New Dihydro and Tetrahydro Derivatives of Desmycosin
III. The Opening of Oxirane Ring of 12,13-Epoxydesmycosin

AMALIA NARANDA*, NEVENKA LOPOTAR and ŽELJKO KELNERIĆ

PLIVA Research Institute,
Prilaz baruna Filipovića 25, 10000 Zagreb, Croatia

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Opening the oxirane ring of 12,13-epoxydesmycosin dimethylacetal (**1**) by catalytic hydrogenation gave the 10,11-dihydro-12,13-epoxy derivative (**3**) as the main product. Reductive oxirane cleavage was accomplished with dissolved metal (Zn) giving the 10,13-dihydro-13-hydroxy compound (**6**). Mild acid hydrolysis of **6** gave expected 10,13-dihydro-13-hydroxydesmycosin (**8**), but hydrolysis of **3**, under the same conditions, gave three tautomeric desepoxy products.

The family of naturally occuring 16-membered macrolide antibiotics with an epoxyenone partial structure in the macrolactone was enlarged by synthetically prepared 12,13-epoxy derivatives.[1] Reductive opening of the oxirane ring of maridomycin II (belonging to the epoxyenol group of 16-membered macrolides) by catalytic hydrogenation was accomplished together with reduction of the C_{10}-C_{11} double bond giving the 13-hydroxy-10,11,12,13-tetrahydro compound.[2] Subjected to mild acid hydrolysis, maridomycin II gave a complex of diol compounds, composed of at least two isomers and another diol, as a result of ring opening and allylic rearrangement. An attempt to cleave the oxirane ring of rosaramycin (belongs to epoxyenone group of 16-membered macrolides) by catalytic hydrogenation gave, contrary to maridomycin II, only the 10,11-dihydro derivative with preserved 12,13-epoxy structure.[3] Reductive opening of the oxirane of naturally occuring macrolides such are deltamycin or angolamycin was performed by microbial deepoxidation[4] and with dissolving metals[5] giving enol type of derivatives at the C-11, C-12 position, which spontaneously were converted to geometric isomers. Macrolides with a C-12 methyl substituent could not be isomerized because of the absence of the hydrogen at C-12. Erythromycin, representative of 14-membered macrolides was easily converted into 6, 9 or 9, 12 cyclic hemiacetal tautomers in non-aqueous or aqueous solutions[6] or in acidic conditions to 8,9-anhydro derivatives[7].

In the preceding paper[8] we described the synthesis and structure-activity relationship of 10,11,12,13-tetrahydro derivatives of tylosin.

Now, we wish to report our investigations on the cleavage of the oxirane ring of 12,13-epoxydesmycosin, the structural and antimicrobial evaluation of the resultant dihydro and tetrahydro compounds, and structure-activity relationships.

