PHOTOCHEMICALLY OBTAINED *N*-DEMETHYL DERIVATIVES OF ANTHRACYCLINES

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(Received for publication April 8, 1992)

New *N*-monodemethyl and *N*-didemethyl derivatives were obtained from seven *N*-dimethylamino sugar (rhodosamine)-containing anthracyclines by photochemical reaction and their *in vitro* bioactivities against L1210 cell culture were compared with those of their *N*-dimethyl parent compounds. *N*-Demethyl derivatives obtained from betaclamycin T (7-*O*-rhodosaminyl-β-rhodomycinone) were much more cytotoxic while those from the other six antibiotics were rather less active as compared with their parent compounds. The *N*-demethylation also gave a considerably greater decrease in the inhibitory activity on RNA synthesis as compared to DNA synthesis, so that the *N*-demethyl derivatives showed smaller IC_{50} ratios on DNA/RNA than their parent compounds.

Recently we have isolated the intensely potent anthracycline antibiotic oxaunomycin from the culture broth of a blocked mutant of a daunorubicin producer[1]. It was identified as 7-*O*-daunosaminyl-β-rhodomycinone, and found to exhibit about a 30-fold greater cytotoxicity against L1210 cell culture than its *N*-dimethyl derivative 7-*O*-(*N*-dimethyldaunosaminyl-β-rhodomycinone; betaclamycin T). This finding led us to suppose that *N*-demethylation of anthracycline aminosugars would improve antitumor potency. Accordingly, *N*-demethylation of rhodosamine (*N*-dimethyldaunosamine)-containing anthracyclines would be a target for improved therapeutic efficacy of antitumor anthracycline antibiotics. As naturally occurring *N*-demethyl anthracyclines are now limited to a daunorubicin group of antibiotics, we tried to prepare them by chemical *N*-demethylation of rhodomycin group of antibiotics which contained rhodosamine as a dimethylamino sugar.

We have found that anthracycline antibiotics aclarubicin yields *N*-monodemethyl (MA144 L1) and *N*-didemethyl (MA144 K1) derivatives when it was exposed to light in ether or chloroform solutions[2]. As shown in Fig. 1, the photochemical *N*-demethylation proceeds stepwise first by detachment of one methyl and then by that of remainding one on exposure to light. We applied this photochemical reaction to prepare *N*-demethyl derivatives from *N*-dimethyl compounds.

The purpose of this study was to obtain such *N*-demethyl derivatives from the rhodomycin groups of seven antibiotics, betaclamycin T[3] (**1a**), obelmycin A[4] (**2a**), yellamycins A and C[5] (**3a** and **4a**), alldimycins A and C[6] (**5a** and **6a**), and iremycin[7] (**7a**), and assess the biological activity *in vitro* against L1210 cell culture. As a result, we prepared the fourteen *N*-demethyl derivatives (**1b**～**7b** and **1c**～**7c**) shown in Table 1, among which eleven were structurally identified as new compounds.

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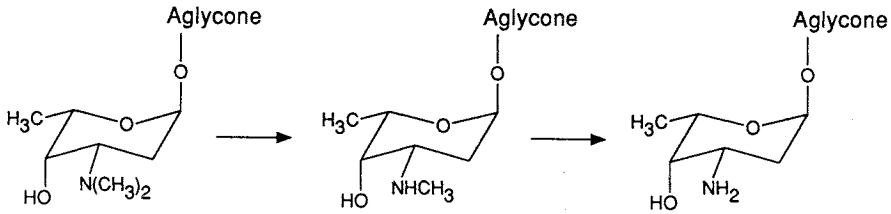
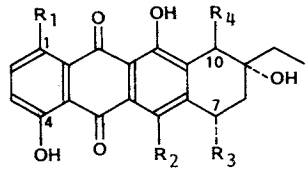
Fig. 1. Photochemical *N*-demethylation or rhodosamine moiety.



L-Rhodosamine (RN) — *N*-Monomethyl-L-daunosamine (mDN) — L-Daunosamine (DN)

Table 1. Structures of seven parent compounds and their *N*-demethyl products.



Compound[a]		R_1	R_2	R_3	R_4
Betaclamycin T	(**1a**)	H	OH	RN[b]	OH
LB-1	(**1b**)	H	OH	mDN[b]	OH
LB-2	(**1c**)	H	OH	DN[b]	OH
Obelmycin A	(**2a**)	OH	OH	RN	OH
ELB-1	(**2b**)	OH	OH	mDN	OH
ELB-2	(**2c**)	OH	OH	DN	OH
Yellamycin A	(**3a**)	H	H	RN	OH
LCS-1	(**3b**)	H	H	mDN	OH
LCS-2	(**3c**)	H	H	DN	OH
Yellamycin C	(**4a**)	H	H	OH	RN
LC-1	(**4b**)	H	H	OH	mDN
LC-2	(**4c**)	H	H	OH	DN
Alldimycin A	(**5a**)	OH	H	RN	OH
ALC-1	(**5b**)	OH	H	mDN	OH
ALC-2	(**5c**)	OH	H	DN	OH
Alldimycin C	(**6a**)	OH	H	OH	RN
ELC-1	(**6b**)	OH	H	OH	mDN
ELC-2	(**6c**)	OH	H	OH	DN
Iremycin	(**7a**)	H	OH	H	RN
IRC-1	(**7b**)	H	OH	H	mDN
IRC-2	(**7c**)	H	OH	H	DN

[a] **a**: Parent compounds, **b** and **c**: Products.
[b] RN, mDN and DN: See Fig. 1.

Results and Discussion

Photochemical *N*-Demethylation

The photochemical conditions for *N*-demethylation were optimized using betaclamycin T as substrate and a high pressure Hg lamp with broad spectra from 260 to 500 nm as light source. Effect of solvent in which the substrate was dissolved was first examined. Seventeen solvents ($CHCl_3$, CH_2Cl_2, CCl_4, MeOH, Me_2CO, CH_3CN, *n*-BuOH, 1,2-dichloroethane, toluene, EtOAc, dioxane, DMF, DMSO, ethyl ether, THF,

Table 2. Chromatographic data on parent compounds and their *N*-demethyl products.

