Cladinose Analogues of Sixteen-membered Macrolide Antibiotics

I. Synthesis of 4-*O*-Alkyl-L-cladinose Analogues *via* Glycosylation

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The synthesis and biological evaluation of sixteen-membered macrolides possessing a 4-*O*-alkyl-α-L-cladinosyl moiety as the neutral sugar are described. The nine novel derivatives have been synthesized by glycosylation with 1-thio sugars. The most active derivative of them showed prolonged antibacterial activity in rat plasma *in vitro* and improved pharmacokinetics.

Sixteen-membered macrolide antibiotics[1] are regarded as important chemotherapeutics from a clinical viewpoint. However, they do not always exhibit satisfactory pharmacokinetics,[2] even when chemically modified for effective chemotherapy. One explanation concerning the poor pharmacokinetics involves an *in vivo* deacylation at the 4″-(sometimes 3″-)position of the neutral sugar moiety.[3] Introduction of alkyl substituents at the 3″- and the 4″-position in the neutral sugar could be expected to improve the pharmacokinetics of these sixteen-membered macrolides. Several 4″-mono-substituted derivatives of spiramycin have been synthesized which possess beneficial therapeutic effects.[4] In another investigation, 3″-*O*-methylcarbomycin B has been synthesized,[5] but its biodynamics, however, were not described. The previously mentioned biological 4″-deacylation and the fact that erythromycin A having L-cladinose was more effective *in vitro* than erythromycin C having L-mycarose,[6] and that modifications at the 3″-hydroxyl group improved the efficacy *in vivo* of sixteen-membered macrolides,[7~10] led us to design new compounds modified at both the 3″- and the 4″-position with *O*-alkyl groups in order to improve the pharmacokinetics.

The synthesis of sixteen-membered macrolides having 4-*O*-alkyl-L-cladinose instead of the acylated L-mycarose moiety is described. We wish to demonstrate here a long duration of antibacterial activity in rat plasma *in vitro* and an improved urinary recovery *in vivo*.

Chemistry

We have selected a glycosylation method for the preparation of the title compounds because it would be rather difficult to introduce a methyl group directly into the 3″-tertiary hydroxyl group without any degradation of the lactone ring. Moreover, structural determination of the products would be simplified.

Acid solvolysis of erythromycin A in the presence of ethanol gave ethyl β-L-cladinoside (**1**). Compound **1** was alkylated with aliphatic alkyl halides and sodium hydride to give 4-*O*-alkyl-β-L-cladinosides (**2**~**10**) in good yields. Acid hydrolysis of these compounds gave 4-*O*-alkyl-L-cladinoses (**11**~**19**) which were successively converted to corresponding glycosyl donors without any purification. Thus, reducing sugars reacted with 2,2′-dipyridyl disulfide and tributylphosphine (Bu_3P) to afford the 1-(2-pyridylthio) sugars[11] (**20**~**28**) as α/β mixture and these were used in the subsequent glycosylations.[12]

On the other hand, 9-dehydro-demycarosylplatenomycin[13] (**29**) was readily prepared by acid hydrolysis of midecamycin A_3.[14] The dimethylamino group of **29** was protected as its *N*-oxide by reaction with 3-chloroperoxybenzoic acid (mCPBA) to give the glycosyl acceptor (**30**) quantitatively.

Next, 4-*O*-alkyl-L-cladinose was regioselectively introduced into the 4′-position of **30** *via* glycosylation in the presence of anhydrous silver perchlorate and pulverized molecular sieves in dry acetonitrile to afford desired α-glycosides (**31**~**39**) together with the β-anomers. Because each anomer exhibited the different mobility on TLC, the isolation of the α-anomer was easily performed. Low reactivity of the 4′-hydroxyl group, however, resulted in poor glycosylation yields, and high α-stereoselectivity could not be achieved, due to the lack of neighboring group effects in this 2-deoxy donor. In fact, few good examples of high stereoselectivity in the preparation of 2-deoxy glycosides have been reported except in special cases.[15~17] When the glycosylation was started at lower temperatures α-selectivity was improved,

but the coupling reaction of **30** with **23** gave the desired α-anomer (**34**) accompanied by equal amounts of the undesired β-anomer (**40**), even under optimized conditions. Byproduct **40** could be readily converted to **30** quantitatively, giving a 38% yield of **34** based on consumed **30**. Using a single β-isomer of **23** or other activators, the yield of **34** could not be increased. The C-1″ anomeric configuration of these imtermediates

Scheme 1.

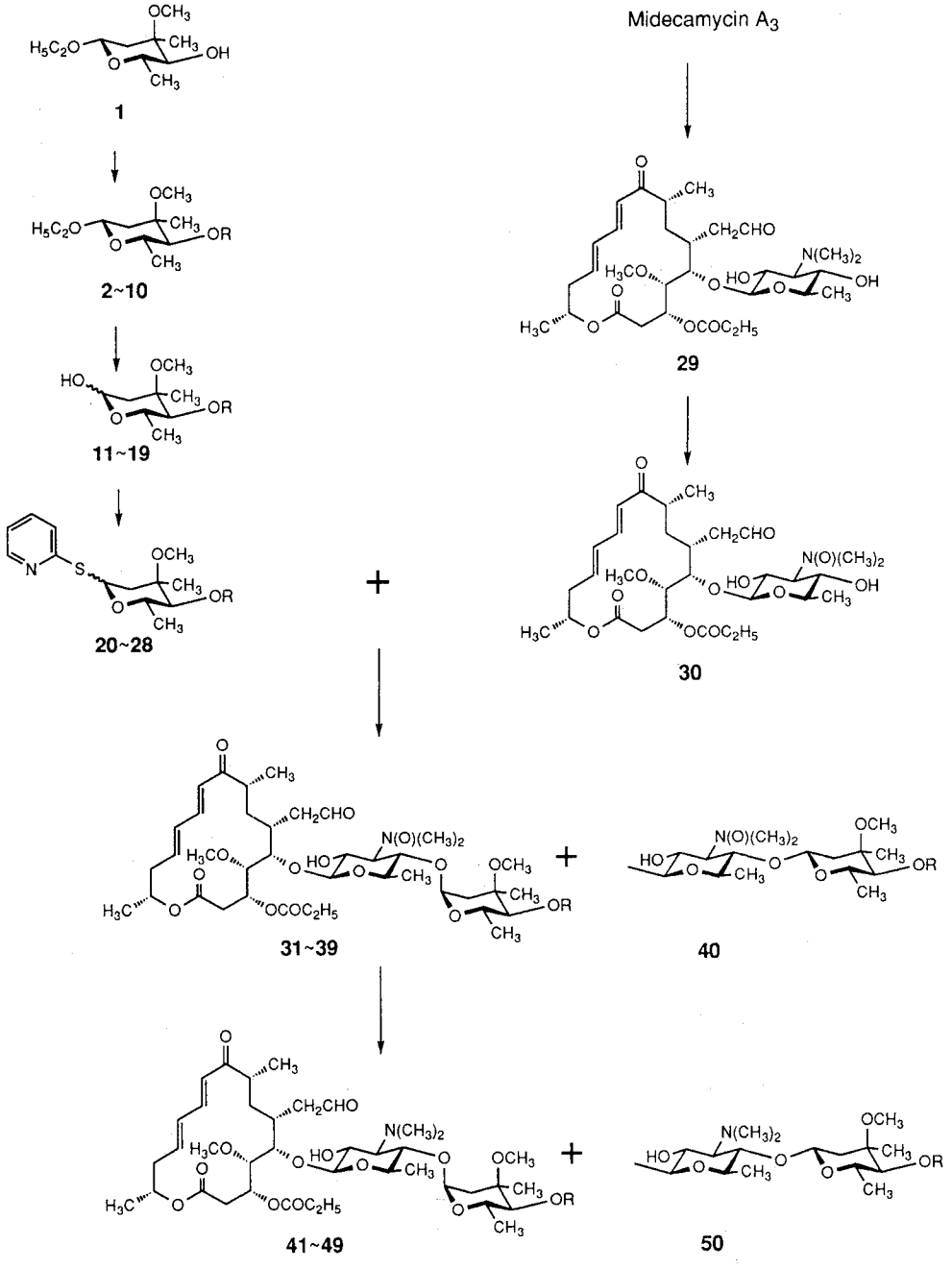


Table 1. Antibacterial activities of **41**~**50** and natural antibiotics (MIC, μg/ml).