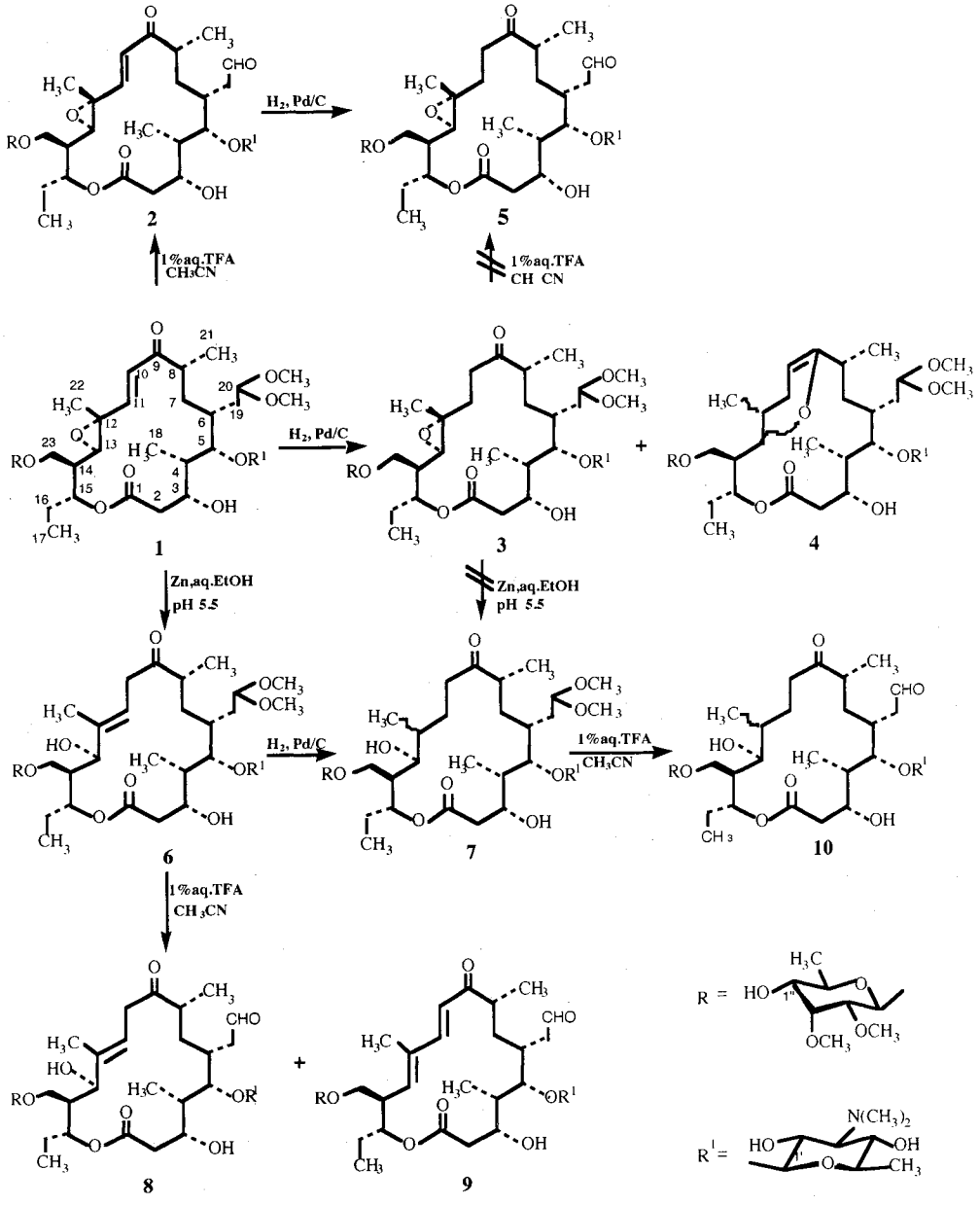
Results and Discussion

Synthesis of 12,13-epoxydesmycosin dimethylacetal (**1**) and its unprotected derivative (**2**) was performed according to the known procedures[1], partially modified in our laboratory.

The change of absorption in UV spectrum and ^{1}H-NMR spectrum of **1** with upfied shifts of H-11, H-14, H-22, especially of H-13 (δ 3.17) in comparison with those of desmycosin confirmed the disappearance of double bond C_{12}-C_{13}. The accordance of $J_{13,14}$ (=9.7 Hz) and $J_{14,15}$ (=9.9 Hz) values with those of other 12,13-epoxy derivatives[9,10] indicates *trans* configuration of H-13 and H-14 as depicted in Fig. 1. This assumption was supported by strong cross peaks of H-11/H-13 and H-13/H-15 in the 2D NOESY spectra.