Compound	HPLC Rt (minutes)	TLC Rf's		Compound	HPLC Rt (minutes)	TLC Rf's	
		System A	System B			System A	System B
1a	8.7	0.20	0.38	**4c**	5.9	0.13	0.13
1b	8.0	0.24	0.16	**5a**	6.8	0.15	0.32
1c	7.3	0.18	0.19	**5b**	6.3	0.20	0.13
2a	9.1	0.19	0.37	**5c**	5.9	0.18	0.15
2b	8.4	0.23	0.15	**6a**	6.4	0.13	0.28
2c	7.6	0.18	0.18	**6b**	5.9	0.18	0.10
3a	7.8	0.15	0.33	**6c**	5.5	0.14	0.13
3b	7.2	0.20	0.16	**7a**	17.9	0.23	0.42
3c	6.5	0.18	0.19	**7b**	15.2	0.27	0.22
4a	6.9	0.12	0.29	**7c**	12.5	0.24	0.25
4b	6.4	0.17	0.11				

methylethylketone and 0.1 M AcOH) were tested and the *N*-demethylation was checked by direct TLC analysis. Among the solvents tested, $CHCl_3$, CH_2Cl_2 and CCl_4 catalyzed the photochemical *N*-demethylation. $CHCl_3$ was the best solvent and catalyzed photochemical production of both *N*-monodemethyl and *N*-didemethyl derivatives of betaclamycin T in similar yield. No other solvents catalyzed *N*-demethylation. DMF and DMSO as solvent caused a rapid undesirable degradation with decoloration, and an unknown orange compound was the main product in 1,2-dichloroethane and methylethylketone. Addition of a small volume of MeOH was needed to obtain the photochemical reaction and to improve the solubility.

In practice, a solution (1 mg/ml) of each parent antibiotic dissolved in $CHCl_3$ - MeOH (10 : 1 ~ 100 : 1) was exposed to the Hg lamp for 1 ~ 2 hours and followed by TLC and HPLC analyses. Two major compounds which showed smaller Rf values (solvent system B) than the parent compound were produced in all reaction mixtures and were designated in the order of decreasing retention time as follows: LB-1 (**1b**) and LB-2 (**1c**) from betaclamycin T (**1a**); ELB-1 (**2b**) and ELB (**2c**) from obelmycin A (**2a**); LCS-1 (**3b**) and LCS-2 (**3c**) from yellamycin A (**3a**); LC-1 (**4b**) and LC-2 (**4c**) from yellamycin C (**4a**); ALC-1 (**5b**) and ALC-2 (**5c**) from alldimycin A (**5a**); ELC-1 (**6b**) and ELC-2 (**6c**) from alldimycin C (**6a**); IRC-1 (**7b**) and IRC-2 (**7c**) from iremycin (**7a**). The total yield of two products was about 60 ~ 70% in the best case.

Isolation and purification was carried out by repeated preparative TLC on Kieselgel PF_{254} plate (E. Merck Co.) using solvent systems A and B. The first alkaline solvent (B) served to separate mainly two products as a mixture from the parent compound. The second solvent (A) was used to separate the two derivatives from each other. Data on their HPLC and TLC are shown in Table 2. All products thus obtained were more than 95% pure as determined by HPLC.

Identification of *N*-Demethyl Derivatives

N-Demethyl derivatives were structurally identified on the basis of their MS, ^1H and ^{13}C NMR analyses and TLC analysis of aglycone and sugar after acid hydrolysis. TLC analysis of aglycone was carried out using two solvent systems. The result revealed that aglycones of all the photochemically obtained products were the same as those of the corresponding parent compounds. UV and visible light absorption spectra of the products in 90% MeOH solution were also similar to those of the parent compounds. On

Table 3. ^{13}C NMR chemical shift assignments of **1b**~**7b** and **4c**~**7c**.

Carbon	**1b**	**2b**	**3b**	**4b**	**4c**	**5b**	**5c**	**6b**	**6c**	**7b**	**7c**
1	119.77	157.85*	119.66	119.70	119.53	158.28*	159.02*	158.25*	156.70	119.33	119.29
2	137.24	129.73	137.05	137.14	136.88	130.13*	130.80*	130.01*	129.49	136.84	136.79
3	124.92	129.73	125.17	125.08	124.93	129.90*	130.40*	129.83*	124.93	124.24	124.21
4	162.56	158.00*	162.70	162.77	162.58	157.95*	158.55*	157.89*	156.70	162.25	162.19
4a	116.16	112.98	116.19	116.34	116.13	112.95*	113.94*	113.01*	113.95*	116.10	116.07
5	190.84	189.20	187.62	187.95	187.63	186.29	187.34	186.39	183.55	190.95	190.92
5a	112.20	112.35	132.12	132.79	132.58	132.51	133.00	133.07*	135.56	110.70	110.64
6	156.69	156.81	120.45	119.98	120.52	120.45	122.02	119.96	114.19	156.08	156.07
6a	135.09	135.17	143.26	150.01	149.30	144.17	147.72	150.42	143.84	136.56	136.58
7	71.08	71.34	73.80	67.00	67.59	74.08	74.89	66.96	66.69	20.85	20.76
8	32.58	32.58	33.76	37.55	36.53	33.98	35.17	37.72	37.27	26.84	26.50
9	72.37	72.69	72.47	72.78	72.73	72.89	69.41	72.79	71.99	71.32	71.20
10	66.07	66.05	66.65	70.68	70.85	66.48	66.53	70.66	74.02	70.69	70.52
10a	138.89	138.63	134.12	131.67	131.34	134.12	133.85	131.48*	131.84	140.89	140.92
11	157.39	157.32	162.27	161.89	161.74	162.59	162.91	161.78	157.74	157.65	157.60
11a	111.63	111.95	115.42	114.96	114.80	115.45	115.97	114.96	114.54	110.27	110.20
12	186.28	189.20	187.87	188.00	187.73	190.93	192.20	191.00	186.23	185.85	185.83
12a	133.55	112.98	133.28	133.59	133.34	112.82*	113.81*	112.87*	113.71*	133.72	133.69
13	30.05*	30.41	30.22*	31.84*	31.24	30.57*	31.31	31.84	31.06	30.93	30.98
14	6.52	6.60	6.56	6.63	6.45	6.65	6.77	6.67	6.63	6.48	6.39
1′	101.64	101.96	98.85	96.68	96.74	99.45	92.18	96.67	98.31	96.93	96.89
2′	30.30*	30.41	30.27*	30.89	33.65	30.47*	31.31	30.92	30.78	30.45	33.63
3′	54.28	54.34	54.10	54.16	46.38	54.18	48.63	54.20	47.34	53.97	46.14
4′	67.10	67.14	66.90	66.76	66.79	67.14	67.29	66.72	66.14	66.68	67.45
5′	67.59	67.95	67.45	67.80	70.54	67.99	68.19	67.85	66.86	67.00	70.35
6′	16.87	16.97	16.96	17.12	16.98	17.04	16.86	17.15	16.94	16.94	16.74
3′-NHMe	32.07	32.05	32.15	31.63*	—	32.01	—	31.72	—	31.90	—
Solvent	[a]	[c]	[a]	[c]	[b]	[c]	[d]	[c]	[e]	[b]	[a]

Spectra were measured at 100 MHz. Chemical shifts are expressed by δ (ppm) from internal TMS. Similar values asterisked may be exchangeable.