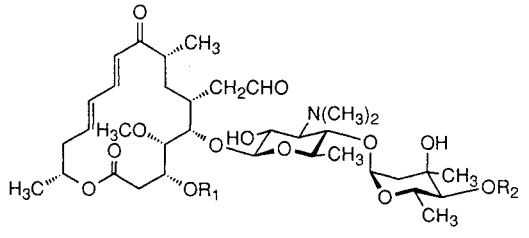
Test organisms	41	42	43	44	45	46	47	48	49	50	Mideca-mycin A_3	Carbo-mycin B	DOP
Staphylococcus aureus 209P JC-1	3.13	3.13	0.20	0.20	0.78	0.39	0.78	6.25	0.20	50	0.20	0.20	1.56
S. aureus M133	3.13	12.5	0.78	0.78	1.56	1.56	1.56	12.5	1.56	>100	0.78	0.78	6.25
S. aureus M126	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
S. aureus MS15026	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
S. aureus MS15027	6.25	12.5	0.78	0.78	1.56	1.56	1.56	12.5	1.56	100	0.78	0.78	6.25
S. epidermidis ATCC14990	12.5	25	1.56	0.78	3.13	1.56	1.56	25	3.13	>100	0.78	0.78	6.25
Micrococcus luteus ATCC9341	0.78	0.39	0.05	0.05	0.10	0.05	0.10	0.78	0.10	12.5	0.05	0.05	0.20
Enterococcus faecalis W-73	3.13	6.25	3.13	1.56	3.13	3.13	6.25	25	1.56	>100	3.13	1.56	3.13
Streptococcus pneumoniae IP692	1.56	1.56	0.10	0.10	0.39	0.20	0.20	0.78	0.20	12.5	0.20	0.10	0.78
S. pneumoniae Type I	1.56	1.56	0.20	0.20	0.39	0.20	0.20	0.78	0.20	12.5	0.39	0.20	0.39
S. pyogenes Cook	0.78	1.56	0.10	0.05	0.20	0.05	0.20	0.78	0.20	12.5	0.20	0.10	0.39
Escherichia coli NIHJ JC-2	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
Klebsiella pneumoniae PCI602	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
Branhamella catarrhalis W-0500	3.13	12.5	0.78	0.78	1.56	1.56	1.56	25	1.56	>100	1.56	0.78	12.5
B. catarrhalis W-0506	6.25	6.25	0.78	0.78	1.56	1.56	1.56	12.5	1.56	>100	3.13	0.78	6.25
Haemophilus influenzae 9334	100	NT	6.25	6.25	12.5	12.5	12.5	100	6.25	>100	3.13	1.56	50

NT; Not tested

could be determined by means of ^{1}H NMR spectra at this stage. The C-1″ anomeric proton of **34** appeared as a narrow doublet ($J_{1'',2''}=5.0$ Hz), but that of **40** showed a wide double doublet ($J_{1'',2''ax}=9.4$ Hz, $J_{1'',2''eq}=1.8$ Hz) indicating the axial-axial relationship between 1″-H and one of 2″-Hs.

Finally, the isolated *N*-oxides (**31**~**40**) having an unnatural L-sugar were reduced to their free dimethylamino derivatives (**41**~**50**) with excess triphenylphosphine (Ph_3P). Acetylation of **44** without any additional bases gave its 2′-*O*-acetyl derivative: ^{1}H NMR δ 4.88 (1H, dd, 2′-H, $J_{1',2'}=7.8$ Hz, $J_{2',3'}=10.4$ Hz), thus showing that the 4-*O*-alkyl-L-cladinose was exclusively introduced onto the 4′-hydroxyl group in the mycaminose moiety.

Fig. 1. Natural occuring antibiotics having a carbonyl group at the C-9 position in sixteen-membered macrolides.



	R_1	R_2
Midecamycin A_3	$COCH_2CH_3$	$COCH_2CH_3$
Carbomycin B	$COCH_3$	$COCH_2CH(CH_3)_2$
DOP	$COCH_2CH_3$	H

Biological Evaluation

The antibacterial activities *in vitro* of the novel 4-*O*-alkyl-α-L-cladinosyl derivatives (**41**~**49**) and one of β-anomers (**50**), compared with those of natural antibiotics which possess a carbonyl group at the C-9 position, are shown in Table 1. The activities of some of the novel derivatives were clearly improved based on that of DOP[18] (9-dehydro-3-*O*-propionylleucomycin V) having a diol structure in the neutral sugar. Compound **44** having the isoamyl (3-methylbutyl) chain at the 4″-hydroxyl group showed the most potent activity *in vitro*. The activity has been optimized with similar alkyl chain length (C_4~C_6) at the 4″-position to those found among the 4″-*O*-acyl analogues,[19] except the case of a highly polar derivative (**48**).

Then the most potent analog, **44**, was incubated in rat plasma to determine its metabolic stability to esterase. Fig. 2 shows changes in the relative antibacterial activities against *Micrococcus luteus*, expressed by referring the starting activity of each compound in the plasma to 100%. The activity of **44** was hardly decreased compared with a structurally related 4-*O*-acyl-α-L-mycarosyl compound, midecamycin A_3 or carbomycin B, since the neutral sugar moiety of **44** could not be attacked by the esterase. Thus, the long duration of activity has been achieved *in vitro* by introducing 4-*O*-alkyl-L-cladinose instead of 4-*O*-acyl-L-mycarose in a number of sixteen-membered macrolides.

Preliminary pharmacokinetics of **44** were examined

Fig. 2. Time course of relative potency (t=0; 100%).

○ **44**, ● midecamycin A_3, ■ carbomycin B. Rat plasma, 37°C.

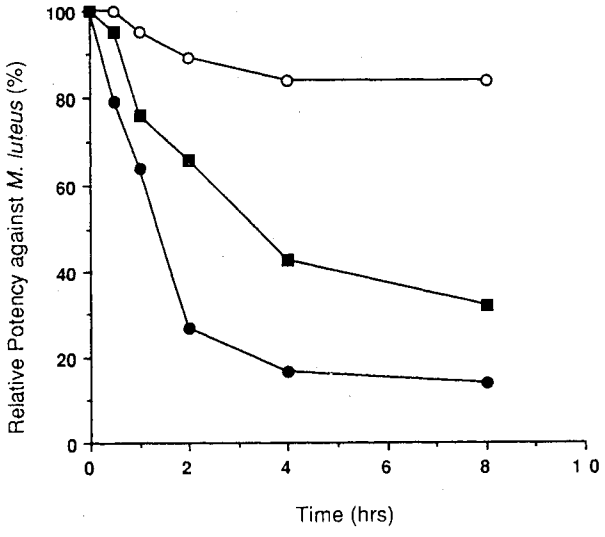
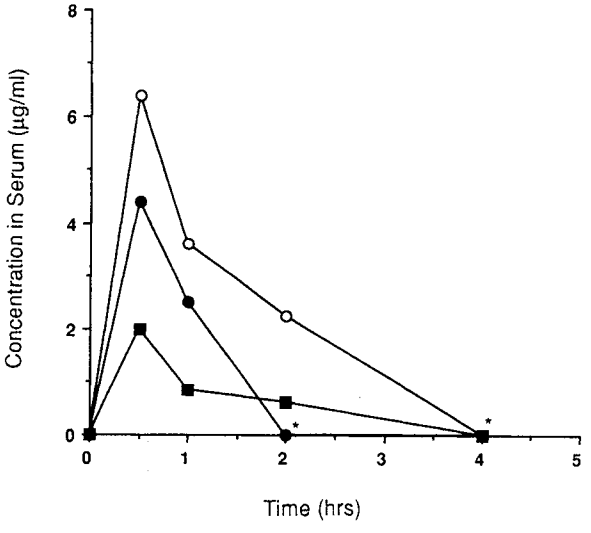


Fig. 3. Concentration in serum.

○ **44**, ● midecamycin A_3, ■ carbomycin B. 200 mg/kg, mouse, n=2, p.o.



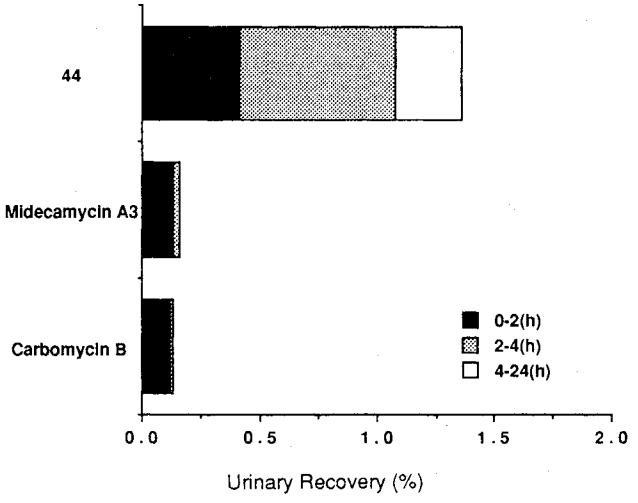
*; Not detected (<0.5 μg/ml).

with the two natural antibiotics. Concentrations† of antibiotics in serum and urinary excretion by mice are shown in Fig. 3 and 4, respectively. The concentration of **44** in serum was higher and it lasted longer than midecamycin A_3 or carbomycin B. The urinary recovery of **44** in mice was greatly improved in sixteen-membered macrolides having a carbonyl group at the C-9 position.

Further investigations of sixteen-membered macrolides possessing the 4-*O*-alkyl-α-L-cladinosyl moiety are under way as potentially useful agents for chemotherapy.

Fig. 4. Urinary recovery.

200 mg/kg, mouse, n=3, p.o.



Experimental

General Methods

MP's were determined with a Yanagimoto micro melting point apparatus and were uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Mass spectra were obtained on a Hitachi M-80A or M-80B mass spectrometer for EI-MS or FD-, SI-MS, respectively. ^1H NMR spectra were measured with a Jeol JNM-GSX 400 NMR spectrometer for 400 MHz in $CDCl_3$ using TMS as internal standard. Silica gel chromatography and preparative TLC were performed on Merck Kieselgel 60 and Merck TLC $60F_{254}$, respectively. In general, organic layer was dried with anhydrous Na_2SO_4, evaporation and concentration were carried out under reduced pressure below 30°C, unless otherwise noted.

Antibacterial Activity *In Vitro*

Minimum inhibitory concentration (MIC) was determined by the agar plate dilution method. Test strains were subjected to seed culture using Sensitivity test broth (STB, Nissui Pharmaceutical) except that the strains belonging to the genus *Streptococcus*, *Branhamella* and *Haemophilus* were cultured on blood agar plate. A 5 μl portion of cell suspension of the test strains having about

† The concentration was determined by the bioassay (*cf.* experimental). Because sixteen-membered macrolides are metabolized to weaker active metabolite(s), especially the natural compounds, an exact concentration will be less than the value shown (especially for midecamycin A_3 and carbomycin B).

