Synthesis and Antibacterial Activity of 6-Deoxysporeamicin A

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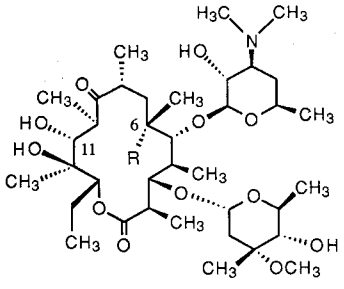
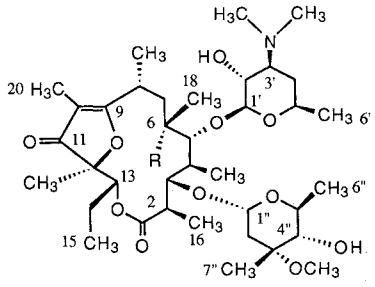
Erythromycin (**1**) is a well established macrolide antibiotic of major therapeutic importance because of its effective antibacterial profile and safety. These properties have prompted several research groups to explore modifications of **1** or isolation of new macrolides[1~4] with the hopes of discovering analogs with improved properties over the parent compound. One novel macrolide resulting from such efforts is **2**, which was synthesized from erythromycin A[5] and later isolated from *Saccharopolyspora* sp. L53-18 and named sporeamicin A.[6,7] Compound **2** is more acid stable than **1**, has higher oral bioavailability and shows better efficacy[8] in animal models of bacterial infections.

Recently, Abbott scientists reported the isolation of 6-deoxyerythromycin A[9] (**3**). Compound **3** was produced via an ingenious genetic manipulation of *Saccharopolyspora erythraea*. This compound was also a more acid stable congener of erythromycin, however its antibacterial potency was significantly lower than that of **1**. The unique structural features of **3** led us to embark on a structure modification program with a view to

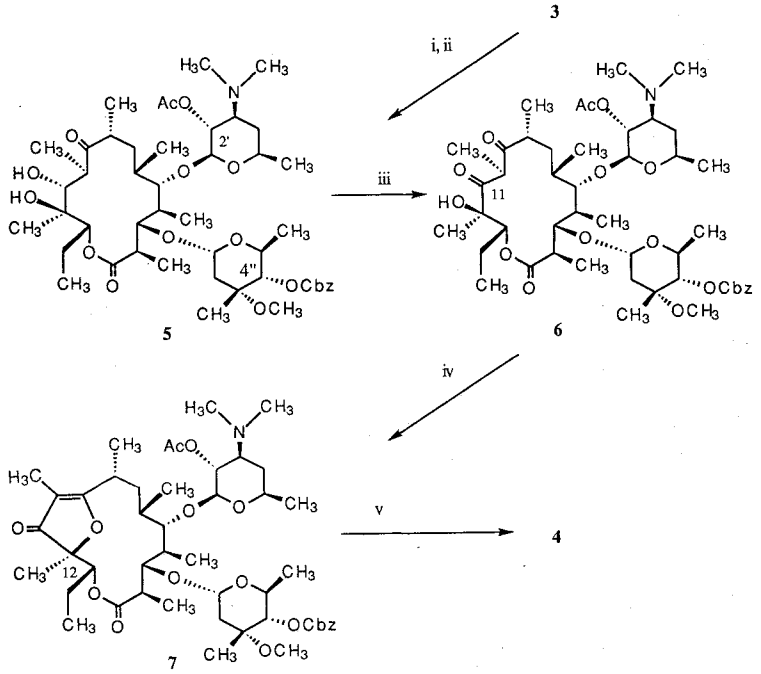


1 R=OH
3 R=H



2 R=OH
4 R=H

Scheme 1.



i, Ac_2O, CH_2Cl_2; ii, CbzCl, DMAP, CH_2Cl_2, 0°C; iii. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C~0°C; iv. $CHCl_2CO_2H$, CH_3CN; v. H_2, Pd-C, CH_3OH.

† Deceased.

Table 1. ^{1}H NMR chemical shifts and assignments for 6-deoxysporeamicin (**4**) ($CDCl_3$, 500 MHz).

