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Synthesis of Ring-Contracted Erythromycin A Derivatives via Microwave-Assisted Intramolecular Transesterification

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Abstract: The synthesis of ring-contracted derivatives of erythromycin A via intramolecular transesterification under microwave irradiation of 8,9-anhydro-erythromycin A 6,9-hemiketal and its derivatives is described. It was found that microwave irradiation could significantly improve the yields and shorten the reaction times under either solvent-containing (method A) or solvent-free (method B) conditions.

Keywords: Ring-contracted derivatives of erythromycin; transesterification; microwave irradiation.

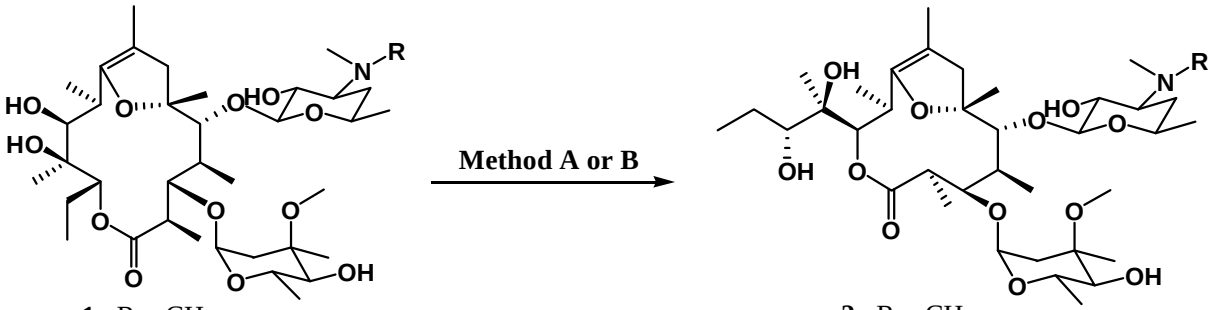
Introduction

Erythromycin, a typical macrolide antibiotic, was the first employed clinically and it has provided new opportunities for the discovery of potential therapeutic agents [1]. Over the past decades, numerous clinical studies have confirmed that erythromycin and its derivatives have additional anti-inflammatory and prokinetic activity [2-3]. The ring-contracted erythromycin derivative **2a** came to our attention on the basis of its anti-inflammatory activity, and was selected as one of our target compounds.

In 1987, Kibwage *et al*. observed that 8,9-anhydroerythromycin A 6,9-hemiketal (**1a**) and its intramolecular transesterification (translactonization) product **2a** could be obtained in *ca*. 18 and 71 % yields, respectively, after chromatographic purification of the mixture of products formed when erythromycin A was heated in a 3:1 mixture of pyridine and acetic acid at 70°C for 24 h [4]. It was also noted that this translactonization was a reversible equilibrium reaction, since when either pure **1a** or **2a** were heated under the same conditions a 20:80 equilibrium mixture of the two compounds (by HPLC) was always produced. Independently and almost simultaneously Kirst and co-workers reported that the translactonization of **1a** catalyzed by potassium carbonate in refluxing methanol gave compound **2a** in 54% yield after 90 min [5].

Recently, an ever growing interest in the application of microwave irradiation in organic synthesis has led to the development of a variety of extremely useful synthetic transformations [6-7]. In 1998, Limousin *et al*. reported that microwaves promoted intermolecular transesterifications catalyzed by K_2CO_3 and a phase transfer catalyst in DMF between methyl benzoate and carbohydrates and that yields as high as 96% could be achieved within 15 min [8]. To the best of our knowledge, microwave assisted intramolecular transesterifications have never been described. Herein, we wish to report a facile and straightforward synthesis of **2a** from **1a** under microwave irradiation via such a reaction (Scheme 1).

Scheme 1. The synthetic route for compounds **2a-2g**.



