Novel 3-*O*-α-L-Cladinosyl Sixteen-membered Macrolide Antibacterials

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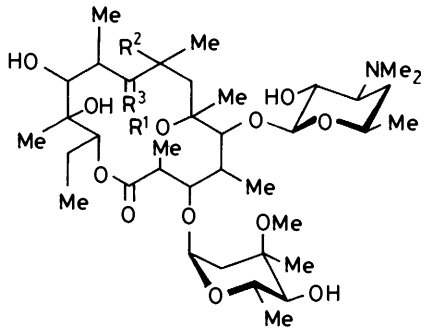
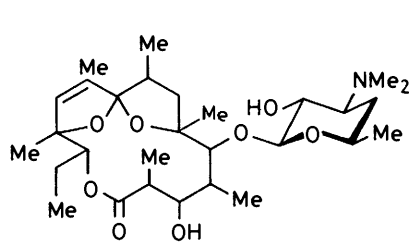
A novel series of 3-*O*-α-L-cladinosyl sixteen-membered macrolide antibacterials has been synthesized by glycosidation of the 3-hydroxy group of 12,13-de-epoxy-12,13-didehydrorosaramicin, 12,13-de-epoxy-12,13-didehydro-20-deoxorosaramicin, desmycosin, 20-deoxodesmycosin, and 19-deformyl-desmycosin. The glycosidation was effected by reaction of the suitably protected macrolide substrates with the 1-*S*-pyridyl derivative of L-cladinose in the presence of either anhydrous silver perchlorate or anhydrous silver trifluoromethanesulphonate to afford the 3-*O*-α-glycosides in good yield.

Although 3-*O*-glycosylated derivatives are commonly found among the naturally occurring twelve-membered macrolides (methymycin,[1] neomethmycin,[2] and antibiotic YC-17)[3] and among fourteen-membered macrolides (erythromycins,[4] megalomicins,[5] oleandomycins,[6] and lankamycins),[7] none have yet been found to occur naturally, nor have they been synthesized, among the sixteen-membered macrolides.[8] The presence of a 3-*O*-α-L-cladinosyl moiety in the clinically important macrolide antibiotic erythromycin A (**1**) prompted us to select L-cladinose as the sugar of choice for our studies. It is well known that erythromycin A (1) readily undergoes conversion under acidic conditions to give the inactive spiroketal erythralosamine (**5**).[9] In recent years considerable effort has gone into finding derivatives of erythromycin A (**1**) which are more acid stable in order to increase its bioavailability. In this connection 9-deoxo-9-(2-methoxyethoxymethoxyimino)erythromycin A (**2**),[10,11] 6-*O*-methylerythromycin A (**3**),[12] and (8*S*)-8-fluoroerythromycin A (**4**)[13–15] have all been synthesized and are currently undergoing preclinical or clinical testing. All three are more stable towards acidic conditions and show greatly enhanced bioavailability.

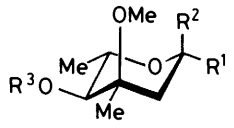


(**1**) $R^1 = R^2 = H$, $R^3 = O$
(**2**) $R^1 = R^2 = H$, $R^3 = NOCH_2OCH_2CH_2OMe$
(**3**) $R^1 = Me$, $R^2 = H$, $R^3 = O$
(**4**) $R^1 = H$, $R^2 = F$, $R^3 = O$



(**5**)

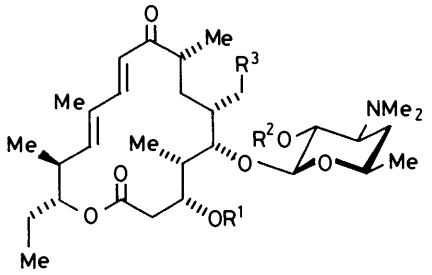
We reasoned that by synthesizing a series of carefully targeted 3-*O*-α-L-cladinosyl sixteen-membered macrolides we might well obtain a novel group of hybrid antibacterials in which the right-hand portion (C-1 to C-9) would closely mimic erythromycin A (**1**). Such compounds would be inherently more acid stable as they would not contain the 6- and 11-hydroxy groups which are needed to form the spiroketal in erythralosamine (**5**). Such novel 3-*O*-glycosyl macrolides might reasonably be expected to exhibit broad-spectrum Gram-positive activity and show enhanced serum levels relative to the parent sixteen-membered macrolides. The availability of powerful new glycosidation reactions[16–18] made the approach even more attractive.



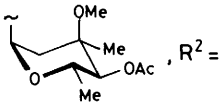
(**6**) $R^1 = R^3 = H$, $R^2 = OH$
(**7**) $R^1 = OH$, $R^2 = R^3 = H$
(**8**) $R^1 = OAc$, $R^2 = H$, $R^3 = Ac$
(**9**) $R^1 = H$, $R^2 = OH$, $R^3 = Ac$
(**10**) $R^1 = OH$, $R^2 = H$, $R^3 = Ac$
(**11**) $R^1 = H$, $R^2 =$ 2-pyridylthio, $R^3 = Ac$
(**12**) $R^1 =$ 2-pyridylthio, $R^2 = H$, $R^3 = Ac$
(**13**) $R^1 = R^3 = H$, $R^2 = OMe$
(**14**) $R^1 = H$, $R^2 = OMe$, $R^3 = Ac$
(**15**) $R^1 = OMe$, $R^2 = R^3 = H$
(**16**) $R^1 = OMe$, $R^2 = H$, $R^3 = Ac$
(**17**) $R^1 = OCOCH_2OPh$, $R^2 = H$, $R^3 = COCH_2OPh$
(**18**) $R^1 = H$, $R^2 = OH$, $R^3 = COCH_2OPh$
(**19**) $R^1 = OH$, $R^2 = H$, $R^3 = COCH_2OPh$
(**20**) $R^1 = H$, $R^2 =$ 2-pyridylthio, $R^3 = COCH_2OPh$
(**21**) $R^1 =$ 2-pyridylthio, $R^2 = H$, $R^3 = COCH_2OPh$

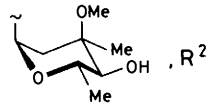
α- and β-L-Cladinose (**6**)/(**7**) was readily available by subjecting erythromycin A (**1**) to acidic hydrolysis.[19] Treatment of (**6**)/(**7**) with acetic anhydride in pyridine afforded 1,4-di-*O*-acetyl-β-L-cladinose (**8**),[19] which on mild acidic hydrolysis gave 4-*O*-acetyl-α- and -β-L-cladinose (**9**)/(**10**).[19] The latter reacted with 2,2′-dipyridyl disulphide and tributylphosphine[19,20] to give the α- and β-1-*S*-pyridyl derivatives (**11**) and (**12**) respectively.[19] The ^{13}C n.m.r. data are given in a supplementary publication.