10^6 CFU/ml was inoculated into Sensitivity disk agar (SDA, Nissui Pharmaceutical) supplemented with 5% horse blood and incubated at 37°C for 20 hours. The MIC was then measured.

Metabolic Stability in Rat Plasma *In Vitro*

A solution of each test compound (500 μg) in CH_3OH (50 μl) was added to thawed rat plasma (950 μl) and the mixture was incubated at 37°C. A 20 μl portion of the mixture was sampled after 0, 0.5, 1, 2, 4 and 8 hours and added to 0.05 M phosphate buffer (pH 7.6, 980 μl) including a small amount of DFP. A 20 μl portion of the sample solution was used to measure antibacterial activity against *M. luteus* ATCC9341. The starting activity of each compound in rat plasma was reffered to as 100%.

Pharmacokinetics Tests in Mice *In Vivo*

A test compound was mixed with a 0.2% aqueous solution of CMC to give a concentration of 4.0 mg/ml and a 1.0 ml portion of the resulting emulsion was orally administrated to 4 weeks old male Jcl : ICR mice. Blood was collected from the armpits of the mice 0.5, 1, 2 and 4 hours after the administration of the test compound (n=2). The collected blood was allowed to stand at 0°C for 2 hours and centrifuged at 3000 rpm for 20 minutes to obtain serum. To the serum was added an equivalent volume of 50% CH_3CN-0.05 M phosphate buffer (pH 7.0). The resulting mixture served as a serum sample. The concentration of the test compound in the serum sample was measured by a bioassay method using *M. luteus* ATCC9341.

Subsequently, 200 mg/kg of a test compound was orally administrated to three mice in the same manner as described above. The three mice were put in a metabolic cage MM type (Sugiyamagen Co., Tokyo, Japan) and urine was collected 2, 4 and 24 hours after the administration. The collected urine was filtered through a filter having a pore size of 0.45 μm (Millipore) and was mixed with an equivalent volume of 50% CH_3CN-0.05 M phosphate buffer (pH 6.5) to serve as an urine sample. The bioassay was carried out by *M. luteus* to determine the concentration of the test compound in the urine sample and the recovery in the urine was calculated.

Ethyl β-L-Cladinoside (**1**)

Erythromycin A (50.0 g) was dissolved in dry EtOH (100 ml) and dry CH_3CN (400 ml), and *p*-toluenesulfonic acid (23.5 g) was added to the solution. The reaction mixture was allowed to stand at room temperature for one hour and poured into saturated aqueous $NaHCO_3$ (5.0 liters). The mixture was extracted with $CHCl_3$ (5.0 liters, 1.3 liters). The combined organic layer was dried and concentrated to give a residue which was roughly chromatographed on silica gel (1.0 kg, $CHCl_3$-MeOH, 30 : 1) to give crude ethyl L-cladinoside (14.3 g). This was further purified on silica gel column chromatography (1.5 kg, PhH-EtOAc, 8 : 1 ~ 3 : 1) to afford **1** (12.8 g, 92%) as a colorless oil: $[\alpha]_D^{19}$ +35° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 1.22 (3H, t, 1-OCH_2CH_3), 1.24 (3H, s, 3-CH_3), 1.30 (3H, d, 6-H), 1.40 (1H, dd, 2-H_{ax}), 2.09 (1H, d, 4-OH), 2.24 (1H, dd, 2-H_{eq}), 2.97 (1H, dd, 4-H), 3.25 (3H, s, 3-OCH_3), 3.50 and 3.93 (each 1H, 2×dq, 1-OCH_2CH_3), 3.59 (1H, dq, 5-H), 4.57 (1H, dd, 1-H).

Ethyl 4-*O*-(3-Methylbutyl)-β-L-cladinoside (**5**)

To a stirred mixture of **1** (7.50 g) and oily sodium hydride (7.34 g of a 60% suspension) in dry DMF (180 ml) at 0°C was added 1-iodo-3-methylbutane (29.0 g). The mixture was stirred at room temperature for 2 hours, which spontaneously heated up to accelerate the reaction. Evaporation at 40°C gave a residue which was extracted with EtOAc (2.4 liters). The organic layer was successively washed with 5% aqueous $KHSO_4$, saturated aqueous $NaHCO_3$ and brine. After drying the organic layer, evaporation gave a residue which was purified by silica gel column chromatography (900 g, PhH-EtOAc, 10 : 1 ~ 5 : 1) to afford **5** (9.05 g, 90%) as a colorless oil: $[\alpha]_D^{18}$ +16° (*c* 1.0, $CHCl_3$); SI-MS *m/z* 275 (MH^+); ^{1}H NMR δ 0.91 (6H, d, –$CH(CH_3)_2$), 1.23 (3H, t, 1-OCH_2CH_3), 1.28 (3H, s, 3-CH_3), 1.31 (3H, d, 6-H), 1.42 (1H, dd, 2-H_{ax}), 1.52 (2H, m, 4-OCH_2CH_2–), 1.73 (1H, m, –$CH(CH_3)_2$), 2.14 (1H, dd, 2-H_{eq}), 2.78 (1H, d, 4-H), 3.31 (3H, s, 3-OCH_3), 3.52 and 3.93 (each 1H, 2×dq, 1-OCH_2CH_3), 3.59 and 3.65 (each 1H, dt and ddd, 4-OCH_2–), 3.88 (1H, dq, 5-H), 4.69 (1H, dd, 1-H).

Ethyl 4-*O*-Ethyl-β-L-cladinoside (**2**)

Reaction of **1** with 1-iodoethane gave **2** as a colorless oil in 90% yield by a similar procedure to **5**.

$[\alpha]_D^{25}$ +19° (*c* 1.0, $CHCl_3$); SI-MS *m/z* 233 (MH^+); ^{1}H NMR δ 1.22(6H, t, 1-OCH_2CH_3, 4-OCH_2CH_3), 1.26 (3H, s, 3-CH_3), 1.29 (3H, d, 6-H), 1.39 (1H, dd, 2-H_{ax}), 2.15 (1H, dd, 2-H_{eq}), 2.78 (1H, d, 4-H), 3.29 (3H, s, 3-OCH_3), 3.51 and 3.92 (each 1H, 2×dq, 1-OCH_2CH_3), 3.62 and 3.68 (each 1H, 2×dq, 4-OCH_2CH_3), 3.87 (1H, dq, 5-H), 4.66 (1H, dd, 1-H).

Ethyl 4-*O*-(2-Propenyl)-β-L-cladinoside (**3**)

Reaction of **1** with 3-iodo-1-propene gave **3** as a colorless oil in 95% yield by a similar procedure to **5**.

$[\alpha]_D^{21}$ +19° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 1.22 (3H, t, 1-OCH_2CH_3), 1.26 (3H, s, 3-CH_3), 1.30 (3H, d, 6-H), 1.40 (1H, dd, 2-H_{ax}), 2.14 (1H, dd, 2-H_{eq}), 2.86 (1H, d, 4-H), 3.29 (3H, s, 3-OCH_3), 3.51 and 3.92 (each 1H, 2×dq, 1-OCH_2CH_3), 3.90 (1H, dq, 5-H), 4.08 and 4.18 (each 1H, 2×br dd, 4-OCH_2–), 4.67 (1H, dd, 1-H), 5.16 and 5.24 (each 1H, 2×br d, –CH=CH_2), 5.94 (1H, ddt, –CH=CH_2).

Ethyl 4-*O*-Butyl-β-L-cladinoside (**4**)

Reaction of **1** with 1-bromobutane gave **4** as a colorless oil in 94% yield by a similar procedure to **5**.

$[\alpha]_D^{25}$ +17° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 0.91 (3H, t, 4-$O(CH_2)_3CH_3$), 1.22 (3H, t, 1-OCH_2CH_3), 1.26 (3H, s, 3-CH_3), 1.29 (3H, d, 6-H), 1.40 (1H, dd, 2-H_{ax}), 2.13

(1H, dd, 2-H_{eq}), 2.76 (1H, d, 4-H), 3.29 (3H, s, 3-OCH_3), 3.51 and 3.91 (each 1H, 2×dq, 1-OCH_2CH_3), 3.54 and 3.61 (each 1H, 2×dt, 4-OCH_2–), 3.87 (1H, dq, 5-H), 4.66 (1H, dd, 1-H).

Ethyl 4-*O*-(3-Methyl-2-butenyl)-β-L-cladinoside (**6**)

Reaction of **1** with 4-bromo-2-methyl-2-butene gave **6** as a colorless oil in 96% yield by a similar procedure to **5**.

$[\alpha]_D^{25}$ +17° (*c* 1.0, $CHCl_3$); EI-MS *m/z* 272 (M^+); ^1H NMR δ 1.21 (3H, t, 1-OCH_2CH_3), 1.26 (3H, s, 3-CH_3), 1.30 (3H, d, 6-H), 1.39 (1H, dd, 2-H_{ax}), 1.66 and 1.73 (each 3H, 2×br s, –CH=$C(CH_3)_2$), 2.14 (1H, dd, 2-H_{eq}), 2.82 (1H, d, 4-H), 3.28 (3H, s, 3-OCH_3), 3.51 and 3.91 (each 1H, 2×dq, 1-OCH_2CH_3), 3.89 (1H, dq, 5-H), 4.09 and 4.13(each 1H, 2×br dd, 4-OCH_2–), 4.66 (1H, dd, 1-H), 5.37 (1H, br t, –CH=$C(CH_3)_2$).

Ethyl 4-*O*-(4-Methylpentyl)-β-L-cladinoside (**7**)

Reaction of **1** with 1-bromo-4-methylpentane gave **7** as a colorless oil in 87% yield by a similar procedure to **5**.