Number	δ (ppm)	J (Hz)	Number	δ (ppm)	J (Hz)
2	2.35 (1H, m)		21	1.34 (3H, s)	
3	4.06 (1H, t)	3.0	1′	4.29 (1H, d)	7.0
4	1.58 (1H, m)		2′	3.37 (1H, dd)	7.0, 10.0
5	3.53 (1H, d)	5.0	3′	2.50 (1H, m)	
6	1.99 (1H, m)		4′a	1.30 (1H, m)	
7a	2.0 (1H, m)		4′b	1.62 (1H, m)	
7b	2.15 (1H, m)		5′	3.50 (1H, m)	
8	2.60 (1H, m)		6′	1.25 (3H, d)	7.0
13	5.17 (1H, dd)	3.0, 10.5	3′-$N(CH_3)_2$	2.31 (6H, s)	
14a	1.83 (1H, m)		1″	4.85 (1H, d)	4.5
14b	1.99 (1H, m)		2″a	1.50 (1H, dd)	4.5, 10.0
15	0.84 (3H, t)	7.5	2″b	2.29 (1H, m)	
16	1.10 (3H, d)	7.0	4″	3.0 (1H, t)	10.0
17	1.02 (3H, d)	7.5	5″	3.92 (1H, m)	
18	1.15 (3H, d)	7.0	6″	1.28 (3H, d)	7.0
19	1.40 (3H, d)	7.0	7″	1.20 (3H, s)	
20	1.78 (3H, s)		3″-OCH_3	3.30 (3H, s)	

Table 2. Antibacterial activity of **4** compared to 6-deoxyerythromycin A (**3**), sporeamicin (**2**) and erythromycin (**1**).

Organism	Strain	**4**	**3**	**2**	**1**
Enterococcus faecium	3519	0.2	1.0	0.2	0.2
Streptococcus bovis	A-5169	0.02	0.5	0.1	0.02
Streptococcus agalactiae	CMX 508	0.05	0.12	0.1	0.05
Streptococcus pyogenes	EES 61	0.05	0.25	0.05	0.05
Streptococcus pyogenes	PIU 2548	1.56	4.0	1.56	3.1
Streptococcus pyogenes	930	>100	>100	>100	>100
Micrococcus luteus	ATCC 4698	0.1	0.5	0.1	0.1
Staphylococcus aureus	ATCC 6538	0.39	1.0	0.78	0.2
Staphylococcus aureus	A5177	6.2	8.0	12.5	1.56
Staphylococcus aureus	CMX 553	0.39	0.5	0.78	0.2
Staphylococcus aureus	CMX 642A	0.39	1.0	0.78	0.2
Escherichia coli	JUHL	>100	>100	>100	>100
Escherichia coli	SS	0.78	2.0	0.78	0.2

improving its activity. In this paper, we describe the conversion of **3** to 6-deoxysporeamicin A (**4**) and the evaluation of its *in vitro* antibacterial profile.

The 2′-OH and 4″-OH groups of **3** were sequentially and selectively protected with an acetyl and a benzyloxy carbonyl group, (Scheme 1) to provide **5** in 80% yield. Oxidation of the 11-OH via the Swern procedure gave compound **6** in 73% yield. Treatment of **6** with dichloroacetic acid led to ring closure between the 12-OH and the 9-ketone to establish the dihydrofuranyl moiety as part of the macrolactone. Thus **7** was obtained in 90% yield. Hydrogenolysis of **7** over Pd-C in methanol afforded **4** in 87% yield; $[\alpha]_D$ −24.5° (*c* 1.0, $CHCl_3$); MP 130~135°C; MS *m/z* 698 $(M+H)^+$. The ^{1}H NMR characteristics of **4** are given in Table 1. Some of the diagnostic features of the NMR spectrum include the three proton H-20 singlet at δ 1.78, loss of the H-10 resonance and the H-6 multiplet at δ 1.99.

Table 2 shows the minimum inhibitory concentrations (MICs)[10] of **4** compared to **3**, **2** and **1** against a number of laboratory bacterial strains. As shown in Table 2, the antibacterial spectrum of **4** was similar to those of **2**, **3** and **1**, there being no significant improvement in activity against the macrolide-resistant Streptococci (PIU 2548 and 930), *S. aureus* A-5177 or the typical Gram-negative bacterium *E. coli* (JUHL). However, **4** showed improved potency compared to its parent **3** against susceptible Streptococci, wherein 2 to 25 fold improvement in activity was observed. Similarly, **4** had better activity than its 6-hydroxy congener **2** against most of the susceptible organisms and an overall potency similar to that of **1**.

Hence modifications of the novel, but otherwise less active, 6-deoxy congener of erythromycin has led to a compound with improved potency. The pharmacokinetics and efficacy of this new derivative in animal models of bacterial infections will be reported in due course.

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