12,13-De-epoxy-12.13-didehydrorosaramicin (**22**)[21,22] was converted into the 2′-*O*-acetyl derivative (**23**).[22] 12,13-De-epoxy-12,13-didehydrorosaramicin 20-dimethyl acetal (**24**)[23] was also converted into the 2′-*O*-acetyl derivative (**25**). Glycosidation of either compound (**23**) or (**25**) with a mixture of the pyridyl thioglycoside (**11**) and (**12**) in the presence of anhydrous silver perchlorate in dry acetonitrile,[19] afforded the protected 3-

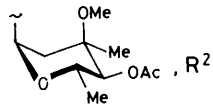


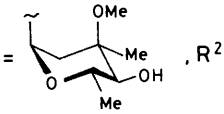
(22) $R^1 = R^2 = H, R^3 = CHO$
(23) $R^1 = H, R^2 = Ac, R^3 = CHO$
(24) $R^1 = R^2 = H, R^3 = CH(OMe)_2$
(25) $R^1 = H, R^2 = Ac, R^3 = CH(OMe)_2$

(26) R^1 =  , $R^2 = Ac, R^3 = CHO$

(27) R^1 =  , $R^2 = H, R^3 = CHO$

(28) $R^1 = R^2 = H, R^3 = Me$
(29) $R^1 = H, R^2 = Ac, R^3 = Me$

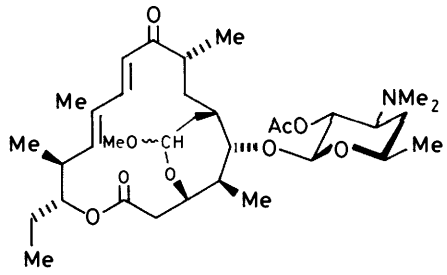
(30) R^1 =  , $R^2 = Ac, R^3 = Me$

(31) R^1 =  , $R^2 = H, R^3 = Me$

O-α-L-cladinosyl derivative (**26**) in both instances. The 20-acetal was unstable to the mildly acidic (pH 3—4) reaction conditions and thus could not be usefully elaborated. An undesired 20-*O*-methyl 3,20-hemiacetal derivative (**32**) was also formed during the glycosidation of compound (**25**). No 3-*O*-β-glycoside was observed in either of the above reactions, as anticipated. Deprotection of compound (**26**) using twenty equivalents of triethylamine in methanol (2% w/v solution) at 25 °C failed to remove the 4′-*O*-acetyl group in the cladinose moiety. Similar resistance to basic hydrolysis has been noted in the erythromycin series.[24] More vigorous basic hydrolysis conditions using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in methanol at 25 °C gave the desired 3-*O*-α-L-cladinosyl-12,13-de-epoxy-12,13-didehydrorosaramicin (**27**). No opening of the lactone ring was observed in the rosaramicin series under the above conditions. The anomeric linkage at C-3 in both (**26**) and (**27**) was assigned the α-configuration from the ^{13}C n.m.r. data (supplementary publication) and from the signal at δ_H 4.99 ($J_{1'eq.,2'eq.}$ 1.5, $J_{1'eq.,2'ax.}$ 4 Hz) in the ^1H n.m.r. spectrum of compound (**26**), and from the signal at δ_H 4.94 ($J_{1'eq.,2'eq.}$ 1, $J_{1'eq.,2'ax.}$ 4 Hz) in the ^1H n.m.r. spectrum of compound (**27**).

Methyl α- and β-L-cladinoside, (**13**) and (**15**), were converted into the 4-*O*-acetyl derivatives (**14**) and (**16**) respectively and the molecular rotations of compounds (**13**)—(**16**) were determined (Table). The application of Klyne's Rule[26] to both compounds (**26**) and (**27**) lent further support to the assignment of an α-L-configuration to the 3-*O*-cladinosyl moiety in these compounds (Table).

The glycosidation of 12,13-de-epoxy-12,13-didehydro-20-de-



(**32**)

oxorosaramicin (**28**)[23,27,28] was studied next. Conversion of (**28**)* into the 2′-*O*-acetate (**29**), followed by glycosidation with a mixture of (**11**) and (**12**) in the presence of anhydrous silver perchlorate,[19] afforded the protected 3-*O*-α-L-cladinosyl derivative (**30**) in good yield. Deprotection as described above with DBU in methanol afforded the desired 3-*O*-α-L-cladinosyl derivative (**31**). The ^1H n.m.r., ^{13}C n.m.r. (supplementary publication) and molecular rotation data (Table), all supported the α-L-configuration for the cladinose at C-3 in structures (**30**) and (**31**). The proton assignments for compound (**30**) were confirmed by means of a 2D-n.m.r. experiment.

Desmycosin (**33**),[29] on treatment with acetic anhydride in pyridine, gave 2′,4′,4″-tri-*O*-acetyldesmycosin (**34**). Glycosidation of the latter with compounds (**11**) and (**12**) in the presence of anhydrous silver perchlorate gave the protected 3-*O*-α-L-cladinosyl derivate (**35**), deprotection of which with DBU in methanol, as before, gave a low yield of the desired 3-*O*-α-L-cladinosyldesmycosin (**36**), which was contaminated with the seco acid ester (**49**). The latter was present to the extent of ~5—10% and co-chromatographed with compound (**36**) in all of the systems studied. Clearly the lactone ring in the desmycosin series was not surviving the DBU hydrolysis and a more labile ester was needed to protect the 4-hydroxy group of the cladinose moiety. We selected the phenoxyacetyl group as it is known to be about 59-times more labile than the acetyl group[30,31] and has the advantage of being stable to normal handling conditions. 1,4-Di-*O*-phenoxyacetyl-β-L-cladinose (**17**) was prepared by reaction of L-cladinose (**6**)/(**7**) with either phenoxyacetyl chloride in the presence of pyridine, or with phenoxyacetic anhydride in pyridine. Mild acidic hydrolysis of compound (**17**) afforded 4-*O*-phenoxyacetyl-α- and -β-L-cladinose (**18**) and (**19**), which were in turn converted into the corresponding 1-*S*-pyridyl derivatives (**20**) and (**21**). Glycosidation of 2′,4′,4″-tri-*O*-acetyldesmycosin (**34**) with a mixture of compounds (**20**) and (**21**) in the presence of anhydrous silver trifluoromethanesulphonate afforded the protected 3-*O*-α-L-cladinosyl derivative (**37**) in high yield. The latter could be readily deprotected by treatment with triethylamine (20 mol equiv.) in methanol (2% w/v solution) at 25 °C for 70 h to give compound (**36**) in high yield. No opening of the lactone was observed under these conditions. The ^1H n.m.r., ^{13}C n.m.r. (supplementary publication), and molecular rotation data (Table) for compounds (**35**)—(**37**) all supported the α-L-configuration for the 3-*O*-glycoside in these compounds.

When desmycosin (**33**) was treated with five mol equiv. of DBU in methanol at 25 °C for 49 h, the seco acid ester aldol product (**51**) was formed, lending support to the fact that desmycosin (**33**) was reacting with DBU when the latter was used to effect removal of the ester protecting groups.

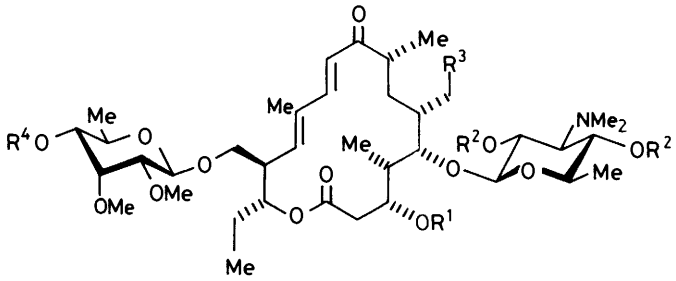
20-Deoxodesmycosin (**38**) was converted into the 2′,4′-diacetyl derivative (**39**) which was then selectively acetylated at

* Kindly provided by Mr. R. S. Jaret.

Table. $[\alpha]_D$, $[M]_D$ and Klyne's Rule[26]

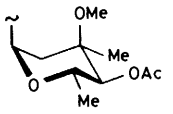
Compound	$[\alpha]_D$[a] (°)	$[M]_D$ (°)	$[M]_D$ (°) Glycoside − Aglycone	3-*O*-Glycoside
(**14**)	−168.1	−390.5		
(**16**)	−3.9	−9.1		
(**13**)	−132.1	−251.3		
(**15**)	+30.7	+58.4		
(**23**)	−4.4	−26.7		
(**26**)	−46.5	−375.7	(**26**) − (**23**) −349.0°	α-L
(**22**)	−29.3	−165.5		
(**27**)	−51.0	−369.2	(**27**) − (**22**) −203.7°	α-L
(**29**)	+7.9	+46.9		
(**30**)	−91.2	−724.2	(**30**) − (**29**) −771.1°	α-L
(**28**)	−6.5	−35.9		
(**31**)	−47.2	−335.1	(**31**) − (**28**) −299.2°	α-L
(**34**)	−3.1	−27.8		
(**35**)	−35.1	−385.5	**35**) − (**34**) −357.7°	α-L
(**33**)	−20.9	−161.3		
(**36**)	−43.8	−407.4	(**36**) − (**33**) −246.1°	α-L
(**38**)	−10.0[b]	−75.8		
(**43**)	−45.0	−412.3	(**43**) − (**38**) −336.5°	α-L
(**44**)	0	0		
(**48**)	−35.6	−321.2	(**48**) − (**44**) −321.2°	α-L

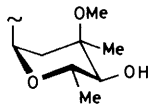
[a] $CHCl_3$. [b] Ref. 25.

