LANDOMYCINS, NEW ANGUCYCLINE ANTIBIOTICS FROM *STREPTOMYCES* SP.

I. STRUCTURAL STUDIES ON LANDOMYCINS A~D

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The chemical structure of the new angucycline antibiotic landomycin A has been elucidated *via* chemical and spectroscopic methods, in particular by 2D NMR correlation spectroscopy, *e.g.*, $^{1}H,^{1}H$-COSY, $^{13}C,^{1}H$-COSY, correlation spectroscopy *via* long-range-couplings and heteronuclear multiple bond connectivity spectroscopy sequences. The spectroscopic investigations were carried out principally with the octaacetyl derivative of landomycin A, which is more soluble in organic solvents than landomycin A itself. The structure consists of a new, unusual angucyclinone, landomycinone A, and of six deoxy sugars, four D-olivoses and two L-rhodinoses, which are all assembled in one chain thus forming the sequence (olivose-4→1-olivose-3→1-rhodinose)$_2$. This long sugar chain is bonded as a phenolic glycoside to the aglycone moiety, a unique structural feature among quinone glycoside antibiotics. By comparison with the main component landomycin A, the structures of three minor congeners, namely landomycins B, C and D, could be proposed.

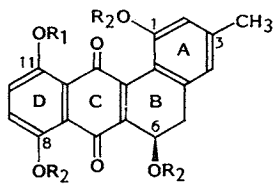
Angucycline antibiotics[1] are a growing group of antibiotic glycosides with interesting and diverse biological activities including antibacterial, enzyme inhibitory and cytostatic effects. Recent examples of this group of antibiotics also show activity as platelet aggregation inhibitors[2,3].

In our screening program for antitumor compounds we found an orange solid as the major bioactive metabolite of *Streptomyces* sp. (DSM 5087). This compound was subsequently named landomycin A. While the fermentation and biological properties of the strain DSM 5087 as well as the isolation of the crude product and the biological activities of the antibiotic compounds will be a subject of an additional paper[4], we report here the physico-chemical characterization and the structure elucidation of the landomycins A~D.

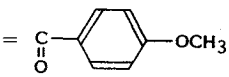
Results

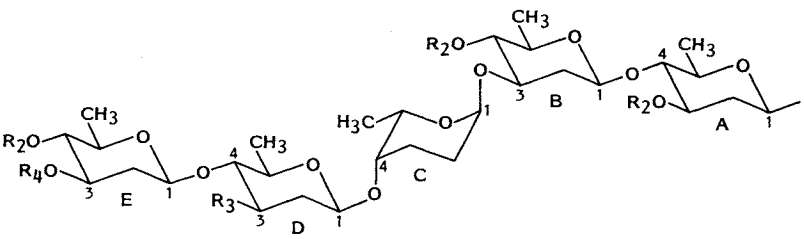
The FAB-MS of landomycin A (**1**) gave both *m/z* 1,089 ($(M+2H+H)^+$, positive ions) and *m/z* 1,087 ($(M+2H-H)^-$, negative ions). Using the FAB method, quinone antibiotics commonly give molecular

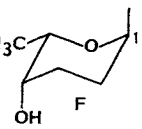
Scheme 1.



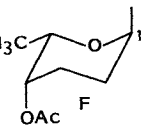
2 $R_1=H$ $R_2=H$

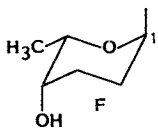
6 $R_1=H$ $R_2=$ 

1, 3, 7, 8, 9 $R_1=$ 

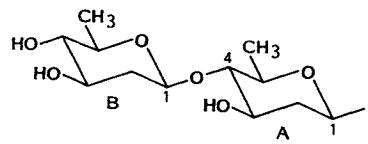
1 $R_2=H$ $R_3=OH$ $R_4=$ 

8 $R_2=Ac$ $R_3=OAc$ $R_4=Ac$

3 $R_2=Ac$ $R_3=OAc$ $R_4=$ 

9 $R_2=H$ $R_3=H$ $R_4=$ 

7 $R_2=H$ $R_3=OH$ $R_4=H$

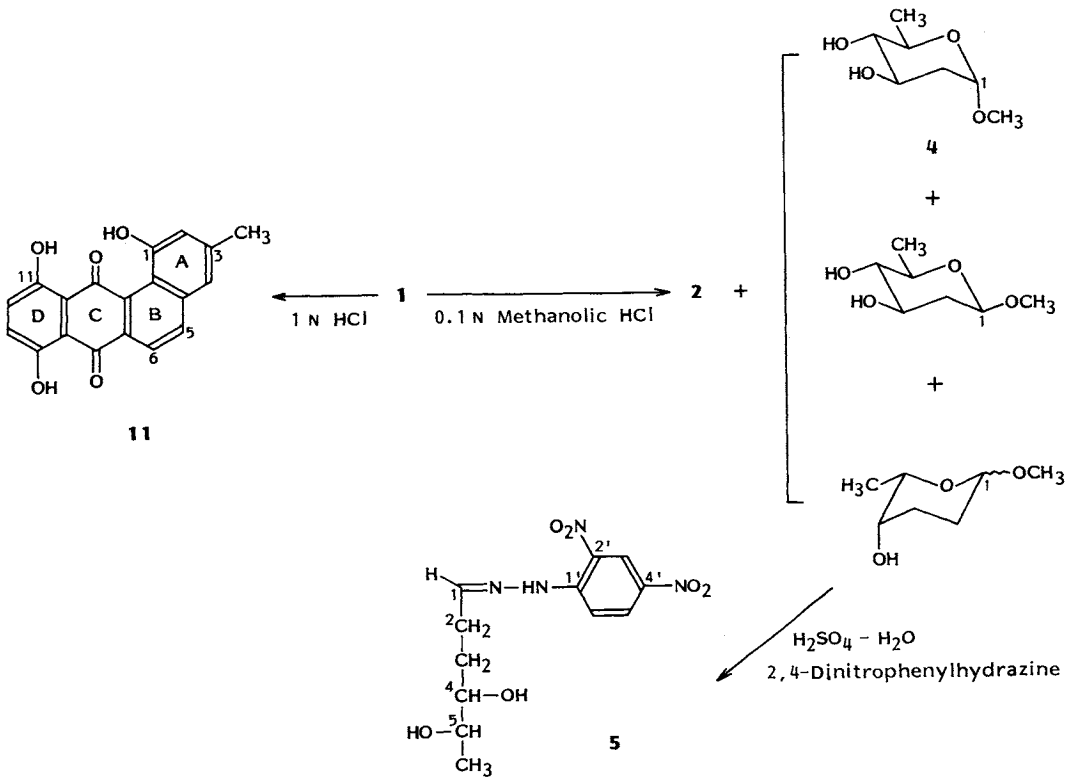
10 $R_1=$  $R_2=H$

ions as hydroquinones[5,6]. With other ionization methods (FD-MS, EI-MS), neither the molecular nor the reduced molecular ions could be observed, but the most intense fragment ions, namely the anhydro-aglycone at *m/z* 320 (HR gave $C_{19}H_{12}O_5$) as well as a disaccharide unit, containing a dideoxy- and a trideoxy-sugar, were detected. From the FAB-MS and the elemental analysis it was possible to determine the molecular formula as $C_{55}H_{74}O_{22}$.

