) R^1 = CH=N—N⟨ ⟩SO$_2$, R^2 = OH, R^3 = H

(81) R^1 = CH_2OH, R^2 = OH, R^3 = H
(82) R^1 = CH_2OH, R^2 = H, R^3 = OH
(83) R^1 = Ac, R^2 = OH, R^3 = H

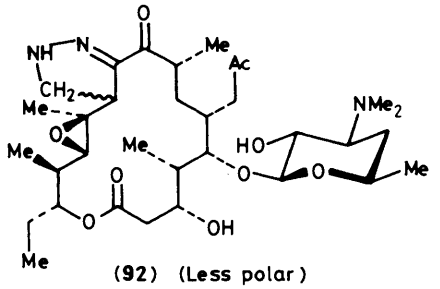


(85)

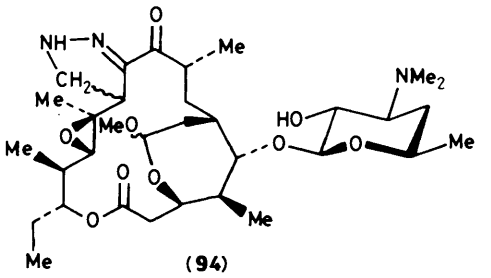


(86) R^1 = CHO, R^2 = H, R^3 = OH
(87) R^1 = CHO, R^2 = OH, R^3 = H
(88) R^1 = CH_2OH, R^2 = H, R^3 = OH
(89) R^1 = CH_2OH, R^2 = OH, R^3 = H
(90) R^1 = Ac, R^2 = H, R^3 = OH
(91) R^1 = Ac, R^2 = OH, R^3 = H

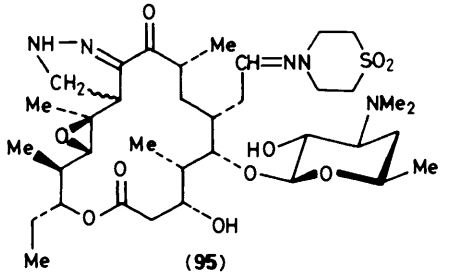
afforded both the 9*R*-dihydro acetal (**76**) and the 9*S*-dihydro acetal (**77**). The $J_{9,10}$ values were used to assign the absolute stereochemistry at C-9.[31] Treatment of (**76**) and (**77**) with mercury(II) chloride and mercury(II) oxide liberated the free aldehydes (**78**) and (**79**) respectively. The hydrazone (**80**) was also prepared from the aldehyde (**78**). An alternative route to (**78**) and (**79**) was also explored. Thus, de-epoxyrosaramicin (**15**) on treatment with acetic anhydride and potassium carbonate,[32] gave 2',20-di-*O*-acetyl-12,13-de-epoxy-12,13-dehydrorosaramicin 3,20-hemiacetal (**84**) with borohydride exchange resin followed by deprotection with triethylamine in methanol, afforded an inseparable mixture of 9*R*- and 9*S*-dihydrode-epoxyrosaramicin (**78**) and (**79**) as the major product, together with 9*R*- and 9*S*-tetrahydro derivatives (**81**) and (**82**) which again were inseparable. Traces of (**15**) were also isolated. When the reduction of (**84**) was carried out using sodium borohydride in isopropyl alcohol, 20-*O*-acetyl-12,13-de-epoxy-12,13-dehydro-20-dihydrorosaramicin (**18**), de-epoxyrosaramicin (**15**) and the 9*S*-tetrahydro derivative (**82**) were the only products isolated. Treatment of 9*R*-dihydrode-epoxyrosaramicin (**78**) with diazomethane, gave the 20-methyl ketone (**83**). Oxidation of (**83**) with chromium trioxide in pyridine containing some water[34] gave 20-*C*-methylde-epoxy-rosaramicin (**16**). The latter was converted into the hydrazone (**19**) by treatment with 4-aminothiomorpholine *S,S*-dioxide and toluene-*p*-sulphonic acid.



(92) (Less polar)
(93) (More polar)



(94)



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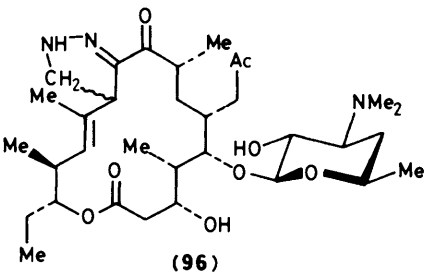
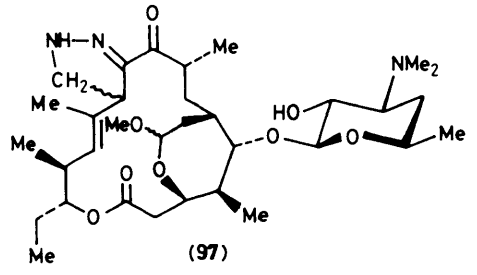


(96)



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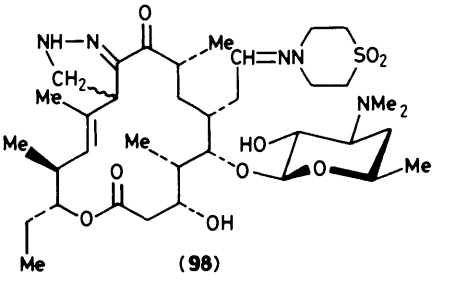
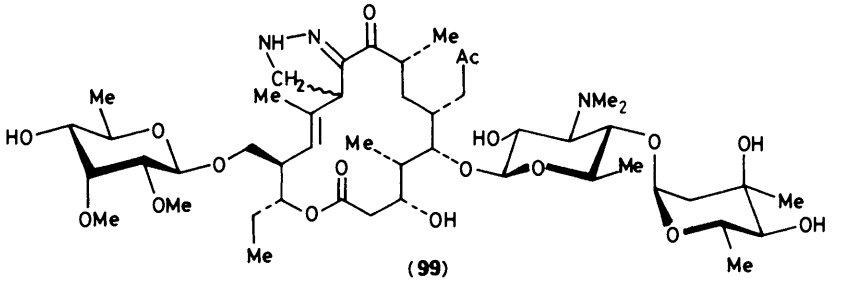
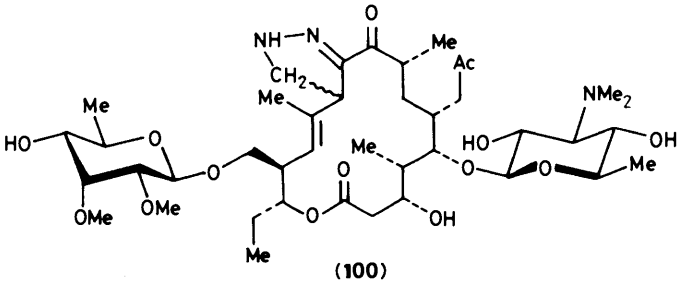


(98)



(99)



(100)

De-epoxidation of 20-*C*-butylrosaramicin (**10**) with chromous ions at acidic pH[29] afforded (**20**), which was in turn converted into the hydrazone derivative (**21**).

The preparation of 20-*C*-methyltylosin (**28**) was carried out by the following routes. Treatment of (11*S*)-11-acetylthio-10,11-dihydrotylosin (**64**) with diazomethane, gave the ketone (**66**), which was in turn deprotected with tetrabutylammonium fluoride to give (**28**). An alternative route involved the preparation of 20,2′,4″,4‴-tetra-*O*-acetyltylosin 3,20-hemiacetal (**85**) by treatment of tylosin (**26**) with acetic anhydride and sodium carbonate.[32,35] 2′,4″,4‴-Tri-*O*-acetyltylosin (**29**) was formed as a by-product in the above reaction. Reduction of (**85**) with sodium borohydride in methanol gave 9*S*-dihydrotylosin (**86**), 9*R*-dihydrotylosin (**87**), 9*S*-tetrahydrotylosin (**88**), and 9*R*-tetrahydrotylosin (**89**) all of which could be separated chromatographically. A mixture of (**86**) and (**87**) on treatment

with diazomethane, afforded the 20-*C*-methyl derivatives (**90**) and (**91**). Oxidation of the latter with either 4-dimethylaminopyridinium chlorochromate,[36] or with chromium trioxide in pyridine containing some water,[34] gave 20-*C*-methyltylosin (**28**).

The 20-*C*-alkyl desmycosin derivatives were prepared by treating the 11*S*-acetylthio derivative (**68**) with the appropriate diazoalkane[26-28] to give the protected 20-*C*-methyl (**72**), 20-*C*-ethyl (**73**), 20-*C*-propyl (**74**), and 20-*C*-butyl (**75**) derivatives. Each of these was in turn deprotected with tetrabutylammonium fluoride to give the desired methyl ketone (**33**), ethyl ketone (**34**), propyl ketone (**35**), and butyl ketone (**36**), respectively.

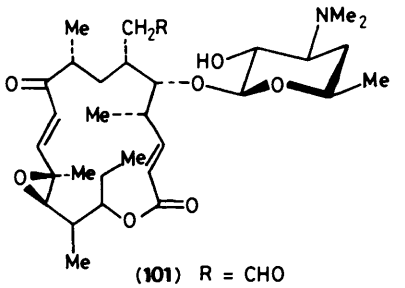
The synthesis of the 18-ketones in the leucomycin series could be carried out using diazomethane without protection, since they have no oxo group at C-9. Thus 3″-*O*-propionyl leucomycin A_5 (**45**)[37,38] on treatment with diazomethane afforded the methyl ketone (**46**) directly.

When 16-membered macrolides having α,β-unsaturated oxo groups in the molecule, were treated with diazomethane, dihydropyrazole derivatives were formed.[23,39,40] Thus, rosaramicin (**7**) on treatment with diazomethane, afforded a pair of diastereoisomeric (at C-11) dihydropyrazole 20-methyl ketone derivatives (**92**) and (**93**), as well as the hemiacetal dihydropyrazole derivative (**94**). The physical data supported the assigned structures and in all cases the double bond was located between C-10 and the nitrogen atom of the dihydropyrazole ring. When rosaramicin (**7**) was treated with diazomethane in the presence of palladium(II) acetate,[41,42] in the hopes of preparing the 10,11-cyclopropyl derivative, only rosaramicin (**7**), 20-*C*-methylrosaramicin (**8**), and the hemiacetal dihydropyrazole derivative (**94**) were obtained. When rosaramicin hydrazone (**12**) was treated with diazomethane and palladium(II) acetate a single diastereoisomeric dihydropyrazole (**95**) was obtained. The absolute stereochemistry at C-11 could not be assigned for any of these dihydropyrazoles.

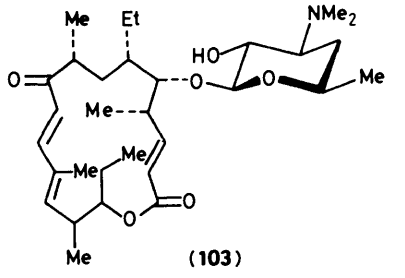
De-epoxyrosaramicin (**15**) on treatment with diazomethane gave a single diastereoisomeric 20-oxodihydropyrazole derivative (**96**) and a dihydropyrazole hemiacetal (**97**). Reaction of de-epoxyrosaramicin hydrazone (**22**) with diazomethane and palladium(II) acetate afforded a single diastereoisomeric dihydropyrazole (**99**) and (**100**) respectively.

We next turned out attention to the preparation of the 20-deoxo-20-dihydro macrolides and the 2,3-dehydro-3-deoxy macrolides, to see what effect these modifications would have on the antibacterial spectrum, potency, and absorption characteristics of these macrolides. 2,3-Dehydro-3-deoxyrosaramicin (**101**) had been prepared in these laboratories[19] some years ago and was available to us.[43] 20-Deoxo-20-dihydrorosaramicin (**13**) had also previously been isolated from *Micromonospora rosaria*[19,43] and it has also been synthesized in these laboratories[44] by the reduction of the hydrazone with bis(triphenylphosphine)copper(I) borohydride.[45] Treatment of (**13**) with chromous ions at acidic pH[29] afforded the de-epoxy derivative (**23**). 20-Deoxo-20-dihydrorosaramicin (**13**) [containing 40% of the de-epoxy derivative (**23**)][19,43] was acetylated with acetic anhydride in acetone to give the 2′-*O*-acetyl derivative (**14**).* The latter was heated with methanesulphonyl chloride in pyridine and then deprotected by heating with triethylamine in methanol to give (**102**).* The resulting mixture was reduced with chromous ions at acidic pH[29] to give (**103**).

Our next objective was to replace the 20-formyl group with a halogenomethyl group and this was achieved as follows. 12,13-De-epoxy-12,13-dehydrorosaramicin (**15**) was selectively



(**101**) R = CHO
(**102**) R = Me



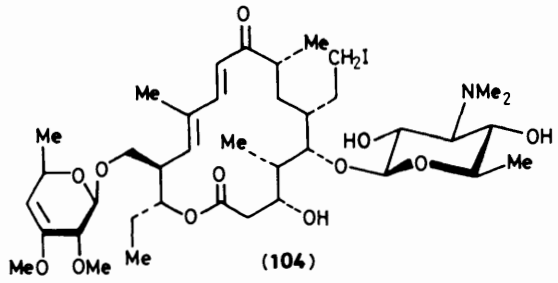
(**103**)

reduced using sodium borohydride in a pH 7.5 buffer[46] to give 12,13-de-epoxy-12,13-dehydro-20-dihydrorosaramicin (**24**). The latter was treated with tris(dimethylamino)phosphorus amide and carbon tetrachloride[47,48] to afford the desired 20-chloro-12,13-de-epoxy-12,13-dehydro-20-deoxy-20-dihydrorosaramicin (**25**) in high yield without the need for any protection of the remaining hydroxy groups.

In order to determine what effect the presence of a 23-*O*-mycinosyl unit would have on the structure–activity relationships of these macrolides, we next turned out attention to the preparation of a series of desmycosin derivatives that incorporated the modifications described above.

Desmycosin (**32**) was selectively reduced using sodium borohydride in a pH 7.5 buffer[46] to give 20-dihydrodesmycosin (**37**). The latter was treated with tris(dimethylamino)phosphorus amide and carbon tetrachloride[47,48] to give the desired 20-chloro-20-deoxy-20-dihydrodesmycosin (**38**). When the above reaction was carried out using tris(dimethylamino)phosphorus amide and carbon tetrabromide, the corresponding 20-bromo-20-deoxy-20-dihydrodesmycosin (**39**) was obtained. In both of the above reactions only the primary hydroxy group at C-20 reacted to give the 20-halogeno derivatives, indicating that no protection of the secondary hydroxy groups was needed. When 20-dihydrodesmycosin (**37**) was treated with methyl triphenoxyphosphonium iodide (2.4 equiv.),[49,50] the principal product of the reaction was 20-deoxy-20-dihydro-20-iododesmycosin (**40**). However, some iodination had occurred at C-4″ with subsequent elimination of hydriodic acid to give 3″,4″-dehydro-20,4″-dideoxy-20-dihydro-20-iododesmycosin (**104**) as a by-product of the reaction. Improved yields of (**40**) were obtained by reducing the amount (2 equiv.) of methyltriphenoxyphosphonium iodide. The ^1H and ^{13}C n.m.r. (Table 1) parameters were in agreement with the assigned structures for the 20-halogeno derivatives. The presence of a doublet at δ_H 4.68 ($J_{4'',5''}$ 2 Hz) due to the vinylic proton at C-4″ and the presence of secondary methyl doublets at δ_H 1.20 and 1.28 (*J* 6 Hz), one of which belonged to the 6-Me group, as well as the presence of a vinylic carbon signal at δ_C 102.6 (C-4″), a vinylic ether carbon signal at δ_C 152.1 (C-3″), and a methyl signal at δ_C 22.9 (C-6″), all lent support to the location of the 3″,4″-double bond in (**104**). The 3″-OMe in (**104**) was strongly shielded (δ_C 54.7). Reduction of 20-deoxy-20-dihydro-20-iododesmycosin (**40**) with tributyltin hydride[51] afforded a high yield of the desired 20-deoxo-20-

* Containing *ca.* 40% of the corresponding 12,13-de-epoxy-12,13-dehydro derivative.



