URDAMYCINS, NEW ANGUCYCLINE ANTIBIOTICS FROM *STREPTOMYCES FRADIAE*

III. THE STRUCTURES OF URDAMYCINS C AND D

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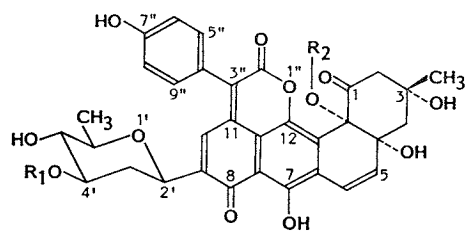
In our recent report of structural studies of urdamycins B to F[1], we published partial structures of urdamycins C and D, the two largest molecules among the complex of angucycline antibiotics produced by *Streptomyces fradiae* (strain Tü 2717)[2]. Now we can complete both structures, which are represented by the formulae **1** (urdamycin C) and **2** (urdamycin D).



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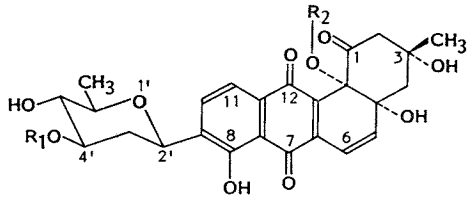

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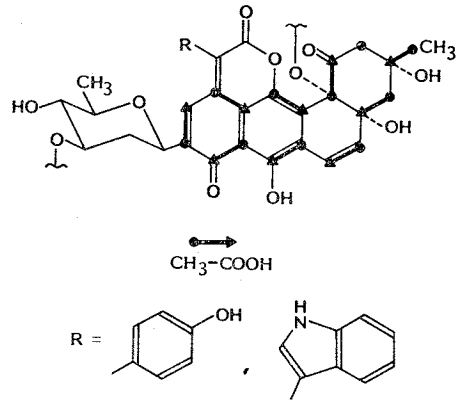
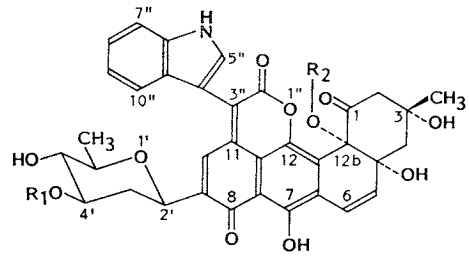
After several unsuccessful attempts to obtain crystals of either the natural products themselves or of derivatives, we tried to solve the structures by a biosynthetic approach. Comparison of the NMR data of urdamycin C (**1**) and of urdamycin D (**2**) with those of urdamycin A (**3**) showed that both antibiotics possess the complete angucycline[2] 4-ring system and the same sugar pattern. Additional structural elements ($C_8H_5O_3$ in the case of **1**, $C_{10}H_6NO_2$ in the case of **2**) are linked to the C-11/C-12 region[1].

It was not possible to assign all carbon signals,

Fig. 1. Labeling pattern of urdamycins C and D biosynthesized from [^{13}C]acetate.





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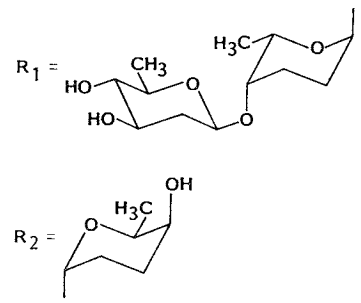


i.e., those of the additional structural moieties and the carbons through which they are linked with the angucycline ring system. The biosynthetic studies showed that the angucycline ring system of the urdamycins derives from acetate units[3] which are connected in the same way as in the angucycline antibiotic vineomycin A_1[4], while the extra structural units of urdamycins C and D were not labeled by acetate (Fig. 1).

Thus it was possible to distinguish between the carbon signals deriving from the unknown parts of the structure and those belonging to the angucycline moiety. The latter also can now be assigned completely (see Table 1).