$[\alpha]_D^{24}$ +10° (*c* 1.0, $CHCl_3$); SI-MS *m/z* 289 (MH^+); ^1H NMR δ 0.88 (6H, d, –$CH(CH_3)_2$), 1.22 (3H, t, 1-OCH_2CH_3), 1.26 (3H, s, 3-CH_3), 1.29 (3H, d, 6-H), 1.40 (1H, dd, 2-H_{ax}), 2.13 (1H, dd, 2-H_{eq}), 2.76 (1H, d, 4-H), 3.29 (3H, s, 3-OCH_3), 3.51 and 3.91 (each 1H, 2×dq, 1-OCH_2CH_3), 3.52 and 3.59 (each 1H, 2×dt, 4-OCH_2–), 3.87 (1H, dq, 5-H), 4.67 (1H, dd, 1-H).

Ethyl 4-*O*-Hexyl-β-L-cladinoside (**8**)

Reaction of **1** with 1-iodohexane gave **8** as a colorless oil in 98% yield by a similar procedure to **5**.

$[\alpha]_D^{21}$ +12° (*c* 0.5, $CHCl_3$); EI-MS *m/z* 288 (M^+); ^1H NMR δ 0.88 (3H, t, 4-$O(CH_2)_5CH_3$), 1.22 (3H, t, 1-OCH_2CH_3), 1.26 (3H, s, 3-CH_3), 1.29 (3H, d, 6-H), 1.39 (1H, dd, 2-H_{ax}), 2.13 (1H, dd, 2-H_{eq}), 2.76 (1H, d, 4-H), 3.29 (3H, s, 3-OCH_3), 3.50 and 3.91 (each 1H, 2×dq, 1-OCH_2CH_3), 3.53 and 3.60 (each 1H, 2×dt, 4-OCH_2–), 3.87 (1H, dq, 5-H), 4.66 (1H, dd, 1-H).

Ethyl 4-*O*-(2-(2-Methoxyethoxy)ethyl)-β-L-cladinoside (**9**)

Reaction of **1** with 1-bromo-2-(2-methoxyethoxy)-ethane gave **9** as a colorless oil in 64% yield by a similar procedure to **5**.

$[\alpha]_D^{28}$ +19° (*c* 1.0, $CHCl_3$); ^1H NMR δ 1.21 (3H, t, 1-OCH_2CH_3), 1.28 (3H, s, 3-CH_3), 1.30 (3H, d, 6-H), 1.40 (1H, dd, 2-H_{ax}), 2.13 (1H, dd, 2-H_{eq}), 2.85 (1H, d, 4-H), 3.29 (3H, s, 3-OCH_3), 3.37 (3H, s, –$O(CH_2)_2OCH_3$), 3.50 and 3.91 (each 1H, 2×dq, 1-OCH_2CH_3), 3.88 (1H, dq, 5-H), 4.66 (1H, dd, 1-H).

Ethyl 4-*O*-Benzyl-β-L-cladinoside (**10**)

Reaction of **1** with α-bromotoluene gave **10** as colorless needles in 92% yield by a similar procedure to **5**.

MP 51~55°C; $[\alpha]_D^{28}$ +28° (*c* 1.0, $CHCl_3$); ^1H NMR δ 1.20 (3H, s, 3-CH_3), 1.22 (3H, t, 1-OCH_2CH_3), 1.31 (3H, d, 6-H), 1.41 (1H, dd, 2-H_{ax}), 2.13 (1H, dd, 2-H_{eq}), 2.99 (1H, d, 4-H), 3.30 (3H, s, 3-OCH_3), 3.51 and 3.92 (each 1H, 2×dq, 1-OCH_2CH_3), 3.95 (1H, dq, 5-H), 4.60 and 4.69 (each 1H, 2×d, 4-OCH_2Ph), 4.69 (1H, dd, 1-H), 7.34 (5H, m, Ph).

1-Deoxy-4-*O*-(3-methylbutyl)-1-(2-pyridylthio)-L-cladinoside (**23**) *via* 4-*O*-(3-Methylbutyl)-L-cladinose (**14**)

To a solution of **5** (5.70 g) in 1,4-dioxane (100 ml) was added 1.0 M HCl (100 ml). The mixture was stirred at 30°C for 24 hours. After addition of saturated aqueous $NaHCO_3$ (250 ml), the mixture was extracted with CH_2Cl_2 (2×200 ml). The combined organic layer was washed with brine, dried and concentrated to afford a colorless oil of **14** (5.12 g) as α/β (*ca.* 1:4) mixture: ^1H NMR δ 0.89 (4.8H, d, –$CH(CH_3)_2$), 0.91 (1.2H, d, –$CH(CH_3)_2$), 1.27 (2.4H, s, 3-CH_3), 1.29 (2.4H, d, 6-H), 1.31 (0.6H, d, 6-H), 1.32 (0.6H, s, 3-CH_3), 1.33 (0.8H, dd, 2-H_{ax}), 1.66 (0.2H, dd, 2-H_{ax}), 1.70 (1H, m, –$CH(CH_3)_2$), 2.04 (0.2H, br d, 2-H_{eq}), 2.23 (0.8H, dd, 2-H_{eq}), 2.77 (0.8H, d, 4-H), 2.79 (0.2H, d, 4-H), 3.29 (2.4H, s, 3-OCH_3), 3.44 (0.6H, s, 3-OCH_3), 3.94 (0.8H, dq, 5-H), 4.12 (0.2H, dq, 5-H), 5.02 (1H, m, 1-H). To a solution of 2,2′-dipyridyl disulfide (8.26 g) in dry CH_2Cl_2 (89 ml) was added at 0°C Bu_3P (12.4 ml). The chilled solution was added to a solution of **14** (3.69 g) in dry CH_2Cl_2 (74 ml) at 0°C under an atmosphere of argon. The solution was allowed to stand at room temperature for 4 hours and concentrated to give a residue which was purified by silica gel column chromatography (1.0 kg, $CHCl_3$-EtOAc, 100:1) to afford an oil of **23** (3.17 g, 62% *via* two steps) as an α/β (*ca.* 2:3) mixture. Each anomer was isolated on preparative TLC ($CHCl_3$-EtOAc, 10:1).

α-Anomer of **23**: Colorless needles; MP 76°C; $[\alpha]_D^{18}$ −311° (*c* 1.0, $CHCl_3$); FD-MS *m/z* 339 (M^+); ^1H NMR δ 0.90 (6H, d, –$CH(CH_3)_2$), 1.26 (3H, d, 6-H), 1.31 (3H, s, 3-CH_3), 1.52 (2H, m, 4-OCH_2CH_2–), 1.73 (1H, m, –$CH(CH_3)_2$), 2.07 (1H, dd, 2-H_{ax}), 2.38 (1H, br d, 2-H_{eq}), 2.82 (1H, d, 4-H), 3.35 (3H, s, 3-OCH_3), 3.60 and 3.67 (each 1H, dt and ddd, 4-OCH_2–), 4.37 (1H, dq, 5-H), 6.33 (1H, br d, 1-H), 6.98 (1H, ddd, 5′-H), 7.27 (1H, dt, 3′-H), 7.49 (1H, dt, 4′-H), 8.45 (1H, ddd, 6′-H).

β-Anomer of **23**: A colorless oil; $[\alpha]_D^{18}$ +27° (*c* 1.0, $CHCl_3$); FD-MS *m/z* 339 (M^+); ^1H NMR δ 0.90 (6H, d, –$CH(CH_3)_2$), 1.30 (3H, d, 6-H), 1.31 (3H, s, 3-CH_3), 1.51 (2H, m, 4-OCH_2CH_2–), 1.71 (1H, m, –$CH(CH_3)_2$), 1.73 (1H, dd, 2-H_{ax}), 2.33 (1H, dd, 2-H_{eq}), 2.83 (1H, d, 4-H), 3.32 (3H, s, 3-OCH_3), 3.59 and 3.65 (each 1H, 2×ddd, 4-OCH_2–), 4.02 (1H, dq, 5-H), 5.59 (1H, dd, 1-H), 7.03 (1H, ddd, 5′-H), 7.32 (1H, dt, 3′-H), 7.55 (1H, ddd, 4′-H), 8.43 (1H, ddd, 6′-H).

1-Deoxy-4-*O*-ethyl-1-(2-pyridylthio)-L-cladinoside (**20**) *via* 4-*O*-Ethyl-L-cladinose (**11**)

Reactions of **2** gave **20** as an α/β (*ca.* 2:3) mixture in 75% yield *via* **11** by a similar procedure to **23**.

20: EI-MS *m/z* 297 (M^+); ^1H NMR δ 1.24 (3H, t, 4-OCH_2CH_3), 1.26 (1.2H, d, 6-H), 1.31 (1.8H, d, 6-H), 1.31 (3H, s, 3-CH_3), 1.72 (0.6H, dd, 2-H_{ax}), 2.06 (0.4H,

dd, 2-H_{ax}), 2.36 (0.6H, dd, 2-H_{eq}), 2.41 (0.4H, br d, 2-H_{eq}), 2.83 (0.4H, d, 4-H), 2.84 (0.6H, d, 4-H), 3.32 (1.8H, s, 3-OCH_3), 3.35 (1.2H, s, 3-OCH_3), 4.03 (0.6H, dq, 5-H), 4.38 (0.4H, dq, 5-H), 5.58 (0.6H, dd, 1-H_{ax}), 6.32 (0.4H, br d, 1-H_{eq}).

1-Deoxy-4-*O*-(2-propenyl)-1-(2-pyridylthio)-L-cladinoside (**21**) *via* 4-*O*-(2-Propenyl)-L-cladinose (**12**)

Reactions of **3** gave **21** as an α/β (*ca.* 1:2) mixture in 80% yield *via* **12** by a similar procedure to **23**.