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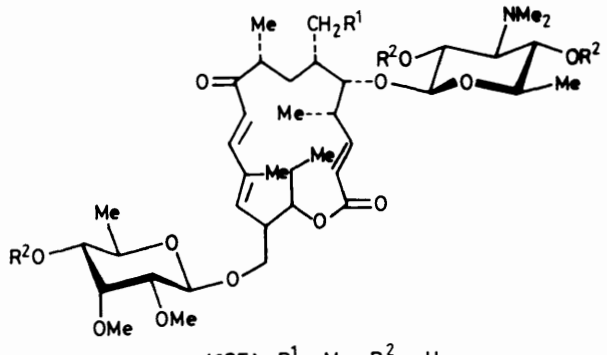
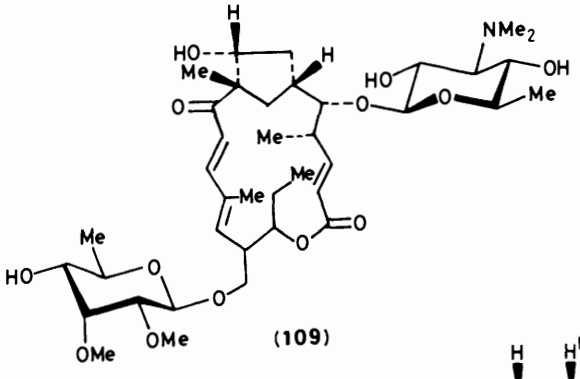
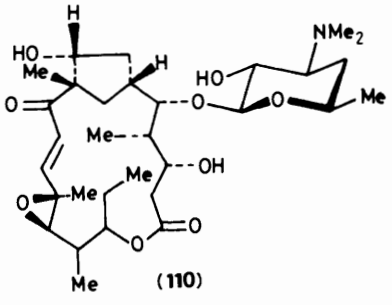


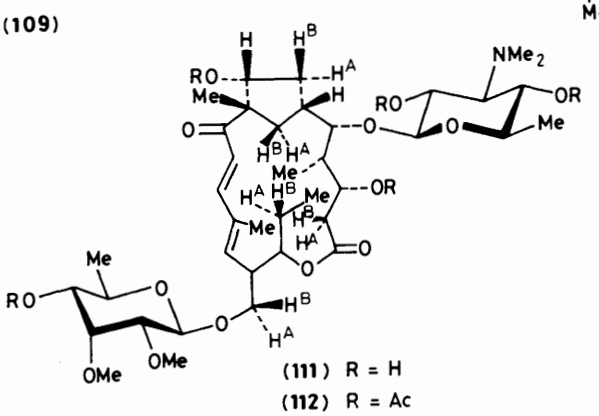
(105) R^1 = Me, R^2 = H
(106) R^1 = CHO, R^2 = Ac
(107) R^1 = $CH(OMe)_2$, R^2 = H
(108) R^1 = CHO, R^2 = H



(109)



(110)



(111) R = H
(112) R = Ac

dihydrodesmycosin (**41**). The latter has also been prepared by reduction of the hydrazone of tylosin[44] to give (**30**), which on mild acidic hydrolysis afforded (**41**). The latter has also been prepared directly by reduction of the hydrazone of desmycosin.[44]

Introduction of the 2,3-double bond into (**41**) was effected by converting (**41**) into the 2′,4′,4″-tri-*O*-acetyl derivative by treatment with acetic anhydride in pyridine. The latter was then directly treated with methanesulphonyl chloride in pyridine, followed by deacetylation with triethylamine in methanol, to give 20-deoxo-3-deoxy-2,3-dehydro-20-dihydrodesmycosin (**105**). The ^{1}H n.m.r. spectrum of (**105**) revealed a doublet at δ_H 5.65 ($J_{2,3}$ 15.5 Hz) due to 2-H and a doublet of doublets at δ_H 6.58 ($J_{2,3}$ 15.5 Hz, $J_{3,4}$ 9.5 Hz) due to 3-H. The presence of a shielded lactone carbonyl (δ_C 166.0) and vinylic carbons at δ_C 120.9 (C-2) and 151.0 (C-3) in the ^{13}C n.m.r. spectrum of (**105**) (Table 1) confirmed the structure. The u.v. spectrum of (**105**) also revealed the characteristic α,β-unsaturated lactone absorption at $\lambda_{max.}$ 213 nm.

Our next objective was to introduce a 2,3-double bond into desmycosin while retaining the 20-aldehyde function. Initially we attempted to do this on the free 20-aldehydo derivatives. Thus desmycosin (**32**) was converted into 2′,4′,4″-tri-*O*-acetyldesmycosin (**42**) by treatment with acetic anhydride in pyridine. The latter on reaction with methanesulphonyl chloride in pyridine at 25 °C, afforded low yields of 2′,4′,4″-tri-*O*-acetyl-2,3-dehydro-3-deoxydesmycosin (**106**). When the mesylation of (**42**) was carried out at 100 °C followed by deprotection either with triethylamine in methanol at 70 °C, or with aqueous methanolic potassium carbonate at 25 °C, a base-catalyzed aldol reaction product (**109**) was obtained as the principal product of the reaction. Analysis of the physical data enabled a gross structure to be assigned to this derivative. The u.v. spectrum revealed the characteristic α,β-unsaturated lactone chromophore at 212 nm and the dienone chromophore at 280 nm. The e.i. mass spectrum of (**109**) revealed a molecular ion at *m/z* 754 consistent with the composition of the proposed structure. The ^{1}H n.m.r. spectrum contained a doublet at δ_H 5.62 ($J_{2,3}$ 15 Hz) due to 2-H and a doublet of doublets at δ_H 6.61 ($J_{2,3}$ 15 Hz, $J_{3,4}$ 10 Hz) due to 3-H, indicating the presence of the 2,3-ene group. The 8-Me group also occurred as a singlet at δ_H 1.29 and there was no signal due to a formyl proton. The ^{13}C n.m.r. data (Table 1) revealed a shielded lactone carbonyl carbon at δ_C 166.1 and vinylic carbons at δ_C 121.9 and 151.0 due to C-2 and

C-3 respectively. The 8-methyl occurred at δ_C 16.9 while C-8 gave rise to a signal at δ_C 59.4. The occurrence of C-9 at δ_C 205.8 suggested that the 20-hydroxy group was hydrogen bonded to the 9-oxo group. The above chemical shifts were in good agreement with those observed in these laboratories[52] for an aldol derivative (**110**) of rosaramicin, which resulted from the degradation of rosaramicin (**7**) tablets. The absolute stereochemistry at C-8 and C-20 in (**110**) had not been established. The assignment of the absolute stereochemistry at C-8 and C-20 in (**109**) and (**110**) followed from 600 MHz ^{1}H n.m.r. studies that were carried out on similar aldol products derived from desmycosin (**32**).

Desmycosin (**32**) reacted with an excess of potassium carbonate in aqueous methanol at 25 °C to form desmycosin-8β,20α-aldol (**111**). The e.i. mass spectrum of (**111**) revealed a molecular ion at *m/z* 771 consistent with the aldol structure. The u.v. spectrum of (**111**) revealed an intact dienone chromophore at 277 nm. The ^{1}H n.m.r. spectrum of (**111**) contained a singlet at δ_H 1.28 due to the 8-methyl group and showed no signal due to a formyl proton. The ^{13}C n.m.r. spectrum of (**111**) (Table 1) revealed the 8-methyl group at δ_C 17.3 while C-8 occurred at δ_C 58.3. The occurrence of C-9 at δ_C 205.6 again suggested that the 20-hydroxy group was hydrogen bonded to the 9-oxo group. In order to determine the absolute stereochemistry at C-8 and C-20, the aldol (**111**) was peracetylated using acetic anhydride in the presence of 4-dimethylaminopyridine and triethylamine. The resulting 3,20,2′,4′,4″-penta-*O*-acetyldesmycosin 8β,20α-aldol (**112**) showed good separation of the proton signals in the ^{1}H n.m.r. spectrum. 2D *J* Spectroscopy and n.O.e. difference spectroscopy[53] at 600 MHz enabled us to assign most of the protons in (**112**) unambiguously and to determine the coupling constants (Table 3).* Five *O*-acetyl groups were present in the molecule and the 20-acetate gave rise to a signal at δ_H 2.00. 20-H

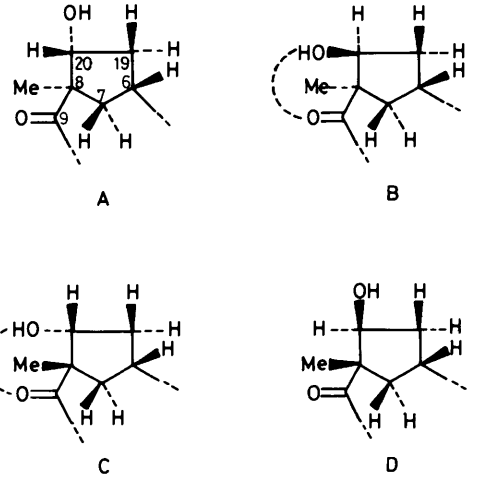
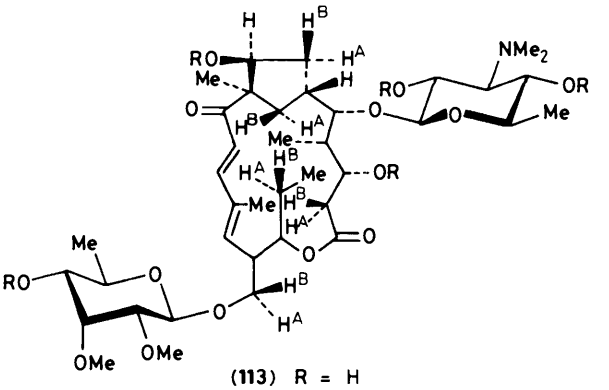


Figure. Possible partial structures for the aldol derivatives

Occurred as a doublet of doublets at δ_H 5.58 ($J_{19^A,20}$ 6.7 Hz, $J_{19^B,20}$ 2.7 Hz). The 8-methyl group gave rise to a singlet at δ_H 1.19. The protons 7^A-H and 7^B-H could not be located. An n.O.e. difference spectrum was run and when the 8-methyl signal was irradiated, a strong n.O.e. was observed at 20-H indicating that the 8-methyl and 20-H were *cis* oriented with respect to each other. Of the four possible structures for the aldol (Figure) only two, namely B and C, have the 8-methyl and 20-H in a vicinal *cis* orientation. The ^{13}C n.m.r. data (Table 1) for (**112**) revealed a signal at δ_C 57.4 for C-8 and a signal at δ_C 17.2 for the 8-methyl. The signal at δ_C 77.8 was assigned to C-20 and C-9 gave rise to a signal at δ_C 203.5, which was shielded relative to C-9 in the aldol (**111**). These data clearly supported the presence of hydrogen bonding between the 20-hydroxy and the 9-oxo group in the aldol (111), which of course was not possible in the peracetylated aldol (**112**). This information again indicated that only structures B and C, which are capable of hydrogen bonding, could accommodate the data. However, it was not possible at this point to decide which of the two structures correctly represented the aldol (**111**). Structures A and D could definitely be ruled out from the above data.

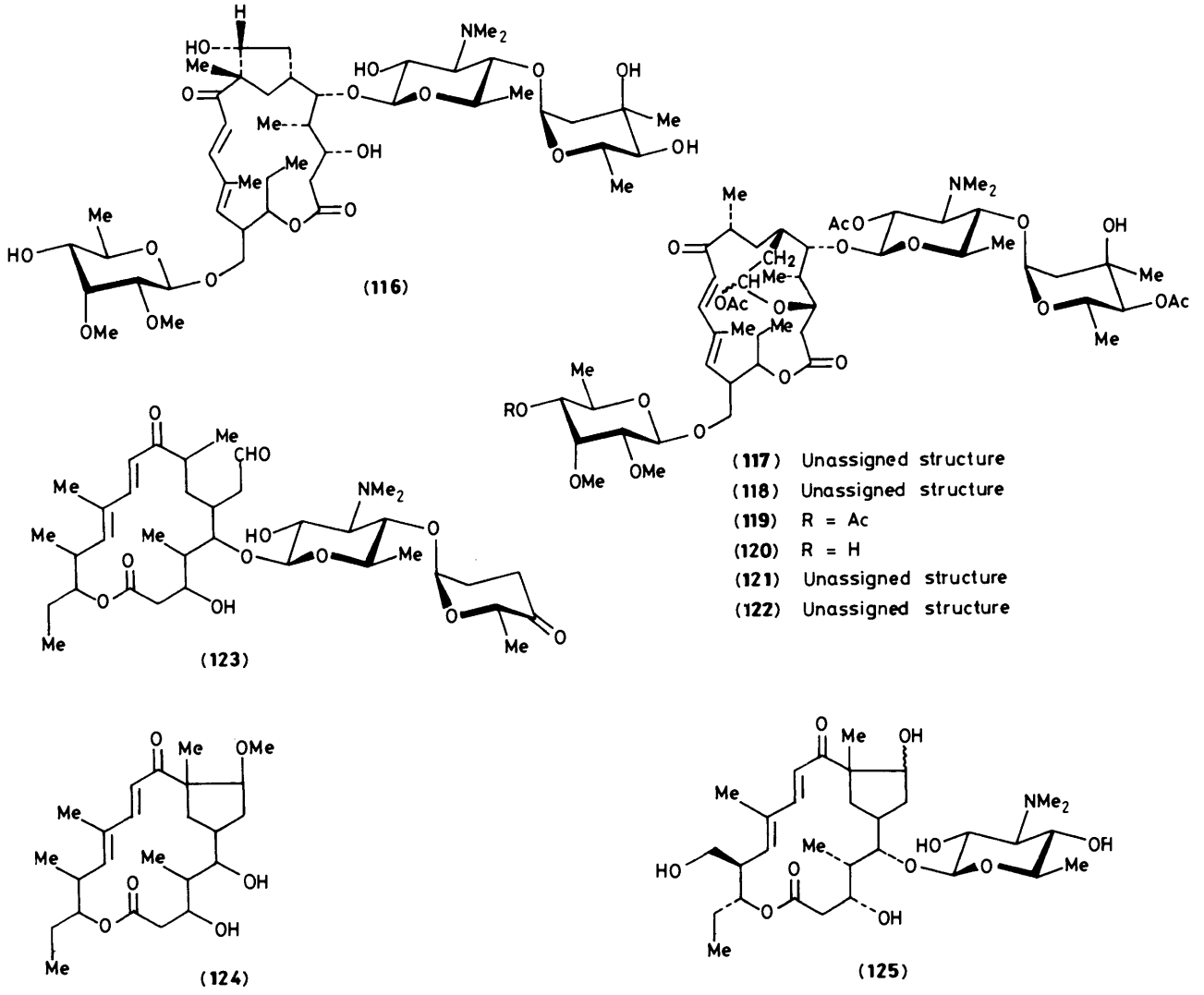
Additional data was therefore needed and it was fortuitous that treatment of desmycosin-8β,20α-aldol (**111**) with tetrabutylammonium fluoride trihydrate in tetrahydrofuran at 25 °C for extended periods afforded an isomeric aldol (**113**). The ^{1}H n.m.r. spectrum of (**113**) contained a singlet at δ_H 1.41 for the 8-



(**113**) R = H
(**114**) R = Ac
(**115**) Structure unassigned

methyl. The ^{13}C n.m.r. spectrum (Table 1) and an SFORD spectrum of (113) showed C-8 as a singlet at δ_C 54.2 clearly indicating that C-8 was a quaternary carbon. The 8-methyl gave rise to a signal at δ_C 19.9 and C-20 gave rise to a signal at δ_C 79.7, the latter being observed as a doublet in the SFORD spectrum. The signal corresponding to C-9 was strongly deshielded (δ_C 209.9) in (**113**) indicating that the 20-hydroxy group was hydrogen bonded to the 9-oxo group in this aldol as well. These data indicate that (**113**) can only have structures B or C (see Figure) since no hydrogen bonding is possible in structures A and D. The e.i. mass spectrum of (**113**) revealed a molecular ion at *m/z* 771 consistent with the assigned structure. The u.v. spectrum of (**113**) was consistent with the presence of a dienone chromophore in the molecule. Acetylation of (**113**) as described earlier, afforded 3,20,2′,4′,4″-penta-*O*-acetyldesmycosin 8α,20β,-aldol (**114**). A 2D ^{1}H n.m.r. spectrum run at 600 MHz enabled all of the protons in (**114**) to be unambiguously assigned and also gave most of the coupling constants. The data are given in Table 3. Five *O*-acetyl groups were again present in the molecule and the acetate at C-20 occurred at δ_H 1.95. 20-H Occurred as a doublet of doublets at δ_H 4.91 and the 8-methyl gave rise to a singlet at δ_H 1.27. The proton 7^A-H gave rise to a doublet of doublets at δ_H 1.47 while 7^B-H occurred as multiplet at δ_H 2.21. An n.O.e. difference spectrum was run and when the 8-methyl signal was irradiated, a strong n.O.e. was observed at 20-H, as well as a weak n.O.e. at 7^A-H. This indicated that both 20-H and 7^A-H were each in a vicinal *cis* orientation with respect to the 8-methyl group. The ^{13}C n.m.r. data for (**114**) revealed a signal at δ_C 55.8 for C-8 and a signal at δ_C 24.3 for 8-Me. The signal at δ_C 83.0 was assigned to C-20, while C-9 gave rise to a signal at δ_C 203.0 which was shielded relative to that in the aldol (**113**). This clearly supported the presence of hydrogen bonding between the 20-hydroxy and the 9-oxo groups in the

* See footnote on p. 12.



aldol (**113**) which, of course, could not occur in the acetate (**114**). It therefore follows that only partial structure B (see Figure) could accommodate the above data, indicating that both (**113**) and (**114**) were, in fact, the 8α,20β-aldols. Hence (**111**) and (**112**) by a process of elimination, must be the 8β,20α-aldols corresponding to partial structure C (see Figure). The c.d. spectra of (**111**) and (**113**) were very similar and did not prove useful in distinguishing between the two structures. The similarities between the chemical shifts of the rosaramicin aldol (**110**)[52] and (**111**) clearly indicate that the former also has the 8β,20α-stereochemistry.

When desmycosin (**32**) was allowed to react with tetrabutylammonium fluoride trihydrate at 25 °C over several days, a new base-catalyzed rearrangement product (**115**) was obtained. The latter contained no fluorine by elemental analysis and had retained the dienone chromophore. The ^{1}H n.m.r. spectrum showed the absence of a formyl proton, while the ^{13}C n.m.r. spectrum (Table 1) contained a signal at δ_C 105.2 which appears to arise from a hemiacetal carbon. The spectrum suggested that (**115**) may be a mixture of isomers, but no separation of the components could be achieved by chromatography. The deshielding observed at C-3 suggested that the 3-hydroxy group might be involved. The f.a.b. mass spectrum of (**115**) showed two intense ions at *m/z* 892 and 890.