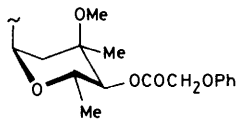


(**33**) $R^1 = R^2 = R^4 = H$, $R^3 = CHO$

(**34**) $R^1 = H$, $R^2 = R^4 = Ac$, $R^3 = CHO$

(**35**) R^1 =  , $R^2 = R^4 = Ac$, $R^3 = CHO$

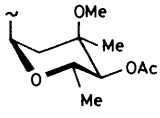
(**36**) R^1 =  , $R^2 = R^4 = H$, $R^3 = CHO$

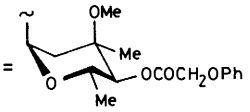
(**37**) R^1 =  , $R^2 = R^4 = Ac$, $R^3 = CHO$

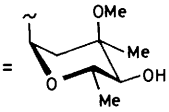
(**38**) $R^1 = R^2 = R^4 = H$, $R^3 = Me$

(**39**) $R^1 = R^4 = H$, $R^2 = Ac$, $R^3 = Me$

(**40**) $R^1 = H$, $R^2 = R^4 = Ac$, $R^3 = Me$

(**41**) R^1 =  , $R^2 = R^4 = Ac$, $R^3 = Me$

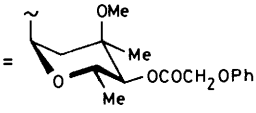
(**42**) R^1 =  , $R^2 = R^4 = Ac$, $R^3 = Me$

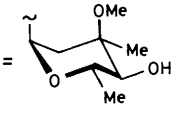
(**43**) R^1 =  , $R^2 = R^4 = H$, $R^3 = Me$

(**44**) $R^1 = R^2 = R^3 = R^4 = H$

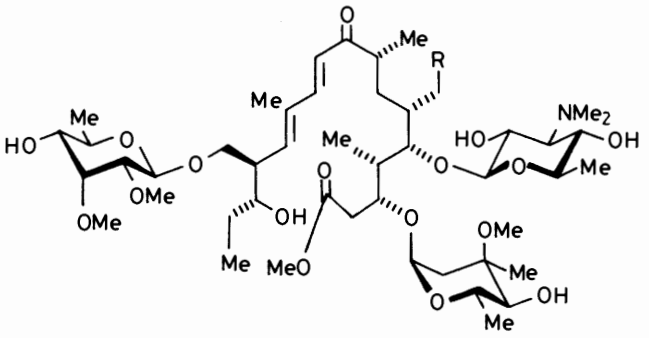
(**45**) $R^1 = R^3 = R^4 = H$, $R^2 = Ac$

(**46**) $R^1 = R^3 = H$, $R^2 = R^4 = Ac$

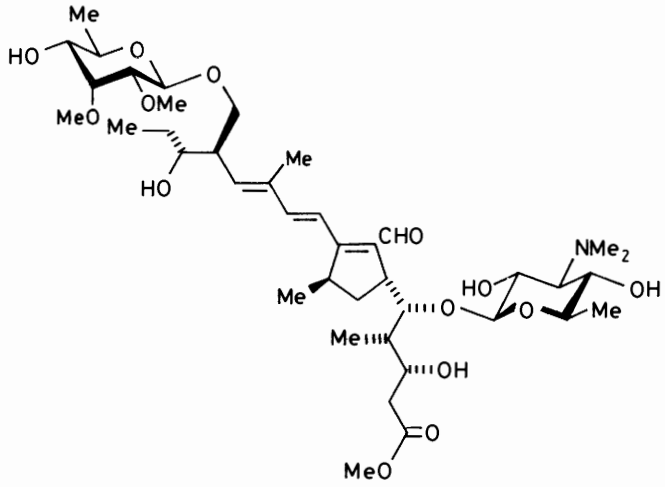
(**47**) R^1 =  , $R^2 = R^4 = Ac$, $R^3 = H$

(**48**) R^1 =  , $R^2 = R^3 = R^4 = H$

the 4″-position to give triacetate (**40**). The triacetate (**40**) was treated with the 4-*O*-acetyl-protected sugars (**11**) and (**12**) in the presence of anhydrous silver perchlorate to give the protected 3-*O*-α-L-cladinosyl derivative (**41**). Deprotection of the latter with DBU (5 mol equiv.) in methanol afforded 3-*O*-α-L-cladinosyl-20-deoxodesmycosin (**43**), which contained ~33% of the corresponding seco acid methyl ester (**50**). The latter co-chromatographed with compound (**43**) in all of the systems



(49) R = CHO
(50) R = Me



(51)

investigated. A peak at *m/z* 948 (MH^+) in the FAB-MS was consistent with the composition of compound (**50**), as were additional signals in both the ^1H n.m.r. and ^{13}C n.m.r. spectra. Glycosidation of compound (**40**) with the phenoxyacetyl-protected sugars (**20**) and (**21**) in the presence of anhydrous silver trifluoromethanesulphonate afforded the protected 3-*O*-α-L-cladinosyl derivative (**42**). The latter was deprotected with triethylamine (20 mol equiv.) in methanol (2% w/v solution) to give a high yield of compound (**43**). No opening of the lactone ring was observed under these conditions. The ^1H n.m.r., ^{13}C n.m.r., and molecular rotation data (Table) of compounds (**41**)—(**43**) were consistent with an α-L-configuration for the newly introduced 3-*O*-glycoside.

Finally the 19-deformyl analogue of desmycosin was prepared as follows. Desmycosin (**33**) was deformylated[32] using tris(triphenylphosphine)rhodium(I) chloride to give 19-deformyldesmycosin (**44**).[32] The latter was converted into the 2′,4′-di-*O*-acetyl derivative (**45**), which was in turn selectively acetylated at the 4″-position to give the triacetate (**46**). Glycosidation of the latter with compounds (**20**) and (**21**) in the presence of silver trifluoromethanesulphonate afforded the 3-*O*-α-L-cladinosyl derivative (**47**), deprotection of which with triethylamine in methanol as described above gave 3-*O*-α-L-cladinosyl-19-deformyldesmycosin (**48**) in high yield. The ^1H n.m.r., ^{13}C n.m.r. and molecular rotation data (Table) were in accord with an α-L-configuration for the cladinose at C-3 in structures (**47**) and (**48**).

The antibacterial activity of these novel 3-*O*-α-L-cladinosyl macrolides was determined.[33] The potency of these derivatives decreased in the order (**27**) > (**31**) > (**36**) > (**48**) > (**43**). The 3-*O*-cladinosyl derivative (**27**) of the de-epoxydidehydrorosaramicin (**22**) was the most potent member of the series and exhibited an antibacterial spectrum similar to that of de-epoxydidehydrorosaramicin (**22**). The derivative (**27**) was about half as active against Gram-negative strains and *Staphylococcus* strains, and about two-to four-fold more potent against *Streptococcus* strains, than was the parent de-epoxydidehydrorosaramicin (**22**). The potency of compound (**27**) was similar to that of roxithromycin (**2**); however, compound (**27**) showed improved Gram-negative activity and also improved activity against erythromycin-resistant strains of *Staphylococcus*. The IV serum levels in mice were similar to those of the mycinamicins.[33] In the non-aldehyde series, compound (**31**) was considerably more potent than the parent (**28**), while both compounds (**43**) and (**48**) were less potent than the parent desmycosin analogues (**38**) and (**44**) respectively. The 3-*O*-α-L-cladinosyldesmycosin (**36**) was also less potent than desmycosin (**33**).