The NMR spectra of landomycin A (**1**) (^{13}C NMR, see Table 2; ^1H NMR, see Table 1) showed the presence of six *O*-glycosidic hexopyranoses, *e.g.*, six anomeric C signals (δ 97.4~101.4) and six anomeric protons (δ 4.48~5.06). Thus a C-19 (55 carbon atoms minus 36 carbon atoms (=6 hexoses)) aglycone moiety was suggested for the landomycin A aglycone. In keeping with this, the weakly soluble landomycinone A (**2**, EI-MS *m/z* 338, $C_{19}H_{14}O_6$, M^+) was liberated by mild acidic methanolysis and characterized by its ^1H NMR spectrum (see Experimental section). Analogous proton signals were also detectable in the NMR spectrum of landomycin A (**1**), confirming that **2** is the aglycone of landomycin A (**1**). Because of the poor solubility of landomycinone A (**2**) a ^{13}C NMR spectrum was not obtained.

The mild methanolysis of landomycin A also yielded the methyl glycosides of only two sugars. Methyl-α-D-olivoside (**4**) was isolated and purified by employing a combination of silica gel and Sephadex LH-20 chromatography and was identified by optical rotation[7~9] ($[\alpha]_D^{20}$ +131°) and ^1H NMR analysis.

Scheme 2.



The two methyl glycosides of L-rhodinose were not separated but could be identified by ^1H NMR analysis of the α/β-anomeric mixture and were characterized by conversion into the known[10] 2,4-dinitrophenylhydrazone (**5**, Scheme 2).

The peracetylation of landomycin A (**1**) with acetic anhydride and *N*,*N*-dimethylaminopyridine gave a well soluble octaacetate (**3**) which proved the existence of eight free hydroxy groups in the molecule. From the ^{13}C NMR and intensive 2D NMR analyses of landomycin A-octaacetate (**3**), one could unequivocally distinguish between sugar moiety and aglycone resonances and allow for the detailed assignments given in Tables 1 and 2.

From the $^1H,^1H$-COSY experiment, the assignments of all protons of every single sugar moiety could be deduced, indicating two rhodinoses and four olivoses (in agreement with the molecular formula). In addition, the assignment of the five acetylated sugar hydroxy groups provided evidence (indirectly) of the interglycosidic linkage positions and thus of the sugars being assembled in one single chain (with an olivose as the sugar connected to the aglycone and a terminal rhodinose). The analysis of the $^1H,^1H$-COSY spectrum of the aglycone moiety resulted in the positioning of the aromatic methyl group between the two meta protons (ring A).

From the 2D-correlation spectroscopy *via* long-range-couplings (COLOC)[11] and 2D-$^{13}C,^1H$-heteronuclear multiple bond connectivity spectroscopy (HMBC)[12] experiments, the sugar sequence could be deduced by the appearance of at least one of the interglycosidic $^3J_{C\text{-}H}$ couplings (see Fig. 1). Furthermore, the linkage position of the sugar chain with the aglycone could be detected, and the constitution of the aglycone moiety (ring B) could be completed. Fig. 1 shows the most important observed $^3J_{C\text{-}H}$ couplings.

Table 1. ^{1}H NMR signals of landomycins A (**1**), B (**7**), C (**9**), D (**10**), A-octaacetate (**3**) and B-octaacetate (**8**).