Tylosin (**26**) on similar treatment with tetrabutylammonium fluoride trihydrate afforded small quantities of tylosin 8β,20α-aldol (**116**) as the more polar product of the reaction. The ^{1}H n.m.r. and ^{13}C n.m.r. data (Table 1) were in agreement with the data previously recorded for desmycosin-8β,20α-aldol (**111**), thus establishing the absolute stereochemistry of (**116**). In addition to (**116**), a less polar product (**117**) was also obtained in low yield, the balance of the material being unchanged tylosin (**26**). The ^{1}H n.m.r. and ^{13}C n.m.r. data (Table 1) for (**117**) closely resembled the data recorded for (**115**). In (**117**) the hemiacetal gave rise to a signal at δ_C 104.6. The f.a.b. mass spectrum showed ions at *m/z* 1036 and 1034. The same product (**117**) was also obtained in good yield when 20,4″-di-*O*-dimethyl-t-butylsilyl-20-imidazolyltylosin (**31**)[35] was treated with tetrabutylammonium fluoride trihydrate at 25 °C for 1.5 h. Peracetylation of (**117**) using acetic anhydride in the presence of 4-dimethylaminopyridine and triethylamine afforded a penta-acetate (**118**) which in a f.a.b. mass spectrum showed ions at *m/z* 1 246 and 1 244, and which was different from an authentic sample of 20,2′,4″,4‴-tetra-*O*-acetyltylosin 3,20-hemiacetal (**119**), prepared by acetylating 20,2′,4″-tri-*O*-acetyltylosin 3,20-hemiacetal (**120**).[32,35] The hemiacetal carbon C-20 gave rise to a signal at δ_C 100.9 in (**118**), while in (**119**) the corresponding signal was at δ_C 95.2. The 3,20-hemiacetal structures for (**115**) and (**117**) can therefore be ruled out.

In order to simplify the spectral analysis the corresponding hemiacetal derivative was prepared from 12,13-de-epoxy-12,13-dehydrorosaramicin (**15**). Thus treatment of (**15**) with tetra-

butylammonium fluoride trihydrate at 25 °C for several days afforded a mixture of isomers that were separated with considerable difficulty by preparative t.l.c. on alumina plates. The less-polar product (**121**) exhibited a signal δ_C 105.1 due to a hemiacetal carbon, while the more polar product (**122**) gave rise to a signal at δ_C 105.2 in the ^{13}C n.m.r. spectra (Table 1). The only significant chemical shift differences between (**121**) and (**122**) in the ^{13}C n.m.r. spectra were observed in the signals assigned to C-5, C-6, C-7, and C-19. The e.i. mass spectra of (**121**) and (**122**) showed peaks above the molecular ion of (**15**), but did not exhibit molecular ions. However, the f.a.b. mass spectra revealed ions at *m/z* 686 and 684. The elucidation of the structures of these novel hemiacetals will have to await *X*-ray studies as their structures are not obvious from the spectral data available at the present time.

De-epoxy antibiotic B-58941 (**123**)[54] when heated under reflux with a sulphonic acid resin in methanol, has been shown to give the 8,20-aldol derivative (**124**).[55] Recently a demycarosyldemycinosyltylosin 8,20-aldol (**125**)[56] has been reported to form during the vigorous acidic hydrolysis of tylosin (**26**), but the absolute stereochemistry of the product was not determined.

In view of the difficulties encountered above in introducing the 2,3-double bond into desmycosin (**32**) in compounds having a free 20-aldehyde group, we decided to first protect the 20-aldehyde group, before attempting to introduce the 2,3-double bond. Thus tylosin (**26**) on treatment with 0.1M hydrogen chloride in methanol afforded desmycosin 20-dimethylacetal (**43**). The latter was treated with acetic anhydride in pyridine to give 2′,4′,4″-tri-*O*-acetyldesmycosin 20-dimethylacetal (**44**). The triacetate (**44**) reacted smoothly with methanesulphonyl chloride in pyridine at 25 °C to give, after deprotection with triethylamine in methanol, 2,3-dehydro-3-deoxydesmycosin 20-dimethylacetal (**107**). Mild acidic hydrolysis of (**107**) with 0.1M aqueous hydrochloric acid gave the desired 2,3-dehydro-3-deoxydesmycosin (**108**). The ^1H n.m.r. and ^{13}C n.m.r. spectra (Table 1) were in agreement with the structure. By protecting the aldehyde group the formation of unwanted aldol by-products was eliminated and good yields of (**108**) were obtained.

After completion of the above studies several reports were published in which the preparation of some of the above derivatives was claimed. Thus the preparation of (**41**) by semisynthesis from desmycosin (**32**) has been described,[56] using different reagents from those described above. The deformyl derivatives (**41**) and (**30**) have also been recently prepared by bioconversion from protylonolide[57] and their demycinosyl analogues have also been reported.[58–60] The preparation of (**41**),[61] (**105**),[62] (**30**),[62] and (**108**)[61,63,64] have all been claimed in the recent patent literature.

In general the 20-*C*-alkyl and 20-deoxo-20-dihydro macrolides described above, exhibited an antibacterial spectrum similar to that of the mycinamicins.[10,65] The most active derivatives were (**33**), (**34**), (**35**), (**36**), and (**41**) which were slightly less potent than the mycinamicins.[10,65]

Experimental

Unless otherwise stated optical rotations were recorded at *c* 0.3%. I.r. spectra were recorded on a Perkin-Elmer Infracord 137, or 221 spectrometer, or on a Pye Unicam 3-200 spectrometer. U.v. spectra were run on a Cary 118 spectrometer. C.d. spectra were run on a Cary 61 spectrometer. Low-resolution e.i. mass spectra were run on a Varian MAT CH5 spectrometer. F.a.b. mass spectra were run on a Finnigan MAT 312 double focussing mass spectrometer, operating at an accelerating voltage of 3 kV. The samples were ionized by bombardment with xenon atoms produced by a saddle-field ion source from Ion Tech operating with a tube current of 2 mA at an energy of 6 keV. ^1H N.m.r. spectra were recorded at 79.5 MHz on a Varian CFT-20 spectrometer; at 100 MHz on a Varian XL-100-15 spectrometer; at 200 MHz on a Varian XL-200 spectrometer; at 400 MHz on a Varian XL-400 spectrometer; and at 600 MHz on a non-commercially available spectrometer at Carnegie-Mellon University, Pittsburgh, Pennsylvania. ^{13}C N.m.r. spectra were obtained on either a Varian FT-80, XL-100-15, XL-200, or XL-400 spectrometer. All chemical shift values are reported in p.p.m. downfield from tetramethylsilane. The ^1H n.m.r. parameters as well as the ^{13}C n.m.r. data (Table 1)* and the 600 MHz ^1H n.m.r. data (Table 3)* are listed in Supplementary Publication No. Sup 56670 (50 pp).* In general the products were worked up by pouring the reaction mixtures into water, adjusting the pH to 10, extracting with dichloromethane, drying the organic layer ($MgSO_4$), filtering, and evaporating to dryness. The products were purified by column chromatography on Baker silica gel, or by preparative t.l.c. on silica gel plates. The column size and eluant are indicated in each case. Wherever possible, reactions were performed in a dry argon atmosphere. Anhydrous tetrabutylammonium fluoride was prepared by azeotroping the trihydrate in tetrahydrofuran and toluene under high vacuum on a rotary evaporator at moderate temperatures of *ca.* 50 °C. In general, the macrolide products were colourless amorphous solids.

(11R)-11-*Acetylthio*-10,11-*dihydrorosaramicin* (**49**).—Thioacetic *S*-acid (2.62 g) was added to rosaramicin (**7**) (10 g) dissolved in dry dichloromethane (50 ml) and the solution was stirred at 25 °C for 21 h. Work-up and chromatography (120 × 5 cm; 2.5% methanol in chloroform) gave unchanged (**7**) (2.22 g, 22%) and the (11*R*)-11-acetylthio derivative (**49**) (8.32 g, 73%) (Found: C, 56.7; H, 7.65; N, 1.65; S, 5.45. $C_{33}H_{55}NO_{10}S{\cdot}0.5CHCl_3$ requires C, 55.24; H, 7.87; N, 1.95; S, 4.47%); *m/z* 658 (MH^+), $[\alpha]_D^{26}$ + 23.9° ($CHCl_3$), $[\theta]_{230}$ + 50 086, $[\theta]_{255}$ −20 670, and $[\theta]_{293}$ + 23 850 (CH_3OH); $\lambda_{max.}$(MeOH) 299 nm (ε 4 695); $\nu_{max.}$($CHCl_3$) 3 500, 1 710, 1 260, and 1 100 cm^{-1}.

General Procedures for the Thioacetic S-*Acid Additions to Dienone Macrolides.—Method 1.* The dienone macrolide (1 equiv.) and thioacetic *S*-acid (20 equiv.) were dissolved in dry dichloromethane (5—8 ml/g macrolide) and the mixture was stirred at 25 °C for 15—40 h. After work-up the product was dissolved in methanol (*ca.* 100 ml/g) and the solution kept at 25 °C for 72 h. Evaporation to dryness afforded the crude products.

Method 2. The dienone macrolide (1 equiv.) was dissolved in thioacetic *S*-acid (20 equiv.) and the mixture was stirred at 25 °C for 40 h. After work-up the product was methanolized as in method 1.

(*a*) The macrolide (**15**) (5.5 g) using method 1 afforded, after chromatography (60 × 5 cm; 3% methanol in chloroform), unchanged (**15**) (1 g, 18%) together with a cut rich in the less-polar diastereoisomer (**56**) and one rich in the more-polar diastereoisomers (**57**). Rechromatography (30 × 1.5 cm; 90% acetone in hexane) of the former gave pure (11*R*)-11-acetylthio derivative (**56**) (1.65 g, 26%) (Found: C, 61.55; H, 8.7; N, 1.95; S, 5.05. $C_{33}H_{55}NO_9S$ requires C, 61.75; H, 8.64; N, 2.18; S, 5.00%); *m/z* 642 (MH^+), $[\alpha]_D^{26}$ +83.8° ($CHCl_3$); $[\theta]_{232}$ +213 967, $[\theta]_{262}$ +19 868, and $[\theta]_{296}$ +51 963 (MeOH); $\lambda_{max.}$(CH_3OH) 231 (ε 4 780) and 286 nm (1 989); $\nu_{max.}$($CDCl_3$) 3 685, 3 460, 1 715, 1 608, 1 265, 1 196, 1 168, 1 112, and 1 052 cm^{-1}. Rechromatography (110 × 2.5 cm; 90% acetone in hexane) of the more-polar diastereoisomer gave the (11*S*)-11-acetylthio

* For details of the Supplementary Publication Scheme, see Instructions for Authors (1987), *J. Chem. Soc., Perkin Trans. 1*, 1987, Issue 1.

derivative (**57**) (964 mg, 5%) (Found: C, 61.35; H, 8.85; N, 1.9; S, 4.55. $C_{33}H_{55}NO_9S$ requires C, 61.75; H, 8.64; N, 2.18; S, 5.00%); *m/z* 642 (MH^+); $[\alpha]_D^{26}$ −5.8° ($CHCl_3$); $[\theta]_{249}$ −38 827 and $[\theta]_{268}$ −51 665 (MeOH), $\lambda_{max.}$(MeOH) 230 (ε 4 921) and 280 nm (2 552); $\nu_{max.}$($CDCl_3$) 3 510, 1 720, 1 595, 1 273, 1 170, 1 114, and 1 052 cm^{-1}.

(*b*) The macrolide (**15**) (5.5 g) using method 2 gave, after chromatography (60 × 5 cm; 80→90% acetone in hexane), unchanged (**15**) (304 mg, 6%), a cut rich in the less-polar diastereoisomer (**56**) and in (**62**), and a cut rich in the more polar diastereoisomer (**57**). Rechromatography of (**56**) and (**62**) (30 × 2.5 cm; 3% methanol in chloroform) afforded (**56**) (385 mg, 6%) and the (11*R*)-11-acetythio-9,19-aldol (**62**) (442 mg, 7%) (Found: C, 61.05; H, 8.6; N, 1.9; S, 4.65. $C_{33}H_{55}NO_9S$ requires C, 61.75; H, 8.64; N, 2.18; S, 5.00%); *m/z* 642 (MH^+), $[\alpha]_D^{26}$ +22.9° ($CHCl_3$), $[\theta]_{236}$ +220 080, $[\theta]_{270}$ −21 397, and $[\theta]_{298}$ +19 868 (MeOH); $\lambda_{max.}$(MeOH) 232 (ε 3 686) and 284 nm (1 177); $\nu_{max.}$($CDCl_3$) 3 460, 1 723, 1 685sh, 1 600, 1 263, 1 110, and 1 050 cm^{-1}. Rechromatography of (**57**) (30 × 2.5 cm; 80% acetone in hexane) gave pure (**57**) (536 mg, 9%).

(*c*) Tylosin (**26**) (5 g) using method 1 gave, after chromatography (110 × 2.5 cm; 4% methanol in chloroform), unchanged (**26**) (1.23 g, 25%), the (11*R*)-11-acetylthio derivative (**63**) (1.2 g, 22%) (Found: C, 56.55; H, 8.25; N, 1.15; S, 4.1. $C_{48}H_{81}NO_{18}S$ requires C, 58.10; H, 8.23; N, 1.41; S, 3.23%); *m/z* 992 (MH^+), $[\alpha]_D^{26}$ +16.7° ($CHCl_3$); $[\theta]_{232}$ +230 811, $[\theta]_{260}$ +35 930, and $[\theta]_{290}$ +97 559 (MeOH); $\lambda_{max.}$(CF_3CH_2OH) 230 (ε 6 022) and 286 nm (1 341); $\nu_{max.}$($CDCl_3$) 3 540, 1 716, 1 685, 1 278, and 1 055 cm^{-1}; and the (11*S*)-11-acetylthio derivatives (**64**) (1.86 g, 34%) (Found: C, 56.5; H, 8.25; N, 1.19; S, 4.13. $C_{48}H_{81}NO_{18}S$ requires C, 58.10; H, 8.23; N, 1.41; S, 3.23%); *m/z* 992 (MH^+); $[\alpha]_D^{26}$ −52.9° ($CHCl_3$); $[\theta]_{250}$ −54 546, $[\theta]_{265}$ −71.902, and $[\theta]_{300}$ +24 794 (MeOH); $\lambda_{max.}$(MeOH) 230 (ε 5 579) and 280 nm (843); $\nu_{max.}$($CDCl_3$) 3 530, 1 725, 1 688, 1 265, and 1 060 cm^{-1}.

(*d*) Desmycosin (**32**) (47.3 g) using method 1 gave, after chromatography (h.p.l.c.; Waters prep. 500; 2 cartridges; 2% methanol in chloroform), unchanged (**32**) (7.78 g, 16%), the (11*R*)-11-acetylthio derivative (**67**) (1.47 g, 3%) (Found: C, 54.6; H; 7.55; N, 1.25; S, 3.7. $C_{41}H_{69}NO_{15}S{\cdot}0.5CHCl_3$ requires C, 54.25; H, 7.65; N, 1.55; S, 3.55%); *m/z* 848 (MH^+); $[\alpha]_D^{26}$ +60.5° ($CHCl_3$); $[\theta]_{233}$ +184 690, $[\theta]_{260}$ +37 692, and $[\theta]_{290}$ +86 691 (MeOH); $\lambda_{max.}$(MeOH) 230 (ε 2 464) and 280 nm (744); $\nu_{max.}$($CDCl_3$) 3 540, 1 698, 1 660, 1 558, and 1 040 cm^{-1}; and the (11*S*)-11-acetylthio derivative (**68**) (21.44 g, 75%) (Found: C, 55.55; H, 7.7; N, 1.5; S, 3.25. $C_{41}H_{69}NO_{15}S{\cdot}0.3CHCl_3$ requires C, 55.71; H, 7.87; N, 1.59; S, 3.63%); *m/z* 848, (MH^+); $[\alpha]_D^{26}$ −25.8° ($CHCl_3$); $[\theta]_{250}$ −51 224, $[\theta]_{265}$ −68 839, and $[\theta]_{300}$ +22 271 (MeOH); $\lambda_{max.}$(MeOH) 230 (ε 4 739) and 280 nm (867); $\nu_{max.}$($CDCl_3$) 3 520, 1 730, 1 695, 1 580, 1 267, 1 080, and 1 065 cm^{-1}.

General Procedures for the Thiophenol Additions to Macrolides.—Method 1. The macrolide (1 equiv.) and thiophenol (20 equiv.) were dissolved in dry dichloromethane (9 ml/g macrolide) and the mixture was stirred at 25 °C for 24 h.

Method 2. The macrolide (1 equiv.) was dissolved in thiophenol (20 equiv.) and the mixture was stirred at 25 °C for 48 h.