[a] $CDCl_3$-CD_3OD (10:1).
[b] $CDCl_3$-CD_3OD (20:1).
[c] $CDCl_3$-CD_3OD (2:1).
[d] AcOH-d_4.
[e] DMSO-d_6.

the other hand, the sugars were found to be *N*-monomethyl-L-daunosamine (Rf value; 0.26) for **1b**~**7b** and L-daunosamine (Rf value; 0.37) for **1c**~**7c** by direct comparison with the authentic samples on TLC.

The chemical shift assignments of ^1H and ^{13}C NMR spectra of the products were carried out by means of DEPT, ^1H-^1H and ^1H-^{13}C COSY. In ^1H NMR spectra, the signal of *N*-methylamino group at about 2.4 ppm which contained three protons was observed with **1b**~**7b**, but not with **1c**~**7c**. The chemical shifts of 3′-H of **1b**~**7b** shifted to lower field (2.7~2.9 ppm) by *N*-monodemethylation and those of **1c**~**7c** to further lower field (3.0~3.5 ppm) by removed of the remaining methyl group, although the other chemical shifts were similar for the parent compound and its *N*-demethyl derivatives. The chemical shift assignments of ^{13}C NMR spectra of new compounds are shown in Table 3. In ^{13}C NMR spectra, the chemical shifts of the aglycone moiety of the products were almost the same as those of the parent compounds, while those of the sugar moiety were different at C-3′ and the *N*-methyl amino group. In *N*-demethyl derivatives, the chemical shifts of both signals shifted to extremely down field, and a signal for the *N*-methyl amino group was not observed with **1c**~**7c**. Furthermore mass analysis of the products

Table 4. Inhibitory activities of parent compounds and their *N*-demethyl products on the growth and nucleic acid synthesis of murine leukemic L1210 cell culture.

Compound	IC_{50} (μg/ml)			DNA/RNA	Compound	IC_{50} (μg/ml)			DNA/RNA
	Growth	DNA synthesis	RNA synthesis			Growth	DNA synthesis	RNA synthesis	
1a	0.01	0.21	0.06	3.5	**5a**	0.05	0.92	0.47	2.0
1b	0.006	0.38	0.26	1.5	**5b**	0.087	1.86	1.36	1.4
1c	0.0003	0.29	0.68	0.4	**5c**	0.057	1.65	2.29	0.7
2a	0.001	0.58	0.14	4.1	**6a**	>1	3.2	3.0	1.1
2b	0.01	0.62	0.45	1.4	**6b**	>1	>10	>10	—
2c	0.005	1.00	0.78	1.3	**6c**	>1	>10	>10	—
3a	0.007	0.28	0.23	1.2	**7a**	0.15	0.80	0.80	1.0
3b	0.026	0.84	0.77	1.1	**7b**	>1	—	—	—
3c	0.006	0.55	4.00	0.1	**7c**	>1	—	—	—
4a	>1	5.0	3.9	1.3	**8**[a]	0.02	1.40	0.55	2.5
4b	>1	>10	>10	—					
4c	>1	>10	>10	—					

In the inhibition test for nucleic acid synthesis, L1210 cell culture (8×10^5 cells/ml) were exposed for 60 minutes to the drugs supplemented with ^{14}C-labeled uridine or thymidine (0.05 μCi/ml), and the incorporation of the radioisotopes into acid insoluble material was measured. For the growth inhibition test, L1210 cell culture (5×10^4 cells/ml) were exposed for 48 hours to the drugs and the viable cells were counted by Coulter counter. IC_{50} is expressed as a drug concentration required to inhibit by a 50% of control growth, and DNA and RNA syntheses of cultured L1210 cells.

[a] Doxorubicin used as reference.

supported that one methyl group and two methyl groups were lost in **1b**~**7b** and **1c**~**7c**, respectively.

From these findings the structures of photochemically obtained *N*-demethyl derivatives were determined as shown in Table 1. Among fourteen derivatives, eleven were new and three were known compounds. Thus, LB-2 (**1c**), ELB-2 (**2c**) and LCS-2 (**3c**) were identical to oxaunomycin[1], 1-hydroxyoxaunomycin[8] and 6-deoxyoxaunomycin[8], respectively.

Biological Activity

The cytotoxic activities of the parent compounds and their *N*-monodemethylated and *N*-didemethylated derivatives against leukemic L1210 cell culture were examined under continuous exposure and are shown in Table 4. In the case of betaclamycin T (β-rhodomycinone glycoside, **1a**), its *N*-monodemethylated derivative **1b** and *N*-didemethylated derivative **1c** exhibited much stronger cytotoxicity than parent compound **1a**. IC_{50} value (μg/ml) of **1b** and **1c** were 0.006 and 0.0003 and that of **1a** was 0.01. In this case, the cytotoxic activity was greatly increased by the *N*-demethylation. In all of the other cases with **2a** (β-isorhodomycinone glycoside), **3a** and **4a** (α-citromycinone glycosides), **5a** and **6a** (α_2-rhodomycinone glycosides) and **7a** (γ-rhodomycinone glycoside), however, the *N*-demethylation decreased the cytotoxic activity, contrary to our expectation. A decrease of the cytotoxicity by *N*-demethylation or the *vice versa* increment by *N*-methylation have been observed with many anthracycline antibiotics[9], *e.g.* aclarubicin and *N*-dimethylated daunorubicin and doxorubicin. This is the first time that *N*-nonmethyl compound **1c** has more potent cytotoxicity than *N*-dimethyl compound **1a**. Regarding their activity on nucleic acid synthesis in L1210 cell culture, all the *N*-demethylated compounds showed a marked decrease in the inhibition on RNA synthesis, but not on DNA synthesis. Therefore, they exhibited smaller IC_{50} ratios on DNA/RNA in comparison with *N*-dimethyl parent compounds although their IC_{50} values on DNA synthesis somewhat increased.