Experimental

Experimental data were recorded as described in the first paper of this series. The ^1H and ^{13}C n.m.r. data are given in Supplementary Publication No. Sup. 56739 (18 pp.).*

General Acylation Procedures for Sugars.—Method 1. The sugar (1 mol equiv.) and acetic anhydride (*x* mol equiv.) were dissolved in dry pyridine (8—20 ml g^{-1} sugar) and the mixture was allowed to remain at 25 °C for 18—19 h. The product was worked up in the usual way to give a solid.

(a) L-Cladinose (**6**)/(**7**) (16.23 g)[9] (*x* = 7.7) gave, after chromatography (45 × 5 cm; 3% EtOAc in $CHCl_3$), the β-1,4-diacetate (**8**)[35] (19.2 g, 80%) (Found: C, 55.8; H, 7.9. Calc. for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74%); *m/z* 201 ($MH^+ - CH_3CO_2$); $[\alpha]_D^{26}$ −41.3° ($CHCl_3$); $\nu_{max.}$($CDCl_3$) 1 750, 1 735, 1 238, and 1 050 cm^{-1}.

(b) Methyl α-L-cladinoside (**13**) (188.5 mg) (*x* = 3) gave, after chromatography (30 × 2 cm; 1.5% Me_2CO in C_6H_{14}), the 4-*O*-*acetate* (**14**) (150.1 mg, 65%) (Found: C, 57.2; H, 8.5. $C_{11}H_{20}O_5$ requires C, 56.88; H, 8.68%); $\nu_{max.}$($CDCl_3$) 1 730, 1 240, and 1 048 cm^{-1}.

(c) Methyl β-L-cladinoside (**15**) (415 mg) (*x* = 3) gave, after chromatography (30 × 2 cm; 1.5% Me_2CO in C_6H_{14}), the 4-*O*-acetate (**16**) (448 mg, 88%) as a gum (Found: C, 52.3; H, 8.1%); $[\alpha]_D^{26}$ −3.9° ($CHCl_3$); $\nu_{max.}$($CDCl_3$) 1 730, 1 240, 1 070, and 1 045 cm^{-1}.

Method 2. L-Cladinose (**6**)/(**7**) (2.85 g)[9] and pyridine (19.65 ml) were dissolved in dry dichloromethane (84 ml) at 0 °C. A solution of phenoxyacetyl chloride (11.2 ml) in dry dichloromethane (84 ml) was added dropwise during 1 h. The mixture was stirred at 0 °C for 2.5 h and worked up in the usual way. Chromatography (30 × 5 cm; 1.5% acetone in chloroform) gave the β-1,4-di-*O*-phenoxyacetate (**17**) (3.3 g, 46%) as a gum (Found: C, 62.0; H, 6.2. $C_{24}H_{28}O_8$ requires C, 64.85; H, 6.35%); *m/z* 293 ($MH^+ - OCOCH_2OC_6H_5$); $[\alpha]_D^{26}$ −26.0° ($CHCl_3$); $\lambda_{max.}$(MeOH) 206 (ε 13 290), 260 (1 420), 266 (2 010), and 273 nm (1 600); $\nu_{max.}$($CDCl_3$) 1 775, 1 598, 1 590, 1 490, 1 273, 1 075, and 1 030 cm^{-1}.

Method 3. L-Cladinose (**6**)/(**7**) (10.82 g)[9] and pyridine (75.2 ml) were dissolved in dry dichloromethane (160 ml). Phenoxyacetic anhydride (87.9 g) in dry dichloromethane (160 ml) was added dropwise at 0 °C during 30 min and the product was worked up in the usual way. Chromatography (h.p.l.c., 2 cartridges; CH_2Cl_2) gave the β-1,4-di-*O*-phenoxyacetate (**17**) (21.75 g, 80%).

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

4-O-*Acetyl*-α- *and* -β-L-*cladinose* (**9**) *and* (**10**).—The diacetate (**8**) (2.18 g) was dissolved in 0.1M aqueous hydrochloric acid (245 ml) and the mixture was kept at 25 °C for 1 h. The usual work-up afforded the α- and β-4-*O*-acetate (**9**) and (**10**)[34] (1.86 g, 100%) as a gum.

4-O-*Acetyl*-1-*deoxy*-1-(2-*pyridylthio*)-α- *and* -β-L-*cladinoside* (**11**) *and* (**12**).—4-*O*-Acetyl-L-cladinose (**9**)/(**10**) (1.84 g) was dissolved in dry dichloromethane (25 ml) and the solution was cooled to 13 °C. After 30 min a chilled solution of 2,2′-dipyridyl disulphide (Aldrithiol-2) (2.8 g) and tributylphosphine (3.45 g) in dry dichloromethane (30 ml) was added in one portion. The mixture was kept at 13 °C for 19 h. Chromatography (twice; 20 × 5 cm; 4% EtOAc in $CHCl_3$ and then 2% EtOAc in $CHCl_3$) gave 4-*O*-acetyl-1-deoxy-1-(2-pyridylthio)-α-L-cladinoside (**11**)[19] (604 mg, 23%) as a gum (Found: C, 58.15; H, 6.8; N, 4.5. Calc. for $C_{15}H_{21}NO_4S$: C, 57.86; H, 6.80; N, 4.50%); *m/z* 312 (MH^+); $[\alpha]_D^{26}$ −339.0° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 239 (9 030) and 282 nm (5 120); $\nu_{max.}$($CDCl_3$) 1 730, 1 580, 1 418, 1 238, 1 063, and 1 045 cm^{-1}; and 4-*O*-acetyl-1-deoxy-1-(2-pyridylthio)-β-L-cladinoside (**12**)[19] (1.02 g, 39%) as a gum (Found: C, 57.5; H, 6.9; N, 4.4. Calc. for $C_{15}H_{21}NO_4S$: C, 57.86; H, 6.80; N, 4.50%); *m/z* 312 (MH^+); $[\alpha]_D^{26}$ −1.1° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 237 (7 810) and 279 nm (4 590); $\nu_{max.}$($CDCl_3$) 1 737, 1 580, 1 418, 1 238, 1 072, and 1 046 cm^{-1}.

4-O-*Phenoxyacetyl*-α- *and* -β-L-*cladinose* (**18**) *and* (**19**).—1,4-Di-*O*-phenoxyacetyl-β-L-cladinose (**17**) (63.35 g) was dissolved in acetonitrile (4.5 l) and 0.1M aqueous hydrochloric acid (4.16 l) was added. The mixture was stirred at 25 °C for 18 h and worked up in the usual way. Chromatography (h.p.l.c., 2 cartridges; CH_2Cl_2→5% Me_2CO in CH_2Cl_2) gave the α- and β-4-*O*-phenoxyacetate (**18**) and (**19**) (32 g, 72%) as a gum.