(*a*) Rosaramicin (**7**) (500 mg) using method 1 gave, after chromatography (60 × 2.5 cm; 3% methanol in chloroform), the (11*R*)-11-phenylthio derivative (**50**) (401 mg, 67%) (Found: C, 63.4; H, 8.25; N, 1.85; S, 4.55. $C_{37}H_{57}NO_9S{\cdot}0.1CHCl_3$ requires C, 63.14; H, 8.16; N, 1.99; S, 4.56%); *m/z* 692 (MH^+); $[\alpha]_D^{26}$ +5.7° ($CHCl_3$); $[\theta]_{230}$ +46 129, $[\theta]_{243}$ +6 151, $[\theta]_{255}$ +26 140, $[\theta]_{268}$ +13 839, and $[\theta]_{298}$ +86 877 (MeOH); $\lambda_{max.}$(MeOH) 255 nm (ε 6 342); $\nu_{max.}$($CDCl_3$) 3 670, 3 470, 1 702, 1 320, 1 255, 1 180, 1 160, 1 100, 1 065, 1 042, and 1 020 cm^{-1}; and the (11*S*)-11-phenylthio derivative (**51**) (74 mg, 12%) (Found: C, 61.0; H, 7.9; N, 1.8; S, 4.0. $C_{37}H_{57}NO_9S{\cdot}0.4CHCl_3$ requires C, 61.07; H, 7.90; N, 1.93; S, 4.41%); *m/z* 692 (MH^+); $[\alpha]_D^{26}$ +4.3° ($CHCl_3$); $[\theta]_{223}$ −315 887, $[\theta]_{255}$ −7 521, $[\theta]_{264}$ −15 042, $[\theta]_{282}$ +18 051, and $[\theta]_{296}$ −15 042 (MeOH); $\lambda_{max.}$(MeOH) 213sh (ε 8 016) and 255 nm (5 632); $\nu_{max.}$($CDCl_3$) 3 680, 3 470, 1 710, 1 600, 1 263, 1 165, 1 110, 1 070, 1 049, and 1 028 cm^{-1}.

(*b*) The macrolide (**15**) (1 g) using method 2 gave, after chromatography (60 × 2 cm; 3% methanol in chloroform), the (11*R*)-11-phenylthio derivative (**58**) (539 mg, 45%) (Found: C, 65.4; H, 8.15; N, 1.9; S, 4.55. $C_{37}H_{57}NO_8S$ requires C, 65.74; H, 8.49; N, 2.07; S, 4.74%); *m/z* 676 (MH^+); $[\alpha]_D^{26}$ +10.7° ($CHCl_3$); $[\theta]_{250}$ −36 050, $[\theta]_{260}$ −45 062, $[\theta]_{286}$ +81 112, and $[\theta]_{305}$ +56 328sh (MeOH); $\lambda_{max.}$(MeOH) 215sh (10 950) and 264 nm (3 650); and $\nu_{max.}$($CDCl_3$) 3 480, 1 712, 1 193, 1 163, 1 108, 1 071, 1 049, and 1 027 cm^{-1}; and the (11*S*)-11-phenylthio derivative (**59**) (200 mg, 17%) (Found: C, 65.35; H, 8.2; N, 1.95; S, 5.7. $C_{37}H_{57}NO_8S$ requires C, 65.74; H, 8.49; N, 2.07; S, 4.74%); *m/z* 676 (MH^+); $[\alpha]_D^{26}$ −8.1° ($CHCl_3$); $[\theta]_{248}$ −19 784, $[\theta]_{286}$ +26 378, and $[\theta]_{300}$ + 21 432sh (MeOH); $\lambda_{max.}$(MeOH) 215sh (ε 12 521) and 257 nm (4 212); $\nu_{max.}$($CDCl_3$) 3 490, 1 718, 1 259, 1 164, 1 110, 1 073, 1 049, and 1 025 cm^{-1}.

(*c*) Desmycosin (**32**) (4 g) using method 2 gave, after chromatography (110 × 2.5 cm; 3% methanol in chloroform), the (11*R*)-11-phenylthio derivative (**70**) (2.15 g, 47%) (Found: C, 58.4; H, 7.5; N, 1.45; S, 3.35. $C_{45}H_{71}NO_{14}S{\cdot}0.3CHCl_3$ requires C, 58.88; H, 7.80; N, 1.53; S, 3.49%); *m/z* 882 (MH^+); $[\alpha]_D^{26}$ +10.3° ($CHCl_3$); $[\theta]_{252}$ −42 007 and $[\theta]_{289}$ +193 231 (MeOH); $\lambda_{max.}$(MeOH), 215sh (ε 11 325) and 263 nm (3 782); $\nu_{max.}$($CDCl_3$) 3 540, 1 714, 1 263, 1 191, 1 176, and 1 060 cm^{-1}; and the (11*S*)-11-phenylthio derivative (**71**) (2.17 g, 47%) (Found: C, 59.0; H, 7.7; N, 1.4; S, 3.55. $C_{45}H_{71}NO_{14}S{\cdot}0.3CHCl_3$ requires C, 58.88; H, 7.80; N, 1.53; S, 3.49); *m/z* 882 (MH^+); $[\alpha]_D^{26}$ −14.4° ($CHCl_3$); $[\theta]_{245}$ −14 114 and $[\theta]_{290}$ +28 228 (MeOH); $\lambda_{max.}$(MeOH) 215sh (ε 12 450) and 257 nm (3 724); $\nu_{max.}$($CDCl_3$) 3 590, 3 540, 3 460, 1 720, 1 260, 1 167, and 1 060 cm^{-1}.

General Procedures for the Reaction of the Macrolides with Diazoalkanes.—Method 1. The macrolide in dry tetrahydrofuran was treated with an excess of diazoalkane in diethyl ether at 25 °C for 14—41 h and the product was worked up in the usual manner.

Method 2. The macrolide in dry tetrahydrofuran was treated with palladium(II) acetate (6 mg/g macrolide) and the mixture was treated with an excess of diazomethane in diethyl ether at 25 °C for 20 h. The product was worked up in the usual manner.

(*a*) Compound (**49**) (5.65 g) with diazomethane using method 1, gave after chromatography (60 × 5 cm; 1.5% methanol in chloroform) the ketone (**52**) (4.05 g, 70%) (Found: C, 60.3; H, 8.35; N, 2.25. $C_{34}H_{57}NO_{10}S$ requires C, 60.78; H, 8.55; N, 2.08%); *m/z* 672 (MH^+); $[\alpha]_D^{26}$ −0.8° ($CHCl_3$); $[\theta]_{231}$ +29 498, $[\theta]_{250}$ −18 027, and $[\theta]_{292}$ +44 247 (MeOH); $\lambda_{max.}$(MeOH) 230 nm (ε 5 183); $\nu_{max.}$($CDCl_3$) 3 490, 1 710, 1 260, 1 110, and 1 045 cm^{-1}.

(*b*) Compound (**49**) (500 mg) with diazobutane using method 1 gave, after chromatography (120 × 2 cm; 2% methanol in chloroform), the ketone (**53**) (291 mg, 54%) (Found: C, 62.45; H, 8.85; N, 1.65; S, 4.6. $C_{37}H_{63}NO_{10}S$ requires C, 62.24; H, 8.89; N, 1.96; S, 4.49%); *m/z* 714 (MH^+); $[\alpha]_D^{26}$ +26.9° ($CHCl_3$); $[\theta]_{231}$ +68 230, $[\theta]_{253}$ +3 411, $[\theta]_{293}$ +75 906, and $[\theta]_{340}$ −3 411 (MeOH); $\lambda_{max.}$(MeOH) 230 (ε 4 702) and 313 nm (873), $\nu_{max.}$($CDCl_3$) 3 470, 1 730, 1 718, 1 695, 1 581, 1 265, 1 115, and 1 055 cm^{-1}.

(*c*) Compound (**56**) (500 mg) with diazomethane using method 1 gave, after chromatography (60 × 2.5 cm; 2% methanol in chloroform), the ketone (**60**) (102 mg, 20%) (Found: C, 62.35; H, 8.9; N, 2.15; S, 4.7. $C_{34}H_{57}NO_9S$ requires C

62.26; H, 8.76; N, 2.14; S, 4.89%); *m/z* 656 (MH^+); $[\alpha]_D^{26}$ +83.9° ($CHCl_3$); $[\theta]_{232}$ +208 976, $[\theta]_{260}$ +34 310, and $[\theta]_{296}$ +90 452 (MeOH); $\lambda_{max.}$(MeOH) 231 (ε 4 397) and 289 nm (1 552); $\nu_{max.}$($CDCl_3$) 3 460, 1 703, 1 270, 1 160, 1 105, and 1 050 cm^{-1}.

(*d*) Compound (**57**) (305 mg) with diazomethane using method 1 gave, after chromatography (60 × 2.5 cm; 2% methanol in chloroform), the ketone (**61**) (122 mg, 39%) (Found: 60.65; H, 8.4; N, 1.95; S, 4.7. $C_{34}H_{57}NO_9S{\cdot}0.2CHCl_3$ requires C, 60.07; H, 8.45; N, 2.06; S, 4.72%); *m/z* 656 (MH^+); $[\alpha]_D^{26}$ −2.9° ($CHCl_3$); $[\theta]_{250}$ −39 939, $[\theta]_{265}$ −46 329, and $[\theta]_{300}$ +15 976 (MeOH); $\lambda_{max.}$(MeOH) 231 (ε 5 147) and 282 nm (1 309); $\nu_{max.}$($CDCl_3$) 3 450, 1 720, 1 260, 1 160, 1 105, and 1 050 cm^{-1}.

(*e*) The macrolide (**78**) (8.8 mg) with diazomethane using method 1 gave the ketone (**83**) (10 mg, 100%); *m/z* 582 (MH^+).

(*f*) Compound (**64**) (1.14 g) with diazomethane using method 1 gave, after chromatography (60 × 2.5 cm; 2% methanol in chloroform), the ketone (**66**) (917 mg, 79%) (Found: 56.95; H, 8.15; N, 1.25; S, 3.8. $C_{49}H_{83}NO_{18}S$ requires C, 58.49; H, 8.31; N, 1.39; S, 3.19%); *m/z* 1 006 (MH^+), $[\alpha]_D^{26}$ −58.9° ($CHCl_3$); $[\theta]_{232}$ −83 012, $[\theta]_{252}$ −50 914, $[\theta]_{265}$ −64 196, and $[\theta]_{300}$ +24 350 (MeOH); $\lambda_{max.}$(MeOH) 231 nm (ε 6 145); $\nu_{max.}$($CDCl_3$) 3 480, 1 720, 1 690, 1 265, 1 170, and 1 065 cm^{-1}.

(*g*) The macrolides (**87**) and (**86**) (88 mg) with diazomethane using method 1, gave after preparative t.l.c. on silica gel plates (20 × 20 cm; 250 μm; 7% methanol in chloroform), the ketones (**91**) and (**90**) (25 mg, 28%); *m/z* 932 (MH^+).

(*h*) Compound (**68**) (3 g) with diazomethane using method 1 gave, after chromatography (110 × 2.5 cm; 4% methanol in chloroform), the ketone (**72**) (2.17 g, 71%) (Found: C, 57.45; H, 8.0; N, 1.6; S, 3.55. $C_{42}H_{71}NO_{15}S$ requires C, 58.5; H, 8.30; N, 1.62; S, 3.72%); *m/z* 862 (MH^+), $[\alpha]_D^{26}$ −32.1° ($CHCl_3$); $[\theta]_{230}$ −72 428, $[\theta]_{253}$ −51 759, $[\theta]_{264}$ −62 081, $[\theta]_{298}$ +24 833, and $[\theta]_{350}$ −4 139 (MeOH); $\lambda_{max.}$(MeOH) 231 nm (ε 5 925); $\nu_{max.}$($CDCl_3$) 3 450, 1 720, 1 695, 1 580, 1 080, and 1 062 cm^{-1}.

(*i*) Compound (**68**) (4 g) with diazomethane using method 1 gave, after chromatography (60 × 2.5 cm; 4% methanol in chloroform), the ketone (**73**) (2.41 g, 58%) (Found: C, 58.5; H, 8.5; N, 1.65; S, 3.95. $C_{43}H_{73}NO_{15}S$ requires C, 58.95; H, 8.40; N, 1.60; S, 3.66%); *m/z* 876 (MH^+); $[\alpha]_D^{26}$ −32.4° ($CHCl_3$); $[\theta]_{231}$ −104 453, $[\theta]_{251}$ −53 506, $[\theta]_{264}$ −70 346, and $[\theta]_{298}$ +23 449 (MeOH), $\lambda_{max.}$(MeOH) 231 (ε 5 749) and 274 nm (594); $\nu_{max.}$($CDCl_3$) 3 470, 1 736, 1 722, 1 692, 1 225, 1 082, and 1 065 cm^{-1}.

(*j*) Compound (**68**) (4 g) with diazopropane using method 1 gave, after chromatography (60 × 2.5 cm; 5% methanol in chloroform), the ketone (**74**) (2.97 g, 71%) (Found: C, 58.35; H, 8.4; N, 1.45; S, 4.35. $C_{44}H_{75}NO_{15}S$ requires C, 59.37; H, 8.49; N, 1.57; S, 3.60%); *m/z* 890 (MH^+); $[\alpha]_D^{26}$ −32.6° ($CHCl_3$); $[\theta]_{232}$ −111 002, $[\theta]_{252}$ −57 636, $[\theta]_{265}$ −74 927, and $[\theta]_{298}$ +21 347 (MeOH); $\lambda_{max.}$(MeOH) 231 nm (ε 6 035); $\nu_{max.}$($CDCl_3$) 3 460, 1 730, 1 718, 1 690, 1 260, and 1 060 cm^{-1}.

(*k*) Compound (**68**) (4 g) with diazobutane using method 1 gave, after chromatography (60 × 2.5 cm; 4% methanol in chloroform), the ketone (**75**) (2.89 g, 68%) (Found: C, 59.45; H, 8.5; N, 1.35; S, 3.8. $C_{45}H_{77}NO_{15}S$ requires C, 59.78; H, 8.58; N, 1.55; S, 3.55%); *m/z* 904 (MH^+); $[\alpha]_D^{26}$ −32.3° ($CHCl_3$); $[\theta]_{230}$ −107 027, $[\theta]_{250}$ −60 894, $[\theta]_{265}$ −75 657, and $[\theta]_{298}$ +19 375 (MeOH); $\lambda_{max.}$(MeOH) 231 nm (ε 6 002); $\nu_{max.}$($CDCl_3$) 3 465, 1 735, 1 720, 1 695, 1 263, 1 080, and 1 065 cm^{-1}.

(*l*) The macrolide (**45**) (500 mg) with diazomethane using method 1 gave, after chromatography (30 × 2 cm; 1% methanol in chloroform), the ketone (**46**) (309 mg, 61%) (Found: C, 60.85; H, 8.4; N, 1.45. $C_{43}H_{71}NO_5$ requires C, 61.34; H, 8.50; N, 1.66%); *m/z* 842 (MH^+); $[\alpha]_D^{26}$ −66.7° ($CHCl_3$); $\lambda_{max.}$(MeOH) 227sh (ε 25 252), 230 (25 873), and 238sh nm (17 800); $\nu_{max.}$($CDCl_3$) 3 600, 2 470, 1 725, 1 150, 1 078, 1 055, and 1 025 cm^{-1}.

(*m*) Rosaramicin (**7**) (500 mg) with diazomethane using method 1 gave, after chromatography (110 × 2.5 cm; 5% methanol in chloroform), the oxo-11,10-methyleneaminoimino derivative (**92**) (171 mg, 31%) (Found: C, 59.8; H, 8.35; N, 6.2. $C_{33}H_{55}N_3O_9{\cdot}0.2CHCl_3$ requires C, 59.90; H, 8.38; N, 6.35%); *m/z* 638 (MH^+); $[\alpha]_D^{26}$ −40.0° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 206 (ε 2 119) and 306 nm (10 627); $[\theta]_{245}$ +16 866, $[\theta]_{275}$ −8 433sh, and $[\theta]_{332}$ −87 394 (MeOH); $\nu_{max.}$($CDCl_3$) 3 500, 3 440, 1 735, 1 720, 1 670, 1 585, 1 420, 1 175, 1 115, and 1 055 cm^{-1}; and the oxo-11,10-methyleneaminoimino derivative (**93**) (99 mg, 18%) (Found: C, 56.4; H, 8.05; N, 5.05. $C_{33}H_{55}N_3O_9{\cdot}0.5CHCl_3$ requires C, 56.82; H, 7.95; N, 6.03%); *m/z* 638 (MH^+); $[\alpha]_D^{26}$ +34.0° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 207 (ε 2 700) and 313 nm (11 650); $[\theta]_{230}$ −51 513, $[\theta]_{270}$ +9 366sh, $[\theta]_{312}$ +162 344, and $[\theta]_{353}$ −42 147 (MeOH); $\nu_{max.}$($CDCl_3$) 3 510, 3 450, 1 730, 1 710, 1 665, 1 580, 1 420, 1 275, 1 175, 1 118, and 1 055 cm^{-1}; and the 20-*O*-methyl-11,10-methyleneaminoimino-3,20-hemiacetal derivative (**94**) (105 mg, 19%) (Found: C, 60.1; H, 8.35; N, 6.05. $C_{33}H_{55}N_3O_9{\cdot}0.2CHCl_3$ requires C, 59.88; H, 8.38; N, 6.35%); *m/z* 638 (MH^+); $[\alpha]_D^{26}$ −21.7° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 210 (ε 898) and 305 nm (ε 12 799); $[\theta]_{230}$ +33 272, $[\theta]_{296}$ −278 272, $[\theta]_{325}$ +375 062, and $[\theta]_{354}$ −93 765 (MeOH); $\nu_{max.}$($CDCl_3$) 3 540, 1 730, 1 720, 1 668, 1 585, 1 420, 1 200, 1 170, 1 115, 1 075, and 1 053 cm^{-1}.