Proton	**1**	**3**[a]	**7**	**8**[b]	**9**	**10**	Multiplicity (J in Hz)
2-H	6.75	6.96	6.68	7.06	6.79	6.70	br s
3-CH_3	2.32	2.33	2.30	2.28	2.32	1.90	s
4-H	6.79	7.04	6.62	7.06	6.76	6.63	br s
5-H_α	2.88	3.04	2.82	2.90	2.88	3.12[g]	dd (15, 4.5)
5-H_β	3.05	3.27	3.05~3.2[c]	3.31	3.07	3.2~3.7[c]	dd (15, 5)
6-H	5.07	6.23	5.03	6.26	5.08	4.80~5.0[c]	dd (5, 4.5)
9-H	7.52	7.62	7.56	7.55	7.54	7.02	d (9.5)
10-H	7.26	7.44	7.45	7.37	7.27	6.70	d (9.5)
1A-H	5.06	5.43	5.26	5.20	5.07	5.13	dd (10, 2)
2A-H_a	1.92[c]	1.93	1.7~2.0[c]	2.0~2.4[c]	1.92[c]	1.82	ddd (12, 12, 10)
2A-H_e	2.72	2.48	2.6~2.8[c]	2.63	2.72	2.60	ddd (12, 5, 2)
3A-H	3.70	5.04	3.60	5.12	3.71	3.67	ddd (12, 8.5, 5)
4A-H	3.09	3.47	3.12	3.3~3.6[c]	3.09	2.94	dd (8.5, 8.5)
5A-H	3.38	3.64	3.2~3.6[c]	3.3~3.6[c]	3.40	3.3~3.6[c]	dq (8.5, 6)
5A-CH_3	1.28	1.32	1.15~1.25[c]	1.36	1.30	1.32	d (6)
1B-H	4.51	4.68	4.62	4.60	4.53	4.66	dd (10, 2)
2B-H_a	1.67[c]	1.37	1.6~2.0[c]	1.5~2.4[c]	1.68[c]	1.54	ddd (12, 12, 10)
2B-H_e	2.23	2.40	2.2~2.6[c]	1.5~2.4[c]	2.24	2.20	ddd (12, 5, 2)
3B-H	3.51	3.85	3.2~3.6[c]	3.82	3.52	3.55	ddd (12, 8.5, 5)
4B-H	3.10	4.55	3.12	4.68	3.11	2.67	dd (8.5, 8.5)
5B-H	3.38	3.46	3.2~3.6[c]	3.3~3.6[c]	3.40	3.3~3.6[c]	dq (8.5, 6)
5B-CH_3	1.38	1.14	1.15~1.25[c]	1.25	1.40	1.28	d (6)
1C-H	4.96	4.87	5.01	4.97	4.97		br s
2C-H_a	1.54[c]	1.32	1.5~2.0[c]	1.8~2.1[c]	1.53[c]		m
2C-H_e	1.9~2.1[c]	1.94	1.8~2.2[c]	1.8~2.1[c]	2.14[c]		m
3C-H_a	1.93[c]	1.82	1.5~2.0[c]	1.4~2.0[c]	1.80[c]		m
3C-H_e	2.13	1.92	2.0~2.2[c]	1.4~2.0[c]	1.9~2.1[c]		m
4C-H	3.64	3.53	3.46	3.46	3.64		br s
5C-H	4.13	3.86	4.16	3.84	4.14		dq (6.5, 2)
5C-CH_3	1.21	1.09	1.02	1.16	1.22		d (6.5)
1D-H	4.48	4.63	4.56	4.53	4.44[d]		dd (10, 2)
2D-H_a	1.66[c]	1.56	1.6~2.0[c]	1.5~2.4[c]	1.66[c]		ddd (12, 12, 10)
2D-H_e	2.31	2.19	2.2~2.6[c]	1.5~2.4[c]	1.92[c]		ddd (12, 5, 2)
3D-H_a	3.58	4.90	3.2~3.6[c]	5.01	1.54[c]		ddd (12, 8.5, 5)
3D-H_e					2.24[c]		m
4D-H	2.97	3.27	2.96	3.3~3.6[c]	3.18[c]		dd (8.5, 8.5)
5D-H	3.28	3.37	3.2~3.6[c]	3.3~3.6[c]	3.34[f]		dq (8.5, 6)
5D-CH_3	1.25	1.24	1.15~1.25[c]	1.29	1.23		d (6)
1E-H	4.48	4.73	4.56	4.59	4.50		dd (10, 2)
2E-H_a	1.66[c]	1.37	1.6~2.0[c]	1.5~2.4[c]	1.61[c]		ddd (12, 12, 10)
2E-H_e	2.22	2.40	2.2~2.6[c]	1.5~2.4[c]	2.17		ddd (12, 5, 2)
3E-H	3.51	3.85	3.2~3.6[c]	3.82	3.49		ddd (12, 8.5, 5)
4E-H	3.10	4.55	2.96	4.70	3.08		dd (8.5, 8.5)
5E-H	3.37	3.48	3.2~3.6[c]	3.3~3.6[c]	3.26		dq (8.5, 6)
5E-CH_3	1.37	1.16	1.15~1.25[c]	1.24	1.35		d (6)
1F-H	4.94[c]	4.94			4.95		br s
2F-H_a	1.56[c]	1.37			1.57[c]		m
2F-H_e	2.04[c]	1.87			2.03[c]		m
3F-H_a	1.76[c]	1.65			1.96[c]		m
3F-H_e	2.01[c]	1.92			2.0~2.2[c]		m
4F-H	3.53	4.71			3.54		br s
5F-H	4.07	3.98			4.09		dq (6.5, 2)
5F-CH_3	1.20	1.02			1.21		d (6.5)

[a] Acetyl signals (3H, s): 1.80, 1.94, 1.96, 1.97, 1.98, 2.03, 2.20, 2.30.
[b] Acetyl signals (3H, s): 1.91, 2.04, 2.07 (6H), 2.08, 2.10, 2.42, 2.43.
[c] Obscured or complex, [d] dd (2, 9), [e] ddd (10, 9, 5), [f] dq (9, 6), [g] dd (8, 8).

Landomycins A (**1**) and C (**9**): 500 MHz, $CDCl_3$, landomycin B (**7**): 200 MHz, DMSO-d_6, landomycin D (**10**): 200 MHz, CD_3OD, landomycin A-octaacetate (**3**): 300 MHz, acetone-d_6, landomycin B-octaacetate (**8**): 200 MHz, $CDCl_3$. δ in ppm relative to internal TMS.

Table 2. ^{13}C NMR signals of the landomycins A (**1**), B (**7**), C (**9**), A-octaacetate (**3**) and B-octaacetate (**8**).

	1	**3**[a]	**7**	**8**[b]	**9**		**1**	**3**[a]	**7**	**8**[b]	**9**
C-1	155.1	149.4	155.0	148.1	155.1	C-4B	80.2	76.0	75.5	74.0	80.4
C-2	119.0	123.4	119.3	122.8	120.1	C-5B	69.2[c]	70.7	70.0[c]	70.0	69.2[c]
C-3	143.6	142.8	141.0	142.2	143.7	C-6B	17.8	18.3	17.6	17.8	17.8[c]
C-4	126.7	127.6	124.5	127.3	126.8	C-1C	97.7	93.8	92.1	92.9	97.7
C-4a	136.6	138.8	138.2	137.3	136.8	C-2C	25.4	25.0	24.0	24.5	25.5
C-5	37.0	34.2	38.4	33.7	37.1	C-3C	25.0	25.2	23.9	24.1	25.1
C-6	62.0	62.0	57.3	61.3	65.6	C-4C	75.7[c]	76.9	73.8[c]	77.2	75.6[c]
C-6a	138.7	138.1	140.2	136.9	138.8	C-5C	67.7	66.8	65.2	66.1	67.8[c]
C-7	182.8	180.8	180.9	180.2	182.9	C-6C	17.0	17.4	16.8	17.2	17.0[c]
C-7a	114.8	122.4	113.1	122.3	114.9	C-1D	101.4	101.6	100.6	101.1	103.5
C-8	150.6	144.6	149.2	144.0	150.7	C-2D	38.2	37.7	38.5	36.7	30.7
C-9	123.7	125.4	120.8	125.3	123.7	C-3D	72.3[c]	71.4	71.8[c]	70.5	30.0
C-10	132.4	131.9	128.3	130.6	132.6	C-4D	88.4	82.7	87.0	82.0	80.7
C-11	159.5	155.2	155.2	154.5	159.6	C-5D	70.8[c]	71.7	68.2[c]	70.7	74.4[c]
C-11a	120.0	126.7	115.4	125.7	119.1	C-6D	17.8	18.5	17.8	18.1	16.9[c]
C-12	190.9	182.7	187.8	181.9	192.7	C-1E	100.9	100.8	99.8	99.8	100.9
C-12a	146.7	142.9	141.7	142.5	146.8	C-2E	37.1	37.2	36.6	36.6	37.2
C-12b	113.2	119.3	115.4	118.1	113.3	C-3E	75.3[c]	72.1	70.1[c]	71.0	75.2[c]
C-13	21.1	20.8	21.0	21.5	21.2	C-4E	80.4	76.0	76.3	75.1	80.5
C-1A	99.5	98.4	97.7	98.3	99.6	C-5E	69.6[c]	70.7	69.6[c]	70.0	71.8[c]
C-2A	37.5	37.1	38.1	35.9	37.6	C-6E	17.8	18.3	17.6	17.9	18.1[c]
C-3A	72.2[c]	70.9	73.2[c]	70.2	72.3[c]	C-1F	97.4	93.5			97.3
C-4A	87.8	82.2	86.3	81.1	87.8	C-2F	24.4	24.9			24.6
C-5A	70.3[c]	72.3	68.6[c]	71.6	70.8[c]	C-3F	24.0	23.4			24.1
C-6A	17.8	18.4	17.7	18.1	17.8[c]	C-4F	67.7[c]	69.8			67.6[c]
C-1B	100.8	100.7	100.1	100.0	100.8	C-5F	67.0	65.8			67.1
C-2B	37.0	37.2	35.7	36.1	36.3	C-6F	17.9	17.3			18.3[c]
C-3B	75.3[c]	71.8	71.8[c]	71.0	75.4[c]						

