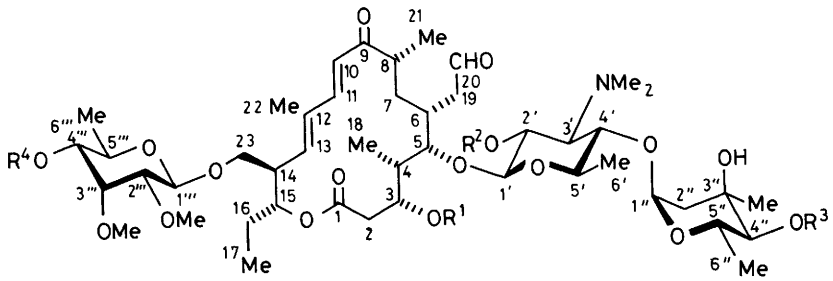
Semisynthetic Macrolide Antibacterials Derived from Tylosin. Synthesis of 23-*O*-Demycinosyltylosin and Related Compounds

Alan K. Mallams * **and Randall R. Rossman**
Research Division, Schering-Plough Corporation, Bloomfield, New Jersey 07003, USA

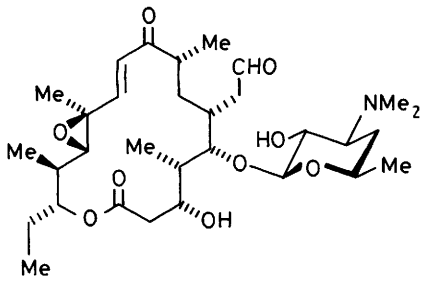
The synthesis of a versatile intermediate 4‴-*O*-(dimethyl-t-butylsilyl)tylosin, directly from tylosin, is described. Its utility in the synthesis of selected acyl derivatives of tylosin, as well as in the synthesis of 23-*O*-demycinosyltylosin, is discussed. Limitations to its use where 3-*O*-acyl groups are present in the macrolide were evident. A number of acyl derivatives and 23-substituted derivatives of 23-*O*-demycinosyltylosin, as well as their hydrazones, have been prepared using the above methodology.

Although the sixteen-membered macrolide antibiotic tylosin (**1**)[1–5] has been widely used to combat bacterial infections in animals, it has never been marketed for human use. Recent attempts aimed at improving the serum levels of tylosin (**1**) have concentrated on the microbial acylation of either tylosin (**1**), or 3-*O*-acetyltylosin (**2**) using a mutant strain of *Streptomyces thermotolerans* ATTC 11416,[6,7] to afford a variety of selectively acylated tylosin derivatives, including (**2**), 4″-*O*-isovaleryltylosin (**3**), and 3-*O*-acetyl-4″-*O*-isovaleryltylosin (**4**). Of these derivatives, one of the most promising candidates was (**4**), which exhibited activity against macrolide-resistant strains of *Staphylococcus aureus* and which showed enhanced serum levels relative to tylosin (**1**) in several species.[8–10] A chemical synthesis of 4″-*O*-acyl derivatives from tylosin (**1**) and of 3,4″-di-*O*-acyl derivatives from 3-*O*-acetyltylosin (**2**) has been patented,[11] utilizing an acetyl protecting group at the 2′-position and a labile monochloroacetyl protecting group at the 4‴-position, which could then be selectively removed in the presence of the 3- and 4″-*O*-acyl groups to give the desired tylosin ester derivatives. In general the 3-, 4″-, and 3,4″-di-*O*-acyl derivatives of tylosin exhibited similar potency to that of (**1**). Work in these laboratories had led to the synthesis of a variety of hydrazone derivatives of rosaramicin (**12**)[12] and 12,13-de-epoxy-12,13-didehydrorosaramicin (**13**) and, of these, the hydrazone (**14**)[13,14] was selected for further study as it retained the potency of rosaramicin (**12**), but exhibited enhanced bioavailability.[15] We were therefore interested in preparing the corresponding hydrazone derivative (**15**) from tylosin (**1**), as well as from selected esters of tylosin, to see whether similar improvements in bioavailability could be realized in the tylosin series.

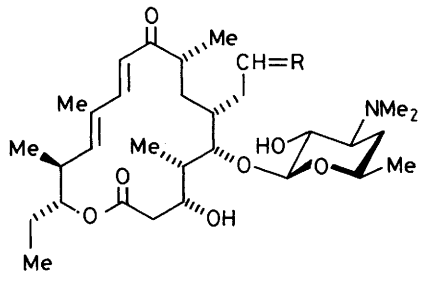
When we started this work in 1979, we and our colleagues[13]



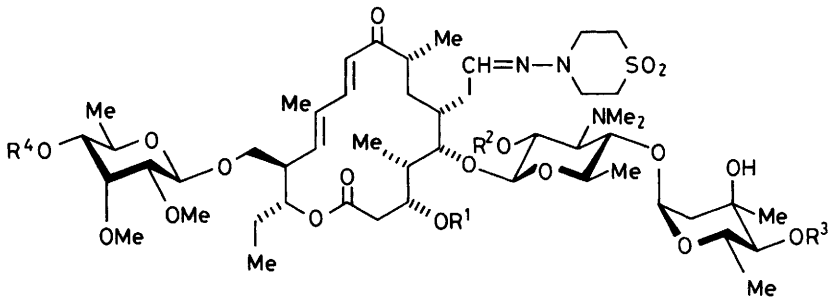
(**1**) $R^1 = R^2 = R^3 = R^4 = H$
(**2**) $R^1 = Ac$, $R^2 = R^3 = R^4 = H$
(**3**) $R^1 = R^2 = R^4 = H$, $R^3 = COCH_2CHMe_2$
(**4**) $R^1 = Ac$, $R^2 = R^4 = H$, $R^3 = COCH_2CHMe_2$
(**5**) $R^1 = R^2 = R^3 = H$, $R^4 = SiMe_2Bu^t$ (BDMS)
(**6**) $R^1 = R^3 = H$, $R^2 = Ac$, $R^4 = BDMS$
(**7**) $R^1 = H$, $R^2 = Ac$, $R^3 = COCH_2CHMe_2$, $R^4 = BDMS$
(**8**) $R^1 = H$, $R^2 = R^3 = Ac$, $R^4 = BDMS$
(**9**) $R^1 = R^4 = H$, $R^2 = Ac$, $R^3 = COCH_2CHMe_2$
(**10**) $R^1 = R^4 = H$, $R^2 = R^3 = Ac$
(**11**) $R^1 = R^2 = R^4 = H$, $R^3 = Ac$



(**12**)



(**13**) R = O
(**14**) R = N–N⟨ ⟩SO$_2$



(15) $R^1 = R^2 = R^3 = R^4 = H$
(16) $R^1 = R^2 = R^4 = H$, $R^3 = COCH_2CHMe_2$
(17) $R^1 = R^4 = H$, $R^2 = Ac$, $R^3 = COCH_2CHMe_2$
(18) $R^1 = R^2 = R^3 = H$, $R^4 = BDMS$
(19) $R^1 = R^3 = H$, $R^2 = Ac$, $R^4 = BDMS$
(20) $R^1 = H$, $R^2 = Ac$, $R^3 = COCH_2CHMe_2$, $R^4 = BDMS$
(21) $R^1 = H$, $R^2 = R^3 = Ac$, $R^4 = BDMS$
(22) $R^1 = R^2 = Ac$, $R^3 = COCH_2CHMe_2$, $R^4 = BDMS$
(23) $R^1 = R^4 = H$, $R^2 = R^3 = Ac$

reasoned that it would also be worthwhile to prepare 23-*O*-demycinosyltylosin (23-DMT) (**24**) and selected ester and hydrazone derivatives thereof, as these compounds had never been prepared at the time, and it was felt that they might well have interesting antibacterial activity. Later that year a paper appeared describing the synthesis of the first 23-DMT derivative (**25**)[16] from tylosin (**1**). In subsequent years, independent research in two other laboratories resulted in the elegant production of 23-DMT (**24**)[17–22] and 23-demycinosyloxytylosin (23-DMOT) (**26**)[17–19,21–23] by mutasynthesis from *Streptomyces fradiae* blocked in specific steps in the biosynthesis of tylosin (**1**). The synthesis of a series of ester derivatives of 23-DMT (**24**) has been reported recently[22,24–27] using different methodology to that described in this and the following paper.[28] 3-*O*-Acetyl-4″-*O*-isovaleryl-23-DMT (**27**) has also recently been mutasynthesized from 5-*O*-mycaminosyltylonolide (OMT) (**42**) using a mutant strain of *Stretomyces thermotolerans*.[29] The synthesis of 23-demycinosyloxy-23-dimethylaminotylosin (**28**) has also been reported.[30] In view of the interest in these compounds resulting from their superior antibacterial properties and serum levels, we were prompted to publish the results of our own studies in this area.

We felt that it might be possible to introduce selectively a dimethyl-t-butylsilyl (BDMS) group onto the 4‴-hydroxy group in tylosin (**1**), due to the unhindered nature of that particular hydroxy group. The BDMS group could later be removed under mild conditions without hydrolysis of other acyl groups in the target structures. Indeed it was found that treatment of tylosin (**1**) with BDMS chloride in the presence of imidazole afforded reasonable yields of the desired 4‴-*O*-BDMS-tylosin (**5**). Acetylation of (**5**) gave the 2′-acetate (**6**). Treatment of the latter with isovaleric anhydride (1 mol equiv.) in the presence of 4-dimethylamino pyridine (DMAP) and triethylamine in dichloromethane afforded the desired 4″-*O*-isovalerate (**7**). The 4″-*O*-acetate (**8**) was also formed as a by-product.*

Reaction of compound (**7**) with anhydrous tetrabutylammonium fluoride gave 2′-*O*-acetyl-4″-*O*-isovaleryltylosin (**9**). When the trihydrate was used some loss of the 2′-*O*-acetyl group was observed. Treatment of the diacetate (**8**) with anhydrous tetrabutylammonium fluoride afforded the desired diacetate (**10**) together with some 4″-*O*-acetate (**11**), the latter presumably arising from inadvertent traces of moisture present in the reaction medium. Methanolysis of compound (**9**) gave 4″-*O*-isovaleryltylosin (**3**). Treatment of compound (**9**) with *N*-amino-4,4-dioxothiomorpholine[13,14] in methanol as solvent afforded the deacetylated hydrazone (**16**) directly. When dichloromethane was used as the solvent the 2′-*O*-acetate group was retained and compound (**9**) was converted smoothly into the corresponding hydrazone (**17**).

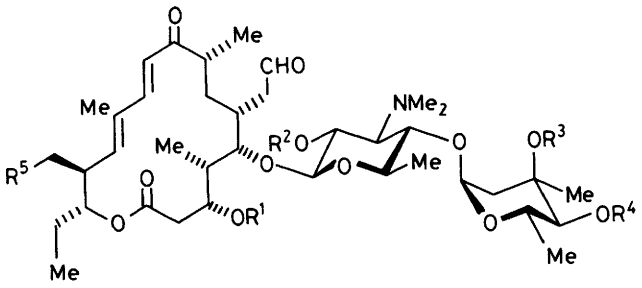
Preliminary studies of the Pfitzner–Moffatt oxidation[31,32] of the 4‴-hydroxy group in (**17**) clearly pointed to the need for protection of the 3-hydroxy group if reasonable yields of 23-DMT derivatives were to be obtained and this was accomplished as follows.