(*n*) Rosaramicin (**7**) (500 mg) using method 2 gave, after chromatography (110 × 2.5 cm; 10% methanol in chloroform), the ketone (**8**) (30 mg, 6%), unchanged (**7**) (33 mg, 7%), and the hemiacetal (**94**) (292 mg, 53%).

(*o*) The macrolide (**12**) (1 g) using method 2 gave, after chromatography (60 × 5 cm; 5% methanol in chloroform), the 11,10-methyleneaminoimino derivative (**95**) (426 mg, 40%) (Found: C, 55.95; H, 7.9; N, 8.5; S, 4.3. $C_{36}H_{61}N_5O_{10}S$ requires C, 57.20; H, 8.13; N, 9.27; S, 4.24%); *m/z* 756 (MH^+); $[\alpha]_D^{26}$ −22.0° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 209 (ε 2 953), 235 (4 523), and 308 nm (9 905); $[\theta]_{247}$ −23 625, $[\theta]_{300}$ +62 370, and $[\theta]_{336}$ −81 269 (MeOH); $\nu_{max.}$($CDCl_3$) 3 420, 1 720, 1 660, 1 578, 1 418, 1 310, 1 130, and 1 050 cm^{-1}.

(*p*) The macrolide (**15**) (2 g) with diazomethane using method 1 gave, after chromatography (106 g; 2% methanol in chloroform), unchanged (**15**) (20 mg, 1%), the oxo-11,10-methyleneaminoimino derivative (**96**) (703 mg, 32%) (Found: C, 63.65; H, 8.85; N, 6.15. $C_{33}H_{55}N_3O_8$ requires C, 63.74; H, 8.92; N, 6.76%); *m/z* 622 (MH^+); $[\alpha]_D^{26}$ −45.0° ($CHCl_3$); $[\theta]_{228}$ +177 220, $[\theta]_{267}$ −54 410, $[\theta]_{305}$ +130 583, and $[\theta]_{345}$ −161 674 (MeOH); $\lambda_{max.}$(CF_3CH_2OH) 220 (ε 4 782) and 309 nm (8 833); $\nu_{max.}$($CDCl_3$) 3 450, 1 700, 1 665, 1 400, 1 190, 1 100, and 1 040 cm^{-1}; the 20-*O*-methyl-11,10-methyleneaminoimino-3,20-hemiacetal (**97**) (1.29 g, 59%) (Found: C, 62.4; H, 8.55; N, 6.25. $C_{33}H_{55}N_3O_8$ requires C, 64.74; H, 8.92; N, 6.76%); *m/z* 622 (MH^+), $[\alpha]_D^{26}$ −38.2° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 230 (ε 4 469) and 282 nm (6 437); $\nu_{max.}$($CDCl_3$) 3 470, 1 695, 1 655, 1 190, 1 090, and 1 063 cm^{-1}.

(*q*) The macrolide (**22**) (1 g) using method 2 gave, after chromatography (60 × 2.5 cm; 5% methanol in chloroform), unchanged (**22**) (249 mg, 25%), and the 11,10-methyleneaminoimino derivative (**98**) (94 mg, 9%) (Found: C, 56.1; H, 8.3; N, 8.35; S, 4.1. $C_{36}H_{61}N_5O_9S{\cdot}0.2CHCl_3$ requires C, 56.60; H, 8.05; N, 9.17; S, 4.20%); *m/z* 740 (MH^+); $[\alpha]_D^{26}$ −40.0° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 235 (ε 3 435) and 310 nm (5 116); $[\theta]_{230}$ +149 710, $[\theta]_{265}$ −71 290, $[\theta]_{307}$ +253 081, and $[\theta]_{347}$ −196 049 (MeOH); $\nu_{max.}$($CDCl_3$) 3 470, 3 400, 1 700, 1 660, 1 580, 1 415, 1 315, 1 195, 1 130, and 1 055 cm^{-1}.

(*r*) Tylosin (**26**) (4.13 g) with diazomethane using method 1 gave, after chromatography (300 g; 5% methanol in chloroform), the oxo-11,10-methyleneaminoimino derivative (**99**) (2.06 g, 47%) (Found: C, 55.45; H, 7.7; N, 2.95. $C_{48}H_{81}$-

N_3O_{17}·0.5$CHCl_3$ requires C, 55.87; H, 7.91; N, 4.07%); *m/z* 972 (MH^+); $[\alpha]_D^{26}$ −80.5° ($CHCl_3$); $\lambda_{max.}$(MeOH) 220sh (ε 4 328) and 309 nm (8 938); $\nu_{max.}$($CDCl_3$) 3 540, 3 470, 3 400, 1 710, 1 660, 1 413, 1 163, 1 080, and 1 055 cm^{-1}.

(*s*) Desmycosin (**32**) (80 mg) with diazomethane using method 1 gave, after chromatography (15 × 2 cm; 3% methanol in chloroform), the oxo-11,10-methyleneaminoimino derivative (**100**) (56 mg, 65%), *m/z* 827 (M^+); $[\alpha]_D^{26}$ −65.7° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 309 nm (ε 9 077); $\nu_{max.}$($CDCl_3$) 3 700, 3 570, 3 420, 1 705, 1 660, 1 190, 1 170, and 1 058 cm^{-1}.

General Procedure for the Deprotection of the 11-*Acetylthio Derivatives.*—The 11-acetylthio derivative (1 equiv.) was dissolved in dry tetrahydrofuran containing anhydrous tetrabutylammonium fluoride (2—4 equiv.) and the mixture was stirred at 25 °C for 1—4.5 h. The product was worked up in the usual way.

(*a*) Compound (**63**) (100 mg) gave, after chromatography (15 × 2 cm; 2.5% methanol in chloroform), tylosin (26) (43 mg, 47%).

(*b*) Compound (**52**) (5.18 g) gave, after chromatography (120 × 2 cm; 1.5% methanol in chloroform), the ketone (**8**) (2.74 g, 60%) (Found: C, 64.15; H, 8.8; N, 2.3. $C_{32}H_{53}NO_9$ requires C, 64.51; H, 8.97; N, 2.35%); *m/z* 596 (MH^+); $[\alpha]_D^{26}$ −19.1° ($CHCl_3$); $[\theta]_{240}$ −187 459 (MeOH); $\lambda_{max.}$(MeOH) 239 nm (ε 12 093); $\nu_{max.}$($CDCl_3$) 3 470, 1 730, 1 710, 1 685, 1 618, 1 180, 1 105, 1 068, and 1 045 cm^{-1}.

(*c*) Compound (**53**) (1.24 g) gave, after chromatography (30 × 6 cm; 2% methanol in chloroform), the ketone (**10**) (850 mg, 77%) (Found: C, 63.35; H, 9.25; N, 2.1. $C_{35}H_{59}NO_9$·0.2$CHCl_3$ requires C, 63.50; H, 8.90; N, 2.12%); *m/z* 638 (MH^+); $[\alpha]_D^{26}$ −20.0° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 239 nm (ε 11 457); $\nu_{max.}$($CDCl_3$) 3 470, 1 740, 1 710, 1 695, 1 625, 1 185, and 1 050 cm^{-1}.

(*d*) Compounds (**60**) and (**61**) (60:40) (120 mg) gave, after chromatography (15 × 2 cm; 2.5% methanol in chloroform), the ketone (**16**) (58 mg, 54%).

(*e*) Compound (**66**) (716 mg) gave, after chromatography (60 × 2.5 cm) (1.5% methanol in chloroform), the ketone (**28**) (442 mg, 67%) (Found: C, 60.4; H, 8.7; N, 1.25. $C_{47}H_{79}NO_{17}$ requires C, 60.69; H, 8.56; N, 1.51%); *m/z* 930 (MH^+); $[\alpha]_D^{26}$ −54.2° ($CHCl_3$); $[\theta]_{230}$ −4 442, $[\theta]_{268}$ +72 183, $[\theta]_{294}$ −78 846, $[\theta]_{320}$ −22 210, and $[\theta]_{345}$ −25 542 (MeOH); $\lambda_{max.}$(CF_3CH_2OH) 286 nm (ε 20 626); $\nu_{max.}$($CDCl_3$) 3 550, 1 715, 1 680, 1 595, 1 165, and 1 060 cm^{-1}.

(*f*) The adduct (**72**) (2.17 g) gave, after chromatography (60 × 2.5 cm; 2% methanol in chloroform), the ketone (**33**) (1.16 g, 59%) (Found: C, 61.15; H, 9.0; N, 2.2. $C_{40}H_{67}NO_{14}$ requires C, 61.13; H, 8.59; N, 1.78%); *m/z* 786 (MH^+); $[\alpha]_D^{26}$ −22.1° ($CHCl_3$); $[\theta]_{228}$ −13 337, $[\theta]_{268}$ +55 255, $[\theta]_{294}$ −80 024, $[\theta]_{325}$ −19 053, and $[\theta]_{340}$ −20 959 (MeOH); $\lambda_{max.}$(MeOH) 283 nm (ε 20 745); $\nu_{max.}$($CDCl_3$) 3 550, 1 705, 1 670, 1 580, 1 165, and 1 060 cm^{-1}.

(*g*) The adduct (**73**) (2.01 g) gave, after chromatography (60 × 2.5 cm; 2.5% methanol in chloroform), the ketone (**34**) (1.46 g, 79%) (Found: C, 61.3; H, 8.8; N, 1.75. $C_{41}H_{69}NO_{14}$ requires C, 61.56; H, 8.69; N, 1.75%); *m/z* 800 (MH^+); $[\alpha]_D^{26}$ −25.5° ($CHCl_3$); $[\theta]_{228}$ −17 857, $[\theta]_{270}$ +69 445, $[\theta]_{294}$ −95 239, $[\theta]_{320}$ −25 794, and $[\theta]_{340}$ −27 778 (MeOH); $\lambda_{max.}$(CF_3CH_2OH) 286 nm (ε 19 248); $\nu_{max.}$($CDCl_3$) 3 550, 1 735, 1 710, 1 675, 1 592, 1 162, 1 080, and 1 060 cm^{-1}.

(*h*) The adduct (**74**) (2.54 g) gave, after chromatography (60 × 2.5 cm; 2.5% methanol in chloroform), the ketone (**35**) (1.13 g, 49%) (Found: C, 61.75; H, 8.9; N, 1.45. $C_{42}H_{71}NO_{14}$ requires C, 61.97; H, 8.79; N, 1.72%); *m/z* 814 (MH^+); $[\alpha]_D^{26}$ −27.5° ($CHCl_3$); $[\theta]_{288}$ −9 798, $[\theta]_{277}$ +54 870, $[\theta]_{294}$ −94 063, $[\theta]_{325}$ −19 596, and $[\theta]_{340}$ −21 556 (MeOH); $\lambda_{max.}$(MeOH) 283 nm (ε 20 880); $\nu_{max.}$($CDCl_3$) 3 550, 1 730, 1 705, 1 678, 1 595, 1 165, and 1 060 cm^{-1}.

(*i*) The adduct (**75**) (2.62 g) gave, after chromatography (60 × 2.5 cm; 1.5% methanol in chloroform), the ketone (**36**) (1.48 g, 62%) (Found: C, 62.2; H, 8.95; N, 1.75. $C_{43}H_{73}NO_{14}$ requires C, 62.37; H, 8.89; N, 1.69%); *m/z* 828 (MH^+), $[\alpha]_D^{26}$ −36.1° ($CHCl_3$); $[\theta]_{228}$ −15 963, $[\theta]_{277}$ +55 869, $[\theta]_{293}$ −118 772, $[\theta]_{322}$ −27 935, and $[\theta]_{340}$ −29 930 (MeOH); $\lambda_{max.}$(MeOH) 283 nm (ε 21 871); $\nu_{max.}$($CDCl_3$) 3 575, 3 480, 1 740, 1 715, 1 688, 1 600, 1 180, and 1 060 cm^{-1}.

De-epoxidation Procedure.—(*a*) 20-*C*-Methylrosaramicin (**8**) (680 mg) was dissolved in 0.5M sulphuric acid (12.5 ml). A solution of chromium(III) chloride hexahydrate (1.37 g) in water (5 ml) was eluted through a zinc-amalgam bed (30 ml)* which was then washed with water (40 ml) and the combined eluates were added to the above solution. The reaction was stirred at 25 °C for 21 h. The aqueous solution was extracted with diethyl ether and the latter was discarded. The aqueous layer was adjusted to pH 10.2 by addition of 50% aqueous sodium hydroxide and was extracted three times with diethyl ether (500 ml). Chromatography (15 × 2 cm; 1.5% methanol in chloroform) gave the ketone (**16**) (480 mg, 72%) (Found: C, 62.25; H, 8.2; N, 2.2. $C_{32}H_{53}NO_8$·0.3$CHCl_3$ requires C, 62.44; H, 8.68; N, 2.28%); *m/z* 580 (MH^+), $[\alpha]_D^{26}$ −19.1° ($CHCl_3$); $[\theta]_{263}$ +26 377; $[\theta]_{293}$ −106 150, $[\theta]_{319}$ −21 873, and $[\theta]_{338}$ −32 167 (MeOH); $\lambda_{max.}$(MeOH) 284 nm (ε 18 612); $\nu_{max.}$($CDCl_3$) 3 490, 1 730, 1 710, 1 678, 1 590, 1 183, 1 170, 1 110, and 1 050 cm^{-1}.

(*b*) 20-*C*-Butylrosaramicin (**10**) (520 mg) was treated as described in (*a*) to give, after chromatography (30 × 2 cm; 1% methanol in chloroform), the ketone (**20**) (366 mg, 72%) (Found: C, 67.2; H, 9.35; N, 1.95; $C_{35}H_{59}NO_8$ requires C, 67.60; H, 9.56; N, 2.25%); *m/z* 622 (MH^+); $[\alpha]_D^{26}$ −38.0° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 228 nm (ε 19 888); $\nu_{max.}$($CDCl_3$) 3 480, 1 740, 1 710, 1 680, 1 600, 1 185, 1 170, and 1 050 cm^{-1}.

(*c*) 20-Deoxo-20-dihydrorosaramicin (**13**) (1.35 g) was treated as described in (*a*) to give, after chromatography (30 × 5 cm; 3% methanol in chloroform), the dienone (**23**) (1.29 g, 96%) (Found: C, 67.1; H, 9.65; N, 2.2. $C_{31}H_{53}NO_7$ requires C, 67.48; H, 9.68; N, 2.54%); $[\alpha]_D^{26}$ −6.5° ($CHCl_3$); $\lambda_{max.}$(MeOH) 282 nm (ε 21 802); $\nu_{max.}$($CHCl_3$) 3 570, 3 490, 2 980, 2 880, 1 715, 1 680, 1 590, 1 310, 1 185, 1 100, and 1 045 cm^{-1}.

General Procedure for the Reaction of Diphenyl Disulphide and Tributylphosphine with Macrolides.—The macrolide (1 equiv.), diphenyl disulphide (1.1 equiv.), and tributylphosphine (1.2 equiv.) were dissolved in dry tetrahydrofuran (2 ml/g macrolide) and the mixture was stirred at 25 °C for 24 h. The product was worked up in the usual manner.

(*a*) Rosaramicin (**7**) (10 g) gave, after chromatography (110 × 5 cm; 2→5% methanol in chloroform), the 20-diphenylthioacetal (**11**) (1.35 g, 10%) (Found: C, 65.5; H, 7.85; N, 1.15. S, 8.75. $C_{43}H_{61}NO_8S_2$ requires C, 65.87; H, 7.84; N, 8.18%); *m/z* 784 (MH^+); $[\alpha]_D^{26}$ −74.2° ($CHCl_3$); $[\theta]_{223}$ −240 749, $[\theta]_{233}$ −147 973, $[\theta]_{253}$ −205 517, $[\theta]_{280}$ −48 933sh, $[\theta]_{305}$ 0, and $[\theta]_{330}$ −15 658 (MeOH); $\lambda_{max.}$(MeOH) 215 (ε 21 898) and 234 nm (19 785); $\nu_{max.}$($CDCl_3$) 3 520, 1 720, 1 690, 1 620, 1 192, 1 075, and 1 050 cm^{-1}; the (11*R*)-11-phenylthio-20-diphenylthioacetal (**54**) (4.01 g, 26%) (Found: C, 65.1; H, 7.45; N, 1.35; S, 10.9. $C_{49}H_{67}NO_8S_3$ requires C, 65.81; H, 7.55; N, 1.57; S, 10.76%); *m/z* 894 (MH^+);

* Preparation of the zinc amalgam. Granular zinc (15 g) was added to a solution of 0.1M mercuric chloride in 1M hydrochloric acid (45 ml) and the mixture was stirred at 25 °C for 10 min. The zinc amalgam was poured onto a column and washed with water (three column volumes) and then 0.5M sulphuric acid (one column volume). The column was kept under positive argon pressure at all times.

$[\alpha]_D^{26}$ −27.0° ($CHCl_3$); $[\theta]_{223}$ −30 300, $[\theta]_{236}$ +84 407, $[\theta]_{277}$ −90 900, and $[\theta]_{305}$ +54 436 (MeOH); $\lambda_{max.}$(CF_3CH_2OH) 215sh (ε 23 903) and 254 nm (13 048); $\nu_{max.}$($CDCl_3$) 3 480, 1 735, 1 720, 1 590, 1 200, 1 180, 1 120, 1 080, 1 060, and 1 035 cm^{-1}; an unknown (**55**) (927 mg, 6%) (Found: C, 65.65; H, 8.4; N, 1.35; S, 10.75. $C_{49}H_{67}NO_8S_3$ requires C, 65.81; H, 7.55; N, 1.57; S, 10.76%); *m/z* 894 (MH^+); $[\alpha]_D^{26}$ −26.3° ($CHCl_3$); $[\theta]_{225}$ −188 202, $[\theta]_{239}$ +19 469, and $[\theta]_{262}$ −140 610 (MeOH); $\lambda_{max.}$(CF_3CH_2OH) 253 nm (ε 12 020); $\nu_{max.}$($CDCl_3$) 3 500, 1 730, 1 710, 1 590, 1 270, 1 173, and 1 050 cm^{-1}; unchanged (**7**) (1.6 g, 16%) and the (11*R*)-11-phenylthio derivative (**50**) (2.74 g, 23%).

