SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF (9*S*)-9-DIHYDROCLARITHROMYCIN

RAMIN FAGHIH, MARK BUYTENDORP, RICHARD STEPHENS, DWIGHT HARDY, JAKE PLATTNER and PAUL LARTEY

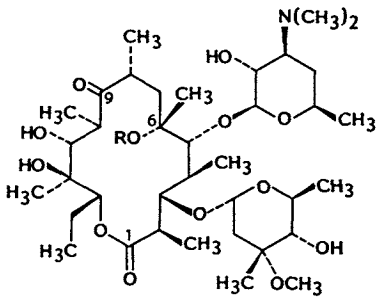
Abbott Laboratories, Anti-infective Research Division, Abbott Park, IL 60064, U.S.A.

(Received for publication April 9, 1990)

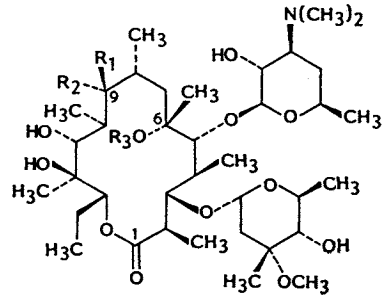
Clarithromycin[1] (**1**, 6-*O*-methylerythromycin A, A-56268, TE-031) is a new macrolide currently undergoing clinical development. The excellent properties[2] of **1** make it attractive for further synthetic modifications. It is known that, reduction of the 9-keto group of erythromycin A (**2**), for example with sodium borohydride, gives the corresponding secondary alcohol, predominantly as the 9(*S*) epimer, known as 9-dihydroerythromycin (**3**)[3~5]. Although **3** has less antibacterial activity than erythromycin[6], the 9-hydroxyl group provides a handle for further chemical transformations[7] to produce compounds with improved activities over **3**. The present paper describes the preparation and antibacterial activity of the analogous reduction product of **1** using nucleophilic hydride.

Synthesis

Upon treatment with 5 equivalents of lithium triethylborohydride[8], in dry THF, clarithromycin (**1**) was readily transformed in 77% yield (after flash



1 R=CH_3
2 R=H



3 R_1=OH R_2=H R_3=H
4 R_1=OH R_2=H R_3=CH_3

Table 1. ^{1}H NMR chemical shifts[a] of **1**, **3** and **4**.

Proton No.	Multiplicity	δ (ppm)			Proton No.	Multiplicity	δ (ppm)		
		3	**1**	**4**			**3**	**1**	**4**
2-H	dq	2.75	2.89	2.98	21-H	s	1.11	1.12	1.11
3-H	dd	4.10	3.77	3.73	6-OCH_3	s	—	3.04	3.38
4-H	ddq	1.89	1.92	2.01	1′-H	d	4.54	4.44	4.49
5-H	d	3.69	3.67	3.83	2′-H	dd	3.31	3.19	3.19
7-H_{eq}	dd	1.30	1.72	1.49	3′-H	ddd	2.53	2.42	2.40
7-H_{ax}	dd	1.67	1.85	1.62	4′-H_{ax}	ddd	—	1.22	1.25
8-H	ddq	2.18	2.59	2.15	4′-H_{eq}	ddd	1.69	1.66	1.67
9-H	ddq	3.38	—	3.30	5′-H	ddq	3.59	3.49	3.50
10-H	dq	1.98	3.00	1.86	6′-H	d	1.24	1.23	1.25
11-H	d	3.75	3.77	3.53	3′-$N(CH_3)_2$	s	2.31	2.29	2.29
13-H	dd	4.89	5.05	5.11	1″-H	dd	4.98	4.93	4.98
14-H	ddq	1.50, 1.96	1.47, 1.92	1.49, 1.95	2″-H_{ax}	dd	1.59	1.59	1.60
15-H	t	0.89	0.84	0.84	2″-H_{eq}	dd	2.38	2.37	2.39
16-H	d	1.22	1.20	1.22	4″-H	dd	3.04	3.03	3.03
17-H	d	1.10	1.10	1.13	5″-H	dq	4.04	4.01	4.05
18-H	s	1.27	1.41	1.37	6″-H	d	1.31	1.31	1.31
19-H	d	1.09	1.13	0.92	7″-H	s	1.25	1.25	1.24
20-H	d	1.18	1.13	1.13	3″-OCH_3	s	3.32	3.33	3.34