Tylosin (**1**) was converted into the hydrazone (**15**) which was in turn converted in high yield into the 4‴-*O*-BDMS derivative (**18**). Conversion into the 2′-*O*-acetate (**19**) followed by acylation as before with isovaleric anhydride, DMAP, and triethylamine gave the desired 4″-*O*-isovalerate (**20**) together with some di-*O*-acetate (**21**). Treatment of compound (**20**) with acetic anhydride, DMAP, and triethylamine gave a high yield of the 3-*O*-acetyl derivative (**22**) at 25 °C. Attempted deprotection of compound (**22**) with anhydrous tetrabutylammonium fluoride gave the 2,3-ene derivative (**58**) as the major product of the reaction, together with some of the corresponding 4‴-*O*-BDMS derivative (**59**). The use of mild acidic and buffered conditions to remove the 4‴-*O*-BDMS group failed to effect deprotection of the group. Methanolysis of compound (**58**) gave the 2,3-ene derivative (**60**). Deprotection of compound (**21**) gave the 2′,4″-di-*O*-acetate (**23**).

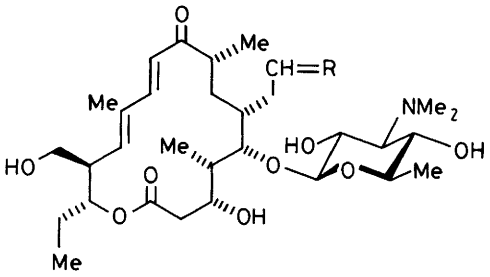
We therefore sought an alternative method for protecting the 3-hydroxy group which would avoid the use of 3-*O*-acyl groups and which would lead to 23-DMT (**24**) itself. Tylosin (**1**) has been shown to react with acetic anhydride in the presence of potassium carbonate to give 2′,4″,4‴, 20-tetra-*O*-acetyltylosin 3,20-hemiacetal in good yield[33] and we elected to apply this methodology to the 4‴-*O*-BDMS derivative (**5**). Reaction of compound (**5**) with acetic anhydride in the presence of potassium carbonate gave a modest yield of the hemiacetal (**61**). The latter on treatment with anhydrous tetrabutylammonium fluoride afforded the 4‴-deprotected derivative (**62**) in high yield. Oxidation of the latter with diethylcarbodi-imide, which is water-soluble and therefore easily removed, afforded as the initial oxidation product the unsaturated ketone (**63**) in 63% yield. The latter was deprotected to give 23-DMT (**24**) together with the seco acid methyl ester derivative (**64**). The latter was being formed by a base-catalysed reaction during the deprotection step.

We next turned our attention to the preparation of selected 23-DMT derivatives and their hydrazones. 23-DMT (**24**) was converted into the 2′-*O*-acetate (**29**) and the latter was selectively acetylated to give the 2′,23-di-*O*-acetate (**30**), acylation of which with isovaleric anhydride in the presence of DMAP and excess of triethylamine afforded, after recycling, the desired 4″-*O*-isovaleryl derivative (**31**) in good yield. Treatment of compound

* The commercial isovaleric anhydride used at the time contained 15–20% acetic anhydride.

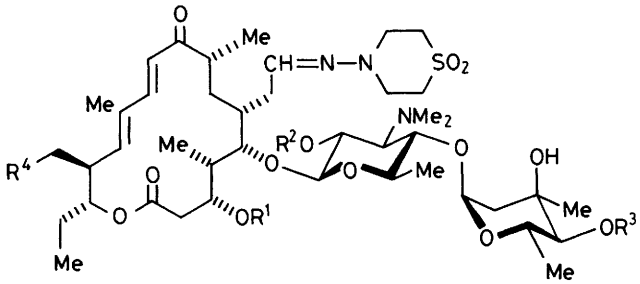


(24) $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = OH$
(25) $R^1 = Ac$, $R^2 = H$, $R^3R^4 = CO$, $R^5 = OH$
(26) $R^1 = R^2 = R^3 = R^4 = R^5 = H$
(27) $R^1 = Ac$, $R^2 = R^3 = H$, $R^4 = COCH_2CHMe_2$, $R^5 = OH$
(28) $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = NMe_2$
(29) $R^1 = R^3 = R^4 = H$, $R^2 = Ac$, $R^5 = OH$
(30) $R^1 = R^3 = R^4 = H$, $R^2 = Ac$, $R^5 = OAc$
(31) $R^1 = R^3 = H$, $R^2 = Ac$, $R^4 = COCH_2CHMe_2$, $R^5 = OAc$
(32) $R^1 = R^2 = R^3 = H$, $R^4 = COCH_2CHMe_2$, $R^5 = OH$
(33) $R^1 = R^3 = R^4 = H$, $R^2 = Ac$, $R^5 = OBz$
(34) $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = OBz$
(35) $R^1 = R^3 = R^4 = H$, $R^2 = Ac$, $R^5 = OCOCH_2CHMe_2$
(36) $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = OCOCH_2CHMe_2$
(37) $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = OCOCH_2Ph$
(38) $R^1 = R^2 = R^3 = Ac$, $R^5 = OH$
(39) $R^1 = R^2 = R^3 = H$, $R^4 = Ac$, $R^5 = I$
(40) $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = I$

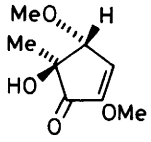


(41) R = N–N(SO$_2$)

(42) R = O



(43) $R^1 = R^2 = H$, $R^3 = COCH_2CHMe_2$, $R^4 = OH$
(44) $R^1 = R^2 = R^3 = H$, $R^4 = OH$
(45) $R^1 = R^2 = R^3 = H$, $R^4 = OBDMS$
(46) $R^1 = R^3 = H$, $R^2 = Ac$, $R^4 = OBDMS$
(47) $R^1 = H$, $R^2 = R^3 = Ac$, $R^4 = OBDMS$
(48) $R^1 = H$, $R^2 = R^3 = Ac$, $R^4 = OH$
(49) $R^1 = R^2 = R^3 = H$, $R^4 = OBz$
(50) $R^1 = R^2 = R^3 = H$, $R^4 = OCOCH_2CHMe_2$
(51) $R^1 = R^2 = R^3 = H$, $R^4 = OCOCH_2Ph$
(52) $R^1 = R^2 = H$, $R^3 = Ac$, $R^4 = OH$
(53) $R^1 = R^2 = H$, $R^3 = Ac$, $R^4 = I$
(54) $R^1 = R^2 = H$, $R^3 = Ac$, $R^4 = NMe_2$
(55) $R^1 = R^2 = R^3 = H$, $R^4 = NMe_2$
(56) $R^1 = H$, $R^2 = R^3 = Ac$, $R^4 = I$

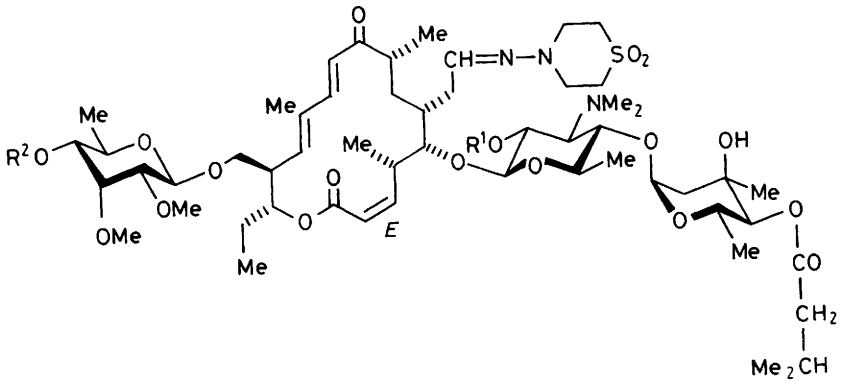


(57)

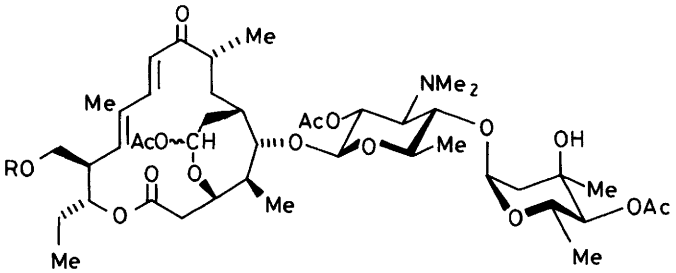
(31) with triethylamine in methanol at 20 °C afforded 4″-*O*-isovaleryl-23-DMT (**32**), which was in turn converted into the hydrazone derivative (**43**). 23-DMT (**24**) was also converted into the corresponding hydrazone (**44**). The latter was also prepared directly from compound (**23**) by oxidation under Pfitzner–Moffatt conditions, followed by base-catalysed deprotection. The hydrazone (**44**) reacted with BDMS chloride and imidazole to give the 23-*O*-BDMS derivative (**45**), which was converted into the 2′-*O*-acetate (**46**). Acetylation of compound (**46**) using acetic anhydride, DMAP, and triethylamine afforded a good yield of diacetate (**47**), deprotection of which with fluoride ion gave compound (**48**).

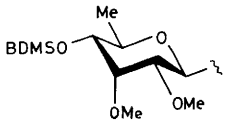
We next synthesized a number of carefully selected 23-substituted DMT derivatives as follows. Benzoylation of compound (**29**) under controlled conditions gave the 2′-*O*-acetyl-23-*O*-benzoyl DMT derivative (**33**), which was subsequently methanolysed to give the 23-*O*-benzoate (**34**). The latter was converted into the corresponding hydrazone (**49**). The acetate (**29**) was also converted into the 23-*O*-isovaleryl derivative (**35**), which was in turn methanolysed to (**36**) and subsequently converted into the hydrazone (**50**). Direct acylation of 23-DMT (**24**) with phenylacetyl chloride in the presence of pyridine gave the 23-*O*-phenylacetyl derivative (**37**). The latter was converted into the hydrazone derivative (**51**).