Catalytic hydrogenation of **1** was performed in ethanol in the presence of palladium on charcoal. Two products (**3**, **4**) (Fig. 1) were obtained in a 5:1 ratio.[11] The disappearance of enone absorption at about 234 nm in the UV spectrum indicated reduction of the C_{10}-C_{11} double bond. Further evidence was obtained by NMR and mass spectra. In the ^{13}C-NMR spectra (Table 1), C-9 shifted downfield to 212.3 ppm, C-10 and C-11 shifted upfield to the 28~35 ppm region, which confirmed hydrogenation of the C_{10}-C_{11} double bond. Preserved singlet at 59.3 ppm and upfield-shifted doublet at 58.3 ppm confirmed the oxirane ring of the main product (**3**). FAB-MS of **3** with its molecular ion peak at *m/z* 836 (MH^+) confirmed the addition of 1 mol of

Fig. 1. Synthesis of dihydro and tetrahydro derivatives of desmycosin.



hydrogen. The minor product **4** with its molecular ion at *m/z* 820 suggested absorption of 2 moles of hydrogen with subsequent elimination of water. NMR spectra contributed to the interpretation of its structure. The absence of a characteristic carbonyl singlet in the NMR spectra in the 200~214 ppm region, a new singlet at 158.6 ppm (^{13}C-NMR spectra) and transformation of the H-22 singlet into an upfield shifted doublet at 0.93 ppm (^{1}H-NMR spectra) is attributed to an internal enol ether structure, suggesting the 9,10-anhydro-9,13-hemiacetal structure for minor compound **4**. Catalytic hydrogenation of **2** gave the 10,11-dihydro compound **5** (*m/z* 790 (MH^+)) as a major product.

Unsuccessful opening of the oxirane ring of **1** or **2** by catalytic hydrogenation was overcome with Zn reduction.[12] Treatment of **1** or **2** with zinc powder in a pH range of 5.0~5.5 gave **6** and **8**, respectively, compounds with molecular ion peaks at *m/z* 836 and *m/z* 790, respectively. Compound **8** was prepared also by hydrolysis of **6**. The ^{13}C-NMR spectrum of **6** with a singlet at 211.4 ppm, attributed to C-9 with an adjacent methylene group, a new doublet at 76.5 ppm attributed to C-13 and a singlet at 139.7 ppm and doublet at 117.3 ppm, attributed to the C_{11}-C_{12} double bond, confirmed that cleavage of the oxirane had occured with allylic rearrangement, giving 10,13-dihydro-13-hydroxy-

Table 1. ^{13}C-NMR chemical shifts[a] of aglycon part[b] of dihydro and tetrahydro desmycosin derivatives.

C	Compounds												
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
1	173.3	172.9	170.3	169.9	170.3	173.1	173.2	172.5	173.5	173.2	170.5	171.5	172.8
2	39.5	39.5	40.4	40.3	40.4	39.3	40.1	39.5	39.4	40.2	41.7	39.1	38.8
3	70.6	70.5	67.9	71.5	67.8	70.7	ND	70.6	67.5	ND	67.8	ND	ND
4	40.8	40.9	39.0	ND	39.1	41.1	ND	41.2	40.5	ND	ND	ND	ND
5	81.8	80.9	83.0	82.4	80.9	80.6	84.8	80.5	81.0	81.5	81.7	81.1	81.8
6	33.1	31.7	32.3	33.3	31.2	34.3	34.3	31.7	31.5	33.1	33.4	ND	ND
7	31.1	31.8	31.7	30.1	30.5	32.1	33.0	31.8	31.6	31.6	33.1	31.2	32.3
8	45.1	45.1	42.6	35.6	42.6	45.5	42.8	45.5	44.7	42.8	39.4	40.0	42.5
9	200.3	200.2	212.3	158.6	212.2	211.4	215.2	211.3	203.2	215.0	113.3	114.6	214.4
10	122.8	122.8	33.9	93.0	33.9	34.0	36.2	33.9	118.2	36.3	34.2	35.9	34.1
11	151.1	151.0	29.0	37.2	28.9	117.3	34.5	117.4	148.0	34.5	29.6	42.3	29.7
							29.8			29.5			
12	59.5	59.4	59.3	28.6	59.3	139.7	38.8	139.6	134.6	38.7	86.4	87.4	73.0
							29.8			29.8			
13	64.3	64.2	58.3	77.1	58.3	76.5	73.3	76.6	143.2	73.3	75.1	79.0	86.6
							72.7			72.5			
14	43.6	43.5	40.5	39.2	40.6	44.0	43.2	43.9	45.1	43.4	44.3	42.8	42.6
15	73.8	73.8	72.5	73.9	72.5	74.2	75.9	74.2	75.2	75.8	75.0	76.9	74.8
16	24.7	24.8	24.7	24.1	24.7	25.0	24.5	25.1	25.5	24.5	25.9	22.4	26.0
17	9.3	9.2	9.1	9.9	9.1	8.6	9.9	8.5	9.7	9.9	9.7	10.5	9.8
18	9.2	9.2	7.8	7.4	7.9	9.0	7.9	9.0	9.0	9.1	8.7	8.2	7.4
19	33.1	43.7	31.5	31.5	43.8	32.1	32.7	43.7	43.7	44.7	45.5	46.6	45.3
20	102.2	202.7	103.9	102.8	202.4	102.2	103.6	202.7	202.7	202.5	203.5	203.0	203.0
21	17.9	17.8	16.7	17.2	16.8	18.0	17.3	18.1	17.4	17.4	17.7	17.7	17.6
22	15.1	15.0	18.4	17.2	18.4	12.5	20.1	12.4	13.0	20.2	16.6	22.2	24.5
							15.9			15.9			
23	67.3	67.4	66.5	64.2	66.5	66.2	66.6	66.3	69.0	66.5	66.3	64.1	66.4