The remaining carbon signals showed an evident similarity to well-known natural product structures, *e.g.*, in the case of urdamycin C (**1**) to the *p*-hydroxyphenyl residues of flavones or phenylcoumarin moieties and in the case of urdamycin D (**2**) to indolyl systems[5~8]. The signals at 159.5 and 159.6 ppm in **1** and **2**, re-

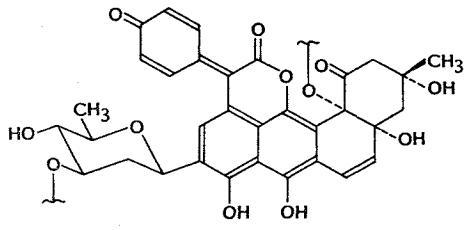
Table 1. ^{13}C NMR assignments of the aglycones of urdamycins C (**1**) and D (**2**) (50.3 MHz, 4.7_{Tesla}; acetone-d_6; 3-CH_3 of **1** in CD_3CN, 3-CH_3 of **2** in DMSO-d_6; multiplicity assignments by distortionless enhancement by polarization transfer).

C-atom	1	2	C-atom	1	2
1	203.8 s	203.9 s	2′	72.1 d	72.2 d
2	54.6 t	54.7 t	3′	40.3 t	40.4 t
3	74.9 s	74.8 s	4′	78.3 d	78.4 d
3-CH_3	29.4 q	29.5 q	5′	79.2 d	79.3 d
4	44.0 t	44.1 t	6′	72.5 d	72.6 d
4a	82.2 s	82.3 s	7′	18.6 q	18.6 q
5	138.8 d	138.3 d	2″	159.5 s	159.6 s
6	118.6 d	118.8 d	3″	132.7 s	127.9 s
6a	125.2 s	123.9 s	4″	123.7 s	109.1 s
7	156.6 s	156.7 s	5″	134.5 d	133.2 d
7a	112.6 s	112.9 s	6″	115.9 d	—
8	187.5 s	187.5 s	6″a	—	137.4 s
9	145.0 s	143.6 s	7″	160.0 s	113.1 d
10	134.7 d	136.1 d	8″	115.9 d	123.5 d
11	133.9 s	130.7 s	9″	134.5 d	121.8 d
11a	116.2 s	116.8 s	10″	—	121.1 d
12	143.7 s	143.1 s	10″a	—	127.8 s
12a	128.9 s	128.4 s			
12b	83.1 s	83.3 s			

Table 2. Assignments of the ^1H NMR signals of urdamycins C (**1**) and D (**2**) in different solvents; downfield region only (in ppm, 200 MHz, TMS as internal standard, *J* (Hz) in brackets).

Position	1		Position	2	
	Acetone-d_6	Acetonitrile-d_3		Acetone-d_6	Dioxane-d_8
5-H	6.20 d (10)	6.24 d (10)	5-H	6.16 d (10)	6.10 d (10)
6-H	7.05 d (10)	7.13 d (10)	6-H	7.06 d (10)	7.03 d (10)
7-OH	13.16 s	13.14 s	7-OH	NO	13.25 br s
10-H[a]	7.96 d (2)	7.89 d (1.5)	10-H[a]	8.25 d (1.5)	8.21 d (1.5)
5″-H	7.47 d (8)	7.51 d (8)	5″-H	8.12 s	8.10 d (2)
6″-H	7.06 d (8)	7.13 d (8)	NH	11.26 br s	10.76 d (2)
7″-OH	9.10 s	7.69 s	7″-H	7.62 dd (8, 2)	7.51 dd (8, 1)
8″-H	7.06 d (8)	7.13 d (8)	8″-H	7.29 ddd (8, 8, 2)	7.28 ddd (8, 8, 1)
9″-H	7.47 d (8)	7.51 d (8)	9″-H	7.20 ddd (8, 8, 2)	7.19 ddd (8, 8, 1)
			10″-H	7.63 dd (8, 2)	7.59 dd (8, 1)

[a] Coupling with 2′-H.
NO: Not observed.