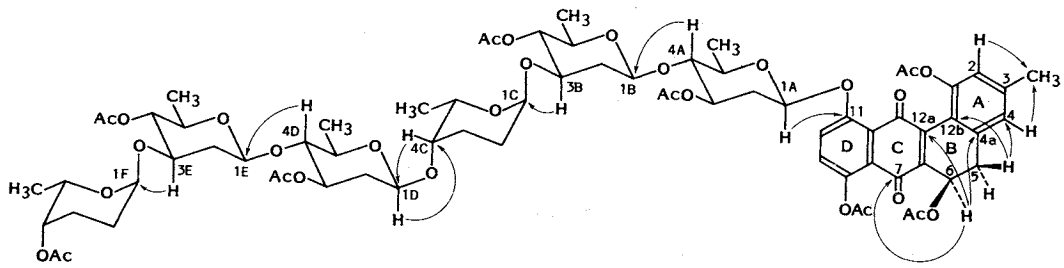
[a] Acetyl-CH_3: 18.0; 18.6; 20.5; 20.9; 20.9; 21.0; 21.3; 21.4, acetyl-C=O: 168.4; 169.9; 170.1; 170.1; 170.3; 170.3; 170.4; 170.7.

[b] Acetyl-CH_3: 20.8; 20.8; 20.9; 21.0; 21.1; 21.2; 21.3; 21.3, acetyl-C=O: 168.4; 169.7; 169.9; 170.1; 170.1; 170.2; 170.3; 170.4.

[c] Assignment uncertain.

Landomycins A (**1**) and C (**9**), and landomycin B-octaacetate (**8**): $CDCl_3$, 50.3 MHz, landomycin B (**7**): DMSO-d_6, 50.3 MHz, landomycin A-octaacetate (**3**): acetone-d_6, 75.4 MHz. δ in ppm relative to internal TMS.

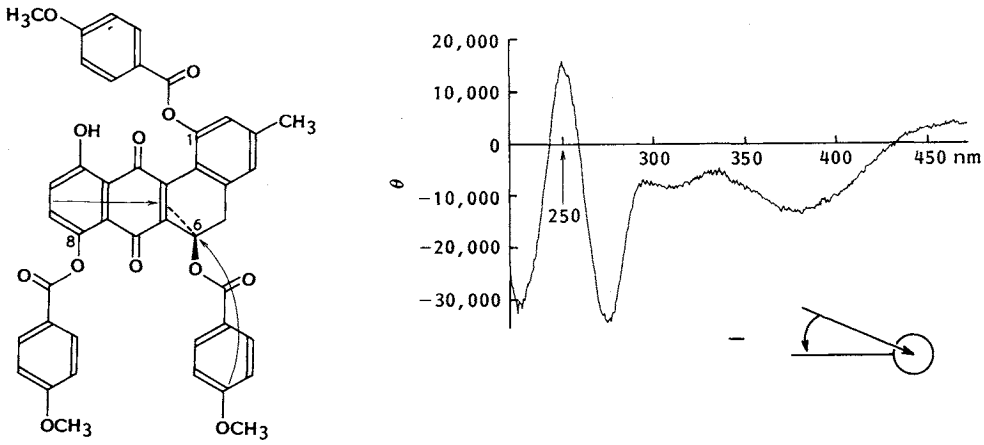
Fig. 1. $^3J_{C\text{-}H}$ couplings observed in landomycin A-octaacetate (**3**), either by COLOC or HMBC.



Only interglycosidic couplings of the sugar chain are shown. Other $^3J_{C\text{-}H}$ couplings in the sugar moieties and $^2J_{C\text{-}H}$ couplings in general are omitted for reasons of clarity.

The only remaining structural problem, namely the absolute configuration of the center at C-6, could be solved by CD-spectroscopy using the modified exciton chirality method of NAKANISHI *et al.*[13]. For that reason landomycin A (**1**) was converted into the 1,6,8-tri-*O*-(*p*-methoxy)benzoyllandomycinone A

Fig. 2. CD curve, transition moments (arrows) and the resulting exciton couplings of landomycinone-1,6,8-tribenzoate (**6**).



The *quasi*-Newman-projection refers to the dotted line in the figure. From the rotation of the chiralities of the two electric transition moments (arrows, in the sense of a counterclockwise twist are in accordance with the negative couplet of the CD-curve) follows the *R*-configuration at C-6.

(**6**) by treatment with *p*-methoxybenzoylchloride and subsequent hydrolysis of the sugars. The observed exciton coupling shows a negative couplet which is in accordance with an *R*-configuration at C-6 (see Fig. 2)[13]. The exciton coupling is primarily due to the interaction between the naphthazarine chromophore and 6-*p*-methoxybenzoate. The interactions of the additional *p*-methoxybenzoyl residues (at C-1 and C-8) with the 6-*p*-methoxybenzoate can be neglected because of the wider distance to C-6 (see Fig. 2), since the exciton effect is inversely proportional to r^2, r being the interchromophoric distance[13].

The structures of the minor congeners of landomycin A were elucidated by comparison of their physico-chemical data with those of landomycin A (**1**).

Landomycin B (**7**): From the FAB-MS (*m/z* 973) and the elemental analysis of its octaacetyl derivative (**8**) a molecular formula $C_{49}H_{64}O_{20}$ could be deduced. Thus landomycin B (**7**) differs from landomycin A (**1**) by one sugar unit. The NMR data of landomycin B (**7**) and of landomycin B-octaacetate (**8**) in comparison with their analog of landomycin A (**1** and **3**, respectively) show that the last sugar of the chain, rhodinose F, is missing in landomycin B (**7**). Methanolysis experiments (yielding the same aglycone **2** and the same sugar derivatives as obtained from **1**) and all other physico-chemical data (see Experimental section) confirm the proposed structure **7**.