[a] δ values in ppm downfield of TMS. Spectra were taken in $CDCl_3$ at 75 MHz as determined from ^{1}H-^{13}C 2D heteronuclear shift correlated experiments.

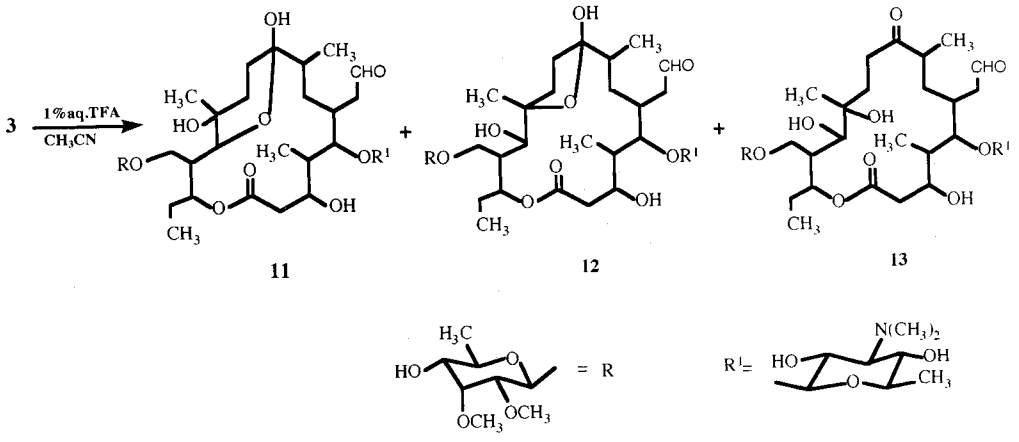
[b] There are no significant changes in sugar part of molecule.

desmycosin. The cross peak between H-11 and H-13 in the 2D NOESY spectra of **6** and **8**, and the absence of NOE H-11/H-22 implied *trans* configuration of the C_{11}-C_{12} double bond. From the magnitude of the coupling constante $J_{13,14}$ (9.7 Hz) *trans* disposition of H-13 and H-14 was deduced, indicating that opening of the oxirane ring proceeded with retention of the configuration at C-13. NOE's of H-13/H-15 and H-13/H-11 support the configuration shown on the Fig. 1. Catalytic hydrogenation of **6** gave a mixture of two isomeric 13-hydroxy-10,11,12,13-tetrahydro compounds **7** (MH^+, *m/z* 838). Because of difficulties in separation (very close Rf values), the proportion of isomers (approximatively 3 : 2) was deduced from quantitative TLC and NMR spectra. ^{13}C-NMR and heteronuclear ^{1}H-^{13}C 2D NMR spectra of chromatographically separated isomers (purity 90%), significantly differ in the chemical shifts C-12 and C-22. The major, more polar isomer is characterised with strongly upfild shifted C-12 (29.8 ppm) and downfield shifted C-22 (20.1 ppm), being very similar to those of the 10,11,12,13-tetrahydrodesmycosin.[8] The other pair of characteristic chemical shifts at 38.8 ppm (C-12) and 15.9 ppm (C-22) is attributed to the minor isomer. In the NOESY spectrum of the major isomer, the cross peak between H-22 and H-14 confirmed their spatial proximity and consequently implied *cis* configuration of H-12 and H-13. An attempt to prepare tetrahydro compound **7** by reductive opening of oxirane ring of dihydro compound **3**, with Zn was unsuccessful.

