SYNTHESES OF 4′-DEOXY-DEMYCAROSYL TYLOSIN AND ITS ANALOGUES

Sir:

In the preceding papers[1,2] it was shown that the 4′-deoxy derivative of mycaminosyl tylonolide and its 23-substituted derivatives exhibit enhanced antibacterial activities in comparison to those of the corresponding 4′-hydroxyl compounds. This paper describes the syntheses of the 4′-deoxygenated derivatives of demycarosyl tylosin[3] (**1**) and its analogues.

Demycarosyl tylosin diethylacetal (**2**) obtained by treating **1** with acidic ethanol was acetylated with acetic anhydride in acetonitrile in the absence of an external base[4] to give 2′,4′-di-*O*-acetyl derivative (**3**), $[\alpha]_D^{22}-3°$ (*c* 1, chloroform); ^{1}H NMR: δ 2.08 (6H, s, Ac). Tetrahydrofuranylation of **3** in dichloromethane with 2,3-dihydrofuran in the presence of pyridinium *p*-toluenesulfonate in a manner already described[1] gave the 3,4′′-bis(*O*-tetrahydrofuranyl) derivative (**4**): Found (Calcd. for $C_{55}H_{87}NO_{17}$): C, 61.86 (62.11); H, 8.59 (8.89); N, 1.37 (1.42)%. Removal of the 2′- and 4′-*O*-acetyl groups (to give **5**), selective 4′-*O*-benzylsulfonylation (to give **6**), replacement of the sulfonyloxy group with iodine (to give **7**), reductive deiodination (to give **8**) and deblocking of the tetrahydrofuranyl and acetal groups were carried out successively as already described[1] to give 4′-deoxy-demycarosyl tylosin (**9**), $[\alpha]_D^{23}-26°$ (*c* 0.8, chloroform); ^{1}H NMR ($CDCl_3$): δ 1.79 (3H, s, 12-Me), 2.30 (6H, s, NMe_2), 3.51 and 3.66 (each 3H, s, OMe), 4.21 (1H, d, $J_{1',2'}$ 7.5 Hz, H-1′), 4.59 (1H, d, $J_{1'',2''}$ 8.0 Hz, H-1′′), 5.92 (1H, d, $J_{13,14}$ 10.5 Hz, H-13), 6.35 (1H, d, $J_{10,11}$ 16 Hz, H-10), 7.42 (1H, d, H-11), 9.80 (1H, s, CHO); Found (Calcd. for $C_{39}H_{65}NO_{13}$): C, 62.06 (61.97); H, 8.67 (8.67); N, 1.66 (1.85)%. The structure was confirmed by the ^{13}C NMR spectrum (Table 1).

Next, 3-*O*-acetyl, 3,4′′-di-*O*-acetyl and 2,3-unsaturated analogues of **9** were prepared.

Table 1. The ^{13}C NMR[a] chemical shifts[b] of 4′-deoxy-demycarosyl tylosin (**9**) in $CDCl_3$ (at 20°C).

Carbon	**9**[c]	Tylosin[6]	Carbon	**9**[c]	Tylosin[6]
1	173.73	173.9	20	203.31[f]	203.0
2	39.55	39.4	21	17.53	17.4
3	67.24	(67.47)[d]	22	12.96	13.0
4	45.09[e]	45.1	23	69.01	68.2
5	81.17	81.6	1′	104.25	(104.31)
6	31.46	32.3	2′	70.41	(70.47)
7	32.55	32.9	3′	65.71	(65.75)
8	41.04	40.3	4′	28.45	(28.73)
9	203.06[f]	202.8	5′	69.59	(69.59)
10	118.31	118.8	6′	21.10	(21.11)
11	147.96	148.0	NMe_2	40.25	(40.32)
12	134.77	134.9	1′′	101.09	101.1
13	142.25	142.2	2′′	81.96	82.0
14	45.05[e]	44.7	3′′	79.88	79.9
15	74.97	75.3 (75.02)	4′′	72.70	72.9
16	25.40	25.5	5′′	70.63	(70.6)
17	8.76	9.0	6′′	17.78	17.8
18	9.68	9.6	2′′-OMe	59.73	59.6
19	43.86	43.9	3′′-OMe	61.71	61.7

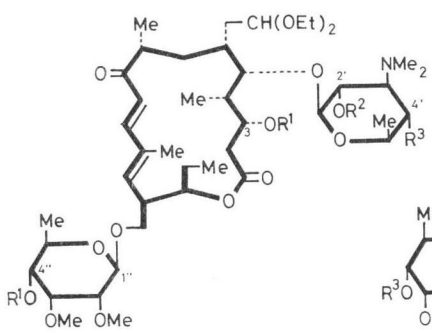
a) Measured at 62.9 MHz with a Bruker WM 250 spectrometer.