1a R= CH_3
1b R= H
1c R= CH_2CH_3
1d R= $CH_2CH_2CH_3$
1e R= $CH_2(CH_3)_2$
1f R= $CH_2CH{=}CH_2$
1g R= $CH_2C{\equiv}CH$

2a R= CH_3
2b R= H
2c R= CH_2CH_3
2d R= $CH_2CH_2CH_3$
2e R= $CH_2(CH_3)_2$
2f R= $CH_2CH{=}CH_2$
2g R= $CH_2C{\equiv}CH$

Method A: TBAF, DMF, MW; **Method B:** Silica gel, MW.

Results and Discussion

In this pursuit, we first tried to prepare **2a** by extending the scope of the Limousin method to intramolecular transesterification (method A). Compound **1a**, which was obtained from erythromycin A under acid treatment [9], could be transformed into **2a** within a few minutes under microwave irradiation by catalysis with potassium carbonate and tetra-*n*-butylammonium bromide (TBAB) in DMF. Further studies suggested that **2a** could also be prepared successfully in the absence of potassium carbonate. In this case, TBAB is a highly polar species and strong specific microwave (i.e. not purely thermal) effects should be considered as a factor in the observed acceleration of the reaction

rate and yield increase [10-11]. It is well-known that fluoride ion acts as a base under aprotic conditions and affects the addition of carbon nucleophiles [12], so tetra-*n*-butylammonium fluoride (TBAF) was therefore employed as a catalyst in our case and it was found that **2a** could be obtained from **1a** in a yield of 72% within 5 minutes.

Up to now, a number of reports have focused on microwave-assisted solvent-free reactions, in which the organic reagents are coated onto the surface of some supports, which absorb little or no microwave energy [13]. In view of the simplicity of this new method, its use for the preparation of **2a** under solvent-free condition (method B) was considered of interest.

In our initial experiments several different solid supports such as silica gel, aluminium oxide and Kieselguhr G were employed, As can be seen from Table 1, only a small quantity of **2a** was obtained when **1a** was absorbed on basic Al_2O_3, acidic Al_2O_3 and Kieselguhr G, even by prolonging the reaction times. When neutral Al_2O_3 (pH 6.5-7.5) was used as a support, the reaction was more efficient and the target compound could be generated in 63% yield. From the data it is obvious that the best result by far involved the use of silica gel as the sorbent, whereby a 76% yield of **2a** was obtained. In addition, we investigated the effect of different reaction times in the silica gel system. The yield increased steadily from 33% to 76% when we extended the reaction time from 10 min to 20 min, but it was observed that reaction times over 20 min resulted in a decrease in the yield of **2a**. It was of interest, however, that when **2a** was adsorbed on silica gel or neutral aluminium oxide and irradiated over 20 minutes, no traces of **1a** were observed, suggesting that under these conditions the intramolecular transesterification of **1a** to **2a** was irreversible.

Table 1. Intramolecular transesterification of **1a** under microwave irradiation.

Method	Reagents	power (W) [a]	Temp.(°C) [b]	Time (min)	Yield (%)
A (solvent-containing)	K_2CO_3,TBAB, DMF	200	130	10	58
	TBAB, DMF	200	130	10	50
	TBAF, DMF	200	130	5	72
B (solvent-free)	Al_2O_3 (pH3.8-4.8)	400	180	20	trace
	Al_2O_3 (pH6.5-7.5)	400	180	20	63
	Al_2O_3 (pH9.0-10)	400	180	20	trace
	Kieselguhr G	400	180	20	trace
	Silica gel	400	180	10	33
		400	180	15	57
		400	180	20	76
		400	180	25	64

[a] The MW power was set at 200W/400W.

[b] The temprature was controlled automatically at 130°C/180°C by intermittent irradiation.

To demonstrate the efficiency of method B, we then extended the scope of substrates to include other 8,9-anhydroerythromycin A 6,9-hemiketal derivatives **2b**-**2g**, which were prepared by the method of Tsuzuki [14], and found the reactions proceeded readily under microwave irradiation.

