Stereoselective Deoxygenation of Erythromycin A at C-12: Effect of Structure and Conformation on Prokinetic Activity

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The macrolide antibiotic erythromycin A **1** is a potent Gram-positive antibacterial agent. Pioneering studies by ŌMURA *et al.*,[1] demonstrated that its 8,9-anhydro-6,9-hemiacetal (enol ether) derivative **2** has diminished antibacterial activity but is a potent motilin receptor agonist (motilide).[2] As such **2** induces contractions in the smooth muscle of the gastrointestinal (GI) tract of dog and is potentially useful as a GI prokinetic agent. In an effort to extend the SAR of the motilides, we decided to determine the effect of C-12 deoxygenation of **2** on both antibacterial and prokinetic activities. The deoxy congener with the natural (*R*) configuration at C-12 **4** is synthetically accessible[3] from erythromycin B **3**, but in order to obtain the (*S*)-epimer, we had to devise methodology for selective deoxygenation of **1**.

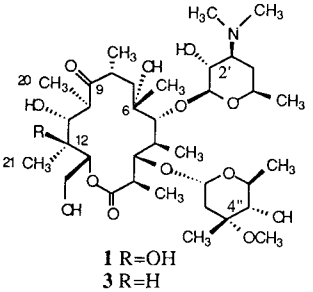
The 12-OH of **1** is hindered and inaccessible selectively, therefore our strategy was to take advantage of the reactivity and *syn*-orientation of the vicinal 11-OH to prepare an 11,12-cyclic thionocarbonate. In accordance with BARTON and MCCOMBIE,[4] a tributylstannyl radical should attack the thiocarbonyl group to generate a radical intermediate which, in this case, could fragment to the secondary radical at C-11 or the tertiary radical at C-12. Since tertiary radicals are more stable than secondary radicals and react faster in both fragmentation and hydrogen abstraction reactions,[5,6] we hoped that the Barton-McCombie deoxygenation would be selective for C-12, to give epimeric 12-deoxy congeners.

Thus the 2′-OH and 4″-OH groups were sequentially and selectively protected with an acetyl and a benzyloxycarbonyl group respectively (Scheme 1) to provide **5**. Treatment of **5** with thiophosgene gave the 11,12-cyclic thionocarbonyl-6,9-hemiacetal intermediate **6**. Deoxygenation of **6** with tri-*N*-butyltin hydride was regioselective for C-12, but to our surprise, enol ether **8** with the unnatural (*S*)-configuration at C-12 was the exclusive deoxygenation product. Hence conditions for the deoxygenation had also resulted in the elimination of the hemiacetal hydroxy group at C-9 of **6** to generate the enol eher. On the other hand, prior conversion of **6** to enol ether **7**, followed by treatment with tri-*n*-butyltin hydride afforded compound **9** with the natural configuration at C-12. These results also demonstrate that formation of the enol ether from **6** occured after the C-12 deoxygenation and that the hemiacetal OH-group played a role in directing the stereoselectivity of the deoxygenation. Removal of the protecting groups in **8** and **9** by treatment with methanol followed by hydrogenolysis afforded **10** [MS *m/z* 400 (M^+)] and **4** respectively, thereby confirming C-12 stereochemistry for **9**.

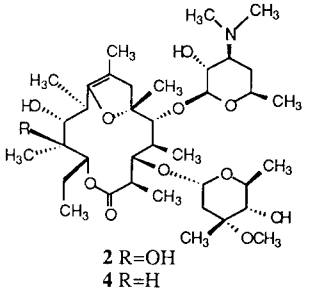
The ^1H resonances for the novel 12-*epi* compound **8** are compared with those of **9** in Table 1. From the COSY spectrum of **8**, the protons pertinent to the determination of C-12 stereochemistry were at (500 MHz, $CDCl_3$) δ 5.55 (1H, d, $J_{11,10}=5.5$ Hz, 11-H), 5.07 (1H, dd, $J_{13,12}=7.5$ Hz, $J_{13,14}=6.0$ Hz, 13-H), 3.57 (1H, m, 10-H), 2.77 (1H, m, 12-H), 1.69 (2H, m, 14-H), 1.19 (3H, d, $J_{21,12}=4.8$ Hz, 21-H), 1.09 (3H, d, $J_{20,10}=5.0$ Hz, 20-H). In the NOESY spectrum, a strong NOE was observed between 13-H and 11-H, suggesting a diaxial arrangement for the two protons. There is also a weak NOE between 20-H and 11-H. A weaker NOE between 11-H and 12-H suggests a *pseudo*-equatorial orientation for 12-H, hence an axial 21-H. These NOEs were consistent with the proposed conformation **11** for **8**, in which the methyl groups C-20 and C-21 are in a 1,3-gauche relationship.

The pertinent resonances in the COSY spectrum for **9** were δ 5.14 (1H, m, 13-H), 3.36 (1H, m, 11-H), 2.61 (1H, m, 10-H), 1.66 (1H, dd, $J_{14a,13}=5.0$ Hz, $J_{14a,14b}=15$ Hz, 14a-H), 1.65 (1H, m, 12-H), 1.48 (1H, m, 14b-H), 1.04 (3H, d, $J_{20,10}=4.5$ Hz, 20-H), 0.83 (3H, d, $J_{21,12}=5.0$ Hz, 21-H). The ROESY spectrum for **9** showed NOEs from 21-H to 10-H and to 11-H. There was also an NOE between 11-H and 13-H, consistent with conformation **12**. Conformation **12** is similar to the X-ray crystallographic structure reported[7] for (9*R*)-9-dihydro-6,9-anhydroerythromycin A. This conformation may have been less favored in the case of **8**, since it would have put C-20 and C-21 in a 1,3-diaxial relationship.