Landomycin C (**9**): From the FAB-MS (*m/z* 1,070) of landomycin C (**9**) a molecular formula of $C_{55}H_{74}O_{21}$ could be deduced, describing **9** as deoxylandomycin A. By comparison of the NMR data of **9** with those of **1** only the differences in the resonances of sugar D are significant, proving sugar D to be an amicetose instead of an olivose. Methanolysis experiments (TLC) show, beside landomycinone A (**2**) and the known methyl glycosides of olivose and rhodinose, a third sugar component whose Rf value and color development (*p*-anisaldehyde) is in agreement with amicetose[14]. Isolation of the amicetose was not possible because of the small amounts of landomycin C (**9**) available.

Landomycin D (**10**): Methanolysis experiments gave, besides **2**, the methyl olivosides (**4** and β-anomer) as the only sugar components. From the FAB-MS (*m/z* 598) a molecular formula of $C_{31}H_{34}O_{12}$ could be deduced which is in agreement with the proposed structure **10**. The ^1H NMR data of landomycin D

(**10**) confirmed this conclusion. Because of the minimal yields of **10**, no useful ^{13}C NMR spectrum could be obtained.

Discussion

While aquayamycin[15] with its benz[a]anthracene (also called isotetracenone[16])-aglycone has been found to be the most common angucyclinone, a larger variety of aglycone structures has been found more recently, *e.g.*, in the urdamycin complex[17,18] or the sakyomicins[19]. Aglycone varieties are also found in the fujianmycins[20] or SF2315A and B[21]. However, the aglycones of the most angucyclinones consist of a naphthoquinone- or an anthraquinone-derived chromophore (rings C, D or B, C, D, respectively) and a ring A which is saturated or partially saturated. With the landomycins we found the first examples of angucycline antibiotics having an aromatic ring A and a dihydroxy naphthoquinone (naphthazarine) chromophore, separated by the saturated 5~6 bond with the secondary alcohol group at C-6. This is unusual, because one would expect a facile dehydration into the hydroxybenz[a]anthracenedione system which has been found, *e.g.*, with tetrangulol[22]. Surprisingly, the aglycone moiety was shown to be reasonably stable, *i.e.* treatment with 1 N HCl is necessary to cause this dehydration, leading to the anhydrolandomycinone A (**11**). A similar structural element occurs on the recently discovered antibiotics of the benz[a]naphthacenequinone type, *e.g.*, KS-619-1[23], SF2446[24], G-2N[25], the benanomicins[26] and the pradimicins[27], all of which have an aglycone similar to that of the landomycins, but an anthraquinone-derived instead of a naphthoquinone-derived chromophore.

A unique and novel structural feature of the landomycins A, B and C is the long sugar chain, connected phenyl glycosidically to the aglycone moiety. Phenyl glycosides are still rare among antibiotics, there are some examples with one sugar moiety, *e.g.* chromocyclomycin[28], elloramycin[29], or the non-natural anthracycline antibiotic 4-*O*-(β-D-glucopyranosyl)-ε-rhodomycinone[30] which could be obtained *via* microbial transformation of rhodomycinone. One of the few examples of a biologically active phenyl glycoside antibiotic with a sugar chain, *i.e.* two sugars, is chartreusin[31]. Among the angucycline antibiotics are several examples with longer sugar chains, but those are either connected *C*-glycosidically or at the tertiary 3-OH of ring A[32,33].

The landomycins have interesting antibacterial and cytotoxic activities which will be reported in the following paper[4].

Experimental

General

TLC: Silica gel plates (Macherey & Nagel Sil G/UV 254+366, 0.25 mm); solvent front distance for Rf values: 15 cm.

MP's were measured with a Reichert hot stage microscope and are uncorrected. FAB- and FD-MS were measured on a Finnigan MAT 8230 with triethylamine or 3-nitrobenzyl alcohol as the matrix, and EI-MS on a Varian 311A. Perfluorokerosine was used as a standard for HR measurements. IR spectra were determined on a Perkin-Elmer Mod. 298; only absorption bands between 4000 and 1500 cm^{-1} are listed. UV spectra were measured on a Kontron Uvikon 860 equipped with a plotter P 800 (Kontron). NMR spectra were determined using a Varian XL 200, a Varian VXR 200, an IBM AF-300 or a Varian XL 500; chemical shifts are in ppm relative to internal TMS. Carbon multiplicities were recorded using the attached proton test (APT) or DEPT sequences. CD spectra were measured on methanol solutions with a Jasco J-500 A in connection with a Jasco if-500 A/D changer and a BMC-if 800 personal computer as the processor. All the extremes between 600 and 220 nm are recorded. The θ-values are in $cm^2 \times deg/10 \times mol$ and were standardized with androsterone (c=0.05%, θ=+11,170 at 304 nm). Optical rotations were determined with a Perkin-Elmer Mod. 241 polarimeter.

Isolation of the Pure Landomycins

To separate the landomycins, the crude product obtained from the fermentation process of *Streptomyces* sp. (DSM 5087) was chromatographed in 100~200 mg portions on silica gel (Kieselgel 60,

<0.08 mm, Merck) using chloroform - methanol (9 : 1) as the eluent. The main fractions containing landomycins A, B, C and D were rechromatographed in 20~50 mg portions on Sephadex LH-20 (Pharmacia) with methanol as the eluent. The solids were obtained as amorphous powders by precipitating the concentrated chloroform solutions into *n*-pentane. One g crude product yielded 400 mg of landomycin A, 90 mg of landomycin B, 17 mg of landomycin C and 10 mg of landomycin D.