Mild acid hydrolysis of **6** gave the expected compound **8** (MH^+, *m/z* 790) and about 30% of compound **9** with a strong absorption at 282 nm in its UV spectrum. Molecular ion of the minor product at *m/z* 772, and spectral data identical in all respects to an authentic sample of desmycosin suggest, that during hydrolysis of acetal group, partial elimination of water occured giving desmycosin (**9**). In the same conditions hydrolysis of **7** gave expected 13-hydroxy-10,11,12,13-tetrahydro-desmycosin isomers (**10**).

In the procedure for the preparation of 12,13-epoxy derivatives of tylosin, before the oxidation step, the aldehyde group is usually protected by acetalation.

Fig. 2. Hydrolysis of 10,11-dihydro-12,13-epoxy-desmycosin dimethylacetal (**3**).



Because of the anticipated next step (paper in preparation) we preserved the acetal in our investigation of oxirane ring cleavage. When we tried to hydrolyse the acetal group of **3** under mild acid conditions, as usual for 12,13-epoxy compounds (**1** to **2**), at least three isomeric diols were obtained as a result of oxirane ring opening by addition of water (Fig. 2). ^{13}C-NMR spectra indicated that these three tautomers have a 9,13-hemiacetal (**11**), 9,12-hemiacetal (**12**) and 9-carbonyl (**13**) structures.

In Vitro Activity

The antibacterial activity of new compounds **4**, **5**, **8**, **10**, **11** and **12** was compared with that of 12,13-epoxy compound (**2**) and desmycosin (Table 2). Dihydro compounds **5** and **8** show 1~3 times decreased antibacterial *in vitro* activity against *Staphylococcus aureus*, *Micrococcus flavus* and *Bacillus* strains in comparison with **2** and desmycosin, and the loss of activity against *Streptococcus* strains (except *S. epidermidis*). Tetrahydro compound **10** has somewhat better activity than corresponding the 13-hydroxy-dihydro compound **8**, but still decreased in comparison with **2** and desmycosin. Tetrahydro compounds **11** and **12** like compound **4**, having hemiketal structures, have negligible antibacterial activity. All new compounds are inactive against standard Gram (−) strains. They show insignificant activity against fresh clinical isolates of *Haemophilus influenzae* and are resistent to clinical isolates of *Streptococcus β-haemolyticus*.

Experimental

Physico-chemical Determination and Chromatography

^{1}H and ^{13}C-NMR spectra were recorded with a VARIAN-GEMINI 300. UV spectra were measured in methanol solution on a SP 8-100 PYE-UNICAM. Mass spectra (MS) were determined using the fast atom bombardment method with an Auto-Spec Q (VG Analytical) mass spectrometer. Thin layer chromatography (TLC) was performed on Silica-gel 60 F_{254} (Merck) in methylene chloride - methanol - ammonium hydroxide (90 : 9 : 1.5) (system E), (90 : 9 : 0.5) (system E_1), or ethyl acetate - methanol - ammonium hydroxide (85 : 10 : 5) (system EA) and column chromatography on Silica-gel 60, 230~400 mesh (Merck) in E or E_1 systems.

In Vitro Evaluation

Antibiotic susceptibility data given in Table 2 were obtained by microdilution methodology recommended by National Commitee for Clinical Laboratory Standards (NCCLS); Methods for Dilution Antibacterial Susceptibility Tests for Bacteria that grow Aerobically (Second Ed.) Document M7-A2 Vol. 10, No. 8, April 1990.