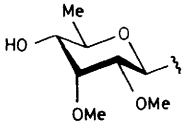
Oxidation of the hemiacetal (**62**) under Pfitzner–Moffatt conditions using *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride, which is water-soluble, afforded the enone (**63**) in high yield. Reaction of compound (**63**) with triethylamine in methanol at 50 °C for 7 h gave a high yield of 4″-*O*-acetyl-23-DMT (**38**). When the hydrolysis was carried out using triethylamine in methanol at 25 °C for 140 h, some bicycloaldehyde (**65**) was formed in addition to (**38**). Base-catalysed β-elimination of 3-*O*-acetyl groups with subsequent Michael addition of the aldehyde to the enelactone to give bicycloaldehydes has been observed in the leucomycin [34] and tylosin [35] series before. The cyclopentenone (**57**) [36] resulting from base-catalysed opening of the ketomycinose moiety, was also isolated in this experiment. It was found to be identical with an authentic sample whose structure had been established in these laboratories [36] by *X*-ray crystallography. The 4″-acetate (**38**) was converted into the hydrazone derivative (**52**). Direct iodination of compound (**38**) with methyltriphenoxyphosphonium iodide in dimethylformamide (DMF) and pyridine gave the 23-iodide (**39**) in high yield. A small amount of the 3,4-ene (**66**) was also formed due to over-reaction at C-3 with subsequent elimination of the 3-iodide. It is interesting to note that in this instance the elimination did not give rise to the conjugated lactone, but instead gave the 3,4-ene. The u.v., ^{1}H n.m.r. and ^{13}C n.m.r. data were all in accord with the assigned structure for compound (**66**). Similarly, the hydrazone (**52**) was converted into the 23-iodide (**53**) by treatment with methyltriphenoxyphosphonium iodide in DMF and pyridine. The hydrazone (**53**) was also prepared by treatment of aldehyde (**39**) with *N*-amino-4,4-dioxothiomorpholine. When hydrazone (**52**) was treated with an excess (4 mol equiv.) of methyltriphenoxyphosphonium iodide, the principal product of the reaction was the 3,4-ene (**67**). The 23-iodide (**53**) reacted with dimethylamine at 80 °C [37] to give the 23-dimethylamino derivative (**54**), which was deacetylated by treatment with triethylamine in methanol to

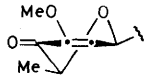


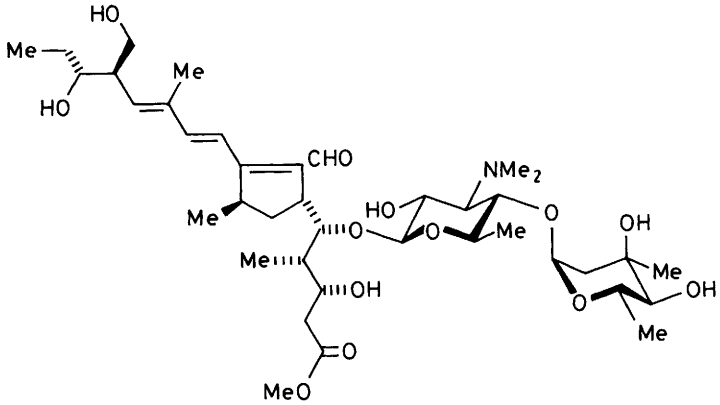
(**58**) R^1 = Ac, R^2 = H
(**59**) R^1 = Ac, R^2 = BDMS
(**60**) R^1 = R^2 = H



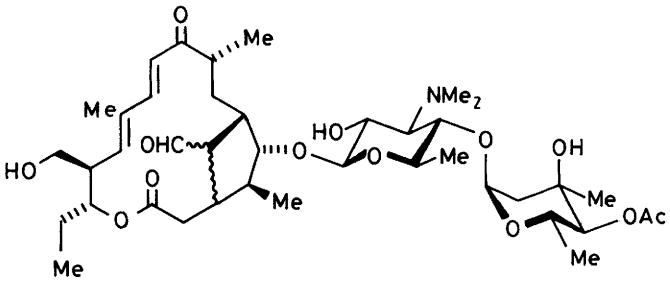
(**61**) R = 

(**62**) R = 

(**63**) R = 



(**64**)



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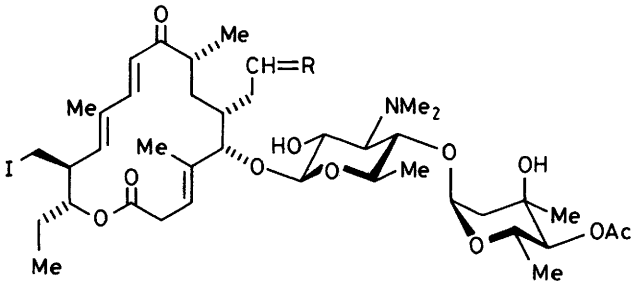
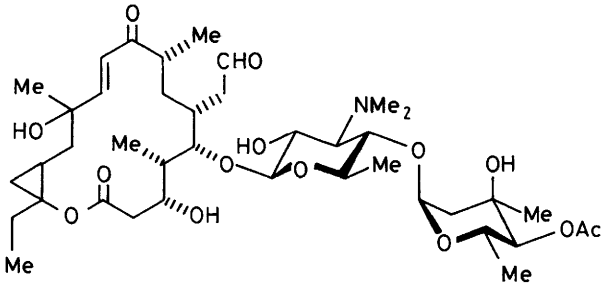
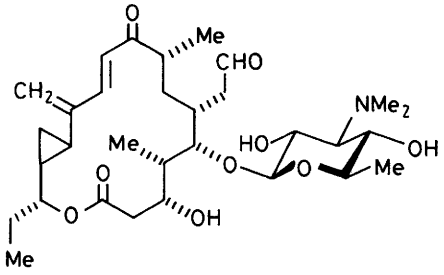


(66) R = O

(67) R = N–N⟨ ⟩SO$_2$



(68) and (69)



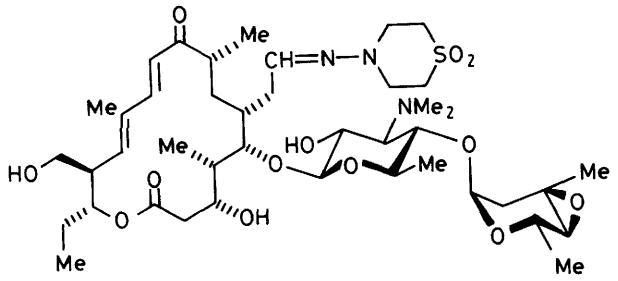
(70)

give compound (**55**).[30] The 4″-*O*-acetate (**39**) was also deacetylated under similar conditions to give 23-iodo-DMT (**40**). When acetate (**39**) was treated with tributyltin hydride at 25 °C in an attempt to prepare 23-DMOT (**26**), the only products isolated were the cyclopropyl derivatives (**68**) and (**69**). The u.v., ^{1}H n.m.r. and ^{13}C n.m.r. data were in accord with the location of the cyclopropyl group at the 14,15-position. The latter may arise from an initially formed 13,14-cyclopropyl-12-peroxyl radical, by a hydrogen transfer from C-15 followed by a shift of the cyclopropyl group to the 14,15-position to give the diastereoisomers (**68**) and (**69**). The APT data clearly supported the presence of tertiary oxygen-bearing carbons at C-12 and C-15. The presence of a cyclopropyl methylene carbon was also confirmed by the ^{13}C n.m.r. data. It is of interest to note that workers at Eli Lilly[26,27,38] found that when 23-*O*-tosyl-OMT was treated with DBU or with nucleophiles such as KCN, rearrangement to the 13,14-cyclopropyl derivative (**70**) occurred.

Attempted iodination of (**44**) with triphenylphosphine and iodine afforded the 3″,4″-epoxy derivative (**71**) and OMT hydrazone (**41**) as the only products of the reaction. No iodination of the 23-hydroxyl group was observed. Presumably the 4″-iodide is being formed and then displaced by the 3″-hydroxy group to give the observed 3″,4″-epoxide (**71**). The generation of hydrogen iodide would account for the rapid acidic hydrolysis of the 2-deoxy sugar to give OMT hydrazone (**41**). When compound (**44**) was treated with 0.1M hydrochloric acid at 25 °C for 105 h the resulting product was OMT (**42**). Similarly, treatment of the 3″,4″-epoxy derivative (**71**) with 0.1M hydrochloric acid afforded the OMT (**42**). By protecting the 4″-hydroxy group and adding an acid scavenger, propylene oxide, successful iodinations could be effected at the 23-hydroxy group using triphenylphosphine and iodine as the reagent. Thus the 2′,4″-di-*O*-acetyl derivative (**48**) on treatment with triphenylphosphine and iodine, in the presence of propylene oxide, gave the 23-iodide (**56**) as the principal product of the reaction. The yields were not as high as with methyltriphenoxyphosphonium iodide.

The synthesis of additional derivatives of tylosin and 23-DMT, as well as their hydrazones and 12,13-epoxy analogues, is described in the following paper.[28]

In general the 4″-*O*-acyl hydrazone derivatives of tylosin



(71)

exhibited a similar antibacterial spectrum and potency to that of the parent aldehydes.[39] They showed improved activity against macrolide-resistant strains of *Staphylococcus aureus* and exhibited higher serum levels than the parent aldehydes, when administered i.v. in mice. The hydrazones, however, showed lower serum levels than the aldehydes when administered orally in squirrel monkeys.[28] The 23-DMT derivatives, their esters and hydrazone derivatives, on the other hand, exhibited a similar antibacterial spectrum to that of tylosin, with the exception of the 23-dimethylamino derivative (**54**) which exhibited improved activity against macrolide-resistant strains of *Staphylococcus aureus*. In general the 23-DMT derivatives were two- to four-fold more potent than their tylosin analogues. The acyl 23-DMT derivatives showed improved serum levels when administered i.v. in mice, or orally in squirrel monkeys. The corresponding hydrazones showed even higher serum levels than the parent 23-DMT aldehydes when administered i.v. in mice. However, their serum levels were lower than those of the aldehydes when administered orally in squirrel monkeys.[28]

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. Low-resolution e.i. mass spectra were run on a Varian Mat CH5 spectrometer. FAB 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. ^{1}H 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; and at 400 MHz on a Varian XL-400 spectrometer. ^{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 ^{1}H n.m.r. and ^{13}C n.m.r. data are given in Supplementary Publication No. SUP 56737 (19 pp).* In general all macrolide reactions were worked up by evaporation to dryness, the residue being taken up in dichloromethane and washed with water, the pH being adjusted to 10. The dichloromethane layer was dried ($MgSO_4$), filtered, and evaporated to dryness. The products were chromatographed on Baker silica gel columns. Unless otherwise stated, the products were colourless amorphous solids. Whenever h.p.l.c. was used the separation was carried out on a Waters Prep 500 instrument using silica gel cartridges.

* For details of the Supplementary Publication Scheme, see section 4 of Instructions for Authors, issue 1.

Anhydrous tetrabutylammonium fluoride was prepared from the trihydrate by azeotroping a solution in toluene–tetrahydrofuran (THF) at *ca.* 50 °C on a rotary evaporator. Wherever possible all reactions were carried out under an inert, dry argon atmosphere.

General Procedure for the Preparation of Dimethyl-t-butylsilyl Macrolides.—The macrolide (1 mol equiv.) and imidazole (*w* mol equiv.) were dissolved in dry DMF (*x* ml g^{-1} macrolide) unless otherwise stated and dimethyl-t-butylsilyl chloride (*y* mol equiv.) was added. The mixture was stirred at 25 °C for *z* h.

(a) Tylosin (**1**) (25 g) (*w* = 10, *x* = 10, *y* = 4.8, *z* = 19) gave, after evaporation, trituration with hot hexane (3 l), and chromatography (160 × 5 cm; 1.5% MeOH in $CHCl_3$), 4‴-O-*dimethyl-t-butylsilyl)tylosin* (**5**) (14.7 g, 47%) (Found: C, 60.6; H, 9.4; N, 1.4. $C_{52}H_{91}NO_{17}Si$ requires C, 60.64; H, 8.84; N, 1.36%); $[\alpha]_D^{26}$ −41.8° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 284 nm (ε 22 620); $\nu_{max.}$($CDCl_3$) 3 500, 2 980, 2 950, 2 910, 1 722, 1 682, 1 600, 1 320, 1 662, 1 220, and 1 050 cm^{-1}.