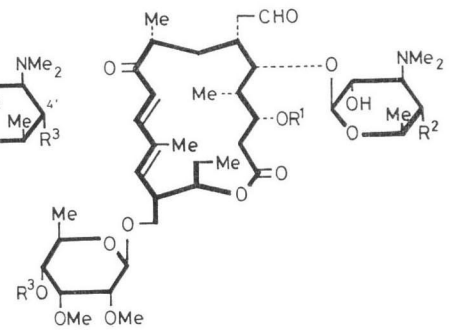
b) In ppm downfield from TMS.

c) Assignments were made by off-resonance method as well as by comparison with the data of tylosin[6] and 4′-deoxymycarosyl tylonolide[1].

d) Data cited in parenthesis are those for 4′-deoxymycaminosyl tylonolide[1].

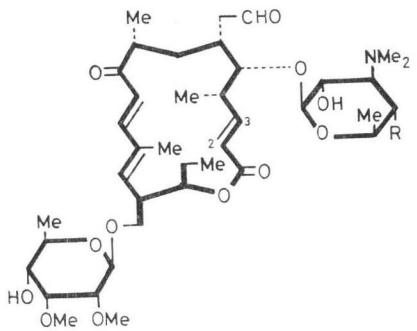
e, f) May be interconvertible.





	R^1	R^2	R^3
2	H	H	OH
3	H	Ac	OAc
4	~THF	Ac	OAc
5	~THF	H	OH
6	~THF	H	$OSO_2CH_2C_6H_5$
7	~THF	H	I
8	~THF	H	H
10	Ac	Ac	OAc
11	Ac	H	OH
14	Ac	H	$OSO_2CH_2C_6H_5$
15	Ac	H	I
16	Ac	H	H

	R^1	R^2	R^3
1	H	OH	H
9	H	H	H
12	Ac	OH	Ac
13	Ac	OH	H
17	Ac	H	Ac
18	Ac	H	H



	R
20	H
21	OH

Treatment of **2** with acetic anhydride in pyridine (50°C, 2 days) gave the 3,2′,4′,4″-tetra-*O*-acetyl derivative (**10**), $[\alpha]_D^{25}$ 0° (*c* 1, chloroform); ^{1}H NMR (in $CDCl_3$ at 40°C at 250 MHz): δ 2.03, 2.04 and 2.09 (each 3H, s, Ac), 2.11 (3H, br s, 3-*O*-Ac; at 20°C, the signal was too broad to be detectable[5]), 2.36 (6H, s, NMe_2). Selective removal of the 2′- and 4′-*O*-acetyl groups by dissolving **10** in methanol (50°C, overnight) (to give **11**) followed by deacetalation (in 0.1 M aqueous HCl - acetonitrile = 1 : 1, room temperature, 1 hour) gave 3,4″-di-*O*-acetyl-demycarosyl tylosin (**12**), $[\alpha]_D^{25}$ +13° (*c* 1, chloroform). ^{1}H NMR (in $CDCl_3$ at 90 MHz): δ 2.13 (6H, s, Ac), 2.52 (6H, s, NMe_2). An aqueous solution of **12** containing *p*-toluenesulfonic acid (1.5 mole equiv. for **12** and 0.035 M solution) was kept at 65°C for 2 days to give 3-*O*-acetyldemycarosyl tylosin (**13**) (70% after purification), $[\alpha]_D^{23}$ −2° (*c* 0.5, chloroform); ^{1}H NMR (in $CDCl_3$ at 90 MHz): δ 2.14 (3H, s, Ac), 5.21 (1H, m, H-3). It is noteworthy that selective deacetylation of C-4″ occurred by the above treatment.