1-*Deoxy*-4-O-*phenoxyacetyl*-1-(2-*pyridylthio*)-α- *and* -β-*cladinoside* (**20**) *and* (**21**).—4-*O*-Phenoxyacetyl-α- and -β-L-cladinose (**18**) and (**19**) (32 g) were dissolved in dry dichloromethane (288 ml) and the solution was cooled to 14 °C. A chilled solution of 2,2′-dipyridyl disulphide (29.53 g) and tributylphosphine (36.3 ml) in dry dichloromethane (288 ml) was added in one portion. The mixture was kept at 14 °C for 20 h. The product was worked up as described earlier and chromatography (h.p.l.c., 2 cartridges; C_6H_{14}→25% CH_2Cl_2 in C_6H_{14}→CH_2Cl_2→2%Me_2CO in CH_2Cl_2) gave a mixture of 1-deoxy-4-*O*-phenoxyacetyl-1-(2-pyridylthio)-α- and -β-L-cladinoside (**20**) and (**21**) (49% α and 39% β) (36.7 g, 88%). Chromatography (20 × 5 cm; 0→0.5% Me_2CO in CH_2Cl_2) gave, from the more polar fractions, the β-*anomer* (**21**), m.p. 74.5—79 °C (Found: C, 62.3; H, 6.3; N, 3.8; S, 7.7. $C_{21}H_{25}NO_5S$ requires C, 62.51; H, 6.25; N, 3.47; S, 7.95%); *m/z* 404 (MH^+); $[\alpha]_D^{26}$ +13.9° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 237 (7 990), 268 (4 480), 274 (5 260), and 280 nm (4 880); $\nu_{max.}$($CDCl_3$) 1 760, 1 734, 1 596, 1 572, 1 190, 1 065, and 1 005 cm^{-1}. The less polar fractions were combined and rechromatographed (15 × 5 cm; 2.5% Me_2CO in C_6H_{14}) to give the pure α-*anomer* (**20**), m.p. 131—133.5 °C (Found: C, 62.7; H, 6.3; N, 3.3; S, 8.2%); *m/z* 404 (MH^+); $[\alpha]_D^{26}$ −272.1° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 237 (15 740), 268 (8 680), 274 (10 070), and 281 nm (9 180); $\nu_{max.}$($CDCl_3$) 1 760, 1 595, 1 575, 1 190, and 1 063 cm^{-1}.

19-*Deformyldesmycosin* (**44**).—Desmycosin (**33**)[29] (18.9 g) was dissolved in degassed benzene (580 ml) and tris(triphenylphosphine)rhodium(I) chloride (29.5 g) was added. The mixture was heated at 90 °C for 16 h. The product was worked up in the usual way and chromatographed (60 × 5 cm; 5% MeOH in $CHCl_3$) to give 19-deformyldesmycosin (**44**)[32] (13.2 g, 73%) (Found: C, 57.05; H, 8.0, N, 1.6 calc. for $C_{38}H_{65}NO_{13}$·0.5 $CHCl_3$: C, 56.79; H, 8.15; N, 1.74%); *m/z* 744 (MH^+); $[\alpha]_D^{26}$ 0° ($CHCl_3$); $\lambda_{max.}$(MeOH) 282 nm (20 680); $\nu_{max.}$($CDCl_3$) 3 540, 3 450, 1 705, 1 670, 1 590, 1 185, 1 163, and 1 055 cm^{-1}.

General Procedure for the Acetylation of the 2′- *and* 2′,4′-*Hydroxy Groups in the Macrolides.*—The macrolide (1 mol equiv.) and acetic anhydride (3 mol equiv.) were dissolved in dry acetone (50 ml g^{-1} macrolide) and the mixture was kept at 25 °C for 17—19 h.

(a) 12,13-De-epoxy-12,13-didehydrorosaramicin (**22**)[21,22] (2 g) gave, after chromatography (60 × 2 cm; 10% Me_2CO in $CHCl_3$), the 2′-*O*-acetate (**23**)[22] (1.79 g, 83%) (Found: C, 62.1; H, 8.3; N, 1.5. Calc. for $C_{33}H_{53}NO_9$·0.2$CHCl_3$: C, 62.75; H, 8.46; N, 2.22%); *m/z* 608 (MH^+); $[\alpha]_D^{26}$ (−4.4° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 288 nm (19 170); $\nu_{max.}$($CDCl_3$) 3 530, 1 740, 1 723, 1 675, 1 593, 1 248, and 1 060 cm^{-1}.

(b) 12,13-De-epoxy-12,13-didehydrorosaramicin 20-dimethyl acetal (**24**)[23] (3.89 g) gave, after chromatography (60 × 2.5 cm; 12% Me_2CO in $CHCl_3$), the 2′-*O*-acetate (**25**) (3.28 g, 79%) (Found: C, 63.0; H, 8.7; N, 1.8. $C_{35}H_{59}NO_{10}$·0.1$CHCl_3$ requires C, 63.14, H, 8.93; N, 2.10%); *m/z* 654 (MH^+); $[\alpha]_D^{26}$ +15.6° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 287 nm (20 570); $\nu_{max.}$($CDCl_3$) 3 505, 1 733, 1 673, 1 590, 1 247, and 1 055 cm^{-1}.

(c) 12,13-De-epoxy-12,13-didehydro-20-deoxorosaramicin (**28**)[23,27,28] (4 g) gave, after chromatography (60 × 2.5 cm; 10% Me_2CO in $CHCl_3$), the 2′-*O-acetate* (**29**) (3.7 g, 85%) (Found: C, 65.1; H, 9.0; N, 2.2. $C_{33}H_{55}NO_8$·0.1$CHCl_3$ requires C, 65.43; H, 9.15; N, 2.31%); *m/z* 594 (MH^+); $[\alpha]_D^{26}$ +7.9° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 287 nm (21 710); $\nu_{max.}$($CDCl_3$) 3 310, 1 737, 1 725, 1 677, 1 592, 1 250, 1 188, and 1 060 cm^{-1}.

(d) 19-Deformyldesmycosin (**44**)[32] (12 g) and acetic anhydride (5 mol equiv.) gave, after chromatography (100 × 2.5 cm; 10% Me_2CO in C_6H_{14}), the 2′,4′-*di*-O-*acetate* (**45**) (11.5 g, 86%) (Found: C, 60.9; H, 8.5; N, 1.9. $C_{42}H_{69}NO_{15}$ requires C, 60.92; H, 8.40; N, 1.69%); *m/z* 828 (*M* H); $[\alpha]_D^{26}$ +11.9° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 283 nm (23 840); $\nu_{max.}$($CDCl_3$) 3 543, 1 742, 1 712, 1 675, 1 590, 1 233, 1 184, 1 174, and 1 055 cm^{-1}.

2′,4′,4″-*Tri*-O-*acetyldesmycosin* (**34**).—Desmycosin (**33**)[29] (3.6 g) and acetic anhydride (1.54 ml) were dissolved in dry pyridine (150 ml) and the mixture was kept at 25 °C for 74 h. The usual work-up followed by chromatography (30 × 5 cm; 15% Me_2CO in $CHCl_3$) gave the 2′,4′,4″-*tri*-O-*acetate* (**34**) (1.91 g, 46%) (Found: C, 60.1; H, 8.1; N, 1.4. $C_{45}H_{71}NO_{17}$ requires C, 60.18; H, 7.97; N, 1.56%); *m/z* 898 (MH^+); $[\alpha]_D^{26}$ −3.1° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 286 nm (22 010); $\nu_{max.}$($CDCl_3$) 3 530, 1 740, 1 678, 1 593, 1 235, 1 167, and 1 050 cm^{-1}.

2′,4′-*Di*-O-*acetyl*-20-*deoxodesmycosin* (**39**).—20-Deoxodesmycosin (**38**)[27,28] (3 g) and pyridine (3.2 ml) were dissolved in dry dichloromethane (430 ml) and acetic anhydride (1.86 ml) was added. The mixture was stirred under dry argon at 25 °C for 42 h. The usual work-up followed by chromatography (30 × 2 cm; 10% Me_2CO in $CHCl_3$) gave the 2′,4′-*di*-O-*acetate* (**39**) (2.92 g, 88%) (Found: C, 60.8; H, 8.3; N, 1.3. $C_{43}H_{71}NO_{15}$·0.1$CHCl_3$ requires C, 60.47; H, 8.38; N, 1.64%); *m/z* 842 (MH^+); $[\alpha]_D^{26}$ −8.2° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 283 nm (22 540); $\nu_{max.}$($CDCl_3$) 3 560, 1 744, 1 720, 1 678, 1 596, 1 235, 1 168, and 1 057 cm^{-1}.

General Procedure for the Acetylation of the 4″-*Hydroxy Group in* 2′,4′-*Di*-O-*acetyl Macrolides.*—The 2′,4′-di-*O*-acetyl macrolide (1 mol equiv.), 4-dimethylaminopyridine (0.2 mol equiv., and triethylamine (10 mol equiv.) were dissolved in dry dichloromethane (30—35 ml g^{-1} macrolide) and acetic anhydride (1 mol equiv.) was added. The mixture was stirred at 25 °C for 20—22 h.