Preparation of 12,13-Epoxy-desmycosin Dimethylacetal (1)

a) Oxidation

Desmycosin dimethylacetal (20.5 g, 0.025 M) was dissolved in methylene chloride (200 ml), *m*-ClPBA (71%) (24 g, 0.1 M) dissolved in methylene chloride (240 ml) was added. The reaction solution was stirred 7 hours at room temperature, 1000 ml of H_2O was added

Table 2. Antibacterial *in vitro* activity of dihydro and tetrahydro desmycosin derivatives.

	MIC (mcg/ml)							
	Desmycosin	**2**	**4**	**5**	**8**	**10**	**11**	**12**
Staphylococcus aureus ATCC 6538	1	2	128	8	8	8	16	16
Micrococcus flavus ATCC 10240	2	4	32	8	8	4	8	8
Bacilllus subtilis ATCC 6633	1	1	32	8	4	4	8	16
Bacillus cereus ATCC 11778	1	2	32	8	8	8	16	32
Bacillus pumilus NCTC 8241	1	2	16	4	8	2	16	16
Streptococcus faecium ATCC 8043	2	4	64	16	32	16	16	64
Streptococcus epidermidis ATCC 12228	2	2	16	4	8	4	2	8
Streptococcus "A" J-21[a]	1	4	128	32	32	32	32	64
Streptococcus "B" J-22[a]	2	2	128	32	32	32	32	64
Gram (−) microorganisms[b]	128	128	128	128	128	128	128	128
Haemophilus influenze[c]	8	8	64	32	64	64	64	64
Streptococcus β-haemolyticus[d]	128	128	128	128	128	128	128	128

[a] Standard from PLIVA culture collection.
[b] *Pseudomonas aeruginosa* NCTC 10490, *Salmonella panama* F 6117, *E. coli* ATCC 10536, *E. coli* (Lac.$^+$) F6131, *E. coli* (Lac$^-$) F 6130.
[c] MIC_{50} of 24 tested fresh clinical isolates.
[d] MIC_{90} of 24 tested fresh clinical isolates.

and solution alkalinized to pH 8.5. After 30 minutes organic layer was separated, washed (1000 ml of saturated solution of $NaHCO_3$, 1000 ml of brine), dried with $CaCl_2$ and evaporated to dryness.

b) Reduction of *N*-oxide

Crude pale yellow product (16.2 g) was dissolved in ethylacetate (250 ml), Ph_3P (29.8 g, 0.114 M) was added and and reaction mixture stirred in N_2 stream at the reflux temperature for 2 hours. After evaporation of EA, MeOH was added (150 ml), obtained precipitate separated by filtration and reaction mixture evaporated to oily product. This crude product was dissolved in toluene (150 ml), H_2O (300 ml) was added and reaction mixture acidified to pH 3.0. After repeated washings with toluene (2 × 100 ml), water layer was alkalinized to pH 8.5 and extracted with $CHCl_3$ (2 × 150 ml). $CHCl_3$ extracts were dried, evaporated to dryness and purified by flash chromatography (solvent system E_1).

Yield: 10.1 g (48.3%) of **1**

^{1}H-NMR ($CDCl_3$) δ 6.57 (1H, d, $J_{10,11}$ = 15.6 Hz, H-11), 6.43 (1H, d, $J_{10,11}$ = 15.6 Hz, H-10), 5.31 (1H, dt, $J_{14,15}$ = 9.9 Hz, H-15), 4.57 (1H, d, 1‴), 4.55 (1H, t, H-20), 4.28 (1H, d, 1′), 3.63 (3H, s, 3‴OMe), 3.56 (3H, s, 2‴OMe), 3.31 (3H, s, 20-OMe), 3.24 (3H, s, 20-OMe), 3.17 (1H, d, $J_{13,14}$ = 9.7 Hz, H-13), 2.52 (6H, s, NMe_2), 1.43 (3H, s, 12-Me).