[a] δ Values in ppm from TMS, measured in $CDCl_3$ at 300 MHz, as determined from ^{1}H-^{1}H 2D homonuclear shift correlated experiments.

chromatography $CHCl_3$ - MeOH - NH_4OH, 40 : 10 : 1) to a single more polar compound **4**. The physico-chemical properties of **4** are as follows: $[\alpha]_D$ −41.9° (*c* 0.96, $CHCl_3$); mp 209°C (crystallized from acetonitrile); IR ($CHCl_3$) cm^{-1} 3520~3280, 2960~2760, 1720, 1455; FAB-MS *m/z* (M^+) 750; *Anal* Calcd for $C_{38}H_{71}NO_{13}$: C 60.86, H 9.54, N 1.87. Found: C 60.58, H 9.33, N 1.80. The ^1H and ^{13}C

Table 2. ^{13}C NMR chemical shifts[a] of **1**, **3** and **4**.

Carbon No.	δ (ppm)			Carbon No.	δ (ppm)		
	3	**1**	**4**		**3**	**1**	**4**
C-1	177.0	175.9	175.2	C-19	20.1	18.0	21.4
C-2	45.7	45.1	45.3	C-20	15.1	12.3	16.8
C-3	79.3	78.4	79.0	C-21	16.6	16.0	16.3
C-4	41.8	39.2	38.5	C-1′	103.4	102.8	102.5
C-5	84.6	80.8	78.4	C-2′	70.8	71.0	70.9
C-6	74.4	78.4	80.3	C-3′	65.1	65.6	65.6
C-7	37.1	39.4	34.6	C-4′	29.0	28.6	28.9
C-8	34.2	45.3	34.7	C-5′	69.3	68.8	68.6
C-9	83.2	221.0	82.0	C-6′	21.2	21.5	21.5
C-10	32.0	37.2	32.5	3′-$N(CH_3)_2$	40.4	40.3	40.3
C-11	70.8	69.1	71.0	C-1″	96.5	96.1	96.5
C-12	75.0	74.3	74.9	C-2″	34.9	34.9	35.1
C-13	77.7	76.6	77.3	C-3″	72.7	72.7	72.7
C-14	21.8	21.0	21.4	C-4″	77.7	78.0	77.8
C-15	11.2	10.6	10.6	C-5″	66.2	65.7	65.9
C-16	14.9	16.0	16.3	C-6″	18.2	18.7	18.7
C-17	9.5	9.1	9.3	C-7″	21.6	21.5	21.5
C-18	25.3	18.0	20.4	3″-OCH_3	49.4	49.5	49.4
6-OCH_3	—	50.6	50.8				

[a] δ Values in ppm from TMS, measured in $CDCl_3$ at 75.46 MHz, as determined from a ^1H-^{13}C 2D heteronuclear shift correlated experiments.

Table 3. Antibacterial activity of erythromycin A (**2**), **3**, clarithromycin (**1**) and **4**.