(a) 2′,4′-Di-*O*-acetyl-20-deoxodesmycosin (**39**) (2.92 g) gave,

after chromatography (30 × 2 cm; 7% Me_2CO in $CHCl_3$), the 2′,4′,4″-*tri*-O-*acetate* (**40**) (2.42 g, 79%) (Found: C, 60.3; H, 8.1; N, 1.6. $C_{45}H_{73}NO_{16}$·0.1$CHCl_3$ requires C, 60.32; H, 8.21; N, 1.56%); *m*/*z* 884 (MH^+); $[\alpha]_D^{26}$ 11.2° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 283 nm (21 720); $\nu_{max.}$($CDCl_3$) 3 540, 1 742, 1 676, 1 593, 1 238, 1 168, and 1 050 cm^{-1}.

(b) 2′,4′-Di-*O*-acetyl-19-deformyldesmycosin (**45**) (10.3 g) gave, after chromatography (60 × 5 cm; 10→15% Me_2CO in C_6H_{14}), the 2′,4′,4″-*tri*-O-*acetate* (**46**) (8.1 g, 75%) (Found: C, 60.9; H, 8.4; N, 1.3. $C_{44}H_{71}NO_{16}$ requires C, 60.74; H, 8.23; N, 1.61%); *m*/*z* 870 (MH^+); $[\alpha]_D^{26}$ +25.3° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 284 nm (22 480); $\nu_{max.}$($CDCl_3$) 3 520, 1 737, 1 672, 1 590, 1 234, 1 181, 1 161, and 1 050 cm^{-1}. The more polar fractions afforded unchanged diacetate (**45**) (1.35 g, 13%).

General Procedure for the 3-O-*Glycosidation of the Protected Macrolides*.—The protected macrolide (1 mol equiv.) and a (4-*O*-acyl R^I)-1-deoxy-1-(2-pyridylthio)-α- and -β-L-cladinose (5.5 mol equiv.) were dissolved in dry acetonitrile (*x* ml g^{-1} macrolide). A solution of the anhydrous silver salt (R^{II}) (6.5 mol equiv.) in dry acetonitrile (*y* ml g^{-1} silver salt) was added and the mixture was stirred under anhydrous conditions at 25 °C for *z* h.

(a) 2′-*O*-Acetyl-12,13-de-epoxy-12,13-didehydrorosaramicin (**23**) (1 g) (R^I = OAc, R^{II} = ClO_4; *x* = 60, *y* = 27.5, *z* = 18) gave, after chromatography (30 × 5 cm; EtOAc), unchanged compound (**23**) (460 mg, 46%) and 2′-O-*acetyl*-3-O-(4-O-*acetyl*-α-L-*cladinosyl*)-12,13-*de-epoxy*-12,13-*didehydrorosaramicin* (**26**) (718 mg, 54%) (Found: C, 62.3; H, 8.3; N, 1.5. $C_{43}H_{69}NO_{13}$·0.2 $CHCl_3$ requires C, 62.08; H, 8.36; N, 1.68%); *m*/*z* 808 (MH^+); $[\alpha]_D^{26}$ −46.5° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 287 nm (17 960); $\nu_{max.}$($CDCl_3$) 1 737, 1 728, 1 673, 1 590, 1 242, and 1 050 cm^{-1}.

(b) 2′-*O*-Acetyl-12,13-de-epoxy-12,13-didehydrorosaramicin 20-dimethyl acetal (**25**) (500 mg) (R^I = OAc, R^{II} = ClO_4; *x* = 60, *y* = 30, *z* = 39) gave, after chromatography (20 × 5 cm; 2.5% Me_2CO in EtOAc), 2′-*O*-acetyl-3-*O*-(4-*O*-acetyl-α-L-cladinosyl)-12,13-de-epoxy-12,13-didehydrorosaramicin (**26**) (193 mg, 31%). The less polar fractions were rechromatographed (15 × 2 cm; 2% Me_2CO in EtOAc and 30 × 2.5 cm; 20% Me_2CO in C_6H_{14}) to give 2′-*O*-acetyl-12,13-de-epoxy-12,13-didehydro-20-*O*-methylrosaramicin 3,20-hemiacetal (**32**) (18 mg, 4%), *m*/*z* 622 (MH^+); $[\alpha]_D^{26}$ −3.9° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 282 nm (21 430); $\nu_{max.}$($CDCl_3$) 1 738, 1 648, 1 630, 1 257, 1 135, 1 064, and 1 043 cm^{-1}.

(c) 2′-*O*-Acetyl-12,13-de-epoxy-12,13-didehydro-20-deoxorosaramicin (**29**) (1.57 g) (R^I = OAc, R^{II} = ClO_4; *x* = 70.7, *y* = 27.7, *z* = 26) gave after chromatography (30 × 5 cm; EtOAc), unchanged reactant (**29**) (471 mg, 30%) and 2′-O-*acetyl*-3-O-(4-O-*acetyl*-α-L-*cladinosyl*)-12,13-*de-epoxy*-12,13-*didehydro*-20-*deoxorosaramicin* (**30**) (1.31 g, 63%) (Found: C, 60.5; H, 8.3; N, 1.2. $C_{43}H_{71}NO_{12}$·0.5$CHCl_3$ requires: C, 60.50; H, 8.38; N, 1.64%); *m*/*z* 794 (MH^+); $[\alpha]_D^{26}$ −91.2° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 286 nm (19 340); $\nu_{max.}$($CDCl_3$) 1 733, 1 673, 1 591, 1 240, 1 160, and 1 048 cm^{-1}.

(d) 2′,4′,4″-Tri-*O*-acetyldesmycosin (**34**) (335 mg) (R^I = OAc, R^{II} = ClO_4; *x* = 60, *y* = 27.5, *z* = 23) gave, after chromatography (60 × 2 cm; 25% Me_2CO in C_6H_{14} and 60 × 2 cm; 15% Me_2CO in $CHCl_3$), 2′,4′,4″-*tri*-O-*acetyl*-3-O-(4-O-*acetyl*-α-L-*cladinosyl*)*desmycosin* (**35**) (167 mg, 41%) (Found: C, 60.1; H, 8.1; N, 1.3. $C_{55}H_{87}NO_{21}$ requires C, 60.15; H, 7.98; 1.28%); *m*/*z* 1 098 (MH^+); $[\alpha]_D^{26}$ −35.1° −35.1° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 285 nm (22 470); $\nu_{max.}$ 1 740, 1 680, 1 595, 1 240, 1 168, and 1 050 cm^{-1}.

(e) 2′,4′,4″-Tri-*O*-acetyldesmycosin (**34**) (2.5 g) (R^I = $OCOCH_2OPh$, R^{II} = OSO_2CF_3; *x* = 20, *y* = 10.8, *z* = 20) gave, after chromatography (15 × 5 cm; 11% Me_2CO in C_6H_{14} and 30 × 2.5 cm; 20% EtOAc in CH_2Cl_2), 2′,4′,4″-*tri*-O-*acetyl*-3-O-(4-O-*phenoxyacetyl*-α-L-*cladinosyl*)*desmycosin* (**37**) (1.99 g, 60%) (Found: C, 61.3; H, 7.8; N, 0.9. $C_{61}H_{91}NO_{22}$ requires C, 61.55; H, 7.71; N, 1.18%); *m*/*z* 1 190 (MH^+); $[\alpha]_D^{26}$ −30.0° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 284 nm (22 450); $\nu_{max.}$($CDCl_3$) 1 740, 1 675, 1 590, 1 230, 1 168, and 1 045 cm^{-1} and unchanged compound (**34**) (190 mg, 8%).