Preparation of Dihydro and Tetrahydro Desmycosin Derivatives: General Methods

Catalytic hydrogenation:

Desmycosin derivative **1**, **2** or **6** (1 g) was dissolved in ethanol (75 ml), 10% Pd/C (5% w/w) was added and hydrogenated 8 hours at ambient temperature. The catalyst was separated, ethanol evaporated to dryness and crude product chromatographed on silica gel column using solvent system E or E_1.

Compound **1** (3 g) yielded 1.56 g (52%) of **3**, Rf (E) 0.47; FAB-MS *m/z* 836 (MH^+); ^{1}H-NMR ($CDCl_3$) δ 4.57 (1H, d, 1‴), 4.55 (1H, t, H-20), 4.25 (1H, d, 1′), 3.64 (3H, s, 3‴OMe), 3.51 (3H, s, 2‴OMe), 3.38 (3H, s, 20-OMe), 3.22 (3H, s, 20-OMe), 2.52 (6H, s, NMe_2), 1.33 (3H, s, 12-Me) and 0.27 (9%) of **4**, Rf (E) 0.25; FAB-MS *m/z* 820 (MH^+); ^{1}H-NMR ($CDCl_3$) δ 4.57 (1H, d, 1‴), 4.52 (1H, t, H-10), 4.50 (1H, t, H-20), 4.25 (1H, d, 1′), 3.65 (3H, s, 3‴OMe), 3.55 (3H, s, 2‴OMe), 3.39 (3H, s, 20-OMe), 3.23 (3H, s, 20-OMe), 2.51 (6H, s, NMe_2), 0.93 (3H, d, 12-Me).

Compound **2** (2.4 g) yielded 1.3 g (54%) of **5**, Rf (E) 0.40; FAB-MS *m/z* 790 (MH^+); ^{1}H-NMR ($CDCl_3$) δ 9.65 (1H, s, H-20), 4.55 (1H, d, 1‴), 4.24 (1H, d, 1′), 3.64 (3H, s, 3‴OMe), 3.51 (3H, s, 2‴OMe), 2.51 (6H, s, NMe_2), 1.34 (3H, s, 12-Me).

Compond **6** (1.5 g) yielded 1.1 g of **7** (73%); Rf (EA) 0.49, Rf (E) 0.45 and 0.42; FAB-MS *m/z* 838 (MH^+); ^{1}H-NMR ($CDCl_3$) δ 4.57 (1H, d, 1‴), 4.55 (1H, t, H-20), 4.24 (1H, d, 1′), 3.65 (3H, s, 3‴OMe), 3.52 (3H, s, 2‴OMe), 3.38 (3H, s, 20-OMe), 3.22 (3H, s, 20-OMe), 2.51 (6H, s, NMe_2), 0.89 (3H, d, 12-Me).

Reductions with Zn:

Desmycosin derivative **1** or **2** (1 equiv) was dissolved in ethanol (17 ml) and water (35 ml) containing am-

monium chloride (0.5 equiv) and Zn powder (10 equiv) in portions was added. The reaction mixture was stirred at room temperature until TLC indicated the completion of reaction (5~6 hours). Zn was separated by filtration, the reaction solution was evaporated to half volume, alkalinized to pH-range of 8.0~8.5 and extracted with $CHCl_3$. The crude pruduct was chromatographed on a silica gel column using solvent system E.

Compound **1** (10.0 g) yielded 6.5 g (65%) of **6**; Rf (E) 0.45, Rf (EA) 0.41; FAB-MS *m/z* 836 (MH^+); ^{1}H-NMR ($CDCl_3$) δ 5.78 (1H, d, H-11, 4.57 (1H, d, 1‴), 4.56 (1H, t, H-20), 4.24 (1H, d, 1′), 3.64 (3H, s, 3‴OMe), 3.51 (3H, s, 2‴OMe), 2.52 (6H, s, NMe_2), 1.68 (3H, s, 12-Me).