21: EI-MS *m/z* 309 (M^+); ^1H NMR δ 1.27 (1H, d, 6-H), 1.32 (3H, s, 3-CH_3), 1.32 (2H, d, 6-H), 1.74 (0.67H, dd, 2-H_{ax}), 2.08 (0.33H, dd, 2-H_{ax}), 2.35 (0.67H, dd, 2-H_{eq}), 2.41 (0.33H, br d, 2-H_{eq}), 2.91 (0.33H, d, 4-H), 2.92 (0.67H, d, 4-H), 3.33 (2H, s, 3-OCH_3), 3.36 (1H, s, 3-OCH_3), 4.07 (0.67H, dq, 5-H), 4.42 (0.33H, dq, 5-H), 5.18 and 5.26 (each 1H, 2×br d, $-CH=CH_2$), 5.62 (0.67H, dd, 1-H_{ax}), 5.95 (1H, m, $-CH=CH_2$), 6.35 (0.33H, br d, 1-H_{eq}).

4-*O*-Butyl-1-deoxy-1-(2-pyridylthio)-L-cladinoside (**22**) *via* 4-*O*-Butyl-L-cladinose (**13**)

Reactions of **4** gave **22** as an α/β (*ca.* 1:2) mixture in 70% yield *via* **13** by a similar procedure to **23**.

22: EI-MS *m/z* 325 (M^+); ^1H NMR δ 0.88 (3H, t, 4-$O(CH_2)_3CH_3$), 1.22 (1H, d, 6-H), 1.27 (2H, d, 6-H), 1.27 (3H, s, 3-CH_3), 1.69 (0.67H, dd, 2-H_{ax}), 2.03 (0.33H, dd, 2-H_{ax}), 2.29 (0.67H, dd, 2-H_{eq}), 2.35 (0.33H, br d, 2-H_{eq}), 2.78 (0.33H, d, 4-H), 2.79 (0.67H, d, 4-H), 3.28 (2H, s, 3-OCH_3), 3.32 (1H, s, 3-OCH_3), 3.53 and 3.59 (each 1H, 2×dt, 4-OCH_2–), 3.98 (0.67H, dq, 5-H), 4.34 (0.33H, dq, 5-H), 5.55 (0.67H, dd, 1-H_{ax}), 6.29 (0.33H, br d, 1-H_{eq}).

1-Deoxy-4-*O*-(3-methyl-2-butenyl)-1-(2-pyridylthio)-L-cladinoside (**24**) *via* 4-*O*-(3-Methyl-2-butenyl)-L-cladinose (**15**)

Reactions of **6** gave **24** as an α/β (*ca.* 2:3) mixture in 48% yield *via* **15** by a similar procedure to **23**.

24: EI-MS *m/z* 337 (M^+); ^1H NMR δ 1.27 (1.2H, d, 6-H), 1.31 (1.8H, d, 6-H), 1.31 (3H, s, 3-CH_3), 1.66 and 1.74 (each 3H, 2×s, $-CH=C(CH_3)_2$), 2.06 (0.4H, dd, 2-H_{ax}), 2.35 (0.6H, dd, 2-H_{eq}), 2.40 (0.4H, br d, 2-H_{eq}), 2.86 (0.4H, d, 4-H), 2.88 (0.6H, d, 4-H), 3.30 (1.8H, s, 3-OCH_3), 3.34 (1.2H, s, 3-OCH_3), 4.04 (0.6H, dq, 5-H), 4.40 (0.4H, dq, 5-H), 5.38 (1H, m, $-CH=C(CH_3)_2$), 5.59 (0.6H, dd, 1-H_{ax}), 6.32 (0.4H, br d, 1-H_{eq}).

1-Deoxy-4-*O*-(4-methylpentyl)-1-(2-pyridylthio)-L-cladinoside (**25**) *via* 4-*O*-(4-Methylpentyl)-L-cladinose (**16**)

Reactions of **7** gave **25** as an α/β (*ca.* 1:3) mixture in 51% yield *via* **16** by a similar procedure to **23**.

25: EI-MS *m/z* 353 (M^+); ^1H NMR δ 0.89 (6H, d, $-CH(CH_3)_2$), 1.31 (2.25H, d, 6-H), 1.32 (3H, s, 3-CH_3), 1.54 (1H, m, $-CH(CH_3)_2$), 1.73 (0.75H, dd, 2-H_{ax}), 2.07 (0.25H, dd, 2-H_{ax}), 2.34 (0.75H, dd, 2-H_{eq}), 2.39 (0.25H, br d, 2-H_{eq}), 2.82 (0.25H, d, 4-H), 2.83 (0.75H, d, 4-H), 3.32 (2.25H, s, 3-OCH_3), 3.35 (0.75H, s, 3-OCH_3), 3.55 and 3.61 (each 1H, 2×dt, 4-OCH_2–), 4.03 (0.75H, dq, 5-H), 4.38 (0.25H, dq, 5-H), 5.59 (0.75H, dd, 1-H_{ax}), 6.33 (0.25H, br d, 1-H_{eq}).

1-Deoxy-4-*O*-hexyl-1-(2-pyridylthio)-L-cladinoside (**26**) *via* 4-*O*-Hexyl-L-cladinose (**17**)

Reactions of **8** gave **26** as an α/β (*ca.* 1:1) mixture in 55% yield *via* **17** by a similar procedure to **23**.

26: EI-MS *m/z* 353 (M^+); ^1H NMR δ 0.93 (3H, t, 4-$O(CH_2)_5CH_3$), 1.31 (3H, s, 3-CH_3), 2.07 (0.5H, dd, 2-H_{ax}), 2.34 (0.5H, dd, 2-H_{eq}), 2.39 (0.5H, br d, 2-H_{eq}), 2.83 (0.5H, d, 4-H), 2.84 (0.5H, d, 4-H), 3.33 (1.5H, s, 3-OCH_3), 3.36 (1.5H, s, 3-OCH_3), 4.03 (0.5H, dq, 5-H), 4.38 (0.5H, dq, 5-H), 5.59 (0.5H, dd, 1-H_{ax}), 6.33 (0.5H, br d, 1-H_{eq}).

1-Deoxy-4-*O*-(2-(2-methoxyethoxy)ethyl)-1-(2-pyridylthio)-L-cladinoside (**27**) *via* 4-*O*-(2-(2-Methoxyethoxy)ethyl)-L-cladinose (**18**)

Reactions of **9** gave **27** as an α/β (*ca.* 1:1) mixture in 93% yield *via* **18** by a similar procedure to **23**.

27: ^1H NMR δ 1.27 (1.5H, d, 6-H), 1.32 (1.5H, d, 6-H), 1.33 (3H, s, 3-CH_3), 1.73 (0.5H, dd, 2-H_{ax}), 2.07 (0.5H, dd, 2-H_{ax}), 2.34 (0.5H, dd, 2-H_{eq}), 2.39 (0.5H, br d, 2-H_{eq}), 2.92 (0.5H, d, 4-H), 2.93 (0.5H, d, 4-H), 3.32 (1.5H, s, 3-OCH_3), 3.35 (1.5H, s, 3-OCH_3), 3.38 (3H, s, $-O(CH_2)_2OCH_3$), 4.04 (0.5H, dq, 5-H), 4.39 (0.5H, dq, 5-H), 5.59 (0.5H, dd, 1-H_{ax}), 6.32 (0.5H, br d, 1-H_{eq}).

4-*O*-Benzyl-1-deoxy-1-(2-pyridylthio)-L-cladinoside (**28**) *via* 4-*O*-Benzyl-L-cladinose (**19**)

Reactions of **10** gave **28** as an α/β (*ca.* 1:1) mixture in 65% yield *via* **19** by a similar procedure to **23**.

28: EI-MS *m/z* 359 (M^+); ^1H NMR δ 1.24 (1.5H, s, 3-CH_3), 1.25 (1.5H, s, 3-CH_3), 1.29 (1.5H, d, 6-H), 1.33 (1.5H, d, 6-H), 1.74 (0.5H, dd, 2-H_{ax}), 2.09 (0.5H, dd, 2-H_{ax}), 2.33 (0.5H, dd, 2-H_{eq}), 2.39 (0.5H, br d, 2-H_{eq}), 3.04 (0.5H, d, 4-H), 3.06 (0.5H, d, 4-H), 3.33 (1.5H, s, 3-OCH_3), 3.36 (1.5H, s, 3-OCH_3), 4.11 (0.5H, dq, 5-H), 4.46 (0.5H, dq, 5-H), 4.62, 4.64, 4.72 and 4.75 (each 0.5H, 4×d, 4-OCH_2Ph), 5.63 (0.5H, dd, 1-H_{ax}), 6.35 (0.5H, br d, 1-H_{eq}), 7.35 (5H, m, Ph).

9-Dehydro-demycarosylplatenomycin (**29**)

To a stirred solution of midecamycin A_3 (5.61 g) in CH_3CN (100 ml) was added 1.0 M HCl (100 ml). The solution was kept at 30°C for 16 hours and poured into saturated aqueous $NaHCO_3$ (1.0 liter). The mixture was extracted with $CHCl_3$ (800 ml, 200 ml). The combined organic layer was dried and concentrated to give a residue which was purified by silica gel column chromatography (250 g, $CHCl_3$ - CH_3OH, 10:1) to afford **29** (3.72 g, 88%) as a colorless solid: MP 108~112°C (Lit.,[13] 108~110°C); EI-MS *m/z* 611 (M^+).