Conclusions

In summary, we have developed two methods for preparing ring-contracted derivatives of erythromycin from 8,9-anhydroerythromycin A 6,9-hemiketal and its *N*-demethylated derivatives via intramolecular transesterification under microwave irradiation in the presence or absence of solvent. The above results suggested that microwave irradiation could improve the yield and accelerate the reaction rate significantly under either solvent-containing or solvent-free conditions. This provided an efficient and environmentally-friendly method for synthesis of the ring-contracted erythromycin derivatives.

Experimental

General

The reactions were carried out in an XH-100 laboratory microwave oven (Beijing Xianghu Science & Technology Development Co., Ltd.). The MW power was set at 200W/400W and the temperature was measured by an immersed platinum resistance thermometer and controlled automatically at 130°C/180°C by intermittent irradiation. Melting points for the compounds were determined on a hot-stage microscope and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ solutions on a Bruker ARX-300 spectrometer operating at 300 (^{1}H) or 75 MHz (^{13}C), with TMS as the internal reference. Coupling constants (*J*) are expressed in Hz. Fast atom bombardment (FAB) mass spectra were obtained using a JMS-DX300 spectrometer. Column chromatography was performed on silica gel (200-300 mesh) obtained from Qingdao Ocean Chemicals. Unless otherwise noted, all the materials were obtained from commercial sources and used without further purification.

Ring-contracted erythromycin (**2a**)

Method A: A mixture of **1a** (200.2 mg, 0.279 mmol), TBAF (7.3 mg, 0.028 mmol) and DMF (1.4 mL) was placed in a flask and then irradiated with microwaves at 200W, 130°C for 5 min. After the mixture had cooled to room temperature, it was diluted with water and extracted with dichloromethane. The organic layer was dried over Na_2SO_4, and concentrated *in vacuo*. The resulting crude product was purified by column chromatography eluting with 10:0.5:0.01 to 10:1:0.05 chloroform-methanol-ammonium hydroxide solution to yield **2a** (144.2 mg, 72%) as a white solid, mp 127.0-130.0°C (lit. [4] mp. 126-130°C); ^{1}H-NMR δ: 5.06 (d, 1H, *J*=2.7, H-11), 4.89 (d, 1H, *J*=7.0, H-1″), 4.33 (d, 1H, *J*=7.0, H-1′), 4.27 (dd, 1H, *J*=10.0, 3.0, H-3), 4.07 (m, 1H, H-5″), 3.70 (d, 1H, *J*=9.5, H-5), 3.27 (s, 3H, 3″-OCH_3), 2.29 (s, 6H, N-CH_3); ^{13}C-NMR δ: 175.72 (C-1), 46.56 (C-2), 80.20 (C-3), 81.22 (C-5), 85.77 (C-6), 43.15 (C-7), 101.04 (C-8), 149.34 (C-9), 103.61 (C-1′), 40.06 (N-CH_3), 97.27 (C-1″), 49.11 (3″-OCH_3); HRMS (FAB) m/z: calcd. for $C_{37}H_{66}NO_{12}$ $[M+H]^+$ 716.4585, found 716.4581.

Method B: Silica gel (200 mg) was added into an EtOAc (2.0 mL) solution containing **1a** (100.0 mg, 0.140 mmol). The mixture was evaporated to dryness and irradiated under microwaves (400W, 180°C) for 20 min. The resulting product was purified by column chromatography on silica gel eluting with

chloroform-methanol-ammonium hydroxide solution (10:0.5:0.01 to 10:1:0.05) to give **2a** (76.1 mg, 76%) as a white solid.