(b) The hydrazone (**15**) (3 g) (*w* = 6.1, *x* = 12, *y* = 6.1, *z* = 18) gave, after chromatography (30 × 5 cm; 30% Me_2CO in C_6H_{14}), 20-*deoxo*-4‴-O-(*dimethyl-t-butylsilyl*)-20-[(4,4-*dioxothiomorpholino*)*imino*]*tylosin* (**18**) (2.44 g, 70%) (Found: C, 58.0; H, 8.1; N, 3.4; S, 2.4. $C_{56}H_{99}N_3O_{18}SSi$ requires C, 57.86; H, 8.58; N, 3.61; S, 2.76%); $[\alpha]_D^{26}$ −47.1° ($CHCl_3$), $\lambda_{max.}$(CF_3CH_2OH) 235 (6 710) and 286 nm (23 080); $\nu_{max.}$($CDCl_3$) 3 500, 2 970, 2 940, 2 900, 1 740, 1 680, 1 595, 1 315, 1 260, 1 130, and 1 052 cm^{-1}.

(c) The hydrazone (**44**) (1.28 g) (*w* = 6, *x* = 46.9, *y* = 3, *z* = 20.5) gave, after chromatography (60 × 2.5 cm; 30% Me_2CO in C_6H_{14}), 23-O-*demycinosyl*-20-*deoxo*-23-O-(*dimethyl-t-butylsilyl*)-20-[(4,4-*dioxothiomorpholino*]*imino*]*tylosin* (**45**) (1.15 g, 79%) (Found: C, 57.4; H, 8.55; N, 4.2; S, 3.3. $C_{48}H_{85}N_3O_{14}SSi$ requires C, 58.33; H, 8.67; N, 4.25; S, 3.24%); *m/z* 988 (MH^+); $[\alpha]_D^{26}$ −62.9° ($CHCl_3$); $\lambda_{max.}$(CH_3OH) 240 (7 330) and 283 nm (21 780); $\nu_{max.}$($CDCl_3$) 3 580, 1 708, 1 673, 1 585, 1 308, 1 258, 1 182, 1 120, and 1 048 cm^{-1}.

General Procedure for the Preparation of 2′-O-*Acetyl Macrolides.*—The macrolide (1 mol equiv.) and acetic anhydride (*w* mol equiv.) were dissolved in dry acetone (*x* ml g^{-1} macrolide) and the mixture was kept at *y* °C for *z* h.

(a) The macrolide (**5**) (15 g) (*w* = 5, *x* = 33, *y* = 25, *z* = 17) gave, after chromatography (70 × 2.5 cm; 20% Me_2CO in C_6H_{14}), the 2′-O-*acetate* (**6**) (15.6 g, 100%) (Found: C, 60.15; H, 8.6; N, 1.4. $C_{54}H_{93}NO_{18}Si$ requires C, 60.48; H, 8.74; N, 1.31%); $[\alpha]_D^{26}$ −45.4° (MeOH); $\lambda_{max.}$(CF_3CH_2OH) 285 nm (22 780); $\nu_{max.}$($CDCl_3$) 3 530, 2 980, 2 960, 2 920, 1 743, 1 720, 1 680, 1 590, 1 230, 1 160, and 1 045 cm^{-1}.

(b) The macrolide (**18**) (1.41 g) (*w* = 4, *x* = 21.3, *y* = 25, *z* = 40) gave, after chromatography (60 × 2 cm; 30% Me_2CO in C_6H_{14}), the 2′-O-*acetate* (**19**) (1.43 g, 98%) (Found: C, 57.5; H, 8.4; N, 3.3; S, 3.0. $C_{58}H_{101}N_3O_{19}SSi$ requires C, 57.88; H, 8.46; N, 3.49; S, 2.66%); $[\alpha]_D^{26}$ −52.2° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 234 (6 370) and 286 nm (22 440); $\nu_{max.}$($CDCl_3$) 3 500, 2 975, 2 950, 2 900, 1 750, 1 715, 1 680, 1 598, 1 318, 1 240, 1 130, and 1 055 cm^{-1}.

(c) 23-*O*-Demycinosyltylosin (**24**) (3.6 g) (*w* = 5, *x* = 41.7, *y* = 25, *z* = 18) gave, after chromatography (30 × 5 cm; 35% Me_2CO in C_6H_{14}), the 2′-*O*-acetate (**29**) (3.1 g, 82%).

(d) The macrolide (**45**) (1.62 g) (*w* = 5.2, *x* = 30.9, *y* = 25, *z* = 24) gave the 2′-*O*-acetate (**46**) (1.69 g, 100%); *m/z* 1 030 (MH^+); $[\alpha]_D^{26}$ −63.7° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 229 (7 090) and 288 nm (20 840); $\nu_{max.}$($CDCl_3$) 3 690, 3 500, 1 735, 1 708, 1 675, 1 588, 1 235, 1 180, 1 120, and 1 048 cm^{-1}.

General Procedure for the Preparation of 4″-O-*Acyl Macrolides.*—The macrolide (1 mol equiv.), DMAP (*v* mol equiv.),

triethylamine (w mol equiv.), and the acid anhydride (x mol equiv.) were dissolved in dry dichloromethane (y ml g^{-1} macrolide) and the mixture was stirred at 25 °C for z h.

(a) The macrolide (**6**) (15.6 g) and isovaleric anhydride (c = 1, w = 14.8, x = 1, y = 76.9, z = 17) gave, after recycling unchanged (**6**) and chromatography (160 × 5 cm; 30% EtOAc in CH_2Cl_2), the 4″-*O*-isovalerate (**7**) (9.7 g, 57%) (Found: C, 60.5; H, 8.7; N, 1.4. $C_{59}H_{101}NO_{19}Si$ requires C, 61.27; H, 8.80; N, 1.21%); $[\alpha]_D^{26}$ −51.7° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 285 nm (23 320); $\nu_{max.}$($CDCl_3$) 3 520, 2 980, 2 950, 2 900, 1 740, 1 720, 1 675, 1 590, 1 235, 1 160, and 1 050 cm^{-1}, and the 4″-O-*acetate* (**8**) (2.03 g, 13%) (Found: C, 60.2; H, 8.4; N, 1.0. $C_{56}H_{95}NO_{19}Si$ requires C, 60.35; H, 8.59; N, 1.26%); $[\alpha]_D^{26}$ −52.1° ($CHCl_3$); $\lambda_{max.}$(MeOH) 283 nm (22 450); $\nu_{max.}$($CDCl_3$) 3 520, 2 980, 2 950, 2 900, 1 740, 1 720, 1 680, 1 590, 1 235, 1 160, and 1 045 cm^{-1}.

(b) The macrolide (**19**) (6 g) and isovaleric anhydride (v = 1, w = 4.3, x = 1, y = 41.7, z = 19.5) gave, after recycling and chromatography (h.p.l.c., 1 cartridge; 22% Me_2CO in C_6H_{14}), the 4″-O-*isovalerate* (**20**) (2.92 g, 46%) (Found: C, 58.6; H, 8.5; N, 3.0; S, 2.6. $C_{63}H_{109}N_3O_{20}SSi$ requires C, 58.77; H, 8.53; N, 3.26; S, 2.49%); $[\alpha]_D^{26}$ −53.4° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 234 (6 460) and 286 nm (22 950); $\nu_{max.}$($CDCl_3$) 3 510, 2 975, 2 940, 2 900, 1 740, 1 720, 1 680, 1 595, 1 315, 1 240, 1 190, 1 170, 1 125, and 1 060 cm^{-1}; and the 4″-O-*acetate* (**21**) (1.39 g, 22%) (Found: C, 57.6; H, 8.0; N, 3.2; S, 2.9. $C_{60}H_{103}N_3O_{20}SSi$ requires C, 57.81; H, 8.33; N, 3.37; S, 2.57%); $[\alpha]_D^{26}$ −56.3° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 234 (6 430) and 286 nm (20 760); $\nu_{max.}$($CDCl_3$) 3 510, 2 975, 2 950, 2 900, 1 740, 1 685, 1 595, 1 317, 1 240, 1 175, 1 130, and 1 050 cm^{-1}; and unchanged (**19**) (2.7 g, 45%).

(c) The macrolide (**46**) (1.69 g) and acetic anhydride (v = 1, w = 5, x = 1.1, y = 47.3, z = 18) gave, after chromatography (90 × 2 cm; 20% Me_2CO in C_6H_{14}), the 4″-O-*acetate* (**47**) (1.29 g, 70%) (Found: C, 58.3; H, 8.2; N, 4.0; S, 3.1. $C_{52}H_{89}N_3O_{16}SSi$ requires C, 58.24; H, 8.36; N, 3.92; S, 2.99%); m/z 1 072 (MH^+); $[\alpha]_D^{26}$ −73.3° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 233 (6 580) and 288 nm (21 160); $\nu_{max.}$($CDCl_3$) 3 500, 1 740, 1 680, 1 595, 1 245, 1 187, 1 128, and 1 050 cm^{-1}.

(d) The macrolide (**30**) (1.5 g) and isovaleric anhydride (v = 0.5, w = 10, x = 1, y = 33.3, z = 19) gave, after recycling unchanged (**30**) and chromatography (60 × 2 cm; 20% Me_2CO in C_6H_{14}), the 4″-*O*-isovaleryl derivative (**31**) (1.02 g, 64%).

2′,3-*Di*-O-*acetyl*-20-*deoxo*-4‴-O-(*dimethyl*-t-*butylsilyl*)-20-[(4,4-*dioxothiomorpholino*)*imino*]-4″-O-*isovaleryltylosin* (**22**).—2′-*O*-Acetyl-20-deoxo-4‴-*O*-(dimethyl-t-butylsilyl)-20-[(4,4-dioxothiomorpholino)imino]-4″-*O*-isovaleryltylosin (**20**) (1.5 g), DMAP (712 mg), and triethylamine (5 ml) were dissolved in dry dichloromethane (100 ml) and acetic anhydride (0.55 ml) was added. The mixture was kept at 25 °C for 19 h. Chromatography (15 × 2 cm; 7% EtOAc in Et_2O) gave the 3-O-*acetate* (**22**) (1.59 g, 98%) (Found: C, 59.0; H, 8.2; N, 2.9; S, 3.3. $C_{65}H_{111}N_3O_{21}SSi$ requires C, 58.71; H, 8.42; N, 3.16; S, 2.41%); $[\alpha]_D^{26}$ −86.4° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 234 (8 115) and 284 nm (24 020); $\nu_{max.}$($CDCl_3$) 3 500, 2 970, 2 940, 2 900, 1 735, 1 680, 1 592, 1 308, 1 240, 1 187, 1 165, and 1 060 cm^{-1}.

