Tetrahedron Letters 52 (2011) 6275–6280

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Transformation of josamycin in alkaline solution—intramolecular S_N2 substitution or E1cB elimination and intramolecular Michael addition?

Piotr Przybylski *, Krystian Pyta

Faculty of Chemistry, A. Mickiewicz University, Grunwaldzka 6, 60-780 Poznan, Poland

ARTICLE INFO

Article history:
Received 21 July 2011
Revised 1 September 2011
Accepted 16 September 2011
Available online 22 September 2011

Keywords:
Josamycin
Macrolides
Intramolecular S_N2
Stereoselective E1cB elimination
Intramolecular Michael addition

ABSTRACT

The conversion of josamycin (**1**) into its α,β-unsaturated derivative **2** was optimized to avoid formation of undesired josamycin bicyclic derivatives of type **3** under alkali treatment. The influence of various **1**:base stoichiometry, temperature and reaction time on the conversion was monitored by ^{1}H NMR spectroscopy. Spectroscopic studies indicated clearly that the transformation of **1** in alkaline solution involves as the first step, the formation of α,β-unsaturated derivative **2** via an E1cB stereoselective elimination and as the second step, the intramolecular Michael addition leading to the formation of two diastereomeric bicyclic derivatives **3a** and **3b**.

Sixteen-membered macrolides such as the leucomycins (josamycin or leucomycin A_3) belong to a wide and structurally diverse group of medically important pharmaceuticals characterized by a wide spectrum of antimicrobial activity against Gram positive and erythromycin-resistant bacteria, for example, *Streptococcus pyogenes* and *Streptococcus pneumoniae*.[1–3] Josamycin (**1**) (Fig. 1),

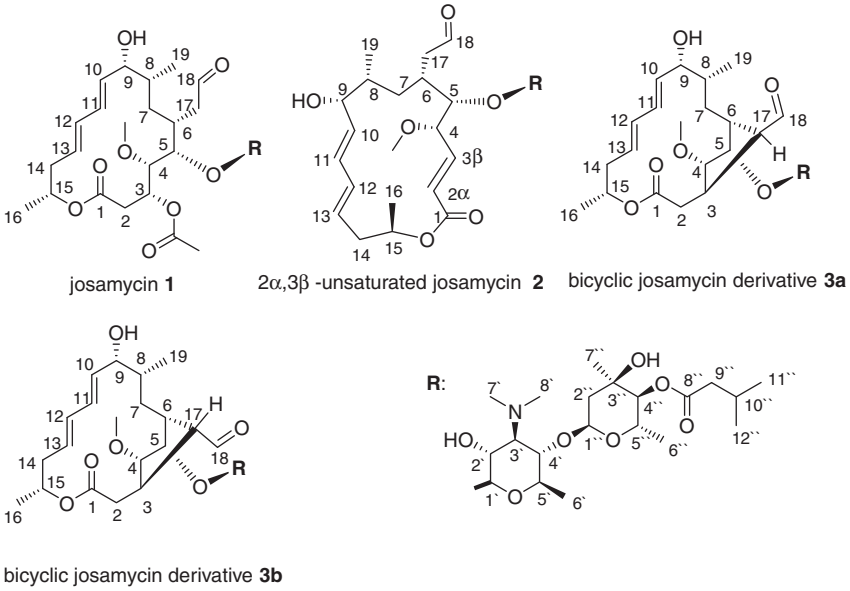

Figure 1. The structures and atom numbering of compounds **1**, **2**, **3a** and **3b**.

* Corresponding author. Tel.: +48 61 829 1252; fax: +48 61 829 1505.
E-mail address: piotrp@amu.edu.pl (P. Przybylski).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.09.086

Table 1
[1]H NMR monitoring of josamycin conversion under alkali treatment in solution taken at various: temperatures (T), reaction time (t) and **1**:KOH stoichiometry

Molar ratio**1**: KOH	Ratio[a] of **1**:**2**:**3a+3b** Temperature reaction time					
	T = 20 °C			T = −20 °C		
	t = 15 min	t = 30 min	t = 60 min	t = 15 min	t = 30 min	t = 60 min
1:0.25	77:20:3	75:21:4	74:21:5	79:21:0	76:24:0	75:25:0
1:0.5	60:31:9	57:33:10	55:33:12	52:48:0	50:50:0	50:50:0
1:0.75	39:45:16	39:43:18	33:46:21	30:70:0	28:72:0	25:75:0
1:1	16:48:36	14:49:37	13:50:37	3:97:0	1:99:0	0:100:0
1:1.25	13:32:55	11:31:58	10:30:60	0:100:0	0:100:0	0:100:0
1:1.5	12:26:62	10:25:65	8:23:69	0:100:0	0:100:0	0:100:0
1:1.75	9:23:68	7:22:71	5:17:78	0:100:0	0:100:0	0:100:0
1:2	1:4:95	0:1:99	0:0:100	0:100:0	0:100:0	0:100:0
1:2.25	0:0:100	0:0:100	0:0:100	0:100:0	0:100:0	0:100:0

[a] Calculated from the H-18 resonance integral for **1**, **2** and diastereomeric bicyclic products **3a** and **3b**.

is a safe and well-tolerated macrolide antibiotic which plays an important role in the treatment of respiratory tract infections[4] and is often used for the treatment of some forms of cancer.[5] The resistance of some bacterial strains, among respiratory tract pathogens and the growing problem of allergic responses to leucomycins have stimulated the search for new alternative agents for the treatment of many bacterial infections.[6]

To date many ether and ester josamycin derivatives have been obtained at C-3″[7] of the isovalerylmycarose moiety, and at the C-9[8,9] and C-3[10] carbon atoms within the aglycone moiety. As established in acidic media this antibiotic undergoes allylic rearrangement yielding isojosamycin,[11] whereas Omura et al.[12] reported the conversion of josamycin into a bicyclic derivative in alkaline solution via S_N2 type intramolecular substitution. Our recent results concerned with the synthesis of a new series of α,β-unsaturated josamycin aza-derivatives via 'one-pot' reductive alkylation and elimination reactions[13] have thrown new light on the mechanism of bicyclic josamycin derivative formation in an alkaline solution and have prompted us to explain this problem.