(f) 2′,4′,4″-Tri-*O*-acetyl-20-deoxodesmycosin (**40**) (800 mg) (R^I = OAc, R^{II} = ClO_4; *x* = 42.5, *y* = 28, *z* = 19) gave, after chromatography (60 × 2 cm; 15% Me_2CO in C_6H_{14}), 2′,4′,4″-tri-*O*-acetyl-3-*O*-(4-*O*-acetyl-α-L-cladinosyl)-20-deoxodesmycosin (**41**) (396 mg, 40%), *m*/*z* 1 084 (MH^+).

(g) 2′,4′,4″-Tri-*O*-acetyl-20-deoxodesmycosin (**40**) (1.83 g) (R^I = $OCOCH_2OPh$, R^{II} = OSO_2CF_3; *x* = 8.2, *y* = 17.4, *z* = 21) gave, after chromatography (60 × 2.5 cm; 5→20% EtOAc in CH_2Cl_2 and 30 × 2.5 cm; 15% EtOAc in CH_2Cl_2), 2′,4′,4″-*tri*-O-*acetyl*-20-*deoxo*-3-O-(4-O-*phenoxyacetyl*-α-L-*cladinosyl*)-*desmycosin* (**42**) (1.26 g, 52%) (Found: C, 62.4; H, 7.9; N, 1.2. $C_{61}H_{93}NO_{21}$ requires C, 62.28; H, 7.97; N, 1.19%); *m*/*z* 1 176 (MH^+); $[\alpha]_D^{26}$ −33.6° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 210 (10 680) and 282 nm (23 150); $\nu_{max.}$($CDCl_3$) 1 740, 1 673, 1 591, 1 235, 1 164, 1 050, and 1 016 cm^{-1} and unchanged compound (**40**) (490 mg, 27%).

(h) 2′,4′,4″-Tri-*O*-acetyl-19-deformyldesmycosin (**46**) (2.5 g) (R^I = $OCOCH_2OPh$, R^{II} = OSO_2CF_3; *x* = 20, *y* = 10.4, *z* = 20) gave, after chromatography (30 × 2.5 cm; 5→20% EtOAc in $CHCl_2$ and 30 × 2.5 cm; 20% EtOAc in CH_2Cl_2) 2′,4′,4″-*tri*-O-*acetyl*-19-*deformyl*-3-O-(4-O-*phenyoxyacetyl*-α-L-*cladinosyl*)*desmycosin* (**47**) (2.04 g, 61%) (Found: C, 62.0; H, 7.8; N, 1.2. $C_{60}H_{91}NO_{21}$ requires C, 62.00; H, 7.89; N, 1.21%); *m*/*z* 1 162 (MH^+); $[\alpha]_D^{26}$ −23.1° ($CHCl_3$); $\lambda_{max.}$(CF_3CH_2OH) 210 (7 560) and 283 nm (17 860); $\nu_{max.}$($CDCl_3$) 1 737, 1 673, 1 590, 1 234, 1 188, 1 160, 1 050, and 1 012 cm^{-1} and unchanged compound (**46**) (450 mg, 18%).

General Procedures for Deprotection of the Acylated Macrolides.—The protected macrolide (1 mol equiv.) was dissolved in a solution of the organic base (*x* mol equiv.) in methanol (*y*% w/v) and the mixture was stirred at 25 °C for *z* h.

(a) The macrolide (**26**) (567 mg) with DBU (*x* = 1, *y* = 0.58, *z* = 43) gave, after chromatography (15 × 5 cm; 2.5% MeOH in $CHCl_3$), 3-*O*-α-L-*cladinosyl*-12,13-*de-epoxy*-12,13-*didehydrorosaramicin* (**27**) (265 mg, 52%) (Found: C, 64.2; H, 9.5; N, 2.0. $C_{39}H_{65}NO_{11}$ requires C, 64.71; H, 9.05; N, 1.93%); *m*/*z* 724 (MH^+); $[\alpha]_D^{26}$ −51.0° ($CHCl_3$); $\lambda_{max.}$(MeOH) 282 nm (19 620); $\nu_{max.}$($CDCl_3$) 3 540, 3 440, 1 728, 1 674, 1 590, 1 160, and 1 050 cm^{-1}.

(b) The macrolide (**30**) (750 mg) with DBU (*x* = 5, *y* = 2.87, *z* = 20) gave, after chromatography (60 × 2 cm; 2% MeOH in $CHCl_3$ and 15 × 2 cm; 2.5→10% MeOH in $CHCl_3$), 3-O-α-L-*cladinosyl*-12,13-*de-epoxy*-12,13-*didehydro*-20-*deoxorosaramicin* (**31**) (428 mg, 64%) (Found: 61.55; H, 8.8; N, 1.6. $C_{39}H_{67}NO_{10}$·0.4$CHCl_3$ requires C, 61.82; H, 8.91; N, 1.85%); *m*/*z* 710 (MH^+); $[\alpha]_D^{26}$ −47.2° ($CHCl_3$); $\lambda_{max.}$(MeOH) 282 nm (20 590); $\nu_{max.}$($CDCl_3$) 3 550, 3 440, 1 730, 1 670, 1 590, 1 160, 1 055, and 1 020 cm^{-1}.

(c) The macrolide (**35**) (602 mg) with DBU (*x* = 3.25, *y* = 1.93, *z* = 44) gave, after chromatography (30 × 2 cm; 3% MeOH in $CHCl_3$), 3-*O*-α-L-cladinosyldesmycosin (**36**) (272 mg, 33%) contaminated with *ca.* 5—10% of 3-*O*-α-L-cladinosyl-desmycosin seco acid methyl ester (**49**) which co-chromatographed with compound (**36**).

(d) The macrolide (**37**) (1.58 g) with triethylamine (*x* = 20, *y* = 2, *z* = 70) gave, after chromatography (60 × 2.5 cm; 4% MeOH in $CHCl_3$), 3-O-α-L-*cladinosyldesmycosin* (**36**) (1.13 g, 91%) (Found: C, 59.15; H, 8.2; N, 1.4. $C_{47}H_{79}NO_{17}$·0.2$CHCl_3$ requires C, 59.17; H, 8.35; N, 1.47%); *m*/*z* 930 (MH^+); $[\alpha]_D^{26}$ −43.8° ($CHCl_3$); $\lambda_{max.}$(MeOH) 283 nm (20 400); $\nu_{max.}$($CDCl_3$) 3 592, 3 550, 1 737, 1 729, 1 674, 1 590, 1 160, and 1 057 cm^{-1}.

(e) The macrolide (**41**) (456 mg) with DBU (*x* = 5, *y* = 1.93,

z = 45) gave, after chromatography (30 × 2 cm; 3.3% MeOH in $CHCl_3$ and 30 × 2 cm; 4% MeOH in $CHCl_3$), 3-*O*-α-L-cladinosyl-20-deoxodesmycosin (**43**) (241 mg) contaminated with *ca.* 33% of 3-*O*-α-L-cladinosyl-20-deoxodesmycosin seco acid methyl ester (**50**), *m/z* 948 (MH^+) which co-chromatographed with compound (**43**).

(f) The macrolide (**42**) (683 mg) with triethylamine (x = 20, y = 2, z = 94) gave, after chromatography (30 × 2.5 cm; 4% MeOH in $CHCl_3$), 3-O-α-L-*cladinosyl*-20-*deoxodesmycosin* (**43**) (458 mg, 86%) (Found: C, 61.1; H, 8.7; N, 1.4. $C_{47}H_{81}NO_{16}$ requires C, 61.62; H, 8.91; N, 1.53%); *m/z* 916 (MH^+); $[\alpha]_D^{26}$ −45.0° ($CHCl_3$); $\lambda_{max.}$(MeOH) 282 nm (19 400); $\nu_{max.}$($CDCl_3$) 3 590, 3 553, 1 736, 1 673, 1 591, 1 160, 1 074, and 1 058 cm^{-1}.