2′,4″,20-*Tri*-O-*acetyl*-4‴-O-(*dimethyl*-t-*butylsilyl*)*tylosin* 3,20-*Hemiacetal* (**61**).—4‴-*O*-(Dimethyl-t-butylsilyl)tylosin (**5**) (5.82 g) and anhydrous potassium carbonate (5.82 g) were treated with acetic anhydride (331 ml) and the mixture was heated at 60—65 °C for 5 h. Chromatography (h.p.l.c., 1 cartridge; 15% Me_2CO in C_6H_{14}) gave the *hemiacetal* (**61**) (2.44 g, 37%) (Found: C, 60.15; H, 8.4; N, 1.0. $C_{58}H_{97}NO_{20}Si$ requires C, 60.24; H, 8.45; N, 1.21%); $[\alpha]_D^{26}$ −79.0°($CHCl_3$), $\lambda_{max.}$(CF_3CH_2OH) 282 nm (24 710); $\nu_{max.}$($CDCl_3$) 3 500, 2 970, 2 930, 2 900, 1 735, 1 650, 1 630, 1 365, 1 240, and 1 050 cm^{-1}.

General Procedure for the Removal of the BDMS Group from Macrolides.—The macrolide (1 mol equiv.) and anhydrous tetrabutylammonium fluoride (1 mol equiv.) were dissolved in dry THF (x ml g^{-1} macrolide) and the mixture was kept at 25 °C for y h.

(a) The macrolide (**7**) (8.25 g) (x = 48.5, y = 16) gave, after chromatography (160 × 2.5 cm; 40% Me_2CO in C_6H_{14}), 2′-O-*acetyl*-4″-*isovaleryltylosin* (**9**) (4.8 g, 65%) (Found: C, 61.3; H, 8.4; N, 1.5. $C_{53}H_{87}NO_{19}$ requires C, 61.08; H, 8.41; N, 1.34%); $[\alpha]_D^{26}$ −66.6° ($CHCl_3$); $\lambda_{max.}$(MeOH) 282 nm (22 640); $\nu_{max.}$($CDCl_3$) 3 550, 2 980, 2 950, 2 900, 1 740, 1 735, 1 730, 1 680, 1 600, 1 248, 1 175, and 1 065 cm^{-1}.

(b) The macrolide (**8**) (1.87 g) (x = 53.5, y = 16) gave, after chromatography (160 × 2.5 cm; 20% Me_2CO in C_6H_{14}), 2′,4″-*di*-O-*acetyltylosin* (**10**) (1 g, 60%) (Found: C, 59.6; H, 8.15; N, 1.3. $C_{50}H_{81}NO_{19}$ requires C, 60.04; H, 8.16; N, 1.40%); $[\alpha]_D^{26}$ −67.7° ($CHCl_3$); $\lambda_{max.}$(MeOH) 282 nm (22 270); $\nu_{max.}$($CDCl_3$) 3 520, 2 980, 2 940, 2 880, 1 730, 1 690, 1 595, 1 240, 1 220, 1 167, and 1 060 cm^{-1}.

(c) The macrolide (**22**) (1.4 g) (x = 114.3, y = 0.25) gave, after chromatography (30 × 2 cm; 35% Me_2CO in C_6H_{14}), 2′-O-*acetyl*-2,3-*didehydro*-20-*deoxo*-3-*deoxy*-20-[(4,4-*dioxothiomorpholino*)*imino*]-4″-O-*isovaleryltylosin* (**58**) (934 mg, 76%) (Found: C, 58.9; H, 7.9; N, 3.4; S, 2.9. $C_{57}H_{93}N_3O_{19}S$ requires C, 59.20; H, 8.11; N, 3.63; S, 2.77%); $[\alpha]_D^{26}$ −89.3° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 208 (22 200) and 286 nm (20 230); $\nu_{max.}$($CDCl_3$) 3 500, 2 980, 2 950, 2 880, 1 740, 1 720, 1 680, 1 595, 1 315, 1 240, 1 170, 1 128, and 1 060 cm^{-1}. The less polar fractions on preparative t.l.c. (r.l.c.) (silica gel; 20 × 20 cm, 250 μ); (40% Me_2CO in C_6H_{14}) and (20 × 20 cm; 25% Me_2CO in C_6H_{14}) gave 2′-O-*acetyl*-2,3-*didehydro*-20-*deoxo*-3-*deoxy*-4‴-O-(*dimethyl*-t-*butylsilyl*)-20-[(4,4-*dioxothiomorpholino*)*imino*]-4″-O-*isovaleryltylosin* (**59**) (109 mg, 8%) (Found: C, 59.5; H, 8.1; N, 2.95; S, 2.4. $C_{63}H_{107}N_3O_{19}SSi$ requires C, 59.55; H, 8.49; N, 3.31; S, 2.52%); $[\alpha]_D^{26}$ −70.0° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 210 (24 980) and 288 nm (20 610); $\nu_{max.}$($CDCl_3$) 3 510, 1 735, 1 680, 1 595, 1 310, 1 240, 1 180, and 1 060 cm^{-1}.

(d) The macrolide (**21**) (2.3 g) (x = 43.5, y = 2) gave, after chromatography (60 × 2 cm; 40% Me_2CO in C_6H_{14}), 2′,4″-*di*-O-*acetyl*-20-*deoxo*-20-[(4,4-*dioxothiomorpholino*)*imino*]*tylosin* (**23**) (1.78 g, 85%) (Found: C, 57.4; H, 8.2; N, 3.7; S, 3.2. $C_{54}H_{89}N_3O_{20}S$ requires C, 57.28; H, 7.92; N, 3.71; S, 2.83%); $[\alpha]_D^{26}$ −71.6° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 232 (7 355) and 286 nm (22 960); $\nu_{max.}$($CDCl_3$) 3 520, 2 980, 2 950, 2 900, 1 740, 1 720, 1 680, 1 595, 1 315, 1 240, 1 170, 1 128, and 1 050 cm^{-1}.

(e) The macrolide (**61**) (1.9 g) (x = 38.4, y = 1) gave, after chromatography (h.p.l.c. 1 cartridge; 30% Me_2CO in C_6H_{14}), 2′,4″,20-*tri*-O-*acetyltylosin*-3,20-*hemiacetal* (**62**) (1.3 g, 76%) (Found: C, 59.6; H, 7.8; N, 1.0. $C_{52}H_{83}NO_{20}$ requires C, 59.93; H, 8.03; N, 1.34%); $[\alpha]_D^{26}$ −94.9° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 281 nm (27 100); $\nu_{max.}$($CDCl_3$) 3 560, 3 500, 2 980, 2 940, 2 890, 1 740, 1 655, 1 373, 1 240, and 1 050 cm^{-1}.

(f) The macrolide (**47**) (1.28 g) (x = 173.4, y = 1) gave, after chromatography (120 × 2 cm; 25% Me_2CO in C_6H_{14}), 2′,4″-di-*O*-acetyl-23-demycinosyl-20-deoxo-20-[(4,4-dioxothiomorpholino)imino]tylosin (**48**) (609 mg, 53%); m/z 958 (MH^+); $[\alpha]_D^{26}$ −76.7° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 230 (6 290) and 285 nm (18 865); $\nu_{max.}$($CDCl_3$) 3 630, 3 500, 1 740, 1 680, 1 590, 1 240, 1 185, 1 125, and 1 050 cm^{-1}.

General Procedure for the Methanolysis of the 2′-O-*Acetates*.—The macrolide (1 mol equiv.) was dissolved in methanol (x ml g^{-1} macrolide) and the solution was kept at 25 °C for y h.

(a) The macrolide (**9**) (854 mg) (x = 177, y = 91) gave, after chromatography (110 × 2.5 cm; 35% Me_2CO in C_6H_{14}), 4″-O-*isovalerytylosin* (**3**) (588 mg, 72%) (Found: C, 61.9; H, 8.6; N, 1.2. $C_{51}H_{85}NO_{18}$ requires C, 61.24; H, 8.57; N, 1.40%) $[\alpha]_D^{26}$ −56.0° ($CHCl_3$); $\lambda_{max.}$(MeOH) 282 nm (21 720); $\nu_{max.}$($CDCl_3$) 3 500,

2 970, 2 930, 2 880, 1 725, 1 680, 1 595, 1 165, and 1 050 cm^{-1}.

(b) The macrolide (**10**) (1 g) (x = 100, y = 25) gave, after chromatography (160 × 2.5 cm; 20→35% Me_2CO in C_6H_{14}), unchanged (**10**) (453 mg, 45%) and 4″-O-*acetyltylosin* (**11**) (448 mg, 47%) (Found: C, 60.0; H, 8.3; N, 1.3. $C_{48}H_{79}NO_{18}S$ requires C, 60.17; H, 8.31; N, 1.46%); $[\alpha]_D^{26}$ −57.4° ($CHCl_3$); $\lambda_{max.}$(MeOH) 282 nm (22 140); $\nu_{max.}$($CDCl_3$) 3 500, 2 980, 2 940, 2 900, 1 720, 1 680, 1 593, 1 245, 1 168, and 1 055 cm^{-1}.

(c) The macrolide (**58**) (900 mg) (x = 55.6, y = 67) gave, after chromatography (30 × 2 cm; 20% Me_2CO in CH_2Cl_2) and (60 × 5 cm; 20→25% Me_2CO in C_6H_{14}), 2,3-*di-dehydro*-20-*deoxo*-3-*deoxy*-20-[(4,4-*dioxothiomorpholino*)*imino*]-4″-O-*isovaleryltylosin* (**60**) (471 mg, 54%) (Found: C, 59.6; H, 8.4; N, 3.5; S, 3.1. $C_{55}H_{91}N_3O_{18}S$ requires C, 59.28; H, 8.23; N, 3.77; S, 2.88%); $[\alpha]_D^{26}$ −84.5° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 204 (22 920) and 288 nm (19 100); $\nu_{max.}$($CDCl_3$) 3 520, 2 970, 2 940, 2 880, 1 720, 1 675, 1 590, 1 303, 1 180, 1 160, 1 120, and 1 050 cm^{-1}.

(d) The macrolide (**31**) (1.02 g) was treated with 5% (v/v) triethylamine in methanol (x = 49, y = 69) to give, after chromatography (90 × 2 cm; 25% Me_2CO in C_6H_{14}), 23-*O*-demycinosyl-4″-*O*-isovaleryltylosin (**32**) (722 mg, 78%).

(e) The macrolide (**33**) (130 mg) (x = 178.6, y = 90) gave, after chromatography (30 × 2 cm; 30% Me_2CO in C_6H_{14}), 23-*O*-benzoyl-23-*O*-demycinosyltylosin (**34**) (107 mg, 86%).

(f) The macrolide (**35**) (808 mg) was treated with 90% methanol–water (x = 61.9, y = 108) to give, after chromatography (60 × 2 cm; 30% Me_2CO in C_6H_{14}), 23-*O*-demycinosyl-23-*O*-isovaleryltylosin (**36**) (684 mg, 79%).

General Procedure for the Preparation of the Hydrazones.—The macrolide (1 mol equiv.) and *N*-amino-4,4-dioxothiomorpholine (x mol equiv.) were dissolved in a suitable solvent and the solution was stirred at 25 °C for y h.