Compound **2** (10.0 g) yielded 6.3 g (63%) of **8**; Rf (E) 0.3; FAB-MS *m/z* 790 (MH^+); ^{1}H-NMR ($CDCl_3$) δ 9.61 (1H, s, H-20), 5.77 (1H, d, H-11), 4.57 (1H, d, 1‴), 4.23 (1H, d, 1′), 3.64 (3H, s, 3‴OMe), 3.51 (3H, s, 2‴OMe), 2.52 (6H, s, NMe_2), 1.69 (3H, s, 12-Me).

Hydrolysis of dimethylacetal group:

Compound **1**, **3**, **6** or **7** (1 g) was dissolved in the mixture of acetonitrile (10 ml) and 1% trifluoroacetic acid in water (15 ml) and stirred at room temperature for 2 hours. The reaction solution was alkalinized to pH 8.5, extracted with $CHCl_3$, evaporated to dryness and chromatographed on a silica gel column in solvent system E.

Compound **1** (5 g) yielded 3.5 g (74%) of **2**; Rf (E) 0.45; FAB-MS *m/z* 788 (MH^+); ^{1}H-NMR ($CDCl_3$) δ 9.65 (1H, s, H-20), 6.61 (1H, d, H-11), 6.46 (1H, d, H-10), 4.57 (1H, d, 1‴), 4.23 (1H, d, 1′), 3.64 (3H, s, 3‴OMe), 3.51 (3H, s, 2‴OMe), 2.51 (6H, s, NMe_2), 1.44 (3H, s, 12-Me).

Compound **3** (3 g) yielded 0.9 g (32%) of **11**; Rf (E) 0.37, FAB-MS *m/z* 808 (MH^+); ^{1}H-NMR ($CDCl_3$) δ 9.68 (1H, s, H-20), 4.57 (1H, d, 1‴), 4.24 (1H, d, 1′), 3.64 (3H, s, 3‴OMe), 3.50 (3H, s, 2‴OMe), 2.52 (6H, s, NMe_2), 1.42 (3H, s, 12-Me) and 0.7 g of a mixture of compounds **12** and **13**; Rf (E) 0.31; FAB-MS *m/z* 808 (MH^+).

Compound **6** (5 g) yielded 1.65 g (35%) of **8**; Rf (E) 0.35; FAB-MS *m/z* 790 (MH^+); ^{1}H-NMR ($CDCl_3$) δ 9.62 (1H, s, H-20), 5.78 (1H, d, H-11), 4.57 (1H, d, 1‴), 4.24 (1H, d, 1′), 3.64 (3H, s, 3‴OMe), 3.51 (3H, s, 2‴OMe), 2.52 (6H, s, NMe_2), 1.68 (3H, s, 12-Me) and 1.63 g (35%) of **9**; Rf (E) 0.40; FAB-MS *m/z* 772 (MH^+); ^{13}C-NMR ($CDCl_3$) δ 203.2 (s, C-9), 202.7 (d, C-20), 173.5 (s, C-1), 148 (d, C-11), 143.2 (d, C-13), 134.6 (s, C-12), 118.2 (d, C-10); ^{1}H-NMR ($CDCl_3$) δ 9.60 (1H, s, H-20), 7.29 (1H, d, H-11), 6.25 (1H, d, H-10), 5.87 (1H, d, H-13), 4.55 (1H, d, 1‴), 4.24 (1H, d, 1′), 3.64 (3H, s, 3‴OMe), 3.52 (3H, s, 2‴OMe), 2.51 (6H, s, NMe_2), 1.72 (3H, s, 12-Me).

Compound **7** (2 g) yielded 1.42 g (75%) of **10**; Rf (EA) 0.38; FAB-MS *m/z* 792 (MH^+); ^{1}H-NMR ($CDCl_3$) δ 9.65 (1H, s, H-20), 4.57 (1H, d, 1‴), 4.25 (1H, d, 1′), 3.65 (3H, s, 3‴OMe), 3.52 (3H, s, 2‴OMe), 2.51 (6H, s, NMe_2), 0.90 (3H, d, 12-Me).

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