9-Dehydro-demycarosylplatenomycin *N*-Oxide (**30**)

To a stirred solution of **29** (1.78 g) in $CHCl_3$ (90 ml) was slowly added at room temperature a solution of mCPBA (502 mg) in $CHCl_3$ (10 ml). After 5 minutes at the temperature, the reaction mixture was successively washed with 10% aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried and concentrated to afford **30** (1.70 g, 93%) as a colorless solid: MP 158~164°C; $[\alpha]_D^{21}$ +43° (*c* 1.0, $CHCl_3$); SI-MS *m/z* 628 (MH^+); ^1H NMR δ 1.14 (3H, t, 3-$OCOCH_2CH_3$), 1.22 (3H, d, 19-H), 1.30 (3H, d, 16-H), 1.32 (3H, d, 6'-H), 1.49 (1H, ddd, 7-H), 1.57 (1H, ddd, 7-H), 1.87 (1H, br t, 6-H), 2.23 (1H, m, 14-H), 2.29 (1H, dd, 2-H), 2.42 and 2.53 (each 1H, 2×dq, 3-$OCOCH_2CH_3$), 2.49 (1H, br dt, 14-H), 2.58 (1H, dd, 17-H), 2.70 (1H, ddd, 17-H), 2.77 (1H, dd, 2-H), 3.20 (1H, t, 3'-H), 3.27 and 3.44 (each 3H, 2×s, $-N(CH_3)_2$), 3.32 (1H, dd, 4-H), 3.40 (1H, dq, 5'-H), 3.47 (1H, dd, 2'-H), 3.56 (3H, s, 4-OCH_3), 3.56 (1H, t, 4'-H), 3.88 (1H, br d, 5-H), 4.39 (1H, d, 1'-H), 4.90 (1H, ddq, 15-H), 5.09 (1H, br dt, 3-H), 6.21 (2H, m, 12-H and 13-H), 6.32 (1H, d, 10-H), 7.37 (1H, dd like, 11-H), 9.58 (1H, br d, 18-H).

9-Dehydro-3''-*O*-methyl-4''-*O*-(3-methylbutyl)-3-*O*-propionylleucomycin V *N*-Oxide (**34**) and Its 4'-*O*-β-Isomer **40**

To a solution of **23** (2.11 g) and **30** (650 mg) in dry CH_3CN (18 ml) well pulverized molecular sieves 4A (6.2 g) were added. The mixture was stirred at room temperature for **10** minutes under an atmosphere of argon and then cooled at −15°C. To the stirred chilled mixture was carefully added anhydrous $AgClO_4$ (2.14 g) and the mixture was stirred at −15°C for 2 hours in a dark place. This was stirred at room temperature for a further 18 hours and poured into a vigorously stirred mixture of CH_2Cl_2 (600 ml) and saturated aqueous $NaHCO_3$ (600 ml). After 30 minutes stirring, the resulting mixture was filtered with Celite and filter cake was washed with CH_2Cl_2 (300 ml). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (300 ml). The combined organic layer was washed with brine (750 ml), dried and concentrated to give a residue which was purified by silica gel column chromatography (250 g, $CHCl_3$ - MeOH, 50 : 1) to afford **34** (177 mg, 20% (38% based on consumed **30**)) as a colorless solid and the same amount of **40**.

34: MP 122~125°C; $[\alpha]_D^{17}$ −26° (*c* 0.8, MeOH); SI-MS *m/z* 856 (MH^+); ^1H NMR δ 0.89 (6H, d, $-CH(CH_3)_2$), 1.13 (3H, t, 3-$OCOCH_2CH_3$), 1.20 (3H, d, 19-H), 1.20 (3H, d, 6'-H), 1.23 (3H, d, 6''-H), 1.28 (3H, s, 3''-CH_3), 1.28 (3H, d, 16-H), 1.51 (2H, m, 4''-OCH_2CH_2–), 1.65 (1H, dd, 2''-H_{ax}), 1.69 (1H, m, $-CH(CH_3)_2$), 1.79 (1H, br t, 6-H), 2.25 (1H, d, 2''-H_{eq}), 2.26 (1H, br d, 2-H), 2.42 and 2.56 (each 1H, 2×dq, 3-$OCOCH_2CH_3$), 2.44 (1H, br dd, 17-H), 2.69 (1H, br dd, 17-H), 2.78 (1H, dd, 2-H), 2.79 (1H, d, 4''-H), 3.24 (1H, t, 3'-H), 3.25 (3H, s, 3''-OCH_3), 3.33 (1H, dd, 4-H), 3.36 (1H, dq, 5'-H), 3.36 and 3.61 (each 3H, 2×s, $-N(CH_3)_2$), 3.55 (1H, t, 4'-H), 3.63 (3H, s, 4-OCH_3), 3.81 (1H, dd, 2'-H), 3.91 (1H, br d, 5-H), 4.06 (1H, dq, 5''-H), 4.65 (1H, d, 1'-H), 4.86 (1H, ddq, 15-H), 4.99 (1H, d, 1''-H), 5.09 (1H, br d, 3-H), 6.21 (2H, m, 12-H and 13-H), 6.35 (1H, d, 10-H), 7.38 (1H, dd, 11-H), 9.53 (1H, br s, 18-H).

40: MP 115~118°C; $[\alpha]_D^{19}$ +8° (*c* 1.0, MeOH); SI-MS *m/z* 856 (MH^+); ^1H NMR δ 0.90 (6H, d, $-CH(CH_3)_2$), 1.14 (3H, t, 3-$OCOCH_2CH_3$), 1.20 (3H, d, 19-H), 1.26 (3H, d, 6'-H), 1.27 (3H, s, 3''-CH_3), 1.29 (3H, d, 16-H), 1.29 (3H, d, 6''-H), 1.36 (1H, dd, 2''-H_{ax}), 1.80 (1H, br t, 6-H), 1.98 (1H, dd, 2''-H_{eq}), 2.27 (1H, br d, 2-H), 2.44 and 2.61 (each 1H, 2×dq, 3-$OCOCH_2CH_3$), 2.72 (1H, d, 4''-H), 2.79 (1H, br dd, 17-H), 2.79 (1H, dd, 2-H), 3.24 and 3.43 (each 3H, 2×s, $-N(CH_3)_2$), 3.29 (3H, s, 3''-OCH_3), 3.34 (1H, dd, 4-H), 3.45 (1H, t, 4'-H), 3.56 and 3.61 (each 1H, 2×dt, 4''-OCH_2–), 3.65 (3H, s, 4-OCH_3), 3.73 (1H, dd, 2'-H), 3.84 (1H, dq, 5''-H), 3.93 (1H, br d, 5-H), 4.63 (1H, d, 1'-H), 4.84 (1H, dd, 1''-H), 4.85 (1H, ddq, 15-H), 5.10 (1H, br d, 3-H), 6.23 (2H, m, 12-H and 13-H), 6.35 (1H, d, 10-H), 7.39 (1H, dd, 11-H), 9.56 (1H, br s, 18-H).

9-Dehydro-3''-*O*-methyl-4''-*O*-(3-methylbutyl)-3-*O*-propionylleucomycin V (**44**)

To a solution of **34** (120 mg) in dry CH_2Cl_2 (16 ml) was added freshly recrystallized Ph_3P (650 mg). The solution was kept at 32°C for 72 hours and concentrated to give a residue which was purified by preparative TLC ($CHCl_3$ - MeOH, 50 : 1, developed twice) to afford **44** (85.0 mg, 72%) as a colorless solid: MP 89~94°C; $[\alpha]_D^{14}$ −23° (*c* 1.0, MeOH); SI-MS *m/z* 840 (MH^+); ^1H NMR δ 0.89 (6H, d, $-CH(CH_3)_2$), 1.14 (3H, t, 3-$OCOCH_2CH_3$), 1.15 (3H, d, 6'-H), 1.19 (3H, d, 19-H), 1.23 (3H, d, 6''-H), 1.24 (3H, s, 3''-CH_3), 1.28 (3H, d, 16-H), 1.51 (2H, m, 4''-OCH_2CH_2–), 1.56 (1H, dd, 2''-H_{ax}), 1.65 (1H, ddd, 7-H), 1.69 (1H, m, $-CH(CH_3)_2$), 1.78 (1H, br t, 6-H), 2.22 (1H, d, 2''-H_{eq}), 2.25 (1H, br d, 2-H), 2.39 (1H, t, 3'-H), 2.43 and 2.58 (each 1H, 2×dq, 3-$OCOCH_2CH_3$), 2.56(6H, s, $-N(CH_3)_2$), 2.76 (1H, br dd, 17-H), 2.77 (1H, d, 4''-H), 2.78 (1H, dd, 2-H), 3.14 (1H, dd, 2'-H), 3.25 (3H, s, 3''-OCH_3), 3.27 (1H, dq, 5'-H), 3.29 (1H, dd, 4-H), 3.46 (1H, t, 4'-H), 3.59 and 3.64 (each 1H, 2×dt, 4''-OCH_2–), 3.60 (3H, s, 4-OCH_3), 3.89 (1H, br dd, 5-H), 4.42 (1H, dq, 5''-H), 4.50 (1H, d, 1'-H), 4.84 (1H, ddq, 15-H), 4.88 (1H, d, 1''-H), 5.09 (1H, br dt, 3-H), 6.22 (2H, m, 12-H and 13-H), 6.34 (1H, d, 10-H), 7.37 (1H, dd, 11-H), 9.54 (1H, br s, 18-H).

9-Dehydro-4''-*O*-ethyl-3''-*O*-methyl-3-*O*-propionylleucomycin V (**41**) *via* 9-Dehydro-4''-*O*-ethyl-3''-*O*-methyl-3-*O*-propionylleucomycin V *N*-Oxide (**31**)

Reaction of **20** and **30** gave **31** in 21% yield by a similar procedure to **34**. Reaction of **31** gave **41** in 71% yield by a similar procedure to **44**.