Experimental

General

MP's were determined on a Kofler hotstage microscope. UV spectra were recorded on a Hitachi EPS 3T and IR spectra (KBr pellet) on a Hitachi EPI-GS spectrophotometer. ^1H and ^{13}C NMR were recorded with a JEOL JNM-GSX400 spectrometer at 400 MHz and 100 MHz, respectively. Chemical shifts were expressed in δ values (ppm) with TMS as an internal standard and coupling constants were given in J (Hz). Mass spectra were recorded with a Hitachi M-80H spectrometer or JEOL JMS SX102A. Specific rotations were recorded on a Jasco DIP-181 Digital Polarimeter. TLC analyses were performed on Kieselgel 60 F_{254} (E. Merck).

Photochemical Reaction

A solution of a parent compound was exposed to a mercury lamp (UVL-400 HA, Riko Science Industry; distance: 8 cm) at 24°C. The reaction was checked by TLC using a developing solvents of $CHCl_3$-MeOH-H_2O-AcOH (40:10:0.4:0.2) (system A) and $CHCl_3$-MeOH-concd NH_4OH (40:10:0.1) (system B).

HPLC Analysis of the Products

Purity of the products was determined by HPLC using a Hitachi 655 liquid chromatographic apparatus with a reverse phase analytical column, A312 (ODS) (6.0 i.d. × 150 mm) (Yamamura Chemical Lab. Co., Ltd.). Acetonitrile-0.04 M ammonium formate (pH 4.0) (30:70) was used as the mobile phase and run at a flow rate of 1.0 ml/minute. Samples were dissolved in the mobile phase and 10 μl of samples were injected. Detection was performed at 254 nm using a UV detector (UVILOG-5III A, Oyo-Bunko Kiki Co., Ltd.).

Qualitative Determination of Aglycones and Sugars

The product (1 mg) in 1 ml of 0.1 N HCl was heated at 85°C for 30 minutes in a water bath. The aglycone thus obtained was extracted with $CHCl_3$. The $CHCl_3$ layer was subjected to TLC using two developing solvents of $CHCl_3$-MeOH (20:1) and EtOAc-benzene-Me_2CO (4:4:1). Rf values of the authentic samples in the two solvent systems were: 0.35 and 0.45 for β-rhodomycinone (reddish orange); 0.35 and 0.42 for β-isorhodomycinone (purple); 0.26 and 0.46 for α-citromycinone (yellow); 0.25 and 0.44 for α_2-rhodomycinone (orange); 0.43 and 0.54 for γ-rhodomycinone (reddish orange).

Alternatively, the aqueous layer containing sugar components was neutralized by adding silver carbonate with a small amount of charcoal and centrifuged. The supernatant fluid was concentrated *in vacuo* and subjected to a TLC plate using a developing solvent of *n*-BuOH-AcOH-H_2O (4:1:1). The sugar spots were detected by spraying with *p*-anisaldehyde-H_2SO_4 (each 5%) in EtOH and heating at 90°C. Aclarubicin, MA144 L1[2] and daunorubicin were also hydrolyzed in the same manner and the aqueous layers were used as a source of authentic sugars including L-rhodosamine, *N*-monomethyl-L-daunosamine and L-daunosamine, located on a TLC plate with Rf values of 0.13, 0.26 and 0.37, respectively.

Biological Activity

In vitro cytotoxicity and inhibition of DNA and RNA syntheses against the cell culture of murine L1210 leukemia were assayed according to the method previously described[10].

7-*O*-(*N*-Monomethyl-α-L-daunosaminyl)-β-rhodomycinone (LB-1) (**1b**) and 7-*O*-(α-L-Daunosaminyl)-β-rhodomycinone (LB-2) (**1c**)

A solution of **1a** (7-*O*-(α-L-rhodosaminyl)-β-rhodomycinone) (200 mg) in 200 ml of $CHCl_3$-MeOH (100:1) was exposed to the mercury lamp for 1 hour and evaporated. The residue was purified by preparative TLC (Kieselgel 60 PF_{254}, E. Merck) with $CHCl_3$-MeOH-H_2O-AcOH (35:10:0.4:0.2). One major red band (LB-1) and a minor one were scraped from the plates separately and extracted with $CHCl_3$-MeOH (6:1). To each eluate was added equal volume of H_2O and the mixture was shaken. The aqueous layer was separated, washed with toluene and extracted with $CHCl_3$ after pH adjustment to 7.5. The $CHCl_3$ layer was washed with saturated aqueous NaCl, dried over Na_2SO_4, concentrated to a small volume and precipitated with an excess of *n*-hexane. This procedure gave 54 mg of **1b** and 7 mg of **1c**. **1b**: Reddish

brown powder; mp 152~155°C (dec); $[\alpha]_D^{20}$ +238° (*c* 0.02, $CHCl_3$); IR (KBr) cm^{-1} 3400, 2930, 1600; UV $\lambda_{max}^{90\%MeOH}$ nm ($E_{1cm}^{1\%}$) 203 (320), 235 (702), 254 (411), 293 (136), 495 (257), 530 (sh, 172); FD-MS *m/z* 529 (M^+, $C_{27}H_{31}NO_{10}$); ^1H NMR (400 MHz, $CDCl_3$-CD_3OD (10:1)) δ 7.81 (1H, d, $J_{1,2}$=8 Hz, 1-H), 7.70 (1H, t, $J_{2,1}=J_{2,3}$=8 Hz, 2-H), 7.29 (1H, d, $J_{3,1}$=8 Hz, 3-H), 5.46 (1H, d, $J_{1',2'b}$=4 Hz, 1'-H), 5.12 (1H, br d, 7-H), 4.84 (1H, s, 10-H), 4.13 (1H, q, $J_{5',6'}$=7 Hz, 5'-H), 3.66 (1H, br s, 4'-H), 2.72 (1H, m, 3'-H), 2.34 (3H, s, 3'-$NHCH_3$), 2.23 (1H, d, $J_{8a,8b}$=15 Hz, 8-Ha), 2.14 (1H, dd, $J_{8b,8a}$=15 Hz, $J_{8b,7}$=4 Hz, 8-Hb), 1.87 (1H, dd, $J_{2'a,2'b}$=12 Hz, $J_{2'a,3'}$=5 Hz, 2'-H), 1.83 (1H, m, $J_{13a,13b}=J_{13a,14}$=7.5 Hz, 13-Ha), 1.78 (1H, m, $J_{13b,13a}=J_{13b,14}$=7.5 Hz, 13-Hb), 1.73 (dt, $J_{2'b,2'a}=J_{2'b,3'}$=12 Hz, $J_{2'b,1'}$=4 Hz, 2'-Hb), 1.35 (3H, d, $J_{6',5'}$=7 Hz, 6'-CH_3), 1.11 (3H, t, $J_{14,13}$=7.5 Hz, 14-CH_3). **1c**: Reddish brown powder; FAB-MS *m/z* 516 ($(M+H)^+$, $C_{26}H_{29}NO_{10}$).