Landomycin A (**1**): MP 152°C; Rf 0.47 ($CHCl_3$ - MeOH, 9 : 1); IR (KBr) cm^{-1} 3420 m, 2970 m, 2935 m, 2880 m, 1765 w, 1725 w, 1645 s, 1615 s, 1595 m, 1565 s; negative FAB-MS *m/z* 1,087 ($(M+2H-H)^-$); positive FAB-MS *m/z* 1,089 ($(M-2H+H)^+$); FD-MS *m/z* (abundance) 320 (80%), 115 (100%); EI-MS (70 eV): Evaporation curve shows the decomposition of the molecule, one can see: After 0 : 45 minutes *m/z* (abundance) 244 (50%, Oliv-Rhod), 170 (30%), 143 (15%), 142 (35%), 128 (20%), 105 (40%), 91 (25%), 77 (22%), 57 (20%), 44 (100%); after 0 : 55 minutes *m/z* (abundance) 244 (60%, Oliv-Rhod), 225 (5%), 185 (20%), 170 (40%), 143 (65%), 128 (60%), 105 (80%), 91 (20%), 77 (5%), 65 (5%), 57 (20%), 43 (100%); after 1 : 40 minutes *m/z* (abundance) 320 (100%, HR, calcd for $C_{19}H_{12}O_5$ and found: 320.06922, M − sugars − H_2O), 160 (5%), 57 (5%), 44 (20%); after 2 : 00 minutes *m/z* (abundance) 243 (6%, Rhod-Oliv), 157 (2%), 131 (80%, Oliv), 115 (60%, Rhod), 113 (100%), 97 (46%), 96 (55%), 81 (20%), 73 (25%), 69 (40%), 57 (75%), 43 (60%); UV λ_{max}^{MeOH} nm (ε) 259 (10,400), 288 (6,900), 448 (4,600); $\lambda_{max}^{MeOH-NaOH}$ nm (ε) 315 (6,600), 534 (4,300); CD $\lambda_{extreme}^{MeOH}$ nm ($[\theta]^{20}$) 233 (−32,000), 274 (−10,900), 286 (−12,600), 312 (−2,500), 404 (−5,200), 476 (+2,500); ^1H NMR (500 MHz, $CDCl_3$) see Table 1; ^{13}C NMR (50.3 MHz, $CDCl_3$) see Table 2.

Anal Calcd for $C_{55}H_{74}O_{22}$: C 60.76, H 6.86.
Calcd for $C_{55}H_{74}O_{22} \cdot H_2O$: C 59.77, H 6.93.
Found: C 59.88, H 7.09.

Landomycin B (**7**): MP 147°C; Rf 0.40 ($CHCl_3$ - MeOH, 9 : 1); IR (KBr) cm^{-1} 3440 m, 2980 m, 2940 m, 2882 m, 1650 sh, 1645 s, 1630 s, 1620 s, 1575 m; negative FAB-MS *m/z* 973, ($(M+2H-H)^-$); UV λ_{max}^{MeOH} nm (ε) 258 (12,000), 286 (9,000), 444 (3,400); $\lambda_{max}^{MeOH-NaOH}$ nm (ε) 291 (7,600), 528 (2,900); CD $\lambda_{extreme}^{MeOH}$ nm ($[\theta]^{20}$) 234 (−22,400), 316 (+3,700), 398 (−7,700), 482 (+4,100); ^1H NMR (200 MHz, DMSO-d_6) see Table 1; ^{13}C NMR (50.3 MHz, DMSO-d_6) see Table 2.

Landomycin C (**9**): MP 176~180°C; Rf 0.49 ($CHCl_3$ - MeOH, 9 : 1); IR (KBr) cm^{-1} 3440 m, 2970 m, 2938 m, 2877 m, 1735 s, 1650 m, 1627 sh, 1618 m, 1570 m; negative FAB-MS *m/z* 1,070 ($(M+H-H)^-$); UV λ_{max}^{MeOH} nm (ε) 261 (14,500), 289 (10,200), 444 (6,500); $\lambda_{max}^{MeOH-NaOH}$ nm (ε) 316 (6,500), 526 (5,200); CD $\lambda_{extreme}^{MeOH}$ nm ($[\theta]^{20}$) 234 (−34,700), 272 (−16,000), 288 (−17,600), 316 (−2,400), 410 (−14,600), 488 (+4,900); ^1H NMR (500 MHz, $CDCl_3$) see Table 1; ^{13}C NMR (50.3 MHz, $CDCl_3$) see Table 2.

Landomycin D (**10**): MP 161°C; Rf 0.28 ($CHCl_3$ - MeOH, 9 : 1); IR (KBr) cm^{-1} 3420 m, 2980 w, 2940 w, 2880 w, 1650 s, 1622 s, 1617 s, 1560 m; negative FAB-MS *m/z* 598 ($(M+H-H)^-$); UV λ_{max}^{MeOH} nm (ε) 262 (13,800), 285 (sh, 9,900), 442 (5,500); $\lambda_{max}^{MeOH-NaOH}$ nm (ε) 238 (24,200), 303 (9,000), 528 (5,100); CD $\lambda_{extreme}^{MeOH}$ nm ($[\theta]^{20}$) 230 (−26,100), 272 (−7,800), 286 (−8,900), 318 (+3,000), 404 (−8,000), 482 (+3,200); ^1H NMR (200 MHz, CD_3OD) see Table 1.

Peracetylation of Landomycins A and B

63 mg landomycin A (**1**) was treated with 5 ml acetic anhydride and 100 mg *N,N*-dimethylaminopyridine. The mixture was stirred at room temperature until it became a clear solution, stirring was continued for another 48 hours. The solution was poured into water and stirred for about 12 hours. Extraction of the products with chloroform, chromatography on silica gel (column 30 × 3 cm, $CHCl_3$ - MeOH, 95 : 5) and Sephadex LH-20 (column 100 × 2.5, MeOH) gave besides incomplete acetylated products landomycin A-octaacetate (**3**). The product was obtained as yellow, amorphous powder by precipitating its concentrated chloroform solution into petroleum ether, yield: 38 mg (46%).

In an analogous procedure one could obtain 28 mg (56% yield) of the landomycin B-octaacetate (**8**) as a yellow amorphous solid, starting from 37 mg landomycin B (**7**). For the Sephadex chromatography step acetone was used instead of methanol as the eluent.

Landomycin A-octaacetate (**3**): MP 158~162°C; Rf 0.89 ($CHCl_3$ - MeOH, 95 : 5); IR (KBr) cm^{-1} 3450 m, 2980 m, 2940 m, 2860 sh, 1775 sh, 1742 s, 1675 m, 1660 sh, 1620 m, 1580 w; negative FAB-MS *m/z* 1,422 ($(M+H-H)^-$); UV λ_{max}^{MeOH} nm (ε) 250 (7,000), 295 (sh, 2,700), 374 (1,900); $\lambda_{max}^{MeOH-NaOH}$ nm (ε) 292 (4,500), 301 (4,300), 375 (1,200), 532 (1,600); CD $\lambda_{extreme}^{MeOH}$ nm ($[\theta]^{20}$) 247 (−81,600), 292 (+15,900), 382

(33,800), 467 (+17,900); ^{1}H NMR (300 MHz, acetone-d_6): See Table 1; ^{13}C NMR (75.4 MHz, acetone-d_6): See Table 2.