41: MP 104~107°C; $[\alpha]_D^{20}$ −22° (*c* 0.7, MeOH); SI-MS *m/z* 798 (MH^+); ^1H NMR δ 1.14 (3H, t, 3-$OCOCH_2CH_3$), 1.15 (3H, d, 6'-H), 1.20 (3H, d, 19-H), 1.23 (3H, d, 6''-H), 1.23 (3H, t, 4''-OCH_2CH_3), 1.24 (3H,

s, 3″-CH_3), 1.28 (3H, d, 16-H), 1.49 (1H, ddd, 7-H), 1.55 (1H, dd, 2″-H_{ax}), 1.64 (1H, ddd, 7-H), 1.78 (1H, br t, 6-H), 2.24 (1H, d, 2″-H_{eq}), 2.26 (1H, br d, 2-H), 2.39 (1H, t, 3′-H), 2.43 and 2.58 (each 1H, 2×dq, 3-OCOC$H_2$$CH_3$), 2.56 (6H, s, –$N(CH_3)_2$), 2.75 (1H, br dd, 17-H), 2.78 (1H, dd, 2-H), 2.78 (1H, d, 4″-H), 3.14 (1H, dd, 2′-H), 3.25 (3H, s, 3″-OCH_3), 3.27 (1H, dq, 5′-H), 3.29 (1H, dd, 4-H), 3.47 (1H, t, 4′-H), 3.60 (3H, s, 4-OCH_3), 3.65 and 3.70 (each 1H, 2×dq, 4″-OC$H_2$$CH_3$), 3.89(1H, br d, 5-H), 4.43 (1H, dq, 5″-H), 4.51 (1H, d, 1′-H), 4.85 (1H, ddq, 15-H), 4.89 (1H, d, 1″-H), 5.09 (1H, br dt, 3-H), 6.21 (2H, m, 12-H and 13-H), 6.34 (1H, d, 10-H), 7.37 (1H, dd, 11-H), 9.54 (1H, br s, 18-H).

9-Dehydro-3″-*O*-methyl-4″-*O*-(2-propenyl)-3-*O*-propionylleucomycin V (**42**) *via* 9-Dehydro-3″-*O*-methyl-4′-*O*-(2-propenyl)-3-*O*-propionylleucomycin V *N*-Oxide (**32**)

Reaction of **21** and **30** gave **32** in 19% yield by a similar procedure to **34**. Reaction of **32** gave **42** in 57% yield by a similar procedure to **44**.

42: MP 160°C; $[\alpha]_D^{17}$ −23° (*c* 1.0, MeOH); FD-MS *m/z* 810 (MH^+); ^{1}H NMR δ 1.28 (3H, d, 16-H), 1.56 (1H, dd, 2″-H_{ax}), 1.64 (1H, ddd, 7-H), 1.78 (1H, br t, 6-H), 2.23 (1H, d, 2″-H_{eq}), 2.26 (1H, br d, 2-H), 2.60 (6H, s, –$N(CH_3)_2$), 2.79 (1H, dd, 2-H), 2.87 (1H, d, 4″-H), 3.17 (1H, dd, 2′-H), 3.25 (3H, s, 3″-OCH_3), 3.30 (1H, dd, 4-H), 3.48 (1H, t, 4′-H), 3.60 (3H, s, 4-OCH_3), 3.89 (1H, br d, 5-H), 4.12 and 4.19 (each 1H, 2×br dd, 4″-OCH_2–), 4.43 (1H, dq, 5″-H), 4.51 (1H, d, 1′-H), 4.85 (1H, ddq, 15-H), 4.89 (1H, d, 1″-H), 5.09 (1H, br d, 3-H), 5.17 and 5.23 (each 1H, 2×br d, –CH=CH_2), 5.96 (1H, ddt, –CH=CH_2), 6.22 (2H, m, 12-H and 13-H), 6.34 (1H, d, 10-H), 7.38 (1H, dd, 11-H), 9.53 (1H, br s, 18-H).

4″-*O*-Butyl-9-dehydro-3″-*O*-methyl-3-*O*-propionylleucomycin V (**43**) *via* 4″-*O*-Butyl-9-dehydro-3″-*O*-methyl-3-*O*-propionylleucomycin V *N*-Oxide (**33**)

Reaction of **22** and **30** gave **33** in 14% yield by a similar procedure to **34**. Reaction of **33** gave **43** in 65% yield by a similar procedure to **44**.

43: MP 93°C; $[\alpha]_D^{17}$ −22° (*c* 1.0, MeOH); SI-MS *m/z* 826 (MH^+); ^{1}H NMR δ 0.91 (3H, t, 4″-O$(CH_2)_3$CH_3), 1.28 (3H, d, 16-H), 1.56 (1H, dd, 2″-H_{ax}), 1.65 (1H, ddd, 7-H), 1.77 (1H, br t, 6-H), 2.22 (1H, d, 2″-H_{eq}), 2.26 (1H, br d, 2-H), 2.58 (6H, s, –$N(CH_3)_2$), 2.78 (1H, d, 4″-H), 2.79 (1H, dd, 2-H), 3.16 (1H, dd, 2′-H), 3.25 (3H, s, 3″-OCH_3), 3.30 (1H, dd, 4-H), 3.47 (1H, t, 4′-H), 3.60 (3H, s, 4-OCH_3), 3.89 (1H, br d, 5-H), 4.41 (1H, dq, 5″-H), 4.51 (1H, d, 1′-H), 4.85 (1H, ddq, 15-H), 4.88 (1H, d, 1″-H), 5.09 (1H, br d, 3-H), 6.22 (2H, m, 12-H and 13-H), 6.34 (1H, d, 10-H), 7.38 (1H, dd, 11-H), 9.53 (1H, br s, 18-H).

9-Dehydro-3″-*O*-methyl-4″-*O*-(3-methyl-2-butenyl)-3-*O*-propionylleucomycin V (**45**) *via* 9-Dehydro-3″-*O*-methyl-4″-*O*-(3-methyl-2-butenyl)-3-*O*-propionylleucomycin V *N*-Oxide (**35**)

Reaction of **24** and **30** gave **35** in 9.5% yield by a similar procedure to **34**. Reaction of **35** gave **45** in 66% yield by a similar procedure to **44**.

45: MP 85°C; $[\alpha]_D^{17}$ −12° (*c* 0.4, MeOH); SI-MS *m/z* 838 (MH^+); ^{1}H NMR δ 1.28 (3H, d, 16-H), 1.56 (1H, dd, 2″-H_{ax}), 1.66 and 1.73 (each 3H, 2×s, –CH=C(CH_3)$_2$), 2.23 (1H, d, 2″-H_{eq}), 2.26 (1H, br d, 2-H), 2.60 (6H, s, –$N(CH_3)_2$), 2.78 (1H, dd, 2-H), 2.83 (1H, d, 4″-H), 3.23 (3H, s, 3″-OCH_3), 3.29 (1H, dd, 4-H), 3.48 (1H, t, 4′-H), 3.60 (3H, s, 4-OCH_3), 3.89 (1H, br d, 5-H), 4.12 and 4.16 (each 1H, 2×br dd, 4″-OCH_2–), 4.40 (1H, dq, 5″-H), 4.51 (1H, d, 1′-H), 4.85 (1H, ddq, 15-H), 4.89 (1H, d, 1″-H), 5.09 (1H, br d, 3-H), 5.38 (1H, br t, –CH=C$(CH_3)_2$), 6.22 (2H, m, 12-H and 13-H), 6.34 (1H, d, 10-H), 7.38 (1H, dd, 11-H), 9.53 (1H, br s, 18-H).

9-Dehydro-3″-*O*-methyl-4″-*O*-(4-methylpentyl)-3-*O*-propionylleucomycin V (**46**) *via* 9-Dehydro-3″-*O*-methyl-4″-*O*-(4-methylpentyl)-3-*O*-propionylleucomycin V *N*-Oxide (**36**)

Reaction of **25** and **30** gave **36** in 17% yield by a similar procedure to **34**. Reaction of **36** gave **46** in 73% yield by a similar procedure to **44**.

46: MP 92~94°C; $[\alpha]_D^{17}$ −17° (*c* 1.0, MeOH); FD-MS *m/z* 854 (MH^+); ^{1}H NMR δ 0.87 (6H, d, –CH(CH_3)$_2$), 1.28 (3H, d, 16-H), 1.56 (1H, dd, 2″-H_{ax}), 1.65 (1H, ddd, 7-H), 1.78 (1H, br t, 6-H), 2.22 (1H, d, 2″-H_{eq}), 2.25 (1H, br d, 2-H), 2.60 (6H, s, –$N(CH_3)_2$), 2.77 (1H, d, 4″-H), 2.79 (1H, dd, 2-H), 3.17 (1H, dd, 2′-H), 3.25 (3H, s, 3″-OCH_3), 3.30 (1H, dd, 4-H), 3.47 (1H, t, 4′-H), 3.60 (3H, s, 4-OCH_3), 3.88 (1H, br d, 5-H), 4.40(1H, dq, 5″-H), 4.51 (1H, d, 1′-H), 4.85 (1H, ddq, 15-H), 4.88 (1H, d, 1″-H), 5.09 (1H, br d, 3-H), 6.21 (2H, m, 12-H and 13-H), 6.34 (1H, d, 10-H), 7.38 (1H, dd, 11-H), 9.54 (1H, br s, 18-H).

9-Dehydro-4″-*O*-hexyl-3″-*O*-methyl-3-*O*-propionylleucomycin V (**47**) *via* 9-Dehydro-4″-*O*-hexyl-3″-*O*-methyl-3-*O*-propionylleucomycin V *N*-Oxide (**37**)

Reaction of **26** and **30** gave **37** in 15% yield by a similar procedure to **34**. Reaction of **37** gave **47** in 70% yield by a similar procedure to **44**.