The activity of **10** was compared to **4** in a rabbit duodenal smooth muscle contractility assay, which serves as an *in vitro* evaluation of prokinetic potency. Compound **10** was much weaker ($pED_{50}=7.0$) than **4** ($pED_{50}=8.7$). Hence, epimerization at C-12 with concomitant conformational change around the C-10 to C-13 region of the macrolactone resulted in a significant decrease in prokinetic activity. The *in vitro* antibacterial activity of **10** as well as its 9-ketone analog (12-



1 R=OH
3 R=H



2 R=OH
4 R=H

This manuscript is a special contribution in honour of Professor SATOSHI ŌMURA's 60th birthday.

Scheme 1.

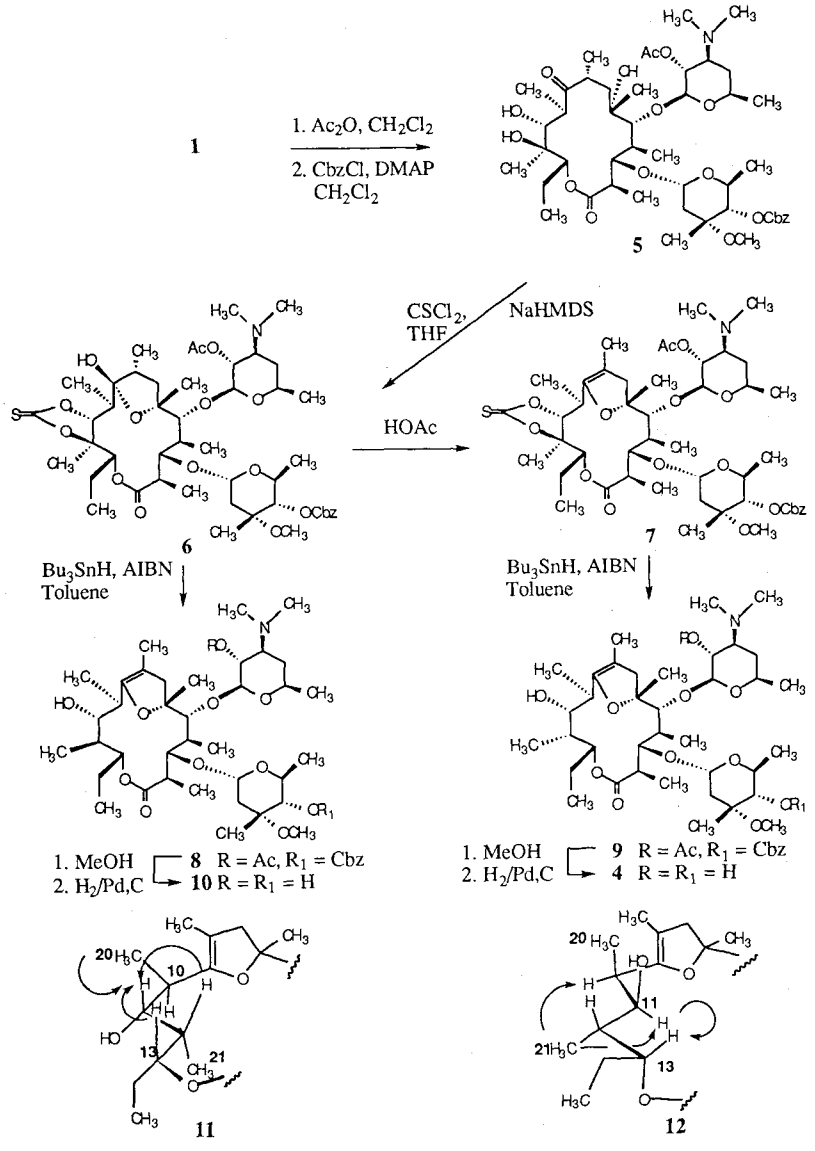


Table 1. Comparison of the ^1H chemical shifts of the epimeric 12-deoxy analogs.

Proton	8	9	Proton	8	9
2	2.75	2.68	1′	4.54	4.64
3	4.10	3.98	2′	4.75	4.76
4	1.62	1.90	3′	2.71	2.74
5	3.46	3.77	4′	1.67, 1.27	1.73, 1.25
7	1.63, 1.45	2.49, 1.94	5′	3.59	3.96
10	3.57	2.61	6′	1.11	1.11
11	5.55	3.36	3′-NMe_2	2.26	2.28
12	2.77	1.65	2′-OAc	2.04	2.05
13	5.07	5.14	1″	4.90	5.13
14	1.69, 1.62	1.66, 1.48	2″	2.39, 1.62	2.44, 1.66
15	0.84	0.89	4″	4.46	4.48
16	1.17	1.24	5″	4.33	4.38
17	0.96	0.93	6″	1.18	1.18
18	1.32	1.30	7″	1.21	1.20
19	1.63	1.54	3″-OMe	3.30	3.34
20	1.09	1.04	4″-OCbz	5.24, 5.13	5.25, 5.13
21	1.19	0.83		7.36	7.35

epierythromycin B) is currently under investigation and will be reported in a later communication.

Dedication

We take this opportunity to wish Professor SATOSHI ŌMURA a happy 60th birthday, long life, continued productivity and prosperity.

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