(*b*) Treatment of tylosin (**26**) (10 g) with diphenyl disulphide (3.3 equiv.) and tributylphosphine (3.6 equiv.) for 66 h gave, after chromatography (160 × 5 cm; 3% methanol in chloroform), the (11*R*)-11-phenylthio-20-diphenylthioacetal (**65**) (2.6 g, 19%) (Found: C, 61.9; H, 7.45; N, 0.95; S, 7.6. $C_{64}H_{93}NO_{16}S_3$ requires C, 62.56; H, 7.63; N, 1.14; S, 7.83%), *m/z* 1 118 (MH^+); $[\alpha]_D^{26}$ −55.1° ($CHCl_3$); $\lambda_{max.}$(MeOH) 258 nm (ε 12 747); $\nu_{max.}$($CDCl_3$) 3 540, 1 710, 1 683, 1 160, and 1 053 cm^{-1}.

(*c*) The macrolide (**15**) (5 g) gave, after chromatography (120 × 5 cm; 3% methanol in chloroform), the 20-diphenylthioacetal (**17**) (3 g, 44%) (Found: C, 67.3; H, 8.0; N, 1.6; S, 9.0. $C_{43}H_{61}NO_7S_2$ requires C, 67.24; H, 8.01; N, 1.82; S, 8.35%); *m/z* 768 (MH^+); $[\alpha]_D^{26}$ −67.3° ($CHCl_3$); $\lambda_{max.}$(MeOH) 275 nm (ε 19 443); $\nu_{max.}$($CDCl_3$) 3 450, 1 705, 1 675, 1 590, 1 180, 1 100, and 1 045 cm^{-1}.

(9R)-12,13-*De-epoxy*-12,13-*dihydro*-20-*deoxo*-9-*dehydrorosaramicin* 20-*Diphenylthioacetal* (**79**) *and* (9S)-12,13-*De-epoxy*-12,13-*dehydro*-20-*deoxo*-9-*dihydrorosaramicin* 20-*Diphenylthioacetal* (**77**).—The macrolide (**17**) (2 g) and sodium borohydride (400 mg) were dissolved in dry methanol (30 ml) and the mixture was stirred at 25 °C for 3.5 h. Chromatography (110 × 2.5 cm; 3% methanol in chloroform) gave the (9*R*)-9-dihydro derivative (**76**) (1.12 g, 56%) (Found: C, 66.75; H, 8.25; N, 1.6; S, 8.65. $C_{43}H_{63}NO_7S_2$ requires C, 67.07; H, 8.25; N, 1.82; S, 8.33%); *m/z* 770 (MH^+); $[\alpha]_D^{26}$ −26.2° ($CHCl_3$); $\lambda_{max.}$(MeOH) 222sh (ε 24 343), 227 (24 822), 232sh (23 959), and 258 nm (8 395); $\nu_{max.}$($CDCl_3$) 3 600, 3 460, 1 705, 1 580, 1 183, 1 100, 1 068, 1 045, and 1 020 cm^{-1}; and the (9*S*)-9-dihydro derivative (**77**) (124 mg, 6%) (Found: C, 67.2; H, 8.15; N, 1.7; S, 8.7. $C_{43}H_{63}NO_7S_2$ requires C, 67.07; H, 8.25; N, 1.82; S, 8.33%); *m/z* 770 (MH^+); $[\alpha]_D^{26}$ 0° ($CHCl_3$); $\lambda_{max.}$(MeOH) 218 (ε 24 067), 227 (22 740), 228 (22 399), 256sh nm (11 939); $\nu_{max.}$($CDCl_3$) 3 460, 1 705, 1 580, 1 160, 1 100, 1 068, and 1 042 cm^{-1}.

(9R)-12,13-*De-epoxy*-12,13-*dehydro*-9-*dihydrorosaramicin* (**78**).—The macrolide (**76**) (600 mg), mercury(II) chloride (529 mg), and mercury(II) oxide (254 mg) were dissolved in 90% tetrahydrofuran–water (30 ml) and the mixture was heated under reflux at 70 °C for 24 h. Chromatography (30 × 2.5 cm; 3% methanol in chloroform) gave the aldehyde (**78**) (110 mg, 25%) (Found: C, 62.25; H, 8.55; N, 1.95. $C_{31}H_{53}NO_8 \cdot 0.2CHCl_3$ requires C, 62.93; H, 9.03; N, 2.37%); *m/z* 568 (MH^+); $[\alpha]_D^{26}$ 0° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 233 nm (ε 21 965); $\nu_{max.}$($CDCl_3$) 3 600, 3 500, 1 720, 1 190, 1 112, 1 070, 1 050, and 1 025 cm^{-1}.

(9S)-12,13-*De-epoxy*-12,13-*dehydro*-9-*dihydrorosaramicin* (**79**).—The macrolide (**77**) (290 mg) was treated as described in the previous experiment and chromatographed (16 g; 5% methanol in chloroform) followed by preparative t.l.c. (20 × 20 cm, 250 μm; 10% methanol in chloroform), to give the aldehyde (**79**) (44 mg, 21%); *m/z* 568 (MH^+).

2′,20-*Di*-O-*Acetyl*-12,13-*de-epoxy*-12,13-*dehydrorosaramicin* 3,20-*Hemiacetal* (**84**).—12,13-De-epoxy-12,13-dehydrorosaramicin (**15**) (4.9 g) and anhydrous potassium carbonate (9.6 g) were added to acetic anhydride (31.8 ml) and the mixture was heated under reflux at 60 °C for 7 h. The solution was evaporated to dryness under reduced pressure and the residue was azeotroped with toluene. Chromatography (30 × 5 cm; 20% acetone in hexane) gave the hemiacetal (**84**) (3.67 g, 65%) (Found: C, 63.35; H, 8.35; N, 1.95. $C_{35}H_{55}NO_{10} \cdot 0.1CHCl_3$ requires C, 63.53; H, 8.38; N, 2.12%); *m/z* 650 (MH^+); $[\alpha]_D^{26}$ −38.5° ($CHCl_3$); $\lambda_{max.}$(EtOH) 285 nm (ε 17 064); $\nu_{max.}$($CDCl_3$) 3 500, 1 740, 1 730, 1 710, 1 650, 1 240, and 1 060 cm^{-1}.

Reduction of 2′,20-*Di*-O-*acetyl*-12,13-*de-epoxy*-12,13-*dehydrorosaramicin* 3,20-*Hemiacetal* (**84**).—(i) The hemiacetal (**84**) (1.9 g) was dissolved in methanol (60 ml) and borohydride exchange resin (5.89 g) was added. The mixture was stirred at 25 °C for 24 h. The resin was filtered off and washed with methanol. The combined filtrates were evaporated to dryness and the residue was taken up in methanol (100 ml) containing triethylamine (10 ml) and the solution was heated under reflux at 65 °C for 48 h. Chromatography (110 × 2.5 cm; 5% methanol in chloroform) gave de-epoxyrosaramicin (**15**) (23 mg, 1%), a mixture of (9*R*/*S*)-9-dihydro derivatives (**78**) and (**79**) (3:2) (733 mg, 44%) (Found: C, 64.99; H, 9.41; N, 2.56. $C_{31}H_{53}NO_8$ requires C, 65.58; H, 9.41; N, 2.47%); *m/z* 568 (MH^+); $[\alpha]_D^{26}$ + 5.7° ($CHCl_3$) ; $\lambda_{max.}$ (MeOH) 231sh (ε22 704) and 235 nm (23 522); $\nu_{max.}$($CDCl_3$) 3 600, 3 480, 1 715, 1 188, 1 110, 1 070, 1 045, and 1 022 cm^{-1}; and a mixture of (9*R*/*S*)-9,20-tetrahydro derivatives (**81**) and (**82**) (1:2) (200 mg, 12%); *m/z* 570 (MH^+).

(ii) The hemiacetal (**84**) (250 mg) was dissolved in dry isopropyl alcohol (7 ml) and the solution was cooled to 0 °C. Sodium borohydride (58.2 mg) was added and the mixture was stirred at 0 °C for 30 min. After work-up the residue was taken up in 2% triethylamine in methanol (50 ml) and heated at 64 °C for 68 h. Chromatography (30 × 5 cm; 2.5% methanol in chloroform) gave the 2′-*O*-acetyl derivative (**18**) (17 mg, 7%) (Found: C, 63.6; H, 8.75; N, 2.5. $C_{33}H_{55}NO_9 \cdot 0.1CHCl_3$ requires C, 63.75; H, 8.92; N, 2.25%); *m/z* 610 (MH^+); $[\alpha]_D^{26}$ −26.0° ($CHCl_3$); $\lambda_{max.}$(MeOH) 282 nm (ε 16 053); $\nu_{max.}$($CDCl_3$) 3 520, 1 720, 1 672, 1 628, 1 590, 1 263, 1 182, 1 108, and 1 048 cm^{-1}; de-epoxyrosaramicin (**15**) (15 mg, 7%); and the (9*S*)-9,20-tetrahydro derivative (**82**) (132 mg, 60%), *m/z* 568 (MH^+); $\nu_{max.}$($CDCl_3$) 3 600, 3 460, 1 707, 1 188, 1 110, 1 074, and 1 058 cm^{-1}.

20,2′,4″,4‴-*Tetra*-O-*acetyltylosin* 3,20-*Hemiacetal* (**85**).—Tylosin (**26**) (20 g) and anhydrous potassium carbonate (24.1 g) were added to acetic anhydride (60 ml) and the slurry was stirred under reflux at 60 °C for 7 h. The slurry was evaporated to dryness and the residue was azeotroped with toluene. Chromatography (160 × 5 cm; 15→70% acetone in hexane) gave the hemiacetal (**85**) (7.84 g, 33%) (Found: C, 59.6; H, 7.65; N, 1.1. $C_{54}H_{85}NO_{21}$ requires C, 59.82; H, 7.90; N, 1.29%); *m/z* 1 084 (MH^+); $[\alpha]_D^{26}$ −75.5° ($CHCl_3$); $\lambda_{max.}$(MeOH) 279 nm (ε 23 139); $\nu_{max.}$($CDCl_3$) 3 470, 1 735, 1 240, and 1 050 cm^{-1}; and the triacetate (**29**) (8.63 g, 38%) (Found: C, 59.8; H, 7.65; N, 1.15. $C_{52}H_{83}NO_{20}$ requires C, 59.93; H, 8.03; N, 1.34%); *m/z* 1 042 (MH^+); $[\alpha]_D^{26}$ −54.7° ($CHCl_3$); $\lambda_{max.}$(MeOH) 281 nm (ε 20 212); $\nu_{max.}$($CDCl_3$) 3 480, 1 735, 1 240, and 1 050 cm^{-1}.

(9S)-9-*Dihydrotylosin* (**86**) *and* (9R)-9-*Dihydrotylosin* (**87**).—20,2′,4″,4‴-Tetra-*O*-acetyltylosin 3,20-hemiacetal (**85**) (6.84 g) was dissolved in dry methanol (50 ml) and sodium borohydride (955 mg) was added. The mixture was stirred at 0 °C for 15 min and at 25 °C for a total of 3.5 h. After work-up the residue was taken up in methanol (100 ml) containing triethylamine (2 ml) and the solution was heated under reflux at 65 °C for 68 h. Chromatography (110 × 5 cm; 30→50% acetone in hexane)

afforded (9*R*/*S*)-9-dihydrotylosin (**87**)/(**86**) (1.39 g, 24%) and (9*R*/*S*)-9,20-tetrahydrotylosin (**89**)/(**88**) (1.64 g, 28%).

A portion of (**87**)/(**86**) (943 mg) was rechromatographed (110 × 2.5 cm; 20%→35% acetone in hexane) to give, (9*S*)-9-dihydrotylosin (**86**) (187 mg) (Found: C, 59.5; H, 8.25; N, 1.3. $C_{46}H_{79}NO_{17}$ requires C, 60.18; H, 8.64; N, 1.53%); *m*/*z* 918 (MH^+); $[\alpha]_D^{26}$ −31.7° ($CHCl_3$); $\lambda_{max.}$(MeOH) 230sh (ε 20 278), 235 (20 999), and 242sh nm (14 645); $\nu_{max.}$($CDCl_3$) 3 530, 3 450, 1 715, 1 600, 1 185, 1 160, and 1 050 cm^{-1}; and (9*R*)-9-dihydrotylosin (**87**) (184 mg) (Found: C, 59.9; H, 8.4; N, 1.4. $C_{46}H_{79}NO_{17}$ requires C, 60.18; H, 8.64; N, 1.53%); *m*/*z* 918 (MH^+); $[\alpha]_D^{26}$ −29.9° ($CHCl_3$); $\lambda_{max.}$(MeOH) 231sh (ε 23 154), 234 (23 567), and 242sh nm (16 506); $\nu_{max.}$($CDCl_3$) 3 540, 3 450, 1 715, 1 600, 1 185, 1 160, and 1 050 cm^{-1}.

A portion of (**89**)/(**88**) (2.03 g) was rechromatographed (110 × 2.5 cm; 35% acetone in hexane) to give (9*S*)-9,20-tetrahydrotylosin (**88**) (318 mg) (Found: C, 59.2; H, 8.5; N, 1.25. $C_{46}H_{81}NO_{17}$ requires C, 60.04; H, 8.87; N, 1.52%); *m*/*z* 920 (MH^+); $[\alpha]_D^{26}$ −27.2° ($CHCl_3$); $\lambda_{max.}$(MeOH) 230sh (ε 23 424), 235 (24 475), and 242sh nm (17 294); $\nu_{max.}$($CDCl_3$) 3 450, 1 705, 1 180, 1 155, and 1 050 cm^{-1}; and (9*R*)-9,20-tetrahydrotylosin (**89**) (385 mg) (Found: C, 58.85; H, 8.45; N, 1.3. $C_{46}H_{81}NO_{17}$ requires C, 60.04; H, 8.87; N, 1.52%); *m*/*z* 920 (MH^+); $[\alpha]_D^{26}$ −24.2° ($CHCl_3$); $\lambda_{max.}$(MeOH) 230sh (ε 25 002), 234 (25 475), and 242sh nm (17 907); $\nu_{max.}$($CDCl_3$) 3 475, 1 712, 1 192, 1 163, and 1 058 cm^{-1}. The balance of the recovered material was a mixture of (**89**) and (**88**) (767 mg).

Oxidation of 9-Dihydromacrolides.—(i) The ketone (**83**) (9 mg) was dissolved in pyridine (0.02 ml). A solution of chromium trioxide (12.4 mg) in water (0.01 ml) was added dropwise to pyridine (0.04 ml) at 0 °C. The latter solution was added to the solution of the macrolide and the mixture was stirred at 25 °C for 2 h. Preparative t.l.c. (20 × 20 cm, 1 000 μm; 20% methanol in chloroform) gave the ketone (**16**) (5 mg, 56%) and unchanged (**83**) (2 mg, 22%).

(ii) (9*R*,*S*)-9-Dihydro-20-*C*-methyltylosin (**91**)/(**90**) (10 mg) and triethylamine (0.5 ml) were dissolved in dry dichloromethane (3 ml). 4-Dimethylaminopyridinium chlorochromate (11.1 mg) was added and the mixture was stirred under dry nitrogen at 25 °C for 23 h. Preparative t.l.c. (20 × 20 cm, 1 000 μm; 7% methanol in chloroform) gave 20-*C*-methyltylosin (**28**) (1 mg, 10%).

(iii) (9*R*,*S*)-9-Dihydro-20-*C*-methyltylosin (**91**)/(**90**) (18 mg) was dissolved in pyridine (0.036 ml). A solution of chromium trioxide (15.3 mg) was dissolved in water (0.018 ml) and the latter was added dropwise to pyridine (0.072 ml) at 0 °C. The latter solution was then added to the solution of the macrolide and the mixture was stirred at 25 °C for 2 h. Preparative t.l.c. (20 × 20 cm, 250 μm; 10% methanol in chloroform) gave 20-*C*-methyltylosin (**28**) (10 mg, 55%).

General Procedures for the Preparation of the Hydrazones.—*Method 1.* The macrolide (1 equiv.) and 4-aminothiomorpholine *S*,*S*-dioxide (1.2 equiv.) were dissolved in dry tetrahydrofuran (50 ml/g macrolide) and the mixture was stirred at 25 °C for 17 h.

(*a*) The macrolide (**68**) (600 mg) gave, after chromatography (60 × 2.5 cm; 3% methanol in chloroform), the hydrazone (**69**) (533 mg, 77%) (Found: C, 54.4; H, 7.55; N, 4.0; S, 6.25. $C_{45}H_{77}N_3O_{16}S_2{\cdot}0.1CHCl_3$ requires C, 54.48; H, 7.82; N, 4.24; S, 6.46%); *m*/*z* 980 (MH^+); $[\alpha]_D^{26}$ −1.4° ($CHCl_3$); $[\theta]_{227}$ −26 293, $[\theta]_{254}$ −102 780, and $[\theta]_{302}$ +23 902 (MeOH); $\lambda_{max.}$(MeOH) 233 (ε 9 902) and 282 nm (2 225); $\nu_{max.}$($CDCl_3$) 3 538, 3 430, 1 712, 1 682, 1 308, 1 258, 1 182, 1 163, 1 122, and 1 058 cm^{-1}.