Organism	MIC (μg/ml)			
	2	**3**	**1**	**4**
Staphylococcus aureus ATCC 6538P	0.2	1.56	0.1	0.39
S. aureus A5177	1.56	50	0.78	6.2
S. aureus 45	0.2	1.56	0.1	0.39
S. aureus 45 RAR2	0.2	1.56	0.1	0.78
S. aureus CMX 553	0.2	1.56	0.1	0.78
S. epidermidis 3519	0.2	1.56	0.1	0.39
Micrococcus luteus ATCC 9341	0.02	0.2	0.01	0.05
M. luteus ATCC 4698	0.1	0.2	0.1	0.1
Enterococcus faecium ATCC 8043	0.1	0.39	0.05	0.1
Streptococcus bovis A5169	0.01	0.2	0.005	0.05
S. agalactiae CMX 508	0.02	0.2	0.02	0.1
S. pyogenes EES61	0.01	0.1	0.01	0.05
S. pyogenes 2548[a]	3.1	6.2	1.56	1.56
Escherichia coli JUHL	25	>100	25	50
E. coli SS	0.2	0.78	0.2	0.39
E. coli DC-2	100	>100	50	>100
E. coli H560	12.5	>100	12.5	50
Pseudomonas aeruginosa BMH10	50	>100	25	50
P. aeruginosa K799/61	1.56	6.2	1.56	3.1
Acinetobacter calcoaceticus CMX 669	3.1	25	3.1	12.5

[a] Inducibly resistant to erythromycin.

NMR spectra of **4** are compared with those of **1** and **3** in Tables 1 and 2.

Antibacterial Activity

The bacterial strains used in this study were clinical isolates or cultures obtained from the American Type Culture Collection (ATCC, Rockville, Maryland, U.S.A.) which are maintained frozen in our laboratory. MICs were determined by the agar† dilution method using brain heart infusion agar. The MICs of **4** against several bacteria are compared with those of **1**, **2** and **3** in Table 3. The antibacterial activity of **4** was less than that of **1** but better than that of **3**. This suggests that further synthetic modifications of **4** could yield compounds with improved potency.

References

1) MORIMOTO, S; Y. TAKAHASHI, Y. WATANABE & S. ŌMURA: Chemical modification of erythromycins. I. Synthesis and antibacterial activity of 6-*O*-methylerythromycins A. J. Antibiotics 37: 187~189, 1984

2) FERNANDES, P. B.; R. BAILER, R. SWANSON, C. W. HANSON, E. MCDONALD, N. RAMER, D. HARDY, N. SHIPKOWITZ, R. R. BOWER & E. GADE: In vitro and in vivo evaluation of Abbott-56268 (TE-031), a new macrolide. Antimicrob. Agents Chemother. 30: 865~873, 1986

3) WILEY, P. F.; K. GERZON, E. H. FLYNN, M. V. SIGAL, O. WEAVER, U. C. QUARCK, R. R. CHAUVETTE & R. MONAHAN: Structure of erythromycin. J. Am. Chem. Soc. 79: 6062~6070, 1957

4) PERUN, T. J.; R. S. EGAN & J. R. MARTIN: Configurational and conformational studies of dihydroerythronolides. Tetrahedron Lett. 1969: 4501~4504, 1969

5) COREY, E. J. & L. S. MELVIN: Selective chromic acid oxidation of alcohols in the erythromycin series in consequence of conformational immobility. Tetrahedron Lett. 1975: 929~932, 1975

6) TADANIER, J.; J. R. MARTIN, A. W. GOLDSTEIN & E. A. HIRNER: Diastereomeric 10,11-epoxyerythromycin B and the preparation of 10-epi-erythromycin B. J. Org. Chem. 43: 2351~2356, 1978

7) HUNT, E.; D. J. C. KNOWLES, C. SHILLINGFORD, J. M. WILSON & I. I. ZOMAYA: 9,11-Cyclic acetal derivatives of (9*S*)-9-dihydroerythromycin A. J. Antibiotics 42: 293~298, 1989

8) BROWN, H. C. & S. KRICHNAMURTHY: Lithium triethylborohydride. An exceptionally powerful nucleophile in displacement reactions with organic halides. J. Am. Chem. Soc. 95: 1669~1671, 1973

† National Committee for Clinical Laboratory Standards. 1985. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved Standard M7-A. National Committee for Clinical Laboratory Standards, Villanova, Pa.