Analytical and spectral data for **2b -2g**

Des(*N-methyl)-ring-contracted erythromycin A* (**2b**): yield 48%; mp. 177-180°C (lit. [15] mp. 193-195°C); ^{1}H-NMR δ: 5.10 (d, 1H, *J*=2.6, H-11), 4.95 (d, 1H, *J*=7.2, H-1″), 4.37 (d, 1H, *J*=7.0, H-1′), 4.23 (dd, 1H, *J*=10.0, 2.8, H-3), 4.12 (m, 1H, H-5″), 3.78 (d, 1H, *J*=9.5, H-5), 3.28 (s, 3H, 3″-OCH_3), 2.38 (s, 3H, N-CH_3); ^{13}C-NMR δ: 175.8 (C-1), 46.76 (C-2), 80.25 (C-3), 38.51 (C-4), 43.22 (C-7), 101.29 (C-8), 149.56 (C-9), 103.27 (C-1′), 32.92 (N-CH_3), 97.38 (C-1″), 49.29 (3″-OCH_3); HRMS (FAB) m/z: calcd. for $C_{36}H_{63}NO_{12}Na$ $[M+Na]^+$ 724.4248, found 724.4230.

Des(*N-methyl)-N-ethyl-ring-contracted erythromycin A* (**2c**): yield 66%; mp. 166-169°C; ^{1}H-NMR δ: 4.98(d, 1H, *J*=2.7, H-11), 4.82 (d, 1H, *J*=7.0, H-1″), 4.27 (d, 1H, *J*=7.0, H-1′), 4.22 (dd, 1H, *J*=10.0, 3.0, H-3), 3.98 (m, 1H, H-5″), 3.61 (d, 1H, J=10.0, H-5), 3.21 (s, 3H, 3″-OCH_3), 2.13 (s, 3H, N-CH_3); ^{13}C-NMR δ: 176.21 (C-1), 46.97 (C-2), 80.39 (C-3), 84.61 (C-5), 101.76 (C-8), 149.66 (C-9), 104.12 (C-1′), 36.47 (N-CH_3), 47.36 (N-$\underline{C}H_2CH_3$), 12.89 (N-$CH_2\underline{C}H_3$), 97.43 (C-1″), 49.36 (3″-OCH_3); HRMS (FAB) m/z: calcd. for $C_{38}H_{68}NO_{12}$ $[M+H]^+$ 730.4738, found 730.4731.

Des(*N-methyl)-N-propyl-ring-contracted erythromycin A* (**2d**): yield 61%; mp. 149-151°C; ^{1}H-NMR δ: 5.00 (d, 1H, *J*=2.7, H-11), 4.82 (d, 1H, *J*=7.2, H-1″), 4.28 (d, 1H, *J*=7.0, H-1′), 4.20 (dd, 1H, *J*=10.0, 3.0, H-3), 3.97 (m, 1H, H-5″), 3.61 (d, 1H, *J*=9.5, H-5), 3.20 (s, 3H, 3″-OCH_3), 2.18 (s, 3H, N-CH_3); ^{13}C-NMR δ: 176.82 (C-1), 46.9 (C-2), 81.17 (C-3), 86.36 (C-6), 101.69 (C-8), 149.82 (C-9), 76.82 (C-11), 104.62 (C-1′), 37.10 (N-CH_3), 55.55 (N-$\underline{C}H_2CH_2CH_3$), 21.74 (N-$CH_2\underline{C}H_2CH_3$), 12.01 (N-$CH_2CH_2\underline{C}H_3$), 97.29 (C-1″), 49.62 (3″-OCH_3); HRMS (FAB) m/z: calcd. for $C_{39}H_{70}NO_{12}$ $[M+H]^+$ 744.4896, found 744.4897.