(g) The macrolide (**47**) (1.9 g) with triethylamine (x = 20, y = 2, z = 72) gave, after chromatography (60 × 2.5 cm; 4% MeOH in $CHCl_3$ and 15 × 2.5 cm; EtOAc), 3-O-α-L-*cladinosyl*-19-*deformyldesmycosin* (**48**) (1.28 g, 87%) (Found: C, 61.4; H, 9.0; N, 1.45. $C_{46}H_{79}NO_{16}$ requires C, 61.24; H, 8.83; N, 1.55%); *m/z* 902 (MH^+); $[\alpha]_D^{26}$ −35.6° ($CHCl_3$); $\lambda_{max.}$(MeOH) 382 nm (20 940); $\nu_{max.}$($CDCl_3$) 3 600, 3 558, 3 450, 1 738, 1 732, 1 674, 1 592, 1 160, 1 058, and 1 010 cm^{-1}.

Reaction of Desmycosin (**33**) *with DBU.*—Desmycosin (**33**) (200 mg) was dissolved in methanol (4.9 ml) containing DBU (0.093 ml) and the mixture was kept at 25 °C for 49 h. Chromatography (30 × 2 cm; 2% MeOH in $CHCl_3$) gave *methyl* 5-β-D-*desosaminyloxy*-5-[2-*formyl*-3-(6-*hydroxy*-3-*methyl*-5-β-D-*mycinosyloxyocta*-1,3-*dienyl*)-4-*methylcyclopenta*-2-*dienyl*]-3-*hydroxy*-4-*methylvalerate* (**51**) (58.2 mg, 29%) (Found: C, 56.1; H, 7.8; N, 1.7. $C_{40}H_{67}NO_{14}$·0.6$CHCl_3$ requires C, 56.02; H, 7.88; N, 1.63%); *m/z* 786 (MH^+); $[\alpha]_D^{26}$ +11.4° ($CHCl_3$); $\lambda_{max.}$(MeOH) 240 (11 110) and 325 nm (17 550); $\nu_{max.}$($CDCl_3$) 3 480, 1 720, 1 642, 1 600, 1 163, and 1 060 cm^{-1}.

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References

1 C. Djerassi and J. A. Zderic, *J. Am. Chem. Soc.*, 1956, **78**, 6930.
2 C. Djerassi and O. Halpern, *Tetrahedron*, 1958, **3**, 255.
3 A. Kinumaki and M. Suzuki, *J. Chem. Soc., Chem. Commun.*, 1972, 744.
4 P. F. Wiley, K. Gerzon, E. H. Flynn, M. V. Segal, Jr., O. Weaver, U. C. Quarck, R. R. Chauvette, and R. Monahan, *J. Am. Chem. Soc.*, 1957, **79**, 6062.
5 P. Bartner, D. L. Boxler, R. Brambilla, A. K. Mallams, J. B. Morton, P. Reichert, F. D. Sancilio, H. Surprenant, G. Tomalesky, G. Lukacs, A. Olesker, T. T. Thang, and L. Valente, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1600.
6 F. A. Hochstein, H. Els, W. D. Celmer, B. L. Shapiro, and R. B. Woodward, *J. Am. Chem. Soc.*, 1960, **82**, 3225.
7 R. S. Egan and J. R. Martin, *J. Am. Chem. Soc.*, 1970, **92**, 4129.
8 A. K. Mallams, Kirk Othmer: 'Encyclopedia of Chemical Technology,' 3rd Edn., Wiley, 1978, vol. 2, p. 937.
9 E. H. Flynn, M. V. Segal, Jr., P. F. Wiley, and K. Gerzon, *J. Am. Chem. Soc.*, 1954, **76**, 3121.
10 J. F. Chantot, J. C. Gasc, S. Gouin D'Ambrieres, and A. Lutz, 23rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Las Vegas, Nevada, 1983, Paper 447.
11 R. N. Jones, A. L. Barry, and C. Thornsberry, *Antimicrob. Agents Chemother.*, 1983, **24**, 209.
12 S. Morimoto, Y. Takahashi, Y. Watanabe, and S. Omura, *J. Antibiot.*, 1984, **37**, 187.
13 L. Toscano, G. Fioriello, S. Silingardi, and M. Inglesi, *Tetrahedron*, 1984, **40**, 2177.
14 L. Toscano, G. Fioriello, R. Spagnoli, L. Cappelletti, and G. Zanuso, *J. Antibiot.*, 1983, **36**, 1439.
15 L. Toscano, G. Fiorello, R. Spagnoli, and L. Cappelletti, *J. Antibiot.*, 1983, **36**, 1585.
16 T. Mukaiyama, T. Nakatsuka, and S. Shoda, *Chem. Lett.*, 1979, 487.
17 S. Hanessian, C. Bacquet, and N. Lehong, *Carbohydr. Res.*, 1980, **80**, C17.
18 K. C. Nicolaou, S. P. Seitz, and D. P. Papahatjis, *J. Am. Chem. Soc.*, 1983, **105**, 2430.
19 R. B. Woodward, E. Logush, K. P. Nambiar, K. Sakan, D. E. Ward, B.-W. Au-Yeung, P. Balaram, L. J. Browne, P. J. Card, C. H. Chen, R. B. Chenevert, A. Fliri, K. Frobel, H.-J. Gais, D. G. Garratt, K. Hayakawa, W. Heggie, D. P. Hesson, D. Hoppe, I. Hoppe, J. A. Hyatt, D. Ikeda, P. A. Jacobi, K. S. Kim, Y. Kobuke, K. Kojima, K. Krowicki, V. J. Lee, T. Leutert, S. Malchenko, J. Martens, R. S. Matthews, B. S. Oong, J. B. Press, T. V. Rajan Babu, G. Rousseau, H. M. Sauter, M. Suzuki, K. Tatsuta, L. M. Tolbert, E. A. Truesdale, I. Uchida, Y. Ueda, T. Uyehara, A. T. Vasella, W. C. Vladuchick, P. A. Wade, R. M. Williams, and H. N.-C. Wong, *J. Am. Chem. Soc.*, 1981, **103**, 3215.
20 M. Tayaki and M. Takagi, *Chem. Lett.*, 1979, 767.
21 A. K. Ganguly and O. Sarre, U.S.P. 3 975 372 August 17, 1976.
22 H. Reimann and R. S. Jaret, unpublished observations.
23 D. J. Schumacher and R. S. Jaret, unpublished observations.
24 P. H. Jones, T. J. Perun, E. K. Rowley, and E. J. Baker, *J. Med. Chem.*, 1972, **15**, 631.
25 A. K. Ganguly and O. Z. Sarre, unpublished observations.
26 W. Klyne, *Biochem. J.*, 1950, **47**, xli.
27 A. K. Ganguly, Y.-T. Liu, and O. Z. Sarre, *J. Chem. Soc., Chem. Commun.*, 1983, 1166.
28 A. G. Fishman, A. K. Mallams, M. S. Puar, R. R. Rossman, and R. L. Stephens, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1189.
29 R. L. Hamill, M. E. Haney, Jr., M. Stamper, and P. F. Wiley, *Antibiot. Chemother.*, 1961, **11**, 328.
30 C. B. Reese and J. C. M. Stewart, *Tetrahedron Lett.*, 1968, 4273.
31 C. B., Reese, J. C. M. Stewart, J. H. van Boom, H. P. M. de Leeuw, J. Nagel, and J. F. M. de Rooy, *J. Chem. Soc., Perkin Trans. 1*, 1975, 934.
32 H. Sakakibara, T. Fujiwara, O. Okegawa, E. Honda, S. Watanabe, and T. Matsuda, U.S.P. 4 345 069 August 17, 1982.
33 R. R. Rossman, A. K. Mallams, G. H. Miller, R. S. Hare, D. Loebenberg, A. F. Cacciapuoti, E. L. Moss, Jr., F. W. Menzel, Jr., J. A. Rudeen, C. L. Cramer, and L. R. Naples, 27th Interscience Conference on Antimicrobial Agents and Chemotherapy, New York, N.Y., 4—7th October, 1987, Abtract 218.
34 K. Tatsuta, K. Fujimoto, M. Kinoshita, and S. Umezawa, *Carbohydr. Res.*, 1977, **54**, 85.

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