(a) The macrolide (**9**) (700 mg) in methanol (100 ml) (x = 1, y = 75) gave, after chromatography (110 × 2.5 cm; 30% Me_2CO in C_6H_{14}), 20-*deoxo*-20-[(4,4-*dioxothiomorpholino*)-*imino*]-4″-O-*isovaleryltylosin* (**16**) (487 mg, 64%) (Found: C, 58.05; H, 8.2; N, 3.4; S, 3.05. $C_{55}H_{93}O_{19}S$ requires C, 58.33; H, 8.28; N, 3.71; S, 2.83%); $[\alpha]_D^{26}$ −62.1° ($CHCl_3$);$\lambda_{max.}$(MeOH) 240 (7 580) and 283 m, (23 150); $\nu_{max.}$($CDCl_3$) 3 510, 2 975, 2 950, 2 900, 1 725, 1 685, 1 600, 1 320, 1 190, 1 170, 1 130, and 1 060 cm^{-1}. Some hydrolysis of the hydrazone occurred during the chromatography to give the less polar 4″-*O*-isovaleryltylosin (**3**) (183 mg, 27%).

(b) The macrolide (**9**) (1.8 g) in dry dichloromethane (50 ml) (x = 1.8, y = 212) gave, after chromatography (11 × 2.5 cm; 30% Me_2CO in C_6H_{14}), 2′-O-*acetyl*-20-*deoxo*-20-[(4,4-*dioxothiomorpholino*)*imino*]-4″-O-*isovaleryltylosin* (**17**) (1.57 g, 77%) (Found: C, 58.0; H, 8.1; N, 3.4; S, 3.2. $C_{57}H_{95}N_3O_{20}S$ requires C, 58.26; H, 8.15; N, 3.58 S, 2.73%); $[\alpha]_D^{26}$ −71.3°($CHCl_3$); $\lambda_{max.}$(MeOH) 240 (8 030) and 283 nm (23 100); $\nu_{max.}$($CDCl_3$) 3 510, 2 980, 2 950, 2 900, 1 740, 1 720, 1 680, 1 600, 1 223, 1 192, 1 172, 1 130, and 1 060 cm^{-1}.

(c) Tylosin (**1**) (30 g) in ethanol (310 ml) (x = 1, y = 42) gave, after chromatography (120 × 5 cm; 1.5% MeOH in $CHCl_3$), 20-*deoxo*-20-[4,4-*dioxothiomorpholino*)*imino*]*tylosin* (**15**) (25 g, 73%) (Found: C, 55.9; H, 7.7; N, 3.8; S, 3.0. $C_{50}H_{85}N_3O_{18}S$·0.3$CHCl_3$ requires C, 55.39; H, 7.90; N, 3.88; S, 2.96%); $[\alpha]_D^{26}$ −56.8° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 235 (6 630) and 286 nm (21 765); $\nu_{max.}$($CDCl_3$) 3 580, 2 980, 2 950, 2 900, 1 710, 1 675, 1 585, 1 305, 1 160, 1 120, and 1 040 cm^{-1}.

(d) Tylosin (**1**) (30 g) in ethanol (250 ml) (x = 1, y = 42) gave, after chromatography (90 × 2 cm; 2.5% MeOH in $CHCl_3$), 23-O-*demycinosyl*-20-*deoxo*-20-[(4,4-*dioxothiomorpholino*)-*imino*]*tylosin* (**44**) (8.37 g, 92%) (Found: C, 57.4; H, 8.1; N, 4.9; S, 3.9. $C_{42}H_{71}N_3O_{14}S$ requires C, 57.71; H, 8.19; N, 4.81; S, 3.67%); m/z (MH^+); $[\alpha]_D^{26}$ −66.7° ($CHCl_3$); $\lambda_{max.}$(MeOH) 240 (6 990) and 283 nm (20 560); $\nu_{max.}$($CDCl_3$) 3 475, 1 708, 1 673, 1 588, 1 305, 1 180, 1 120, and 1 056 cm^{-1}.

(e) The macrolide (**32**) (737 mg) in dry THF (50 ml) (x = 2, y = 22) gave, after chromatography (30 × 2 cm; 30% Me_2CO in C_6H_{14}), 23-O-*demycinosyl*-20-*deoxo*-20-[(4,4-*dioxothiomorpholino*)*imino*]-4″-O-*isovaleryltylosin* (**43**) (592 mg, 72%) (Found: C, 57.3; H, 8.4; N, 3.9. $C_{50}H_{77}N_3O_{15}S$·0.3$CHCl_3$ requires C, 58.40; H, 7.55; N, 4.09%); m/z 992 (MH^+), $[\alpha]_D^{26}$ −44.7° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 240 (8 660) and 283 nm (18 630); $\nu_{max.}$($CDCl_3$) 3 480, 1 725, 1 675, 1 590, 1 310, 1 262, 1 185, 1 160, 1 125, and 1 050 cm^{-1}.

(i) The macrolide (**38**) (500 mg) in dry THF (7.5 ml) (x = 1.1, y = 18) gave, after chromatography (30 × 2.5 cm; 25% Me_2CO in C_6H_{14}), 4″-*O*-acetyl-23-*O*-demycinosyl-20-deoxo-20-[(4,4-dioxothiomorpholino)imino]tylosin (**52**) (467 mg, 80%), m/z 916 (MH^+); $[\alpha]_D^{26}$ −70.1° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 235 (6 590) and 285 nm (19 270); $\nu_{max.}$($CDCl_3$) 3 500, 1 730, 1 710, 1 675, 1 590, 1 420, 1 275, 1 180, 1 120, and 1 050 cm^{-1}.

(j) The macrolide (**39**) (1.1 g) in dry THF (20 ml) (x = 1.1, y = 19) gave, after chromatography (15 × 1 cm; 25% Me_2CO in C_6H_{14}), 4″-*O*-acetyl-23-demycinosyloxy-20-deoxo-20-[(4,4-dioxothiomorpholino)imino]-23-iodotylosin (**53**) (1.2 g, 95%).

Preparation of 23-O-*Demycinosyltylosin Derivatives by Pfitzner–Moffatt Oxidation.*—The macrolide (1 mol equiv.) and the carbodi-imide (u mol equiv.) were dissolved in the solvent. A solution of pyridine (v mol equiv.) and trifluoroacetic acid (w mol equiv.) in dimethyl sulphoxide (DMSO) (x ml) was added and the mixture was stirred at 25 °C for y h.

(a) The macrolide (**62**) (5 g) and diethylcarbodi-imide in 30% (v/v) DMSO in dry toluene (150 ml) (u = 18, v = 6, w = 3, x = 5, y = 42) gave, after chromatography (90 × 5 cm, 14% Me_2CO in C_6H_{14}), 2′,4″,20-*tri*-O-*acetyl*-2‴,3‴-*didehydro*-2‴-*demethoxy*-4‴-*deoxy*-4‴-*oxotylosin* 3,20-*hemiacetal* (**63**) (2.25 g, 63%) (Found: C, 58.9; H, 7.45; N, 1.6. $C_{51}H_{77}NO_{19}$·0.2$CHCl_3$ requires C, 58.67; H, 7.43; N, 1.34%); $[\alpha]_D^{26}$ −70.7° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 279 nm (24 750); $\nu_{max.}$($CDCl_3$) 3 500, 1 735, 1 650, 1 240, 1 070, and 1 050 cm^{-1}; and unchanged (**62**) (0.53 g, 11%).

The ketone (**63**) (2.13 g) was dissolved in methanol (100 ml) containing 1.45% (w/v) sodium methoxide in methanol (2.13 ml) and the mixture was kept under dry argon at 25 °C for 1 h. After work-up, the product was dissolved in methanol (100 ml) containing triethylamine (4 ml) and heated at 40 °C for 67 h. Chromatography (30 × 5 cm; 25% Me_2CO in C_6H_{14}) gave 23-O-*demycinosyltylosin* (**24**) (1.1 g, 71%) (Found: C, 59.5; H, 8.2; N, 1.2. $C_{38}H_{63}NO_{13}$·0.2$CHCl_3$ requires C, 59.60; H, 8.29; N, 1.83%); $[\alpha]_D^{26}$ −41.9° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 284 nm (18 240); $\nu_{max.}$($CDCl_3$) 3 490, 2 980, 2 940, 2 900, 1 720, 1 680, 1 595, 1 250, 1 188, 1 165, and 1 050 cm^{-1}. The more polar fractions were rechromatographed (60 × 2 cm; 2.5% MeOH in $CHCl_3$) to give *methyl* 5-[2-*formyl*-3-(6-*hydroxy*-5-*hydroxymethyl*-3-*methylocta*-1,3-*dienyl*)-4-*methylcyclopent*-2-*enyl*]-5-[α-L-*mycarosyl*-(1→4)-β-D-*mycaminosyloxy*]*valerate* (**64**) (323 mg, 17%) (Found: C, 59.8; H, 8.2; N, 1.3. $C_{39}H_{65}NO_{13}$·0.2$CHCl_3$ requires C, 60.07; H, 8.40; N, 1.80%); m/z 756 (MH^+); $[\alpha]_D^{26}$ +2.8° ($CHCl_3$); $\lambda_{max.}$(MeOH) 241 (11 470) and 327 nm (17 950); $\nu_{max.}$($CDCl_3$) 3 450, 1 720, 1 640, 1 600, 1 200, 1 160, and 1 050 cm^{-1}.

(b) The macrolide (**23**) (415 mg), and diethylcarbodi-imide in 15% (v/v) DMSO in dry toluene (10 ml) (u = 3, v = 1, w = 0.5, x = 1.2 of 15% DMSO in dry toluene, y = 42) gave, after work-up, a product, which was dissolved in methanol (40 ml) containing triethylamine (1 ml) (dried over KOH pellets) and the mixture was kept at 25 °C for 108 h, then heated at 50 °C for 7 h and chromatographed (60 × 2 cm; 3% MeOH in

$CHCl_3$) to give 23-*O*-demycinosyl-20-deoxo-20-[(4,4-dioxothiomorpholino)imino]tylosin (**44**) (70 mg, 22%).

(c) The macrolide (**62**) (10 g) and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodi-imide hydrochloride in DMSO (250 ml) (u = 12, v = 4, w = 2, x = 10, y = 19) gave, after work-up and chromatography (h.p.l.c., 1 cartridge; 20% Me_2CO in C_6H_{14}), 2′,4″,20-tri-*O*-acetyl-2‴,3‴-didehydro-2‴-demethoxy-4‴-deoxy-4‴-oxotylosin 3,20-hemiacetal (**63**) (8.4 g, 86%).

The ketone (**63**) (5.9 g) was dissolved in methanol (1 l) containing triethylamine (14.5 ml) and the solution was heated at 52 °C for 7 h. Chromatography (h.p.l.c., 1 cartridge; 1.5→5% MeOH in $CHCl_3$) gave 4″-O-*acetyl*-23-O-*demycinosyltylosin* (**38**) (3.2 g, 70%) (Found: C, 58.15; H, 8.05; N, 1.6. $C_{40}H_{65}NO_{14}$·0.3$CHCl_3$ requires C, 57.76; H, 7.88; N, 1.68%); m/z 724 ($MH^+ - 60$); $[\alpha]_D^{26}$ −41.5° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 285 nm (19 200); $\nu_{max.}$($CDCl_3$) 3 590, 3 470, 1 720, 1 675, 1 590, 1 245, 1 180, and 1 050 cm^{-1}.