7-*O*-(*N*-Monomethyl-α-L-daunosaminyl)-β-isorhodomycinone (ELB-1) (**2b**) and 7-*O*-(α-L-Daunosaminyl)-β-isorhodomycinone (ELB-2) (**2c**)

A solution of **2a** (7-*O*-(α-L-rhodosaminyl)-β-isorhodomycinone) (150 mg) in 150 ml of $CHCl_3$-MeOH (10:1) was exposed to the lamp for 1 hour and purified in the same way as described above to give 39 mg of **2b** and 4 mg of **2c**. **2b**: Dark purple powder; mp 176~179°C (dec); $[\alpha]_D^{20}$ −355° (*c* 0.002, $CHCl_3$); IR (KBr) cm^{-1} 3400, 2950, 1585; UV $\lambda_{max}^{90\%MeOH}$ nm ($E_{1cm}^{1\%}$) 205 (326), 241 (895), 298 (131), 523 (325), 550 (305), 561 (324); FD-MS *m/z* 546 ($(M+H)^+$, $C_{27}H_{31}NO_{11}$); ^1H NMR (400 MHz, $CDCl_3$-CD_3OD (2:1)) δ 7.24 (2H, s, 2-H and 3-H), 5.45 (1H, d, $J_{1',2'b}$=4 Hz, 1'-H), 5.11 (1H, br s, 7-H), 4.80 (1H, s, 10-H), 4.15 (1H, q, $J_{5',6'}$=7 Hz, 5'-H), 3.68 (1H, br s, 4'-H), 2.72 (1H, br d, $J_{3',2'b}$=13 Hz, 3'-H), 2.36 (3H, s, 3'-$NHCH_3$), 2.25 (1H, d, $J_{8a,8b}$=15 Hz, 8-Ha), 2.16 (1H, dd, $J_{8b,8a}$=15 Hz, $J_{8b,7}$=4 Hz, 8-Hb), 1.91 (1H, dd, $J_{2'a,2'b}$=13 Hz, 2'-Ha), 1.83 (1H, m, $J_{13a,13b}=J_{13a,14}$=7 Hz, 13-Ha), 1.81 (1H, m, $J_{13b,13a}=J_{13b,14}$=7 Hz, 13-Hb), 1.73 (1H, dt, $J_{2'b,2'a}$=13 Hz, $J_{2'b,3'}$=13 Hz, $J_{2'b,1'}$=4 Hz, 2'-Hb), 1.35 (3H, d, $J_{6',5'}$=7 Hz, 6'-CH_3), 1.12 (3H, t, $J_{14,13}$=7 Hz, 14-CH_3). **2c**: Dark purple powder; FAB-MS *m/z* 532 ($(M+H)^+$, $C_{26}H_{29}NO_{11}$).

7-*O*-(*N*-Monomethyl-α-L-daunosaminyl)-α-citromycinone (LCS-1) (**3b**) and 7-*O*-(α-L-Daunosaminyl)-α-citromycinone (LCS-2) (**3c**)

A solution of **3a** (7-*O*-(α-L-rhodosaminyl)-α-citromycinone) (84 mg) in 80 ml of $CHCl_3$-MeOH (15:1) was exposed to the light for 1 hour and purified in the same way as described above to give 25 mg of **3b** and 3 mg of **3c**. **3b**: Reddish brown powder; mp 132~135°C (dec); $[\alpha]_D^{20}$ −55° (*c* 0.02, $CHCl_3$); IR (KBr) cm^{-1} 3400, 2920, 1625, 1605, 1580; UV $\lambda_{max}^{90\%MeOH}$ nm ($E_{1cm}^{1\%}$) 206 (373), 230 (692), 258 (459), 435 (215); FD-MS *m/z* 514 ($(M+H)^+$, $C_{27}H_{31}NO_9$); ^1H NMR (400 MHz, $CDCl_3$-CD_3OD (10:1)) δ 7.86 (1H, dd, $J_{1,2}$=8 Hz, $J_{1,3}$=1.5 Hz, 1-H), 7.80 (1H, s, 6-H), 7.71 (1H, t, $J_{2,1}=J_{2,3}$=8 Hz, 2-H), 7.34 (1H, dd, $J_{3,2}$=8 Hz, $J_{3,1}$=1.5 Hz, 3-H), 5.33 (1H, br s, 1'-H), 4.94 (1H, 7-H), 4.93 (1H, s, 10-H), 4.06 (1H, q, $J_{5',6'}$=7 Hz, 5'-H), 3.66 (1H, d, $J_{4',3'}$=3 Hz, 4'-H), 2.81 (1H, dt, *J*=8 and 3 Hz, 3'-H), 2.37 (3H, s, 3'-$NHCH_3$), 2.29 (1H, dd, $J_{8a,8b}$=15 Hz, $J_{8a,7}$=5 Hz, 8-Ha), 2.19 (1H, dd, $J_{8b,8a}$=15 Hz, $J_{8b,7}$=2 Hz, 8-Hb), 1.88 (1H, m, $J_{13a,13b}=J_{13a,14}$=7 Hz, 13-Ha), 1.78 (2H, dd, *J*=10 and 3 Hz, 2'-CH_2), 1.73 (1H, m, $J_{13b,13a}=J_{13b,14}$=7 Hz, 13-Hb), 1.37 (3H, d, $J_{6',5'}$=7 Hz, 6'-CH_3), 1.12 (3H, t, $J_{14,13}$=7 Hz, 14-CH_3). **3c**: Reddish brown powder; FAB-MS *m/z* 500 ($(M+H)^+$, $C_{26}H_{29}NO_9$).

