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STRUCTURE DETERMINATION OF LUSTROMYCIN, AN ANTIBIOTIC AGAINST ANAEROBIC BACTERIA

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Abstract – Extensive homo and heteronuclear two-dimensional NMR studies revealed lustromycin, an anti-anaerobic antibiotic. Its structure consists of a decaline ring system fused to a 10-membered macrolactone and a 14-membered macrolactone having an enol ether moiety conjugated with a maleic anhydride functionality.

In the course of screening of anti-anaerobic antibiotics from actinomycetes, we have found novel antibiotics, thiotetromycin,[1] clostomicin,[2] lustromycin (**1**),[3] and luminamicin (**2**).[4] Luminamicin (**2**) was identical with coloradocin whose structure was determined by McAlpine.[5] The biological properties of **1** were found to be similar to those of **2**.[3] This paper deals with the structure elucidation of lustromycin (**1**). Structure determination of **1** ($C_{32}H_{38}O_{13}$) was performed based on the NMR spectral analyses. As described in the preceding paper,[3] the structure of **1** was expected to resemble **2** ($C_{32}H_{38}O_{12}$) closely. ^{1}H and ^{13}C NMR spectral signals of both compounds observed in $CDCl_3$ were assigned by various 1D- and 2D-NMR spectral experiments (Table 1).[6] Comparison of MS and NMR spectral data of **1** and **2** revealed that **1** contained another O-methyl group instead of a C-methyl group present in **2**. ^{1}H- and ^{13}C-NMR spectral analyses of **1** indicated the presence of a 14-membered lactone ring (C-16~C-29) containing an enol ether moiety conjugated with an unsaturated cyclic anhydride, and also the presence of an isopentenyl unit (C-13~C-16, CH_3-14). The spectral NMR data of these parts shown by **1** are in fair agreement with those of **2** as shown in Table 1. Connectivity of the remaining part (C-1~C-12) was further analyzed using ^{1}H-^{1}H COSY and HMBC experiments (Figure 1). The partial structures including C-4~C-6, C-7~C-8 and C-9~C-11 were assigned by interpretation of the COSY cross-peaks. HMBC experiments revealed the partial structure C-4 to C-8 by correlations between H-8/C-6, H-5/C-7 and H-6/C-7, and confirmed the direct linkage of C-7 to C-12 by correlations H-6 to C-12 and H-12 to C-8. The

Table 1 ^{1}H- and ^{13}C-NMR Spectral Data of **1** and **2**, and ^{1}H-NMR Spectral Data of **3**