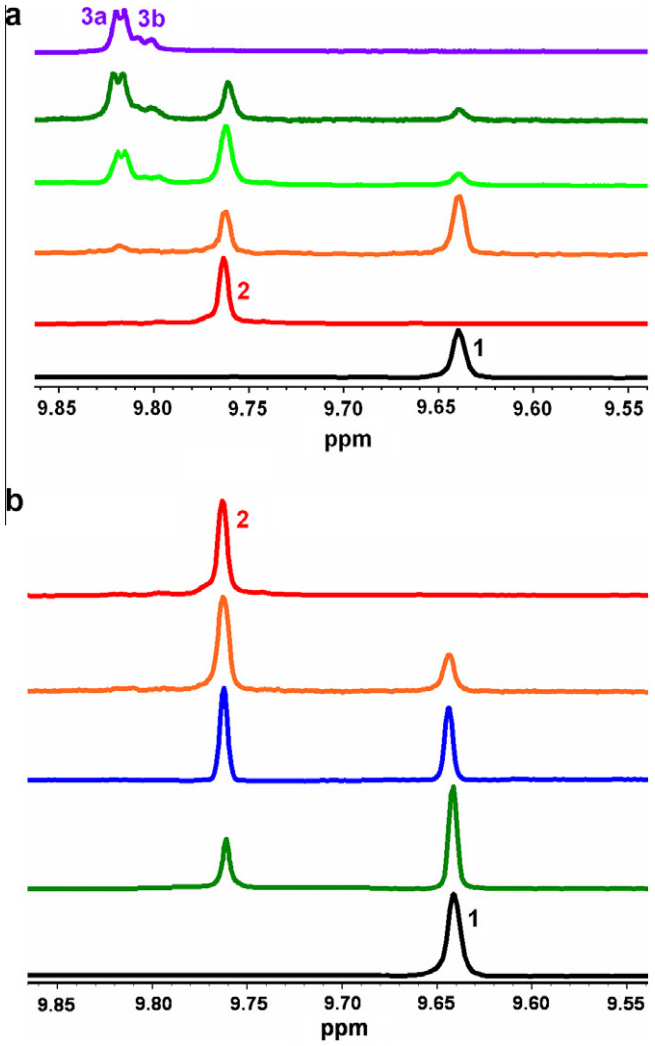

Figure 2. [1]H NMR spectra ($CDCl_3$) in the 9.9–9.5 ppm range of **1**:KOH mixtures: (a) at 20 °C after t = 60 min, taken at various **1**:KOH ratios: 1:0.5 (orange), 1:1 (pale green), 1:1.5 (green), 1:2 (violet) and for comparison **1** (black) and **2** (red); (b) at −20 °C after t = 60 min taken at various **1**:KOH ratios: 1:0.25 (green), 1:0.5 (blue), 1:0.75 (orange), 1:1 (red) and for comparison **1** (black).

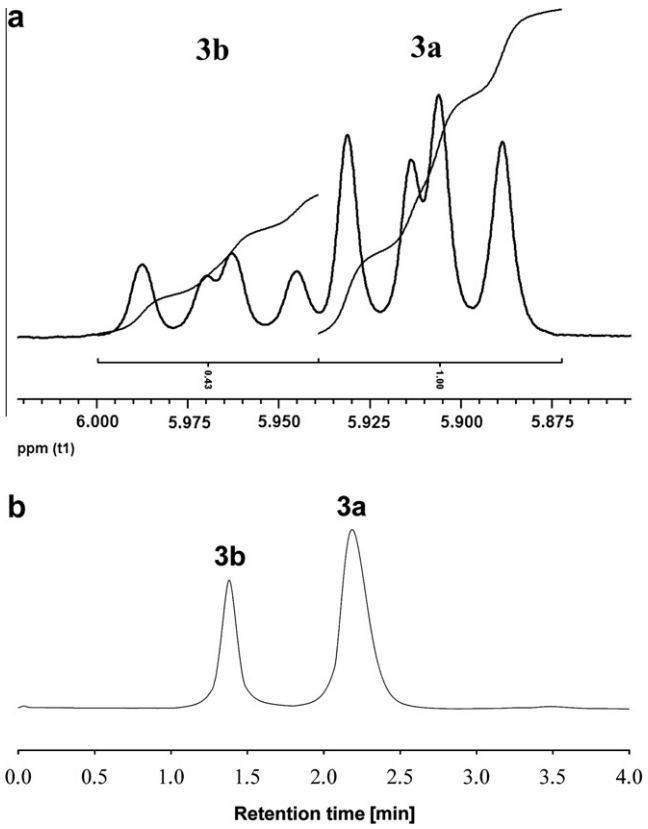

Figure 3. Comparison of: (a) H-12 integrals in the [1]H NMR spectrum and (b) HPLC for the mixture of diastereomers **3a** and **3b** obtained after conversion of josamycin in an alkaline solution at 1:2 stoichiometry of **1**:KOH (T = 20 °C, t = 60 min).