10-*O*-(*N*-Monomethyl-α-L-daunosaminyl)-α-citromycinone (LC-1) (**4b**) and 10-*O*-(α-L-Daunosaminyl)-α-citromycinone (LC-2) (**4c**)

A solution of **4a** (10-*O*-(α-L-rhodosaminyl)-α-citromycinone) (101 mg) in 100 ml of $CHCl_3$-MeOH (15:1) was exposed to the light for 2 hours and evaporated. The residue containing two major products was purified in the same way as described above to give 15 mg of **4b** and 24 mg of **4c**. **4b**: Yellowish brown powder; mp 143~147°C (dec); $[\alpha]_D^{20}$ +80° (*c* 0.02, $CHCl_3$); IR (KBr) cm^{-1} 3400, 2930, 1625, 1605, 1580; UV $\lambda_{max}^{90\%MeOH}$ nm ($E_{1cm}^{1\%}$) 206 (382), 231 (727), 257 (468), 291 (sh, 158), 436 (220); SI-MS *m/z* 514 ($(M+H)^+$, $C_{27}H_{31}NO_9$); ^1H NMR (400 MHz, $CDCl_3$-CD_3OD (10:1)) δ 8.02 (1H, s, 6-H), 7.81 (1H, d, $J_{1,2}$=8 Hz, 1-H), 7.69 (1H, t, $J_{2,1}=J_{2,3}$=8 Hz, 2-H), 7.30 (1H, d, $J_{3,2}$=8 Hz, 3-H), 5.25 (1H, d, $J_{1',2'a}$=3.5 Hz, 1'-H), 5.06 (1H, s, 10-H), 4.89 (1H, dd, $J_{7,8a}$=6 Hz, $J_{7,8b}$=3.5 Hz, 7-H), 3.99 (1H, q, $J_{5',6'}$=7 Hz, 5'-H), 3.65 (1H, br s, 4'-H), 2.77 (1H, br d, $J_{3',2a}$=13 Hz, 3'-H), 2.42 (1H, dd, $J_{8a,8b}$=15 Hz, $J_{8a,7}$=6 Hz, 8-Ha), 2.35 (3H, s, 3'-$NHCH_3$), 1.96 (1H, dd, $J_{8b,8a}$=15 Hz, 8-Hb), 1.82 (2H, q, $J_{13,14}$=8 Hz, 13-CH_2), 1.62 (1H, dt, $J_{2'a,2'b}$=13 Hz, $J_{2'a,1'}$=3.5 Hz, 2'-Ha), 1.53 (1H, dd, $J_{2'b,2'a}$=13 Hz, $J_{2'b,3'}$=4 Hz, 2'-Hb), 1.31 (3H, d,

$J_{6',5'}=7$ Hz, 6'-CH_3), 1.10 (3H, t, $J_{14,13}=8$ Hz, 14-CH_3). **4c**: Yellowish brown powder; mp indistinct; $[\alpha]_D^{20}$ $+80°$ (*c* 0.02, $CHCl_3$); IR (KBr) cm^{-1} 3400, 2930, 1620, 1600, 1580; UV $\lambda_{max}^{90\%MeOH}$ nm ($E_{1cm}^{1\%}$) 204 (367), 231 (708), 258 (466), 291 (sh, 158), 436 (224); FD-MS *m/z* 500 ($(M+H)^+$, $C_{26}H_{29}NO_9$); ^1H NMR (400 MHz, $CDCl_3$-CD_3OD (25:1)) δ 7.99 (1H, s, 6-H), 7.82 (1H, d, $J_{1,2}=8$ Hz, 1-H), 7.68 (1H, t, $J_{2,1}=J_{2,3}=8$ Hz, 2-H), 7.30 (1H, d, $J_{3,2}=8$ Hz, 3-H), 5.27 (1H, d, $J_{1',2'a}=4$ Hz, 1'-H), 5.01 (1H, s, 10-H), 4.84 (1H, dd, $J_{7,8a}=6$ Hz, $J_{7,8b}=3$ Hz, 7-H), 4.00 (1H, q, $J_{5',6'}=7$ Hz, 5'-H), 3.43 (1H, br s, 4'-H), 3.02 (1H, m, $J_{3',2'a}=13$ Hz, $J_{3',2'b}=5$ Hz, $J_{3',4'}=3$ Hz, 3'-H), 2.36 (1H, dd, $J_{8a,8b}=15$ Hz, $J_{8a,7}=6$ Hz, 8-Ha), 2.01 (1H, br d, $J_{8b,8a}=15$ Hz, 8-Hb), 1.80 (1H, m, $J_{13a,13b}=J_{13a,14}=8$ Hz, 13-Ha), 1.79 (1H, m, $J_{13b,13a}=J_{13b,14}=7$ Hz), 1.66 (1H, dt, $J_{2'a,2'b}=13$ Hz, $J_{2'a,1'}=4$ Hz, 2'-Ha), 1.43 (1H, dd, $J_{2'b,2'a}=13$ Hz, $J_{2'b,3'}=5$ Hz, 2'-Hb), 1.30 (3H, d, $J_{6',5'}=7$ Hz, 6'-CH_3), 1.08 (3H, t, $J_{14,13}=7$ Hz, 14-CH_3).

7-*O*-(*N*-Monomethyl-α-L-daunosaminyl)-α_2-rhodomycinone (ALC-1) (**5b**) and 7-*O*-(α-L-Daunosaminyl)-α_2-rhodomycinone (ALC-2) (**5c**)