(*b*) The macrolide (**78**) (729 mg) gave, after chromatography (50 g; 5% methanol in chloroform), the hydrazone (**80**) (900 mg, 100%) (Found: C, 55.8; H, 8.25; N, 6.25; S, 5.7. $C_{35}H_{61}N_3O_9S{\cdot}0.5CHCl_3$ requires C, 55.34; H, 8.09; N, 5.53; S, 4.22%); *m*/*z* 700 (MH^+); $[\alpha]_D^{26}$ +2.6° ($CHCl_3$); $[\theta]_{245}$ −263 077 (MeOH); $\lambda_{max.}$(MeOH) 234 nm (ε 27 344); $\nu_{max.}$($CDCl_3$) 3 480, 1 710, 1 460, 1 310, 1 190, 1 129, 1 075, and 1 050 cm^{-1}.

Method 2. The macrolide (1 equiv.), toluene-*p*-sulphonic acid (0.1—1 equiv.), and 4-aminothiomorpholine *S*,*S*-dioxide (2—10 equiv.) were dissolved in ethanol (50 ml/g macrolide) and the mixture was either allowed to stand at 25 °C for 40—69 h, or it was heated at 60 °C for 25 h.

(*a*) The macrolide (**8**) (100 mg) gave, after chromatography (90 × 2 cm; 1.4% methanol in chloroform), the hydrazone (**9**) (62 mg, 51%) (Found: C, 58.6; H, 8.25; N, 5.15. $C_{36}H_{61}N_3O_{10}S$ requires C, 59.40; H, 8.45; N, 5.77%); *m*/*z* 728 (MH^+); $[\alpha]_D^{26}$ −60.0° ($CHCl_3$); $\lambda_{max.}$(MeOH) 240 (ε 12 156) and 283 nm (3 895); $\nu_{max.}$($CDCl_3$) 3 520, 1 720, 1 710, 1 690, 1 620, 1 580, 1 195, 1 128, and 1 053 cm^{-1}.

(*b*) The macrolide (**16**) (125 mg) gave, after preparative t.l.c. (20 × 20 cm, 250 μm; 10% methanol in chloroform) and chromatography (15 × 1 cm; 2.5% methanol in chloroform), the hydrazone (**19**) (74 mg, 48%) (Found: C, 60.9; H, 8.7; N, 5.85. $C_{36}H_{61}N_3O_9S$ requires C, 60.73; H, 8.64; N, 5.90%); *m*/*z* 712 (MH^+); $[\alpha]_D^{26}$ −86.7° ($CHCl_3$); $\lambda_{max.}$(MeOH) 281 nm (ε 20 624); $\nu_{max.}$($CDCl_3$) 3 480, 1 705, 1 675, 1 590, 1 295, 1 183, 1 115, and 1 048 cm^{-1}.

(*c*) The macrolide (**20**) (250 mg) gave, after chromatography (30 × 2 cm; 2.5% methanol in chloroform), the hydrazone (**21**) (187 mg, 62%) (Found: C, 56.0; H, 8.05; N, 5.2. $C_{39}H_{67}N_3O_9S{\cdot}0.7CHCl_3$ requires C, 55.98; H, 8.06; N, 1.67%); *m*/*z* 754 (MH^+); $[\alpha]_D^{26}$ −111.9° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 285 nm (ε 18 135); $\nu_{max.}$($CDCl_3$) 3 470, 1 720, 1 705, 1 675, 1 590, 1 295, 1 193, 1 120, and 1 045 cm^{-1}.

12,13-*De-epoxy*-2,3:12,13-*dehydro*-20-*deoxo*-3-*deoxy*-20-*di-hydrorosaramicin* (**103**).—20-Deoxo-20-dihydrorosaramicin (**13**)* (4 g) was dissolved in dry acetone (150 ml) and acetic anhydride (5 ml) was added. The mixture was allowed to remain at 25 °C for 17 h. Chromatography (60 × 5 cm; 50% acetone in hexane) gave 2′-*O*-acetyl-20-deoxo-20-dihydrorosaramicin (**14**)* (3 g).

A portion (2 g) of (**14**) was dissolved in dry pyridine (180 ml) and methanesulphonyl chloride (1 ml) was added. The mixture was heated at 80 °C for 48 h. Additional methanesulphonyl chloride (1 ml) was added and the reaction was continued for a further 48 h. After the work-up, the residue was dissolved in methanol (100 ml) and the mixture was heated at 80 °C for 73 h. Chromatography (30 × 5 cm; 3% methanol in chloroform) gave 2,3-dehydro-20-deoxo-3-deoxy-20-dihydrorosaramicin (**102**)* (816 mg). The epoxide (**102**) (816 mg) was de-epoxidised as described earlier to give, after chromatography (30 × 3 cm; 3% methanol in chloroform), the dienone (**103**) (341 mg, 14%) (Found: C, 67.0; H, 8.75; N, 1.75; M^+, 533.3691. $C_{31}H_{51}NO_6$ requires C, 69.76; H, 9.63; N, 2.62%; *M*, 533.3716); $[\alpha]_D^{26}$ +15.3° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 212 (ε 18 710) and 288 nm (14 682); $\nu_{max.}$($CDCl_3$) 3 490, 2 990, 2 950, 2 900, 1 715, 1 700, 1 680, 1 598, 1 322, 1 240, 1 180, 1 110, and 1 050 cm^{-1}.

12,13-*De-epoxy*-12,13-*dehydro*-20-*dihydrorosaramicin* (**24**).—12,13-De-epoxy-12,13-dehydrorosaramicin (**15**) (1 g) was dissolved in methanol (200 ml) and a pH 7.5 buffer solution† (200 ml) was added. Sodium borohydride (33.5 mg) in methanol (25 ml) and pH 7.5 buffer solution† (25 ml) was added dropwise at 25 °C over 1 h to the stirred solution. The stirring was continued at 25 °C for 16 h. The solution was evaporated to dryness. The residue was taken up in chloroform–10% aqueous acetic acid

* Contained 40% of the 12,13-de-epoxy-12,13-dehydro derivative.

† Prepared by mixing 0.1M potassium dihydrogen phosphate (400 ml) with 0.1M sodium hydroxide (330 ml).

and the mixture was shaken. The pH was adjusted to 7.4 with concentrated aqueous sodium hydroxide and the chloroform layer was worked up in the usual way. Chromatography (30 × 5 cm; 4% methanol in chloroform) gave the alcohol (**24**) (834 mg, 83%) (Found: C, 65.15; H, 8.25; N, 2.3. $C_{31}H_{53}NO_8$ requires C, 65.58; H, 9.41; N, 2.47%); $[\alpha]_D^{26}$ +10.6° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 288 nm (ε 21 322); $\nu_{max.}$($CDCl_3$) 3 500, 2 975, 2 950, 2 890, 1 710, 1 680, 1 590, 1 315, 1 183, and 1 040 cm^{-1}.

20-*Dihydrodesmycosin* (**37**).—Desmycosin (**32**) (8 g) was dissolved in methanol (200 ml) and a pH 7.5 buffer solution (200 ml). Sodium borohydride (197 mg) dissolved in methanol (50 ml) and buffer (50 ml) was added dropwise over 1.5 h to the stirred solution at 25 °C. After 1.5 h, additional sodium borohydride (197 mg) in methanol (50 ml) and buffer† (50 ml) was added dropwise over 1.5 h. The mixture was stirred at 25 °C for 16 h. Additional sodium borohydride (40 mg) in methanol (10 ml) and buffer† (10 ml) was added and after 45 min the reaction volume was reduced to 60 ml. The product was worked up as described in the previous experiment. Chromatography (120 × 5 cm; 6% methanol in chloroform) gave 20-dihydrodesmycosin (**37**) (6.1 g, 76%) (Found: C, 59.8; H, 8.6; N, 1.65. $C_{39}H_{67}NO_{14}$ requires C, 60.46; H, 8.73; N, 1.81%); $[\alpha]_D^{26}$ −11.2° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 285 nm (ε 22 711); $\nu_{max.}$($CDCl_3$) 3 570, 3 500, 2 990, 2 950, 2 900, 1 715, 1 680, 1 595, 1 188, 1 170, and 1 060 cm^{-1}.

Preparation of 20-*Halogenomacrolides*.—*Method 1*. The 20-dihydromacrolide (1 equiv.) and carbon tetrahalide (*x* equiv.) were dissolved in dry dimethylformamide (100 ml/1.5 g macrolide). The mixture was cooled to −45 °C and a solution of tris(dimethylamino)phosphorus amide (1.6 equiv.) in dry dimethylformamide (50 ml) was added over a period of 1 h. The mixture was allowed to warm to 25 °C after which it was heated at 80 °C for 20 h. The product was worked up in the usual way.

(*a*) 12,13-De-epoxy-12,13-dehydro-20-dihydrorosaramicin (**24**) (1.8 g) and CCl_4 (*x* = 6) gave, after chromatography (60 × 5 cm; 2% methanol in chloroform), the 20-chloro macrolide (**25**) (1.64 g, 94%) (Found: C, 62.25; H, 8.65; Cl, 5.65; N, 1.5. $C_{31}H_{52}ClNO_7$ requires C, 63.52; H, 8.94; Cl, 6.05; N, 2.39%); $[\alpha]_D^{26}$ −29.7° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 286 nm (ε 20 506); $\nu_{max.}$($CDCl_3$) 3 580, 2 980, 2 950, 2 885, 1 710, 1 678, 1 590, 1 315, 1 183, and 1 045 cm^{-1}.

(*b*) 20-Dihydrodesmycosin (**37**) (1.5 g) and CCl_4 (*x* = 2) gave, after chromatography (110 × 2.5 cm; 3% methanol in chloroform), the 20-chloro macrolide (**38**) (1.03 g, 67%) (Found: C, 58.0; H, 8.25; Cl, 4.75; N, 1.4. $C_{39}H_{66}ClNO_{13}$ requires C, 59.12; H, 8.40; Cl, 4.47; N, 1.77%); $[\alpha]_D^{26}$ −26.7° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 285 nm (ε 22 582); $\nu_{max.}$($CDCl_3$) 3 570, 3 530, 2 950, 2 905, 2 850, 1 710, 1 672, 1 590, 1 315, 1 185, 1 163, 1 075, and 1 055 cm^{-1}.

(*c*) 20-Dihydrodesmycosin (**37**) (1.5 g) and CBr_4 (*x* = 2) gave, after chromatography (110 × 2.5 cm; 3% methanol in chloroform), the 20-bromo macrolide (**39**) (674 mg, 42%) (Found: C, 55.9; H, 8.05; Br, 10.15; N, 1.6. $C_{39}H_{66}BrNO_{13}$ requires C, 56.21; H, 7.98; Br, 9.59; N, 1.68%); $[\alpha]_D^{26}$ −33.7° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 285 nm (ε 23 090); $\nu_{max.}$($CDCl_3$) 3 570, 2 980, 2 950, 2 895, 1 718, 1 680, 1 598, 1 320, 1 190, 1 170, and 1 060 cm^{-1}.

Method 2. The 20-dihydro macrolide (1 equiv.) and methyltriphenoxyphosphonium iodide (freshly washed with ethyl acetate; *x* equiv.) were dissolved in dry dimethylformamide (100—200 ml/5 g macrolide) and the mixture kept at 25 °C for *y* h. Methanol (50 ml) was added and after 30 min, the solution was evaporated to dryness, taken up in chloroform, and washed with aqueous sodium thiosulphate. The product was worked up in the usual manner.

(*a*) 20-Dihydrodesmycosin (**37**) (2.46 g) (*x* = 2.4, *y* = 18) gave, after chromatography (100 × 2.5 cm; 3% methanol in chloroform), the 20-iodo derivative (**40**) (749 mg, 27%) (Found: C, 52.95; H, 7.4; I, 16.55; N, 1.4. $C_{39}H_{66}INO_{13}$ requires C, 52.98; H, 7.52; I, 14.35, N, 1.58%); $[\alpha]_D^{26}$ −40.6° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 284 nm (ε 23 422); $\nu_{max.}$($CDCl_3$) 3 570, 2 980, 2 940, 2 890, 1 718, 1 680, 1 597, 1 318, 1 188, 1 165, 1 080, and 1 060 cm^{-1}. The forecuts from the column were re-chromatographed twice (110 × 2.5 cm; 3% methanol in chloroform) to give 3″,4″-dehydro-20,4″-dideoxy-20-dihydro-20-iododesmycosin (**104**) (220 mg, 8%) (Found: C, 53.9; H, 7.6; I, 14.77; N, 1.4. $C_{39}H_{64}INO_{12}$ requires C, 54.10; H, 7.45; I, 14.66; N, 1.62%); $[\alpha]_D^{26}$ −49.5° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 284 nm (ε 21 959); $\nu_{max.}$($CDCl_3$) 3 600, 2 980, 2 930, 2 870, 1 720, 1 680, 1 600, 1 322, 1 190, 1 170, and 1 062 cm^{-1}.

(*b*) 20-Dihydrodesmycosin (**37**) (5 g) (*x* = 2, *y* = 4.5) gave, after chromatography, the 20-iodide (**40**) (3.6 g, 62%).

20-*Deoxo*-20-*dihydrodesmycosin* (**41**).—The iodide (**40**) (1 g) was dissolved in dry tetrahydrofuran (150 ml). Freshly distilled tributyltin hydride (10 ml) was added and the mixture stirred at 60 °C for 70 h. Chromatography (30 × 5 cm; 2% methanol in chloroform) gave 20-deoxo-20-dihydrodesmycosin (**41**) (830 mg, 99%) (Found: C, 59.5; H, 8.6; N, 1.5. $C_{39}H_{67}NO_{13}$·0.25$CHCl_3$ requires C, 59.85; H, 8.55; N, 1.78%); *m/z* 757 (M^+); $[\alpha]_D^{26}$ −10.9° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 286 nm (ε 14 189).

20-*Deoxo*-3-*deoxy*-2,3-*dehydro*-20-*dihydrodesmycosin* (**105**).—20-Deoxo-20-dihydrodesmycosin (**41**) (1 g) was dissolved in dry pyridine (75 ml). Acetic anhydride (0.62 ml) was added and the mixture was stirred at 25 °C for 48 h. Additional acetic anhydride (0.62 ml) was added and the mixture was stirred at 25 °C for a further 77 h. After work-up the residue (861 mg) was dissolved in dry pyridine (80 ml) and methanesulphonyl chloride (0.75 ml) was added. The mixture was heated at 80 °C for 46 h. Additional methanesulphonyl chloride (0.32 ml) was added and the heating was continued for a further 18 h. The product was worked up and the residue was dissolved in methanol (70 ml) containing triethylamine (10 ml) and the mixture was heated at 65 °C under reflux for 68 h. Additional triethylamine (5 ml) was added and the heating was continued for a further 18 h.

Chromatography (30 × 5 cm; 2.5% methanol in chloroform) gave 20-deoxo-3-deoxy-2,3-dehydro-20-dihydrodesmycosin (**105**) (520 mg, 53%) (Found: C, 62.15; H, 8.6; N, 1.65. $C_{39}H_{65}NO_{12}$ requires C, 63.34; H, 8.86; N, 1.90%); $[\alpha]_D^{26}$ −5.9° ($CDCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 213 (ε 19 769) and 287 nm (19 220); $\nu_{max.}$($CDCl_3$) 3 620, 3 580, 2 970, 2 940, 2 900, 1 708, 1 675, 1 590, 1 320, 1 170, and 1 060 cm^{-1}.

2′,4′,4″-*Tri*-O-*acetyldesmycosin* (**42**).—Desmycosin (**32**) (2 g) was dissolved in dry pyridine (50 ml) and acetic anhydride (873 mg) was added. After 48 h, additional acetic anhydride (221 mg) was added and the mixture was allowed to remain at 25 °C for a total of 86 h. Chromatography (20 × 5 cm; chloroform) gave 2′,4′,4″-tri-*O*-acetyldesmycosin (**42**) (897 mg, 39%) (Found: C, 60.45; H, 8.05; N, 1.15. $C_{45}H_{71}NO_{17}$ requires C, 60.19; H, 7.79; N, 1.56%); $[\alpha]_D^{26}$ −7.7° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 286 nm (ε 22 147); $\nu_{max.}$($CDCl_3$) 3 550, 2 980, 2 940, 2 900, 1 740, 1 720, 1 685, 1 595, 1 235, 1 170, and 1 050 cm^{-1}.

2′,4′,4″-*Tri*-O-*acetyl*-2,3-*dehydro*-3-*deoxydesmycosin* (**106**).—2′,4′,4″-Tri-*O*-acetyldesmycosin (**42**) (1 g) was dissolved in dry pyridine (100 ml) and methanesulphonyl chloride (0.85 ml) was added. The mixture was allowed to remain at 25 °C for 150 h. Repeated chromatography (30 × 5 cm; 20% ethyl acetate in dichloromethane), and preparative t.l.c. (20 × 20 cm, 250 μm;

50% ethyl acetate in dichloromethane) and (30 × 2 cm; 50% ethyl acetate in dichloromethane) gave the 2,3-ene (**106**) (83 mg, 8%) (Found: C, 60.55; H, 7.8; N, 1.4. $C_{45}H_{69}NO_{16}$ requires C, 61.36; H, 7.90; N, 1.59%); $[\alpha]_D^{26}$ −2.3° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 210sh (ε 19 550) and 287 nm (19 550); $\nu_{max.}$($CDCl_3$) 2 980, 2 940, 2 890, 1 735, 1 675, 1 595, 1 235, 1 168, and 1 055 cm^{-1}.