The ketone (**63**) (8.5 g) was dissolved in methanol (200 ml) containing triethylamine (10 ml) and the mixture was kept at 25 °C for 140 h. Chromatography (h.p.l.c., 1 cartridge; 2→3% MeOH in $CHCl_3$) gave the cyclopentenone (**57**) (1.1 g, 77%), identical with that isolated earlier in these laboratories,[35] and 4″-*O*-acetyl-23-*O*-demycinosyltylosin (**38**) (1.35 g). The overlap fractions (4.6 g) were rechromatographed (60 × 2 cm; 2% MeOH in $CHCl_3$) to give 4″-O-*acetyl*-23-O-*demycinosyl*-3-*deoxy*-3,19-*cyclotylosin* (**65**) (150 mg, 2%) (Found: C, 60.9; H, 8.0; N, 1.8. $C_{40}H_{63}NO_{13}$·0.2$CHCl_3$ requires C, 60.83; H, 8.04; N, 1.77%); m/z 766 (MH^+); $[\alpha]_D^{26}$ −59.2° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 281 nm (21 590); $\nu_{max.}$($CDCl_3$) 3 590, 3 480, 1 730, 1 658, 1 598, 1 240, 1 160, and 1 048 cm^{-1}, and 4″-*O*-acetyl-23-*O*-demycinosyltylosin (**38**) (2.5 g) (total 3.85 g, 59%).

General Procedures for the Preparation of 23-O-*Acyl Macrolides*.—(a) The macrolide (**29**) (3.1 g), DMAP (95.3 mg), and triethylamine (2.7 ml) were dissolved in dry dichloromethane (300 ml). Acetic anhydride (0.22 ml) was added and the mixture was stirred at 25 °C for 19 h. Chromatography (30 × 5 cm; 25% Me_2CO in C_6H_{14}) gave 2′,23-di-*O*-acetyl-23-*O*-demycinosyltylosin (**30**). Unchanged (**29**) was recycled twice to give a total yield of compound (**30**) of 2.42 g (70%).

(b) The macrolide (**29**) (158 mg), triethylamine (0.14 ml), and benzoic anhydride (151 mg) were dissolved in dry dichloromethane (4 ml) and the mixture was stirred at 25 °C for 44 h. Chromatography (30 × 2 cm; 25% Me_2CO in C_6H_{14}) gave 2′-*O*-acetyl-23-*O*-benzoyl-23-*O*-demycinosyltylosin (**33**) (112 mg, 63%).

(c) The macrolide (**29**) (632 mg), pyridine (0.101 ml), and DMAP (20.2 mg) were dissolved in dry dichloromethane (15 ml). Isovaleric anhydride (0.0926 ml) was added and the mixture was stirred at 25 °C for 18 h. Chromatography (60 × 2 cm; 25% Me_2CO in C_6H_{14}) gave 2′-*O*-acetyl-23-*O*-demycinosyl-23-*O*-isovaleryltylosin (**35**) (517 mg, 72%).

(d) The macrolide (**24**) (1.1 g) and pyridine (0.3625 ml) were dissolved in dry dichloromethane (10 ml). The solution was cooled to −53 °C and a solution of phenylacetyl chloride (0.2378 ml) in dry dichloromethane (5 ml) was added dropwise. After 55 min additional phenylacetyl chloride (0.2378 ml) in dry dichloromethane (5 ml) was added during 15 min. After an additional 10 min at −53 °C and warming to 25 °C during 30 min, the mixture was worked up and chromatographed (15 × 5 cm; 2% MeOH in $CHCl_3$) to give 23-*O*-demycinosyl-23-*O*-phenylacetyltylosin (**37**) (491 mg, 39%), m/z 860 (MH^+); $[\alpha]_D^{26}$ −33.9° ($CHCl_3$); $\lambda_{max.}$(MeOH) 284 nm (19 700).

General Procedure for the Preparation of 23-*Demycinosyloxy*-23-*iodotylosin Derivatives*.—The macrolide (1 mol equiv.), pyridine (10 mol equiv.), and methyltriphenoxyphosphonium iodide* (x mol equiv.) were dissolved in dry DMF (y ml) and the mixture was stirred in the dark at 25 °C for 18 h. Methanol was added and the product worked up in the usual way.

(a) The macrolide (**38**) (3 g) (x = 2, y = 15) gave, after chromatography (30 × 5 cm; 20% Me_2CO in C_6H_{14}), 4″-O-*acetyl*-23-*demycinosyloxy*-23-*iodotylosin* (**39**) (2.46 g, 72%) (Found: C, 52.4; H, 7.05; N, 1.3. $C_{40}H_{64}INO_{13}$ requires C, 53.75; H, 7.22; N, 1.57%); m/z 894 (MH^+); $[\alpha]_D^{26}$ 5.0° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 286 nm (22 410); $\nu_{max.}$($CDCl_3$) 3 490, 1 720, 1 675, 1 590, 1 240, 1 160, and 1 040 cm^{-1}. Rechromatography (90 × 2 cm; 17% Me_2CO in C_6H_{14}) of the less polar fractions (746 mg) gave 4″-O-*acetyl*-3,4-*didehydro*-23-*demycinosyloxy*-3-*deoxy*-23-*iodotylosin* (**66**) (259 mg, 8%) (Found: C, 54.9; H, 7.1; N, 1.4. $C_{40}H_{62}INO_{12}$ requires C, 54.86; H, 7.14; N, 1.60%); m/z 876 (MH^+); $[\alpha]_D^{26}$ −23.3° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 282 nm (21 290); $\nu_{max.}$($CDCl_3$) 3 600, 3 480, 1 720, 1 675, 1 590, 1 238, 1 155, and 1 040 cm^{-1}.

(b) The macrolide (**52**) (171 mg) (x = 2, y = 0.865) gave, after chromatography (30 × 2 cm; 25% Me_2CO in C_6H_{14}), 4″-O-*acetyl*-23-*demycinosyloxy*-20-*deoxo*-20-[(4,4-*dioxothiomorpholino*)*imino*]-23-*iodotylosin* (**53**) (84 mg, 44%) (Found: C, 51.7; H, 7.15; N, 3.8. $C_{44}H_{72}IN_3O_{14}S$ requires C, 51.51; H, 7.07; N, 4.10%); m/z 1 026 (MH^+); $[\alpha]_D^{26}$ −19.1° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 235 (7 390) and 285 nm (21 900); $\nu_{max.}$($CDCl_3$) 3 500, 1 725, 1 705sh, 1 680, 1 590, 1 310, 1 240, 1 185, 1 125, and 1 045 cm^{-1}.

(c) The macrolide (**52**) (159.4 mg) (x = 4, y = 0.797) gave, after chromatography (30 × 1 cm; 25% Me_2CO in C_6H_{14}) and p.l.c. (silica gel; 20 × 20 cm; 250 μ; 40% Me_2CO in C_6H_{14} and (15 × 0.5 cm; 20% Me_2CO in C_6H_{14}), 4″-*O*-acetyl-3,4-didehydro-23-demycinosyloxy-20-deoxo-3-deoxy-20-[(4,4-dioxothiomorpholino)imino]-23-iodotylosin (**67**) (31 mg, 17%), m/z 1 008 (MH^+); $\lambda_{max.}$(CF_3CH_2OH) 237 (8 090) and 283 nm (20 920); $\nu_{max.}$ ($CDCl_3$) 3 600, 3 490, 1 735, 1 675, 1 690, 1 200, 1 245, 1 125, and 1 050 cm^{-1}.

4″-O-*Acetyl*-23-*demycinosyloxy*-20-*deoxo*-23-*dimethylamino*-20-[(4,4-*dioxothiomorpholino*)*imino*]*tylosin* (**54**).—The macrolide (**53**) (500 mg) and dimethylamine (268 mg) were dissolved in dry acetonitrile (7.9 ml) and the mixture was heated in a sealed bomb at 80 °C for 40 min. Chromatography (90 × 2 cm; 35% Me_2CO in C_6H_{14}) gave the 23-*dimethylamino derivative* (**54**) (429 mg, 93%) (Found: C, 58.8; H, 8.3; N, 4.8. $C_{46}H_{78}N_4O_{14}S$ requires C, 58.58; H, 8.34, N, 5.94%); m/z 943 (MH^+); $[\alpha]_D^{26}$ −38.5° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 225 (6 700) and 277 nm (19 820); $\nu_{max.}$($CDCl_3$) 3 600, 3 500, 1 725, 1 705, 1 675, 1 585, 1 305, 1 240, 1 180, 1 120, and 1 040 cm^{-1}.

23-*Demycinosyloxy*-20-*deoxo*-23-*dimethylamino*-20-[(4,4-*dioxothiomorpholino*)*imino*]*tylosin* (**55**).—The macrolide (**54**) (286 mg) and triethylamine (4.2 ml) were dissolved in methanol (80 ml) and the mixture was stirred at 25 °C for 138 h. Chromatography (90 × 1 cm; 1.5% MeOH in $CHCl_3$) gave the 23-*dimethylamino derivative* (**55**) (111 mg, 41%) (Found: C, 56.4; H, 8.6; N, 5.5; S, 3.2. $C_{44}H_{76}N_4O_{13}S$·0.3$CHCl_3$ requires C, 56.40; H, 8.18; N, 5.98; S, 3.42%); m/z 901 (MH^+); $[\alpha]_D^{26}$ −36.9° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 230 (6 490) and 275 nm (21 050); $\nu_{max.}$($CDCl_3$) 3 475, 1 705, 1 675, 1 590, 1 310, 1 190, 1 125, and 1 045 cm^{-1}.

The forecuts from the column afforded unchanged (**54**) (134 mg, 47%). The latter was recycled as above to give a total yield of compound (**55**) of 61%.

23-*Demycinosyloxy*-23-*iodotylosin* (**40**).—The macrolide (**39**) (70 mg) and triethylamine (1.09 ml) were dissolved in methanol (20.7 ml) and the solution was kept at 25 °C for 24 h.

* Freshly washed with ethyl acetate and dried *in vacuo*.

Chromatography (15 × 2 cm; 2% MeOH in $CHCl_3$) gave the 23-iodide (**40**) (11 mg) and unchanged (**39**). The latter was taken up in methanol (15 ml) and triethylamine (0.8 ml), heated at 40 °C for 25 h, and kept at 25 °C for a further 18 h. Chromatography (30 × 1 cm; 1.5% MeOH in $CHCl_3$) gave a further crop of *compound* (**40**) (total yield 30 mg, 45%) (Found: C, 54.8; H, 8.0; N, 1.2. $C_{38}H_{62}INO_{12}$ requires C, 53.58; H, 7.34; N, 1.64%); *m/z* 852 (MH^+); $[\alpha]_D^{26}$ 0° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 285 nm (16 950); $\nu_{max.}$($CDCl_3$) 3 500, 1 715, 1 695sh, 1 668, 1 585, 1 158, and 1 048 cm^{-1}.