A solution of **5a** (7-*O*-(α-L-rhodosaminyl)-α_2-rhodomycinone) (185 mg) in 180 ml of $CHCl_3$-MeOH (15:1) was exposed to the light for 2 hours and evaporated. The residue containing two major products was purified in the same way as described above to give 26 mg of **5b** and 14 mg of **5c**. **5b**: Reddish purple powder; mp 147~153°C (dec); $[\alpha]_D^{20}$ $+162°$ (*c* 0.02, $CHCl_3$); IR (KBr) cm^{-1} 3400, 2950, 1590; UV $\lambda_{max}^{90\%MeOH}$ nm ($E_{1cm}^{1\%}$) 205 (315), 235 (788), 258 (403), 292 (sh, 138), 492 (250); SI-MS *m/z* 530 ($(M+H)^+$, $C_{27}H_{31}NO_{10}$); ^1H NMR (400 MHz, $CDCl_3$-CD_3OD (2:1)) δ 7.81 (1H, s, 6-H), 7.31 (1H, d, $J_{2,3}=10$ Hz, 2-H), 7.28 (1H, d, $J_{3,2}=10$ Hz, 3-H), 5.34 (1H, d, $J_{1',2'}=3$ Hz, 1'-H), 4.96 (1H, dd, $J_{7,8a}=5$ Hz, $J_{7,8b}=3$ Hz, 7-H), 4.91 (1H, s, 10-H), 4.08 (1H, q, $J_{5',6'}=7$ Hz, 5'-H), 3.69 (1H, br s, 4'-H), 2.82 (1H, br d, $J_{3',2'b}=12$ Hz, 3'-H), 2.38 (3H, s, 3'-$NHCH_3$), 2.32 (1H, dd, $J_{8a,8b}=15$ Hz, $J_{8a,7}=5$ Hz, 8-Ha), 2.19 (1H, br d, $J_{8b,8a}=15$ Hz, 8-Hb), 1.87 (1H, m, $J_{13a,13b}=J_{13a,14}=7.5$ Hz, 13-Ha), 1.76 (1H, m, $J_{13b,13a}=J_{13b,14}=7.5$ Hz, 13-Hb), 1.7~1.9 (2H, 2'-CH_2), 1.36 (3H, d, $J_{6',5'}=7$ Hz, 6'-CH_3), 1.12 (3H, t, $J_{14,13}=7.5$ Hz, 14-CH_3); **5c**: Reddish purple powder; mp 158~162°C (dec); $[\alpha]_D^{20}$ $+135°$ (*c* 0.02, dioxane); IR (KBr) cm^{-1} 3400, 2950, 1590; UV $\lambda_{max}^{90\%MeOH}$ nm ($E_{1cm}^{1\%}$) 203 (332), 235 (791), 258 (405), 292 (139), 492 (253); SI-MS *m/z* 516 ($(M+H)^+$, $C_{26}H_{29}NO_{10}$); ^1H NMR (400 MHz, $CDCl_3$-CD_3OD (2:1)) δ 7.87 (1H, s, 6-H), 7.49 (2H, s, 2-H and 3-H), 5.30 (1H, br d, 1'-H), 4.97 (1H, br, 7-H), 4.93 (1H, s, 10-H), 4.08 (1H, m, 5'-H), 3.48 (1H, br s, 4'-H), 3.05 (1H, br d, 3'-H), 2.32 (1H, dd, $J_{8a,8b}=13$ Hz, $J_{8a,7}=5$ Hz, 8-Ha), 2.18 (1H, d, $J_{8b,8a}=15$ Hz, 8-Hb), 1.7~1.9 (4H, 13-CH_2 and 2'-CH_2), 1.34 (3H, d, $J_{6',5'}=7$ Hz, 6'-CH_3), 1.11 (3H, t, $J_{14,13}=7$ Hz, 14-CH_3).

10-*O*-(*N*-Monomethyl-α-L-daunosaminyl)-α_2-rhodomycinone (ELC-1) (**6b**) and 10-*O*-(α-L-Daunosaminyl)-α_2-rhodomycinone (ELC-2) (**6c**)

A solution of **6a** (10-*O*-(α-L-rhodosaminyl)-α_2-rhodomycinone) (171 mg) in 170 ml of $CHCl_3$-MeOH (15:1) was exposed to the light for 2 hours and evaporated. The residue containing two major products was purified in the same way as described above to give 32 mg of **6b** and 16 mg of **6c**. **6b**: Dark purple powder; mp 145~149°C (dec); $[\alpha]_D^{20}$ $+381°$ (*c* 0.02, $CHCl_3$); IR (KBr) cm^{-1} 3400, 2950, 1590; UV $\lambda_{max}^{90\%MeOH}$ nm ($E_{1cm}^{1\%}$) 205 (316), 235 (829), 258 (415), 292 (142), 493 (259); SI-MS *m/z* 530 ($(M+H)^+$, $C_{27}H_{31}NO_{10}$); ^1H NMR (400 MHz, $CDCl_3$-CD_3OD (2:1)) δ 8.02 (1H, s, 6-H), 7.30 (1H, d, $J_{2,3}=10$ Hz, 2-H), 7.26 (1H, d, $J_{3,2}=10$ Hz, 3-H), 5.23 (1H, d, $J_{1',2'}=4$ Hz, 1'-H), 5.07 (1H, s, 10-H), 4.90 (1H, dd, $J_{7,8a}=6$ Hz, $J_{7,8b}=3$ Hz, 7-H), 4.00 (1H, q, $J_{5',6'}=7$ Hz, 5'-H), 3.66 (1H, br s, 4'-H), 2.78 (1H, br d, $J_{3',2'b}=13$ Hz, 3'-H), 2.43 (1H, dd, $J_{8a,8b}=15$ Hz, $J_{8a,7}=6$ Hz, 8-Ha), 2.36 (3H, s, 3'-$NHCH_3$), 1.95 (1H, dd, $J_{8b,8a}=15$ Hz, $J_{8b,7}=3$ Hz, 8-Hb), 1.83 (2H, q, $J_{13,14}=8$ Hz, 13-CH_2), 1.63 (1H, dt, $J_{2'a,2'b}=J_{2'a,3'}=13$ Hz, $J_{2'a,1'}=4$ Hz, 2'-Ha), 1.54 (1H, dd, $J_{2'b,2'a}=13$ Hz, $J_{2'b,1'}=4$ Hz, 2'-Hb), 1.32 (3H, d, $J_{6',5'}=7$ Hz, 6'-CH_3), 1.10 (3H, t, $J_{14,13}=8$ Hz, 14-CH_3). **6c**: Dark purple powder; mp 148~152°C (dec); $[\alpha]_D^{20}$ $-150°$ (*c* 0.002, MeOH); IR (KBr) cm^{-1} 3400, 2920, 1590; UV $\lambda_{max}^{90\%MeOH}$ nm ($E_{1cm}^{1\%}$) 204 (313), 235 (790), 258 (407), 292 (143), 493 (253); SI-MS *m/z* 516 ($(M+H)^+$, $C_{26}H_{29}NO_{10}$); ^1H NMR (400 MHz, DMSO-d_6) δ 6.79 (1H, s, 6-H), 7.12 (1H, d, $J_{2,3}=9$ Hz, 2-H), 7.09 (1H, d, $J_{3,2}=9$ Hz, 3-H), 5.46 (1H, s, 1'-H), 4.64 (1H, s, 10-H), 4.27 (1H, br, 7-H), 3.88 (1H, q, $J_{5',6'}=7$ Hz, 5'-H), 3.52 (1H, br s, 4'-H), 3.47 (1H, br d, 3'-H), 2.03 (1H, dd, $J_{8a,8b}=14$ Hz, $J_{8a,7}=5$ Hz, 8-Ha), 1.70 (1H, m, $J_{13a,13b}=J_{13a,14}=7$ Hz, 13-Ha), 1.66 (1H, d, $J_{8b,8a}=14$ Hz, 8-Hb), 1.56 (1H, m, $J_{13b,13a}=J_{13b,14}=7$ Hz, 13-Hb), 1.5~1.7 (2H, 2'-CH_2), 1.12 (3H, d, $J_{6',5'}=7$ Hz, 6'-CH_3), 0.96 (3H, t, $J_{14,13}=7$ Hz, 14-CH_3).