47: MP 86°C; $[\alpha]_D^{17}$ −19° (*c* 1.0, MeOH); FD-MS *m/z* 854 (MH^+); ^{1}H NMR δ 0.90 (3H, t, 4″-O$(CH_2)_5$CH_3), 1.58 (1H, dd, 2″-H_{ax}), 1.66 (1H, ddd, 7-H), 1.79 (1H, br t, 6-H), 2.24 (1H, d, 2″-H_{eq}), 2.28 (1H, br d, 2-H), 2.61 (6H, s, –$N(CH_3)_2$), 2.80 (1H, d, 4″-H), 2.81 (1H, dd, 2-H), 3.18 (1H, dd, 2′-H), 3.27 (3H, s, 3″-OCH_3), 3.31 (1H, dd, 4-H), 3.49 (1H, t, 4′-H), 3.62 (3H, s, 4-OCH_3), 3.91 (1H, br d, 5-H), 4.42 (1H, dq, 5″-H), 4.53 (1H, d, 1′-H), 4.87 (1H, ddq, 15-H), 4.90 (1H, d, 1″-H), 5.11 (1H, br d, 3-H), 6.24 (2H, m, 12-H and 13-H), 6.36 (1H, d, 10-H), 7.40 (1H, dd, 11-H), 9.55 (1H, br s, 18-H).

9-Dehydro-4″-*O*-(2-(2-methoxyethoxy)ethyl)-3″-*O*-methyl-3-*O*-propionylleucomycin V (**48**) *via* 9-Dehydro-4″-*O*-(2-(2-methoxyethoxy)ethyl)-3″-*O*-methyl-3-*O*-propionylleucomycin V *N*-Oxide (**38**)

Reaction of **27** and **30** gave **38** in 22% yield by a similar procedure to **34**. Reaction of **38** gave **48** in 57% yield by a similar procedure to **44**.

48: MP 75~76°C; $[\alpha]_D^{17}$ −20° (*c* 1.0, MeOH); EI-MS *m/z* 871 (M^+); ^{1}H NMR δ 1.28 (3H, d, 16-H), 1.56 (1H, dd, 2″-H_{ax}), 1.64 (1H, ddd, 7-H), 1.77 (1H, br t, 6-H), 2.22 (1H, d, 2″-H_{eq}), 2.26 (1H, br d, 2-H), 2.58 (6H, s, –$N(CH_3)_2$), 2.78 (1H, dd, 2-H), 2.89 (1H, d, 4″-H), 3.16 (1H, dd, 2′-H), 3.24 (3H, s, 3″-OCH_3), 3.30 (1H, dd, 4-H), 3.38 (3H, s, –$O(CH_2)_2OCH_3$), 3.47 (1H, t, 4′-H), 3.60 (3H, s, 4-OCH_3), 3.89 (1H, br d, 5-H), 4.42 (1H, dq, 5″-H), 4.50 (1H, d, 1′-H), 4.85 (1H, ddq, 15-H), 4.88 (1H, d, 1″-H), 5.09 (1H, br d, 3-H), 6.22(2H, m, 12-H and 13-H), 6.34 (1H, d, 10-H), 7.38 (1H, dd, 11-H), 9.53 (1H, br s, 18-H).

4″-*O*-Benzyl-9-dehydro-3″-*O*-methyl-3-*O*-propionylleucomycin V (**49**) *via* 4″-*O*-Benzyl-9-dehydro-3″-*O*-methyl-3-*O*-propionylleucomycin V *N*-Oxide (**39**)

Reaction of **28** and **30** gave **39** in 21% yield by a similar procedure to **34**. Reaction of **39** gave **49** in 59% yield by a similar procedure to **44**.

49: MP 95~97°C; $[\alpha]_D^{17}$ −14° (*c* 1.0, MeOH); FD-MS *m/z* 860 (MH^+); ^{1}H NMR δ 1.28 (3H, d, 16-H), 1.56 (1H, dd, 2″-H_{ax}), 1.65 (1H, ddd, 7-H), 1.78 (1H, br t, 6-H), 2.21 (1H, d, 2″-Heq), 2.26 (1H, br d, 2-H), 2.56 (6H, s, –$N(CH_3)_2$), 2.79 (1H, dd, 2-H), 2.99 (1H, d, 4″-H), 3.16 (1H, dd, 2′-H), 3.25 (3H, s, 3″-OCH_3), 3.29 (1H, dd, 4-H), 3.47 (1H, t, 4′-H), 3.60 (3H, s, 4-OCH_3), 3.89 (1H, br d, 5-H), 4.48 (1H, dq, 5″-H), 4.50 (1H, d, 1′-H), 4.62 and 4.70 (each 1H, 2×d, 4″-OCH_2Ph), 4.85 (1H, ddq, 15-H), 4.89 (1H, d, 1″-H), 5.09 (1H, br d, 3-H), 6.21 (2H, m, 12-H and 13-H), 6.34 (1H, d, 10-H), 7.34 (5H, m, Ph), 7.38 (1H, dd, 11-H), 9.52 (1H, br s, 18-H).

9-Dehydro-1″-*epi*-3″-*O*-methyl-4″-*O*-(3-methylbutyl)-3-*O*-propionylleucomycin V (**50**)

Reaction of **40** gave **50** in 79% yield by a similar procedure to **44**.

MP 93~99°C; $[\alpha]_D^{13}$ +10° (*c* 1.0, MeOH); SI-MS *m/z* 840 (MH^+); ^{1}H NMR δ 0.89 (6H, d, –CH $(CH_3)_2$), 1.14 (3H, t, 3-$OCOCH_2CH_3$), 1.19 (3H, d, 19-H), 1.23 (3H, d, 6′-H), 1.25 (3H, s, 3″-CH_3), 1.25 (3H, d, 6″-H), 1.29 (3H, d, 16-H), 1.33 (1H, dd, 2″-H_{ax}), 1.49 (2H, m, 4″-OCH_2CH_2–), 1.62 (1H, ddd, 7-H), 1.70 (1H, m, –$CH(CH_3)_2$), 1.80 (1H, br t, 6-H), 2.16 (1H, dd, 2″-H_{eq}), 2.26 (1H, br d, 2-H), 2.44 and 2.60 (each 1H, 2×dq, 3-$OCOCH_2CH_3$), 2.50 (6H, s, –$N(CH_3)_2$), 2.74 (1H, d, 4″-H), 2.78 (1H, dd, 2-H), 2.79 (1H, br dd, 17-H), 3.21 (1H, dd, 2′-H), 3.27 (3H, s, 3″-OCH_3), 3.28 (1H, dd, 4-H), 3.37 (1H, t, 4′-H), 3.56 and 3.62 (each 1H, 2×dt, 4″-OCH_2–), 3.59 (3H, s, 4-OCH_3), 3.81 (1H, dq, 5″-H), 3.90 (1H, br d, 5-H), 4.46 (1H, d, 1′-H), 4.79 (1H, dd, 1″-H), 4.85 (1H, ddq, 15-H), 5.10 (1H, br d, 3-H), 6.22 (2H, m, 12-H and 13-H), 6.33 (1H, d, 10-H), 7.37 (1H, dd, 11-H), 9.56 (1H, br s, 18-H).

2′-*O*-Acetate of **44**

To a stirred solution of **44** (18.0 mg) in dry CH_3CN (3.6 ml) was added at room temperature Ac_2O (4.2 μl). After stirring at 30°C for 16 hours, 0.13 M NH_4OH (0.34 ml) was added to the resulting solution, which was allowed to stand at room temperature for 20 minutes. Evaporation gave a residue which was extracted with $CHCl_3$ (9.0 ml) and the organic layer was washed with saturated aqueous $NaHCO_3$ and brine. This was dried and concentrated to afford the 2′-*O*-acetate of **44** (18.2 mg, 96%) as a colorless solid: MP 92~97°C; $[\alpha]_D^{18}$ −15° (*c* 1.0, PhH); EI-MS *m/z* 881 (M^+); ^{1}H NMR δ 0.88 (6H, d, –$CH(CH_3)_2$), 1.13 (3H, d, 6′-H), 1.14 (3H, t, 3-$OCOCH_2CH_3$), 1.20 (3H, d, 6″-H), 1.20 (3H, d, 19-H), 1.22 (3H, s, 3″-CH_3), 1.28 (3H, d, 16-H), 1.50 (1H, dd, 2″-H_{ax}), 1.55 (1H, ddd, 7-H), 1.69 (1H, m, –$CH(CH_3)_2$), 2.03 (3H, s, –$COCH_3$), 2.20 (1H, d, 2″-H_{eq}), 2.25 (1H, br d, 2-H), 2.42 (6H, s, –$N(CH_3)_2$), 2.64 (1H, t, 3′-H), 2.73 (1H, dd, 2-H), 2.74 (1H, d, 4″-H), 3.17 (1H, t, 4′-H), 3.20 (1H, dd, 4-H), 3.24 (3H, s, 3″-OCH_3), 3.26 (1H, dq, 5′-H), 3.50 (3H, s, 4-OCH_3), 3.58 and 3.64 (each 1H, 2×dt, 4″-OCH_2–), 3.90 (1H, br d, 5-H), 4.42 (1H, dq, 5″-H), 4.57 (1H, d, 1′-H), 4.76 (1H, d, 1″-H), 4.83 (1H, ddq, 15-H), 4.88 (1H, dd, 2′-H), 5.08 (1H, br d, 3-H), 6.20 (2H, m, 12-H and 13-H), 6.34 (1H, d, 10-H), 7.35 (1H, dd like, 11-H), 9.53 (1H, br s, 18-H).

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