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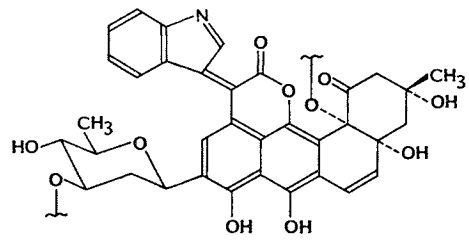

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Fig. 2. $^{3}J_{C-H}$ Long range couplings observed in urdamycin C by the heteronuclear multiple-bond connectivity (HMBC) pulse sequence.

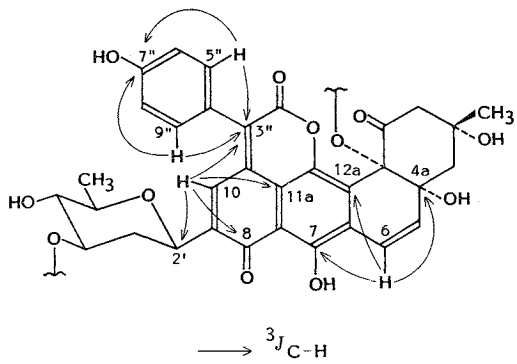
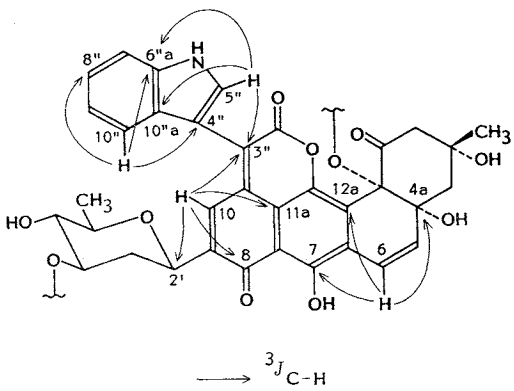


Fig. 3. $^{3}J_{C-H}$ Long range couplings (as Fig. 2; for urdamycin D).



All other $^{3}J_{C-H}$- and some $^{2}J_{C-H}$-couplings are omitted for reasons of clarity. The HMBC spectra were recorded on a Bruker WM 300 instrument at 7_{Tesla} in acetone-d_6.

spectively, are typical for aromatic δ-lactones, as seen in coumarins or in antibiotics of the toromycin (gilvocarcin) group or in chartreusin[9~11]. The connection of these structural elements with the angucycline system as shown in formulae **1** and **2** is biosynthetically reasonable and could be proved by NMR (chemical shift of C-12; heteronuclear multiple-bond connectivity (HMBC) spectra[12,13], showing $^{3}J_{C-H}$ long range couplings as illustrated in Figs. 2 and 3; nuclear Overhauser effect (NOE)-difference spectra, which demonstrated the proximity of 10-H to 5″/9″-H in **1** and of 10-H to 10″-H in **2** (see also Tables 1 and 2).

Thus the additional structural elements of the urdamycins C (**1**) and D (**2**) form quinonemethides with the angucycline backbone, that changes the chromophores drastically in comparison with urdamycin A (**3**). Neither chromophore has been previously found in natural products. Because of their enlarged aglycones, these antibiotics occupy a similarly unique position among the angucycline antibiotics as the nogalamycin-related antibiotics among the anthracyclines[14~16]. While the nogalamycin-related antibiotics have their acetate-derived aglycones enlarged by structural elements coming from the sugar pool[14], we propose that the extra units of **1** and **2** derive biogenetically from the amino acid pool, *i.e.*, from tyrosine and tryptophan. Further studies on the biosynthesis of these antibiotics are in progress. Antibiotics **1** and **2** should exist, at least partially, as their tautomeric structures **4** and **5**, which would provide an explanation for the intense dark red and blue colors, respectively, of these compounds.

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