10-*O*-(*N*-Monomethyl-α-L-daunosaminyl)-γ-rhodomycinone (IRC-1) (**7b**) and 10-*O*-(α-L-Daunosaminyl)-γ-rhodomycinone (IRC-2) (**7c**)

A solution of **7a** (10-*O*-(α-L-rhodosaminyl)-γ-rhodomycinone) (180 mg) in 180 ml of $CHCl_3$-MeOH (15:1) was exposed to the light for 2 hours and evaporated. The residue containing two major products was purified in the same way as described above to give 16 mg of **7b** and 9 mg of **7c**. **7b**: Reddish brown powder; mp 145~149°C (dec); $[\alpha]_D^{20}$ +381° (*c* 0.02, $CHCl_3$); IR (KBr) cm^{-1} 3400, 2950, 1590; UV $\lambda_{max}^{90\%MeOH}$ nm ($E_{1cm}^{1\%}$) 205 (316), 235 (829), 258 (415), 292 (142), 493 (259); FAB-MS *m/z* 530 ($(M+H)^+$, $C_{27}H_{31}NO_{10}$); ^1H NMR (400 MHz, $CDCl_3$-CD_3OD (20:1)) δ 7.88 (1H, dd, $J_{1,2}$=8 Hz, $J_{1,3}$=1 Hz, 1-H), 7.70 (1H, t, $J_{2,1}=J_{2,3}$=8 Hz, 2-H), 7.30 (1H, dd, $J_{3,2}$=8 Hz, $J_{3,1}$=1 Hz, 3-H), 5.37 (1H, d, $J_{1',2'a}$=4 Hz, 1'-H), 4.94 (1H, s, 10-H), 3.99 (1H, q, $J_{5',6'}$=7 Hz, 5'-H), 3.62 (1H, br s, 4'-H), 2.8~3.0 (2H, m, 7-CH_2), 2.80 (1H, ddd, $J_{3',2'a}$=13 Hz, $J_{3',2'b}$=5 Hz, $J_{3',4'}$=3 Hz, 3'-H), 2.37 (3H, s, 3'-$NHCH_3$), 2.0~2.1 (1H, m, 8-Ha), 1.85 (1H, m, $J_{13a,13b}=J_{13a,14}$=7 Hz, 13-Ha), 1.8~1.9 (1H, m, 8-Hb), 1.72 (1H, m, $J_{13b,13a}=J_{13b,14}$=7 Hz, 13-Hb), 1.64 (1H, dt, $J_{2'a,2'b}=J_{2'a,3'}$=13 Hz, $J_{2'a,1'}$=4 Hz, 2'-Ha), 1.57 (1H, dd, $J_{2'b,2'a}$=13 Hz, $J_{2'b,3'}$=5 Hz, 2'-Hb), 1.32 (3H, d, $J_{6',5'}$=7 Hz, 6'-CH_3), 1.08 (3H, t, $J_{14,13}$=7 Hz, 14-CH_3). **7c**: Reddish brown powder; mp 148~152°C (dec); $[\alpha]_D^{20}$ −150° (*c* 0.002, MeOH); IR (KBr) cm^{-1} 3400, 2920, 1590; UV $\lambda_{max}^{90\%MeOH}$ nm ($E_{1cm}^{1\%}$) 204 (313), 235 (790), 258 (407), 292 (143), 493 (253); FAB-MS *m/z* 516 ($(M+H)^+$, $C_{26}H_{29}NO_{10}$); ^1H NMR (400 MHz, $CDCl_3$-CD_3OD (10:1)) δ 7.89 (1H, dd, $J_{1,2}$=8 Hz, $J_{1,3}$=1 Hz, 1-H), 7.71 (1H, t, $J_{2,1}=J_{2,3}$=8 Hz, 2-H), 7.31 (1H, dd, $J_{3,2}$=8 Hz, $J_{3,1}$=1 Hz, 3-H), 5.34 (1H, d, $J_{1',2'a}$=4 Hz, 1'-H), 4.94 (1H, s, 10-H), 4.02 (1H, q, $J_{5',6'}$=7 Hz, 5'-H), 3.44 (1H, br s, 4'-H), 3.04 (1H, ddd, $J_{3',2'a}$=13 Hz, $J_{3',2'b}$=5 Hz, $J_{3',4'}$=3 Hz, 3'-H), 2.8~3.0 (2H, m, 7-CH_2), 1.98~2.06 (1H, m, 8-Ha), 1.8~1.9 (2H, 8-Hb and 13-Ha), 1.71 (1H, m, $J_{13b,13a}=J_{13b,14}$=7 Hz, 13-Hb), 1.68 (1H, dt, $J_{2'a,2'b}=J_{2'a,3'}$=13 Hz, $J_{2'a,1'}$=4 Hz, 2'-Ha), 1.49 (1H, dd, $J_{2'b,2'a}$=13 Hz, $J_{2'b,3'}$=5 Hz, 2'-Hb), 1.29 (3H, d, $J_{6',5'}$=7 Hz, 6'-CH_3), 1.07 (3H, t, $J_{14,13}$=7 Hz, 14-CH_3).

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