2,3-*Dehydro*-3-*deoxydesmycosin* 8β,20α-*Aldol* (**109**).—(i) 2′,4′,4″-Tri-*O*-acetyldesmycosin (**42**) (4.0 g) was dissolved in dry pyridine (350 ml). Methanesulphonyl chloride (4.3 ml) was added and the mixture was stirred at 100 °C under reflux, for 72 h. After work-up the product was dissolved in methanol (200 ml) containing triethylamine (10 ml) and heated at 70 °C for 16 h. Chromatography (120 × 5 cm; 8% methanol in chloroform) and (30 × 5 cm; 5% methanol in chloroform) gave 2,3-dehydro-3-deoxydesmycosin 8β,20α-aldol (**109**) (800 mg, 20%) (Found: C, 61.4; H, 8.5; N, 1.55. $C_{39}H_{63}NO_{13}$ requires C, 62.13; H, 8.42; N, 1.86%); $[\alpha]_D^{26}$ +10.8° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 212 (ε 21 193) and 280 nm (18 761); $\nu_{max.}$($CDCl_3$) 3 610, 3 550, 2 975, 2 940, 2 880, 1 705, 1 675, 1 645, 1 595, 1 185, 1 165, 1 070, and 1 055 cm^{-1}.

(ii) 2′,4′,4″-Tri-*O*-acetyldesmycosin (**42**) (2 g) was dissolved in dry pyridine (200 ml). Methanesulphonyl chloride (2.15 ml) was added and the mixture was heated at 100 °C under argon for 75 h. Chromatography (60 × 5 cm; 40% ethyl acetate in dichloromethane) gave a product (932 mg) which was dissolved in methanol (220 ml); a solution of potassium carbonate (3.73 g) in water (30 ml) was then added to it. The mixture was stirred at 25 °C for 19 h after which chromatography (60 × 5 cm; 10% methanol in chloroform) gave the aldol (**109**) (263 mg, 16%).

Desmycosin 8β,20α-*Aldol* (**111**).—Desmycosin (**32**) (5.3 g) was dissolved in methanol (300 ml) and a solution of potassium carbonate (4.48 g) in water (75 ml) was added. The solution was stirred at 25 °C for 18 h after which chromatography (30 × 5 cm; 7% methanol in chloroform) gave desmycosin 8β,20α-aldol (**111**) (1.87 g, 35%) (Found: C, 60.85; H, 9.5; N, 1.55. $C_{39}H_{65}NO_{14}$ requires C, 60.62; H, 8.49; N, 1.81%); $[\alpha]_D^{26}$ +10.8° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 277 nm (ε 18 613); $[\theta]_{217}$ −1 174, $[\theta]_{270}$ +18 497, and $[\theta]_{323}$ −4 991 (CF_3CH_2OH); $\nu_{max.}$($CDCl_3$) 3 610, 3 540, 2 970, 2 940, 2 890, 1 705, 1 680, 1 600, 1 312, 1 265, 1 185, 1 168, and 1 060 cm^{-1}.

3,20,2′,4′,4″-*Penta*-O-*acetyldesmycosin* 8β,20α-*Aldol* (**112**).—Desmycosin 8β,20α-aldol (**111**) (617 mg), 4-dimethylaminopyridine (960 mg), and triethylamine (2 ml) were dissolved in dry dichloromethane (100 ml). Acetic anhydride (0.8 ml) was added and the mixture was allowed to remain at 25 °C for 18 h. Chromatography (15 × 2 cm; 20% acetone in hexane), (15 × 2 cm; 8% acetone in hexane), and (15 × 2 cm; 7% ethyl acetate in dichloromethane) gave 3,20,2′,4′,4″-penta-*O*-acetyldesmycosin 8β,20α-aldol (**112**) (433 mg, 58%) (Found: C, 59.7; H, 7.75; N, 1.25. $C_{49}H_{75}NO_{19}$ requires C, 59.93; H, 7.70; N, 1.42%); $[\alpha]_D^{26}$ −5.2° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 278 nm (ε 18 997); $\nu_{max.}$($CDCl_3$) 2 970, 2 940, 2 890, 1 735, 1 680, 1 595, 1 235, and 1 050 cm^{-1}.

Desmycosin 8α,20β-*Aldol* (**113**).—Desmycosin 8β,20α-aldol (**111**) (1.1 g) was dissolved in dry tetrahydrofuran (180 ml) and tetrabutylammonium fluoride trihydrate (436 mg) was added. The solution was stirred at 25 °C for 5 days. Chromatography (30 × 5 cm; 3.5% methanol in chloroform) gave desmycosin 8α,20β-aldol (**113**) (258 mg, 24%) (Found: C, 59.7; H, 8.4; N, 1.65. $C_{39}H_{65}NO_{14}$ requires C, 60.62; H, 8.49; N, 1.81%); $[\alpha]_D^{26}$ +4.9° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 281 nm (ε 19 193), $[\theta]_{222}$ +4 463, $[\theta]_{275}$ +19 805, and $[\theta]_{324}$ −5 300 (CF_3CH_2OH); $\nu_{max.}$($CDCl_3$) 3 570, 2 990, 2 950, 2 900, 1 710, 1 672, 1 595, 1 315, 1 165, and 1 060 cm^{-1}.

3,20,2′,4′,4″-*Penta*-O-*acetyldesmycosin* 8α,20β-*Aldol* (**114**).—Desmycosin 8α,20β-aldol (**113**) (618 mg), 4-dimethylaminopyridine (952 mg), and triethylamine (5 ml) were dissolved in dry dichloromethane (100 ml). Acetic anhydride (0.8 ml) was added and the mixture was stirred at 25 °C for 18 h. Chromatography (30 × 2 cm; 5→15% acetone in hexane) gave 3,20,2′,4′,4″-penta-*O*-acetyldesmycosin 8α,20β-aldol (**114**) (103 mg, 14%) (Found: C, 59.55; H, 7.75; N, 1.45. $C_{49}H_{75}NO_{19}$ requires C, 59.93; H, 7.70; N, 1.42%); $[\alpha]_D^{26}$ +27.0° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 282 nm (ε 13 246); $\nu_{max.}$($CDCl_3$) 2 980, 2 950, 2 900, 1 735, 1 680, 1 600, 1 370, 1 240, 1 060, and 1 050 cm^{-1}.

Reaction of Desmycosin (**32**) *with Tetrabutylammonium Fluoride*.—Desmycosin (**32**) (1 g) and tetrabutylammonium fluoride trihydrate (800 mg) were dissolved in dry tetrahydrofuran (100 ml) and the mixture was kept at 25 °C for 4 days. Chromatography (110 × 2.5 cm; 3% methanol in chloroform) gave the product (**115**) (247 mg, 25%) (Found: C, 53.6; H, 6.9; N, 1.45%); *m/z* 892 (MH^+) and 890; $[\alpha]_D^{26}$ +1.1° ($CHCl_3$); $\lambda_{max.}$(MeOH) 281 nm ($E^{1\%}_{1cm}$ 228.1); $\nu_{max.}$($CDCl_3$), 3 450, 3 000, 2 960, 2 910, 1 720, 1 685, 1 595, 1 325, 1 180, and 1 065 cm^{-1}.

Tylosin 8β,20α-*Aldol* (**116**).—Tylosin (**26**) (1 g) was dissolved in dry tetrahydrofuran (100 ml) and tetrabutylammonium fluoride trihydrate (800 mg) was added. The mixture was stirred at 25 °C for 98 h. Chromatography (30 × 5 cm; 2% methanol in chloroform) gave a product (**117**) (42 mg, 5%) and tylosin 8β,20α-aldol (**116**). Rechromatography of the latter (15 × 2 cm; 50% acetone in hexane) gave (**116**) (30 mg, 3%), $[\alpha]_D^{26}$ −23.0° ($CHCl_3$); $[\theta]_{219}$ −3 020, $[\theta]_{270}$ +15 703, and $[\theta]_{320}$ −4 530 (CF_3CH_2OH); $\lambda_{max.}$(CF_3CH_2OH) 278 nm (ε 17 573); $\nu_{max.}$($CDCl_3$) 3 570, 2 990, 2 950, 2 900, 1 715, 1 680, 1 600, 1 315, 1 160, and 1 055 cm^{-1}. The balance of the material recovered consisted of unchanged tylosin (**26**).

Reaction of 20,4‴-*Di*-O-(*dimethyl-t-butylsilyl*)-20-*imidazolyltylosin* (**31**) *with Tetrabutylammonium Fluoride*.—20,4‴-Di-*O*-(dimethyl-t-butylsilyl)-20-imidazolyltylosin (**31**)[35] (2 g) and tetrabutylammonium fluoride trihydrate (2.6 g) were dissolved in dry tetrahydrofuran (50 ml) and the solution was kept at 25 °C for 1.5 h. Chromatography (110 × 2.5 cm; 2% methanol in chloroform) gave (**117**) (945 mg, 63%) (Found: C, 52.95; H, 7.2; N, 1.15%); *m/z* 1 036 (MH^+); $[\alpha]_D^{26}$ −34.4° (MeOH); $\lambda_{max.}$(MeOH) 281 nm ($E^{1\%}_{1cm}$ 221.9); $\nu_{max.}$($CDCl_3$) 3 570, 3 470, 2 980, 2 940, 2 900, 1 715, 1 680, 1 595, 1 410, 1 315, 1 185, 1 160, and 1 045 cm^{-1}.

Acetylation of the Product (**117**).—The product (**117**) (260 mg) was dissolved in dry dichloromethane (50 ml) and 4-dimethylaminopyridine (693 mg) and triethylamine (5 ml) were added. Acetic anhydride (580 mg) was added and the mixture was stirred at 25 °C for 18 h. Chromatography (110 × 2.5 cm; 25% acetone in hexane) gave the peracetate (**118**) (219 mg) (Found: C, 54.95; H, 7.1; N, 1.3%); *m/z* 1 246 (MH^+) and 1 034; $[\alpha]_D^{26}$ −67.8° ($CHCl_3$); $\nu_{max.}$(MeOH) 3 500, 2 980, 2 950, 1 740, 1 680, 1 660, 1 600, 1 382, 1 218, 1 185, and 1 045 cm^{-1}.

20,2′,4″,4‴-*Tetra*-O-*acetyltylosin* 3,20-*Hemiacetal* (**119**).—20,2′,4″-Tri-*O*-acetyltylosin 3,20-hemiacetal (**120**) (400 mg) was dissolved in dry dichloromethane (25 ml) and 4-dimethylaminopyridine (9.4 mg) and triethylamine (0.2 ml) were added. Acetic anhydride (0.7 ml) was added and the mixture was kept at 25 °C for 18 h. Chromatography (60 × 2 cm; 20% acetone in hexane) gave the hemiacetal (**119**) (315 mg, 76%) (Found: C,

59.45; H, 7.9; N, 0.7. $C_{54}H_{85}NO_{21}$ requires C, 59.82; H, 7.90; N, 1.29%); $[\alpha]_D^{26}$ −81.3° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 230 (ε 4 215) and 282 nm (25 290); $\nu_{max.}$($CDCl_3$) 3 460, 2 980, 2 940, 1 730, 1 652, 1 365, 1 238, and 1 045 cm^{-1}.

Reaction of 12,13-*De-epoxy*-12,13-*dehydrorosaramicin* (**15**) *with Tetrabutylammonium Fluoride*.—12,13-De-epoxy-12,13-dehydrorosaramicin (**15**) (1 g) and tetrabutylammonium fluoride trihydrate (496 mg) were dissolved in dry tetrahydrofuran (80 ml) and the mixture was kept at 25 °C for 99 h. Chromatography (30 × 5 cm; 1.5% methanol in chloroform) and preparative t.l.c. (20 × 20 cm, 250 μm; 50% acetone in toluene) gave a less polar product (**121**) (127 mg, 13%) (Found*: C, 56.25; H, 7.75; N, 0.85%); *m/z* 686 (*M*H$^+$) and 684; $[\alpha]_D^{26}$ +16.2° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 287 nm (ε 18 161); $\nu_{max.}$($CDCl_3$) 3 475, 2 980, 2 950, 2 880, 1 708, 1 670, 1 585, 1 312, 1 175, and 1 020 cm^{-1}; and a more polar product (**122**) (102 mg, 10%), *m/z* 686 (*M*H$^+$) and 684; $[\alpha]_D^{26}$ −7.0° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 288 nm (ε 18 239); $\nu_{max.}$($CDCl_3$) 3 420, 2 980, 2 950, 2 890, 1 710, 1 680, 1 588, 1 318, 1 182, 1 100, and 1 042 cm^{-1}. The only other product isolated was unchanged compound (**15**) (150 mg, 15%).

Desmycosin 20-*Dimethylacetal* (**43**).—Tylosin (**26**) (5 g) was dissolved in 0.1M hydrogen chloride in methanol (200 ml) and the solution was kept at 25 °C for 18 h. The reaction was neutralized with Amberlite IRA 401S (OH^-) resin and the resin was filtered off and washed with methanol. Chromatography (100 × 5 cm; 5% methanol in chloroform) gave the acetal (**43**) (3.53 g, 79%) (Found: C, 59.8; H, 8.3; N, 1.6. $C_{41}H_{71}NO_{15}$ requires C, 60.28; H, 8.75; N, 1.71%); $[\alpha]_D^{26}$ −0.8° (MeOH); $\lambda_{max.}$(CF_3CH_2OH) 284 nm (ε 22 023); $\nu_{max.}$($CDCl_3$) 3 580, 2 990, 2 960, 2 900, 1 720, 1 685, 1 600, 1 320, 1 190, 1 170, and 1 060 cm^{-1}.

2′,4′,4″-*Tri*-O-*acetyldesmycosin* 20-*Dimethylacetal* (**44**).—Desmycosin 20-dimethylacetal (**43**) (8.5 g) was dissolved in dry pyridine (300 ml). Acetic anhydride (4.9 ml) was added and the mixture was kept at 25 °C for 18 h. Additional acetic anhydride (2.94 ml) was added and the reaction was allowed to proceed for a further 17 h. Chromatography (30 × 5 cm; 45% ethyl acetate in dichloromethane) gave 2′,4′,4″-tri-*O*-acetyldesmycosin 20-dimethylacetal (**44**) (7.18 g, 73%) (Found: C, 59.85; H, 8.2; N, 1.3. $C_{47}H_{77}NO_{18}$ requires C, 59.82; H, 8.22; N, 1.48%); $[\alpha]_D^{26}$ +11.6° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 284 nm (ε 23 659); $\nu_{max.}$($CDCl_3$) 3 475, 2 975, 2 950, 2 910, 1 730, 1 678, 1 590, 1 225, 1 160, and 1 040 cm^{-1}.

2,3-*Dehydro*-3-*deoxydesmycosin* 20-*Dimethylacetal* (**107**).—2′,4′,4″-Tri-*O*-acetyldesmycosin 20-dimethylacetal (**44**) (3.02 g) was dissolved in dry pyridine (150 ml). Methanesulphonyl chloride (2.5 ml) was added and the mixture was kept at 25 °C for 36 h. Additional methanesulphonyl chloride (0.5 ml) was added and the mixture was kept for a further 6 h. After work-up the product was dissolved in methanol (100 ml) containing triethylamine (2.65 ml) and the mixture was heated at 60 °C for 18 h. Additional triethylamine (0.5 ml) was added and the mixture was heated at 45 °C for 112 h. Chromatography (60 × 5 cm; 4% methanol in chloroform) gave 2,3-dehydro-3-deoxydesmycosin 20-dimethylacetal (**107**) (1.42 g, 56%) (Found: C, 61.1; H, 8.45; N, 1.55. $C_{41}H_{69}NO_{14}$ requires C, 61.56; H, 8.69; N, 1.75%); $[\alpha]_D^{26}$ +2.2° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 212 (ε 19 189) and 286 nm (19 691); $\nu_{max.}$($CDCl_3$) 3 630, 3 580, 2 985, 2 940, 2 900, 1 710, 1 675, 1 653, 1 590, 1 320, 1 182, and 1 052 cm^{-1}.

* Analysis run on 1:1 mixture of (**121**) and (**122**) which was obtained prior to preparative t.l.c. (448 mg, 45%).

2,3-*Dehydro*-3-*deoxydesmycosin* (**108**).—2,3-Dehydro-3-deoxydesmycosin 20-dimethylacetal (**107**) (896 mg) was dissolved in 0.1M aqueous hydrochloric acid (25 ml) and the mixture was kept at 25 °C for 4 h. Chromatography (110 × 2.5 cm; 2% methanol in chloroform) gave 2,3-dehydro-3-deoxydesmycosin (**108**) (680 mg, 81%) (Found: C, 61.5; H, 8.25; N, 1.55. $C_{39}H_{63}NO_{13}$ requires C, 62.13; H, 8.42; N, 1.86%), $[\alpha]_D^{26}$ −21.3° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 212 (ε 16 826) and 287 nm (20 406); $\nu_{max.}$($CDCl_3$), 3 620, 2 985, 2 950, 2 890, 1 720, 1 680, 1 655, 1 592, 1 320, 1 165, and 1 057 cm^{-1}.

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