	1			**2**			**2**[Ref. 5]			**3**
No.	δ_C	(m)	δ_H	δ_C	(m)	δ_H	δ_C	(m)	δ_H	δ_H
1	171.0	(s)	-	173.1	(s)	-	172.8	(s)	-	
2	87.4	(d)	3.73	82.8	(d)	3.75	81.8	(d)	3.79	3.75
3	78.2	(d)	3.93	32.9	(t)	2.46	32.9	(t)	2.43	3.90
						1.41			1.22	
4	45.1	(d)	2.00	38.3	(d)	2.20	37.7	(d)	2.16	1.98
5	123.8	(d)	5.53	128.3	(d)	5.47	128.3	(d)	5.51	5.54
6	130.7	(d)	6.05	130.2	(d)	5.88	129.9	(d)	5.82	6.03
7	28.7	(d)	2.28	29.6	(d)	2.21	29.2	(d)	2.14	2.40
8	32.5	(t)	1.61	27.9	(t)	1.69	27.5	(t)	1.66	1.65
						1.43			1.21	
9	64.8	(d)	4.03	70.5	(d)	3.65	69.6	(d)	3.52	4.03
10	38.2	(t)	2.10	40.9	(d)	1.93	38.8	(d)	1.85	2.06
			1.69							1.74
11	69.3	(d)	3.97	77.4	(d)	3.35	75.3	(d)	3.18	4.86
12	37.9	(d)	2.24	38.0	(d)	1.82	37.9	(d)	1.97	2.27
13	75.3	(s)	-	76.5	(s)	-	75.9	(s)	-	-
14	143.1	(s)	-	142.0	(s)	-	141.5	(s)	-	-
15	122.7	(d)	6.04	123.4	(d)	6.04	121.6	(d)	5.85	5.87
16	36.8	(d)	3.19	37.2	(d)	3.20	36.4	(d)	3.05	2.94
17	64.3	(t)	4.88	64.3	(t)	4.87	63.7	(t)	4.79	4.58
			4.09			4.05			3.97	4.27
18	171.7	(s)	-	172.0	(s)	-	171.0	(s)	-	-
19	33.6	(t)	2.81	33.5	(t)	2.86	32.9	(t)	2.43	2.83
			2.52			2.49			1.22	2.63
20	18.6	(t)	3.46	18.6	(t)	3.29	17.8	(t)	3.37	3.48
			2.72			2.67			2.61	2.71
21	133.5	(s)	-	133.5	(s)	-	133.7	(s)	-	-
22	165.7	(s)	-	165.7	(s)	-	165.5	(s)	-	-
23	164.2	(s)	-	164.3	(s)	-	164.1	(s)	-	-
24	138.5	(s)	-	138.3	(s)	-	137.3	(s)	-	-
25	96.8	(d)	5.66	96.7	(d)	5.63	96.3	(d)	5.62	5.81
26	156.8	(d)	7.86	156.8	(d)	7.84	155.6	(d)	7.71	7.89
27	72.0	(t)	4.19	72.1	(t)	4.19	71.8	(t)	4.09	4.24
28	66.5	(d)	4.51	66.3	(d)	4.49	65.0	(d)	4.26	5.84
29	72.4	(d)	5.36	72.2	(d)	5.42	72.5	(d)	5.26	5.52
2-OCH_3	59.1	(q)	3.35	57.9	(q)	3.24	57.2	(q)	3.18	3.38
3-OCH_3	60.3	(q)	3.43	-		-	-		-	3.41
10-CH_3	-		-	16.0	(q)	0.97	15.6	(q)	0.85	-
11-$OCOCH_3$	-		-	-		-	-		-	2.03
14-CH_3	15.0	(q)	1.68	15.1	(q)	1.72	14.7	(q)	1.64	1.55
28-$OCOCH_3$	-		-	-		-	-		-	2.15

1 and **2** were measured in $CDCl_3$ at 600 MHz (^{1}H) and 150 MHz (^{13}C).

3 was measured in $CDCl_3$ at 400 MHz (^{1}H).

Ref. 5 was measured in DMSO-d_6.

six-membered ring consisting of the C-7 to C-12 chain was proved by correlations between H-8/C-10, H-10/C-8, H-10/C-12 and H-12/C-8. The direct linkages between C-12 to C-13, C-4 to C-13 and C-4 to C-3 were indicated by correlations of H-11 to C-13, H-5 to C-13, and H-3 to C-4, 5 and 13, respectively. An ester bond between C-29 and C-1 was deduced by correlation of H-29 to C-1 as well as from the chemical shift values of C-29 (δ_C 72.4) and H-29 (δ_H 5.36). Additional HMBC experiments also proved the partial

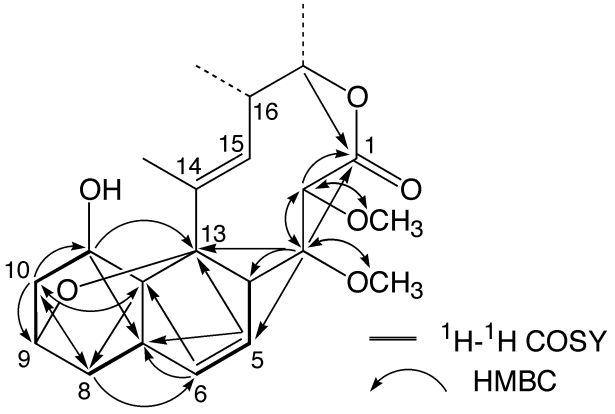

Figure 1 Connection of partial structure of **1**

structure of C-1~C-3. The presence of 2- and 3-OCH_3 in **1** was verified by observation of HMBC cross-peaks between H-2/C-2-OCH, H-2-OCH/C-2, H-3/C-3-OCH and H-3-OCH/C-3, respectively. Substitution of the free hydroxyl groups at C-11 and C-28 was deduced from the lower-field shifts of the respective ^1H signals due to their acetylation. From the molecular formula and the degree of unsaturation of **1**, remaining two oxygen-baring carbons (C-13 and C-19) seemed to form ether ring, although the ether bond linkage between C-9 and C-13 in **1** could not be verified by its NMR spectral analyses. Therefore we present the skeletal structure of lustromycin (**1**) as shown in Figure 2 based on the spectral analogies with those of luminamicin (**2**).