Anal Calcd for $C_{71}H_{90}O_{30}$: C 59.91, H 6.37.
Calcd for $C_{71}H_{90}O_{30} \cdot H_2O$: C 59.16, H 6.43.
Found: C 59.11, H 6.43.

Landomycin B-octaacetate (**8**): MP 152~155°C; Rf 0.91 ($CHCl_3$-MeOH, 95:5); IR (KBr) cm^{-1} 3450 m, 2980 m, 2940 m, 2880 m, 1775 sh, 1743 s, 1675 m, 1640 m, 1580 w; UV λ_{max}^{MeOH} nm (ε) 256 (4,400), 300 (sh, 1,200), 377 (1,600); CD $\lambda_{extreme}^{MeOH}$ nm ($[\theta]^{20}$) 240 (−62,500), 284 (+12,000), 376 (−26,400), 460 (+14,400); ^{1}H NMR (200 MHz, $CDCl_3$): See Table 1; ^{13}C NMR (50.3 MHz, $CDCl_3$): See Table 2.

Anal Calcd for $C_{65}H_{80}O_{28}$: C 59.63, H 6.16.
Found C 59.35, H 6.19.

Hydrolysis of Landomycin A

(a) 10 mg landomycin A (**1**) were dissolved in 5 ml 0.1 M methanolic HCl (prepared by reaction of 0.1 mol acetyl chloride with 1 liter of methanol) and stirred for 5 minutes at room temperature. The mixture was evaporated to dryness, the red solid was chromatographed on silica gel (column 30×3 cm, $CHCl_3$-MeOH-acetic acid, 90:10:1), and on Sephadex LH-20 (column 100×2.5 cm, MeOH-acetic acid, 99:1) to yield 2.3 mg (74%) landomycinone A (**2**).

(b) 100 mg **1** were dissolved in 50 ml 0.1 N methanolic HCl (as in (a)), but stirred for 2 hours. The red solid obtained by removing of the solvents was chromatographed on silica gel (column, 30×3 cm, $CHCl_3$-MeOH, 9:1), to yield methyl-L-rhodinoside, methyl-α,β-D-olivoside and a red dye. The latter was further chromatographed on silica gel (column 30×3 cm, $CHCl_3$), to yield 25 mg anhydrolandomycinone A (**11**). The sugar fractions were finally purified by chromatography on silica gel (column 30×3 cm, $CHCl_3$-MeOH, 95:5) and Sephadex LH-20 (column 100×2.5 cm, MeOH), to yield 6 mg (22%) methyl-α,β-L-rhodinoside, and 11 mg (18%) pure methyl-α-D-olivoside (**4**) besides 21 mg (35%) methyl-α,β-D-olivoside, respectively, as colorless syrups.

(c) 30 mg **1** was dissolved in 2 ml methanol and treated with 2 mg malonic acid for 12 hours at room temperature. The workup procedure was as in (a). Yield: 6 mg (64%) landomycinone A (**2**).

Landomycinone A (**2**): MP 228~230°C; Rf 0.73 ($CHCl_3$-MeOH-acetic acid, 90:10:1); IR (KBr) cm^{-1} 3460 m, 3200 w, 2950 sh, 2920 w, 2850 w, 1705 w, 1640 sh, 1620 sh, 1588 s, 1555 s; EI-MS (70 eV) *m/z* (abundance) 338 (M^+, 8%), 320 ($M-H_2O$, 100%), 302 (30%), 292 (8%), 274 (8%), 189 (9%), 160 (10%), 72 (10%), 60 (32%), 44 (78%); UV λ_{max}^{MeOH} nm (ε) 262 (13,600), 288 (9,600), 368 (3,200), 503 (3,400); $\lambda_{max}^{MeOH-HCl}$ nm (ε) 263 (11,000), 287 (8,700), 368 (3,200), 500 (4,700); $\lambda_{max}^{MeOH-NaOH}$ nm (ε) 255 (sh, 14,200), 291 (8,000), 478 (2,800), 599 (11,300), 640 (10,500); CD $\lambda_{extreme}^{MeOH}$ nm ($[\theta]^{20}$) 230 (−35,600), 272 (−11,600), 284 (−13,300), 326 (−900), 394 (−7,600), 448 (+4,000); ^{1}H NMR (200 MHz, CD_3OD) δ 2.22 (s, 3-CH_3), 2.34 (dd, J=16 and 4 Hz, 5-H_α), 2.82 (dd, J=16 and 2 Hz, 5-H_β), 5.14 (dd, J=4 and 2 Hz, 6-H), 6.41 (br s, 4-H), 6.44 (br s, 2-H), 6.66 (d, J=10 Hz, 9/10-H), 6.82 (d, J=10 Hz, 9/10-H).

Anhydrolandomycinone A (**11**): MP 210~215°C; Rf 0.42 ($CHCl_3$); IR (KBr) cm^{-1} 3440 m, 3050 w, 2960 w, 2920 m, 2860 w, 1610 s, 1590 s, 1560 s, 1500 s; EI-MS (70 eV) *m/z* (abundance) 320 (M^+, 100%), 302 ($M-H_2O$, 90%), 292 (20%), 274 (35%), 189 (35%), 160 (40%); UV λ_{max}^{MeOH} nm (ε) 319 (15,300), 500 (5,900), 516 (6,300), 560 (3,300); $\lambda_{max}^{MeOH-NaOH}$ nm (ε) 304 (sh, 17,500), 585 (10,900), 625 (11,600); CD $\lambda_{extreme}^{MeOH}$ nm ($[\theta]^{20}$) 264 (−600), 310 (−1,300), 400 (+200), 430 (0), 504 (+800); ^{1}H NMR (200 MHz, CD_2Cl_2) δ 2.50 (s, 3-CH_3), 7.15 (d, J=2 Hz, 4-H), 7.32 (d, J=2 Hz, 2-H), 7.34 (2H, s, 9-H and 10-H), 8.18 (d, J=9 Hz, 5-H), 8.34 (d, J=9 Hz, 6-H), 11.06 (s, 1-OH), 12.48 (s, 11-OH), 12.97 (8-OH).

Methyl-α,β-L-rhodinoside: (α:β, 2:1) Rf 0.56 ($CHCl_3$-MeOH, 9:1); ^{1}H NMR (200 MHz, $CDCl_3$, only signals from the methyl-α-L-rhodinoside) δ 1.20 (d, J=7 Hz, 5-CH_3), 1.3~1.5 (2H, m, 2-H_a and 3-H_a), 1.8~2.4 (2H, m, 2-H_e and 3-H_e), 3.36 (s, OCH_3), 3.57 (br s, 4-H), 3.94 (dq, J=7 and 2 Hz, 5-H), 4.70 (dd, J=4 and 1 Hz, 1-H).