Des(*N-methyl)-N-isopropyl-ring-contracted erythromycin A* (**2e**): yield 39%; mp. 112-114°C; ^{1}H-NMR δ: 4.98 (d, 1H, *J*=2.7, H-11), 4.81 (d, 1H, *J*=7.0, H-1″), 4.30 (d, 1H, *J*=7.0, H-1′), 4.21 (dd, 1H, *J*=9.5, 3.0, H-3), 4.02 (m, 1H, H-5″), 3.62 (d, 1H, *J*=9.5, H-5), 3.22 (s, 3H, 3″-OMe), 2.17 (s, 3H, N-Me); ^{13}C-NMR δ: 176.14 (C-1), 46.64 (C-2), 86.12 (C-6), 43.50 (C-7), 101.43 (C-8), 149.46 (C-9), 103.20 (C-1′), 31.99 (N-CH_3), 53.27 (N-$\underline{C}H(CH_3)_2$), 20.61 (N-CH($\underline{C}H_3)_2$), 98.33 (C-1″), 49.40 (3″-OCH_3); HRMS (FAB) m/z: calcd. for $C_{39}H_{70}NO_{12}$ $[M+H]^+$744.4889, found 744.4858.

Des(*N-methyl)-N-allyl-ring-contracted erythromycin A* (**2f**): yield 44%; mp. 106-109°C; ^{1}H-NMR δ: 5.72 (m, 1H, $\underline{CH}=CH_2$), 5.13 (d, 1H, *J*=10.5, CH=$\underline{CH_2}$), 5.04 (d, 1H, *J*=16.8, CH=$\underline{CH_2}$), 4.97 (d, 1H, *J*=2.6, H-11), 4.81 (d, 1H, *J*=7.0, H-1″), 4.27 (d, 1H, *J*=7.0, H-1′), 4.21 (dd, 1H, *J*=10.0, 3.0, H-3), 3.98 (m, 1H, H-5″), 3.61 (d, 1H, *J*=9.8, H-5), 3.20 (s, 3H, 3″-OMe), 2.13 (s, 3H, N-Me); ^{13}C-NMR δ: 176.12 (C-1), 81.07 (C-3), 82.31 (C-5), 86.23 (C-6), 101.49 (C-8), 150.00 (C-9), 77.10 (C-11), 104.46 (C-1′), 30.94 (N-CH_3), 57.52 (N-$\underline{C}H_2CH=CH_2$), 136.66 (N-$CH_2\underline{C}H=CH_2$), 129.24 (N-$CH_2CH=\underline{C}H_2$), 97.89 (C-1″), 49.78 (3″-OCH_3); HRMS (FAB) m/z: calcd. for $C_{39}H_{68}NO_{12}$ $[M+H]^+$ 742.4725, found 742.4711.

Des(*N-methyl*)-*N-propargyl-ring-contracted erythromycin A* (**2g**): yield 58%; mp. 111-113°C; ^{1}H-NMR δ: 4.97 (d, 1H, *J*=2.7, H-11), 4.80 (d, 1H, *J*=7.0, H-1″), 4.28 (d, 1H, *J*=7.0, H-1′), 4.20 (dd, 1H, *J*=10.0, 3.0, H-3), 3.97 (m, 1H, H-5″), 3.62 (d, 1H, *J*=10.0, H-5), 3.34 (s, 2H, N-CH_2), 3.20 (s, 3H, 3″-OCH_3), 2.26 (s, 3H, N-CH_3); ^{13}C-NMR δ: 176.36 (C-1), 81.30 (C-3), 81.09 (C-5), 101.72 (C-8), 150.15 (C-9), 104.18 (C-1′), 32.59 (N-CH_3), 58.53 (N-$\underline{C}H_2C{\equiv}CH$), 82.13 (N-$CH_2\underline{C}{\equiv}CH$), 71.05 (N-$CH_2C{\equiv}\underline{C}H$), 97.97 (C-1″) 49.83 (3″-OCH_3); HRMS (FAB) m/z: calcd. for $C_{39}H_{66}NO_{12}$ $[M+H]^+$ 740.4572, found 740.4565.

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Sample Availability: Samples of the compounds are available from the authors.