Lustromycin (**1**) is related to a class of 10-membered macrolide antibiotics including nodusmicin,[7] nargenicin,[8] and luminamicin (coloradocin) (Figure 2).

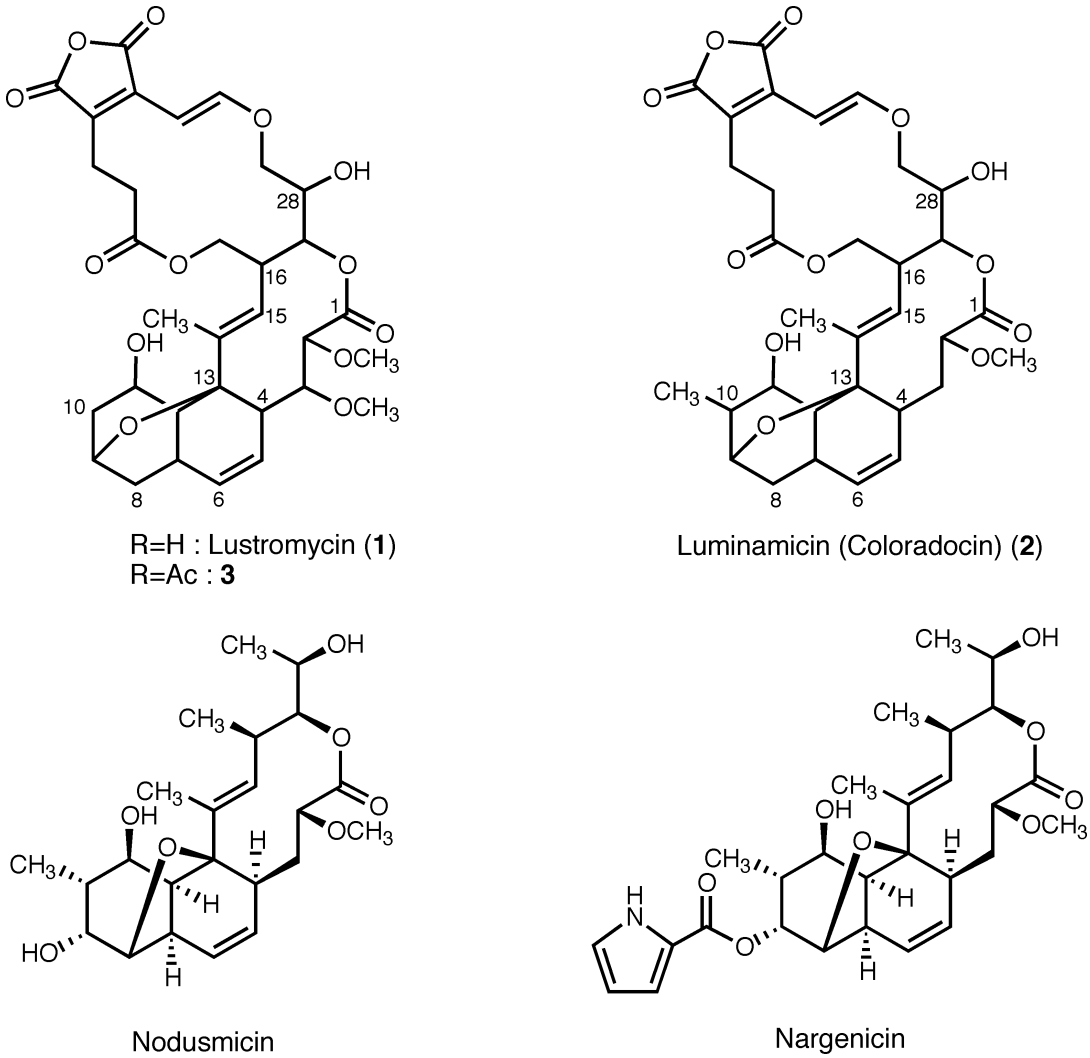

Figure 2 Structures of lustromycin, luminamicin, nodusmicin, and nargenicin

Lustromycin (**1**) could be a new lead compound for the medication to compete with vancomycin which is used clinically in pseudomembranous colitis therapy.

Further efforts to determine its stereochemistry and synthetic studies are in progress.

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