Selective benzylsulfonylation of **11** gave 4′-*O*-benzylsulfonyl derivative (**14**), which, by iodination (to give **15**) followed by reductive deiodination (to give **16**) and deacetalation in a manner as already described[1,2] gave 3,4″-di-*O*-acetyl-4′-deoxy-demycarosyl tylosin (**17**), $[\alpha]_D^{23}$ +16° (*c* 0.5, chloroform); ^{1}H NMR (in $CDCl_3$ at 90 MHz): δ 2.11 (6H, s, Ac); Found (Calcd. for $C_{43}H_{69}NO_{15}$): C, 61.43 (61.48); H, 8.16 (8.28); N, 1.54 (1.67)%. Selective deacetylation at C-4″ of **17** in the manner described above gave 3-*O*-acetyl-4′-deoxy-demycarosyl tylosin (**18**) (54% after purification), $[\alpha]_D^{23}$ +0° (*c* 1, chloroform); ^{1}H NMR (in $CDCl_3$ at 90 MHz): δ 2.12 (3H, s, Ac); Found (Calcd. for $C_{41}H_{67}NO_{14}$): C, 61.39 (61.71); H, 8.52 (8.46); N, 1.64 (1.76)%. Treatment of **16** with 14%

Table 2. Antibacterial spectra of the products (mcg/ml).

Test organisms*	Tylosin	**1**	**9**	**12**	**17**	**13**	**18**	**21**	**20**
Staph. aureus 193	1.56	3.12	0.78	25	12.5	1.56	0.78	3.12	0.78
〃 EMf	6.25	12.5	6.25	>100	>100	12.5	12.5	50	25
〃 209P	1.56	3.12	<0.2	6.25	6.25	0.78	0.39	0.78	0.39
〃 Smith	0.39	0.78	<0.2	6.25	6.25	0.39	0.39	0.78	0.39
〃 MS 8800	>100	>100	>100	>100	>100	>100	>100	>100	>100
Micrococcus flavus FDA 16	<0.2	<0.2	<0.2	6.25	1.56	<0.2	<0.2	<0.2	<0.2
M. luteus PCI 1001	<0.2	<0.2	<0.2	6.25	1.56	<0.2	<0.2	0.2	0.39
B. subtilis NRRL B-558	0.78	1.56	0.39	3.12	1.56	1.56	0.78	0.78	0.39
Coryn. bovis 1810	<0.2	0.78	<0.2	25	6.25	0.39	<0.2	0.39	<0.2
E. coli NIHJ	>100	>100	50	>100	>100	>100	100	>100	>100
〃 K-12	>100	>100	>100	>100	>100	>100	>100	>100	>100
Kl. pneumoniae PCI 602	25	25	12.5	>100	>100	100	50	50	>100
Sh. dysenteriae JS 11910	6.25	6.25	6.25	100	12.5	6.25	6.25	12.5	12.5
Sal. enteritidis 1891	12.5	12.5	12.5	100	25	12.5	6.25	12.5	25
Ps. aeruginosa A3	>100	>100	>100	>100	>100	>100	>100	>100	>100
Mean MIC** (mcg/ml)	4.7	6.8	2.9	41.5	22.8	6.0	4.1	7.2	5.2

* Agar dilution streak method (nutrient agar, 37°C, 17 hours).
** See Ref. 2.

ammonia in aqueous methanol (1: 1) (room temperature, overnight) gave 3,4′-dideoxy-2,3-didehydro-demycarosyl tylosin diethylacetal (**19**) (59% after purification), which, on deacetalation, gave 3,4′-dideoxy-2,3-didehydro-demycarosyl tylosin (**20**), $[\alpha]_D^{23}-16°$ (*c* 0.5, chloroform); ^{1}H NMR (in $CDCl_3$ at 90 MHz): δ 5.68 (1H, d, $J_{2,3}$ 15.5 Hz, H-2), 5.85 (1H, d, $J_{13,14}$ 10 Hz, H-13), 6.25 (1H, d, $J_{10,11}$ 15.5 Hz, H-10), 6.88 (1H, dd, $J_{3,4}$ 9.5 Hz, H-3), 7.27 (1H, d, H-11), 9.80 (1H, s, H-20); Found (Calcd. for $C_{39}H_{63}NO_{12}$): C, 63.23 (63.48); H, 8.45 (8.61); N, 1.81 (1.90)%. As a reference compound, 3-deoxy-2,3-didehydro-demycarosyl tylosin (**21**), $[\alpha]_D^{25}-14°$ (*c* 0.5, chloroform) was prepared from **11** by similar treatment with ammonia.

Antibacterial spectra of the products (Table 2) indicate that 4′-deoxy-demycarosyl tylosin (**9**) has the best antibacterial activity among the products tested, including tylosin. Moreover it was again observed that the 4′-deoxy series of compounds (**9**, **17**, **18** and **20**) were always superior, in the antibacterial activity, to the corresponding 4′-hydroxyl series of compounds (**1**, **12**, **13** and **21**).

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