Methyl-α-D-olivoside (**4**): Rf 0.34 ($CHCl_3$-MeOH, 9:1); $[\alpha]_D^{20}$ +131° (*c* 1.1, EtOH); +125° (*c* 0.9, acetone); EI-MS (70 eV) *m/z* (abundance) 131 (M−OMe, 14%, HR calcd for $C_6H_{11}O_3$ and found: 131.1013), 104 (30%), 59 (100%); ^{1}H NMR (200 MHz, CD_3OD) δ 1.23 (d, J=7 Hz, 5-CH_3), 1.58 (ddd, J=14, 12 and 4 Hz, 2-H_a), 2.04 (ddd, J=14, 6 and 1 Hz, 2-H_e), 2.92 (dd, J=9 and 9 Hz, 4-H), 3.29 (s, OCH_3), 3.55 (dq, J=9 and 7 Hz, 5-H), 3.74 (ddd, J=12, 9 and 6 Hz, 3-H), 4.70 (dd, J=4 and 1 Hz, 1-H).

Methyl-β-D-olivoside: Rf 0.38 ($CHCl_3$ - MeOH, 9 : 1); ^1H NMR (signals from the α/β (1 : 3) mixture, β-methylolivoside signals only, 200 MHz, CD_3OD) δ 1.28 (d, $J=7$ Hz, 5-CH_3), 1.43 (ddd, $J=13$, 13 and 10 Hz, 2-H_a), 2.10 (ddd, $J=13$, 5 and 2 Hz, 2-H_e), 3.88 (dd, $J=9$ and 9 Hz, 4-H), 3.24 (dq, $J=9$ and 7 Hz, 5-H), 3.51 (ddd, $J=13$, 9 and 5 Hz, 3-H), 4.42 (dd, $J=10$ and 2 Hz, 1-H).

L-Rhodinose-2,4-dinitrophenylhydrazone (**5**): 10 mg of the methylrhodinoside-mixture were dissolved in 3 ml of ethanol and treated with 400 mg dinitrophenylhydrazine (dissolved in 1 ml ethanol), 1 ml conc H_2SO_4 and 2 ml of water. After stirring for 2.5 hours at room temperature the mixture was poured into 200 ml of water. Extraction with $CHCl_3$ (3 ×) and evaporation of the combined organic layers to dryness gave a yellow solid which was chromatographed on silica gel (column 30 × 3 cm, $CHCl_3$ - MeOH, 95 : 5). The second fraction was a mixture of yellow compounds which could be separated on Sephadex LH-20 (column 100 × 2.5 cm, $CHCl_3$). The third of 5 yellow fractions was the desired L-rhodinose-2,4-dinitrophenylhydrazone (**5**, NMR control). Yield: 9.3 mg (43%).

MP 115°C; Rf 0.44 ($CHCl_3$ - MeOH, 9 : 1); $[\alpha]_D^{20}$ −17° (*c* 0.5, pyridine); EI-MS (70 eV) *m/z* (abundance) 312 (M^+, 3%, HR calcd for $C_{12}H_{16}N_4O_6$ and found: 312.1069), 115 (100%, rhodinose), 97 (80%); ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (d, $J=7$ Hz, 5-CH_3), 1.6~2.0 (m, 3-H_2), 2.5~2.7 (m, 2-H_2), 3.46 (m, 4-H), 3.68 (dq, $J=7$ and 6 Hz, 5-H), 7.64 (dd, $J=5$ and 5 Hz, 1-H), 7.91 (d, $J=10$ Hz, 6'-H), 8.31 (dd, $J=10$ and 3 Hz, 5'-H), 9.12 (d, $J=3$ Hz, 3'-H), 11.04 (br s, NH).

Landomycinone-1,6,8-tri-*O*-(4-*O*-methyl)benzoate (**6**): 45 mg landomycin A (**1**) was dissolved in 1.5 ml pyridine and treated with 100 mg 4-methoxybenzoyl chloride. After 3 hours stirring at room temperature the mixture was poured into 200 ml ice-water and allowed to stand overnight (*ca.* 12 hours). The products were extracted with chloroform and evaporated to dryness, residual pyridine was removed azeotropically with toluene. The solid residue was dissolved in a mixture of 3 ml 2 N methanolic HCl and 1 ml chloroform and stirred for 1 hour (hydrolysis of the sugars). The solvents were removed *in vacuo*, and the solid residue was chromatographed on silica gel (column 30 × 3 cm, $CHCl_3$ - MeOH; 95 : 5). Those fractions containing the main yellow zone were collected, evaporated to dryness and chromatographed on Sephadex LH-20 (column 100 × 2.5 cm, acetone) and silica gel (column 40 × 2.5 cm, ethyl acetate - hexane, 1 : 1), to yield 8.8 mg (29%) landomycinone-1,6,8-tri-*O*-(4-*O*-methyl)benzoate (**6**).

MP 118~122°C; Rf 0.53 (EtOAc - *n*-hexane, 1 : 1); IR (KBr) cm^{-1} 3440 m, 3080 w, 3000 w, 2960 m, 2936 m, 2840 w, 1735 s, 1720 sh, 1675 m, 1634 s, 1609 s, 1581 m, 1513 s; negative FAB-MS *m/z* 740 ($(M+H-H)^-$); UV λ_{max}^{MeOH} nm (ε) 259 (41,600), 422 (3,200); $\lambda_{max}^{MeOH-NaOH}$ nm (ε) 256 (39,100), 320 (sh, 5,200), 528 (3,000); CD $\lambda_{extreme}^{MeOH}$ nm ($[\theta]^{20}$) 227 (−32,100), 251 (+15,700), 276 (−34,900), 297 (−5,900), 320 (−7,100), 345 (−5,300), 382 (−13,700), 470 (+2,400); ^1H NMR (200 MHz, $CDCl_3$) δ 2.34 (s, 3-CH_3), 3.05 (dd, $J=18$ and 4 Hz, 5-H_α), 3.42 (dd, $J=18$ and 2 Hz, 5-H_β), 3.79 (s, OCH_3), 3.89 (s, OCH_3), 3.91 (s, OCH_3), 6.64 (dd, $J=4$ and 2 Hz, 6-H), 6.82 (4H, m) and 6.86 (2H, m, benzoyl-H), 7.00 (br s, 4-H), 7.10 (br s, 2-H), 7.28 (d, $J=9$ Hz, 9/10-H), 7.42 (d, $J=9$ Hz, 9/10-H), 7.71 (2H, m), 7.81 (2H, m) and 7.90 (2H, m, benzoyl-H), 12.51 (s, 11-OH).

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