4″-O-*Acetyl*-23-*demycinosyloxy*-12,13-*dihydro*-12-*hydroxy*-14,15-*methylenetylosin* (**68**) *and* (**69**).—The macrolide (**39**) (200 mg) and tributyltin hydride (1.8 ml) were dissolved in dry THF (1.8 ml) and the mixture was kept at 25 °C for 52 h. Chromatography (15 × 2 cm; 4% MeOH in $CHCl_3$) gave a 1:1 mixture of title products (**68**) and (**69**). P.l.c. (silica gel; 20 × 20 cm; 250 μ; 10% THF in Et_2O) and chromatography of each band (15 × 1 cm; 2% MeOH in $CHCl_3$) gave the less polar diastereoisomer (**68**) (50.9 mg, 30%), *m/z* 784 (MH^+); $[\alpha]_D^{26}$ −34.0° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 230 nm (8 630); $\nu_{max.}$($CDCl_3$) 3 610, 3 490, 1 730, 1 700, 1 680, 1 625, 1 245, 1 170, and 1 050 cm^{-1}, and the more polar diastereoisomer (**69**) (51.1 mg, 29%), *m/z* 784 (MH^+); $[\alpha]_D^{26}$ −24.7°($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 235 nm (9 790); $\nu_{max.}$($CDCl_3$) 3 600, 3 500, 1 730, 1 700, 1 608, 1 250, 1 190, 1 170, and 1 050 cm^{-1}.

3″,4″-*Anhydro*-23-O-*demycinosyl*-20-*deoxo*-20-[(4,4-*dioxothiomorpholino*)*imino*]*tylosin* (**71**).—The macrolide (**44**) (400 mg) was dissolved in dry acetonitrile (20 ml) and a solution of triphenylphosphine (132 mg) and iodine (128 mg) in dry acetonitrile (70 ml) was added. After 1 h at 25 °C the mixture was treated with methanol and the reaction mixture was worked up. Chromatography (60 × 2 cm; 3% MeOH in $CHCl_3$ gave the *epoxide* (**71**) (141 mg, 36%) (Found: C, 58.3; H, 7.9; N, 4.5. $C_{42}H_{69}N_3O_{13}S$ requires C, 58.93; H, 8.12; N, 4.91%); *m/z* 856 ($M^{+\bullet}$); $\lambda_{max.}$(MeOH) 282 nm (21 530); $\nu_{max.}$($CDCl_3$) 3 600, 3 450, 1 720, 1 673, 1 585, 1 308, 1 183, 1 120, and 1 055 cm^{-1}, and 20-*deoxo*-20-[(4,4-*dioxothiomorpholino*)*imino*]-5-O-β-D-*mycaminosyltylonolide* (**41**) (134 mg, 40%) (Found: C, 54.55; H, 7.65; N, 4.8; S, 3.6. $C_{35}H_{59}N_3O_{11}S{\cdot}0.3CHCl_3$ requires C, 54.90; H, 7.77; N, 5.49; S, 4.19%); *m/z* 729 ($M^{+\bullet}$); $[\alpha]_D^{26}$ −32.1° ($CHCl_3$); $\lambda_{max.}$(MeOH) 283 nm (21 260); $\nu_{max.}$($CDCl_3$) 3 600, 3 450, 1 710, 1 675, 1 590, 1 305, 1 185, 1 125, and 1 060 cm^{-1}.

5-O-β-D-*Mycaminosyltylonolide* (**42**).—(i) The macrolide (**44**) (500 mg) was dissolved in 0.1M hydrochloric acid (50 ml) and the solution was kept at 25 °C for 105 h. Chromatography (30 × 2.5 cm; 3% MeOH in $CHCl_3$) gave compound (**42**) (250 mg, 73%) (Found: C, 58.0; H, 7.9; N, 2.2. Calc. for $C_{31}H_{51}NO_{10}{\cdot}0.4CHCl_3$: C, 57.70; H, 7.96; N, 2.17%); *m/z* 597 ($M^{+\bullet}$); $[\alpha]_D^{26}$ −2.9°($CHCl_3$); $\lambda_{max.}$(MeOH) 282 nm (20 590); $\nu_{max.}$($CDCl_3$) 3 590, 3 430, 1 715, 1 693, 1 590, 1 315, 1 185, and 1 055 cm^{-1}.

(ii) The macrolide (**71**) (61.4 mg) was dissolved in 0.1M hydrochloric acid (10 ml) and the solution was kept at 25 °C for 8 days. The product was isolated as in (i) above to give compound (**41**) (9.1 mg, 21%).

2′,4″-*Di*-O-*acetyl*-23-*demycinosyloxy*-20-*deoxo*-20-[(4,4-*dioxothiomorpholino*)*imino*]-23-*iodotylosin* (**56**).—The macrolide (**48**) (92.9 mg), triphenylphosphine (50.8 mg), and propylene oxide (0.0128 ml) were dissolved in dry DMF (0.1818 ml). A solution of iodine (49.19 mg) in dry DMF (0.0929 ml) was added and the mixture kept at 25 °C for 0.75 h. The reaction was quenched with methanol (2 ml) and the mixture was worked up in the usual way. Chromatography (15 × 1 cm; 30% Me_2CO in C_6H_{14}) gave the iodide (**56**) (35 mg, 34%), *m/z* 1 068 (MH^+).

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References

1 R. B. Morin and M. Gorman, *Tetrahedron Lett.*, 1964, 2339.
2 R. B. Morin, M. Gorman, R. L. Hamill, and P. V. Demarco, *Tetrahedron Lett.*, 1970, 4737.
3 S. Omura, A. Nakagawa, A. Neszmelyi, S. D. Gero, A. M. Sepulchre, F. Piriou, and G. Lukacs, *J. Am. Chem. Soc.*, 1975, **97**, 4001.
4 S. Omura, A. Nakagawa, M. Machida, and H. Imai, *Tetrahedron Lett.*, 1977, 1045.
5 S. Omura, H. Matsubara, A. Nakagawa, A. Furusaki, and T. Matsumoto, *J. Antibiot.*, 1980, **33**, 915.
6 R. Okamoto, H. Nomura, M. Tsuchiya, H. Tsunekawa, T. Fukumoto, T. Inui, T. Sawa, T. Takeuchi, and H. Umezawa, *J. Antibiot.*, 1979, **32**, 542.
7 R. Okamoto, T. Fukumoto, H. Nomura, K. Kiyoshima, K. Nakamura, A. Takamatsu, H. Naganawa, T. Takeuchi, and H. Umezawa, *J. Antibiot.*, 1980, **33**, 1300.
8 R. Okamoto, M. Tsuchiya, H. Nomura, H. Iguchi, K. Kiyoshima, S. Hori, T. Inui, T. Sawa, T. Takeuchi, and H. Umezawa, *J. Antibiot.*, 1980, **33**, 1309.
9 M. Tsuchiya, K. Suzukake, M. Hori, T. Sawa, T. Takeuchi, H. Umezawa, R. Okamoto, H. Nomura, H. Tsunekawa, and T. Inui, *J. Antibiot.*, 1981, **34**, 305.
10 M. Tsuchiya, T. Sawa, T. Takeuchi, H. Umezawa, and R. Okamoto, *J. Antibiot*, 1982, **35**, 673.
11 S. Mori, R. Okamoto, T. Inui, and T. Takeuchi, U.S.P. 4 205 163/May 27, 1980.
12 A. K. Ganguly, Y.-T. Liu, O. Sarre, R. S. Jaret, A. T. McPhail, and K. K. Onan, *Tetrahedron Lett.*, 1980, **21**, 4699.
13 A. K. Ganguly, O. Z. Sarre, and Y.-T. Liu, unpublished observations.
14 A. K. Ganguly and Y.-T. Liu, U.S.P. 4 279 896/July 21, 1981.
15 J. A. Waitz, G. H. Miller, and D. M. Loebenberg, unpublished observations.
16 A. A. Nagel and L. A. Vincent, *J. Org. Chem.*, 1979, **44**, 2050.
17 R. H. Baltz and E. T. Seno, *Antimicrob. Agents Chemother.*, 1981, **20**, 214.
18 H. A. Kirst, G. M. Wild, R. H. Baltz, R. L. Hamill, J. L. Ott, F. T. Counter, and E. E. Ose, *J. Antibiot.*, 1982, **35**, 1675.
19 H. A. Kirst, G. M. Wild, R. H. Baltz, E. T. Seno, R. L. Hamill, J. W. Paschal, and D. E. Dorman, *J. Antibiot.*, 1983, **36**, 376.
20 R. H. Baltz, G. M. Wild, and E. T. Seno, U.S.P. 4 321 361/March 23, 1982.
21 R. Okamoto, K. Kiyoshima, M. Yamamoto, K. Takada, T. Ohnuki, T. Ishikura, H. Naganawa, K. Tatsuta, T. Takeuchi, and H. Umezawa, *J. Antibiot.*, 1982, **35**, 921.
22 R. Okamoto, M. Yamamoto, K. Kiyoshima, T. Ishikura, K. Tatsuta, T. Takeuchi, and H. Umezawa, Eur.P. 96 900/December 28, 1983.
23 R. H. Baltz, G. M. Wild, and E. T. Seno, U.S.P. 4 321 362/March 23, 1982.
24 H. A. Kirst, U.S.P. 4 396 613/August 2, 1983.
25 H. A. Kirst, U.S.P. 4 436 733/ March 13, 1984.
26 H. A. Kirst, M. Debono, J. E. Toth, B. A. Treudell, J. A. Wind, and K. E. Willard, 190th ACS National Meeting, Chicago, Illinois, September 8–13, 1985, Abstract 76.
27 H. A. Kirst, M. Debono, J. E. Toth, B. A. Truedell, K. E. Willard, J. L. Ott, F. T. Counter, A. M. Felty-Duckworth, and R. S. Pekarek, *J. Antibiot.*, 1986, **39**, 1108.
28 A. G. Fishman, A. K. Mallams, and R. R. Rossman, following paper.
29 R. Okamoto, T. Fukumoto, T. Inui, and T. Takeuchi, Jap.P. 85 16 960/April 30, 1985.
30 S. Sakamoto, T. Tsuchiya, T. Miyake, A. Tanaka, and S. Umezawa, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 3536.
31 K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, 1965, **87**, 5661.
32 K. E. Pfitzner and J. G. Moffatt, *J. Am. Chem. Soc.*, 1965, **87**, 5670.
33 H. Sakakibara, T. Fujiwara, O. Okegawa, T. Watanabe, S. Watanabe, and T. Matsuda, U.S.P. 4 268 665/May 19, 1981.

34 S. Omura, A. Nakagawa, K. Suzuki, and T. Hata, *J. Antibiot.*, 1974, **27**, 370.
35 H. Matsubara, K. Miyano, A. Nakagawa, and S. Omura, *Chem. Pharm. Bull.*, 1982, **30**, 97.
36 A. K. Ganguly, Y.-T. Liu, A. T. McPhail, and O. Sarre, *J. Chem. Soc., Chem. Commun.*, 1982, 853.
37 A. Tanaka, T. Tsuchiya, T. Okada, S. Umezawa, M. Hamada, and H. Umezawa, *J. Antibiot.*, 1982, **35**, 113.
38 H. A. Kirst and J. E. Toth, Eur.P. 99 747/February 1, 1984.
39 A. F. Cacciapuoti, D. Loebenberg, E. L. Moss, Jr., F. W. Menzel, Jr., J. A. Rudeen, L. R. Naples, C. L. Cramer, R. S. Hare, and G. H. Miller, manuscript in preparation.

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