

A Facile and Scaleable Synthesis of 3-*O*-Decladinose-6-methyl-10,11-dehydrate-erythromycin-3-one-2'-acetate, an Important Intermediate for Ketolide Synthesis

Xin Wei and Qidong You*

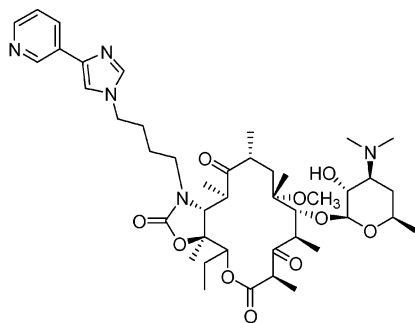
Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing, Jiangsu 210009, PR, China

Abstract:

A facile and scaleable synthetic process of compound **2**, an important intermediate for synthesis of ketolide semisynthetic antibiotics, was developed starting from commercially available clathromycin with an overall yield of ~74%. This synthetic pathway was composed of four steps from compound **3** which could be prepared from clathromycin without using expensive reagents such as EDC·HCl (1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride) or more active reagents such as methanesulfonic anhydride. This new process was efficient and practical as demonstrated by scale-up to prepare more than 1 kg of pure compound **2**.

Introduction

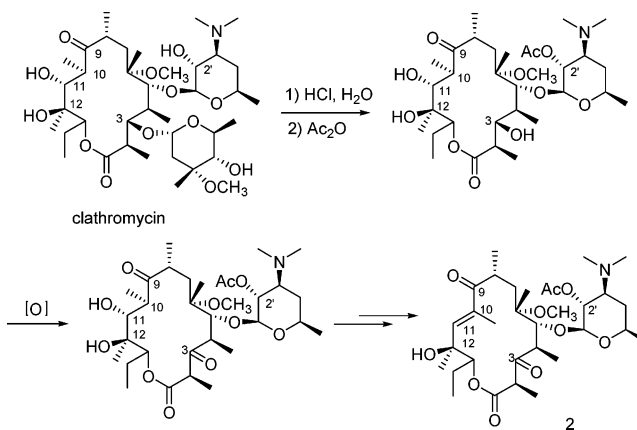
Ketolides, such as telithromycin (**1**), were called the third generation of semisynthetic macrolide derivatives with excellent activity against susceptible and resistant strains to erythromycin in vitro and in vivo.

Telithromycin(**1**)

These new compounds were generated from erythromycin, in which the cladinose-sugar moiety at the 3-position was changed to a carbonyl group. Telithromycin was approved for marketing in Germany and the UK in 2001. In the preparation of ketolides, compound **2**, 10,11-didehydro-11-deoxy-3-*O*-de-[(2,6-dideoxy-3-methyl-3-*O*-methyl- α -L-ribohexopyranosyl)oxy]-6-*O*-methyl-3-oxoerythromycin-2'-acetate, is an important intermediate.^{1–2}

The strategy of most synthetic pathways to **2** in the literature was composed of decladinose on the 3-position to form the 3-hydroxy group, oxidation of the 3-hydroxy group

Scheme 1



to the carbonyl group, and dehydration of the 11-hydroxy group to produce a double bond at the 10,11-position (Scheme 1).

In this strategy for synthesizing **2**, the oxidation of the 3-hydroxy group should be carried out with a selective oxidizing agent since there are another two hydroxy groups at the 11 and 12 positions at the same time. Another problem in this strategy was the dehydration of the 11-hydroxy group to form the 10,11-double bond. The hydroxy group on the 11-position was inactive for dehydration and should be converted to ester (such as mesylate), an easily leaving group, to increase its dehydration ability. In this paper, we describe the successful development of a practical and scaleable process for the synthesis of **2**.

Results and Discussion

It was reported that compound **2** was usually synthesized^{3–6} from clathromycin as starting material through decladinose on the 3-position to form the 3-hydroxy group, selective oxidation of the 3-hydroxy group to the carbonyl group by EDC·HCl/DMSO, selective methanesulfonylation of the 11-hydroxy group by the active reagent methanesulfonic anhydride, and then formation of the double bond on the 10,11-positions by removing the formed methanesulfonic acid ester group in the presence of DBU (1,5-diazabicyclo[5,4,0]undecen-5-ene) (Scheme 2).

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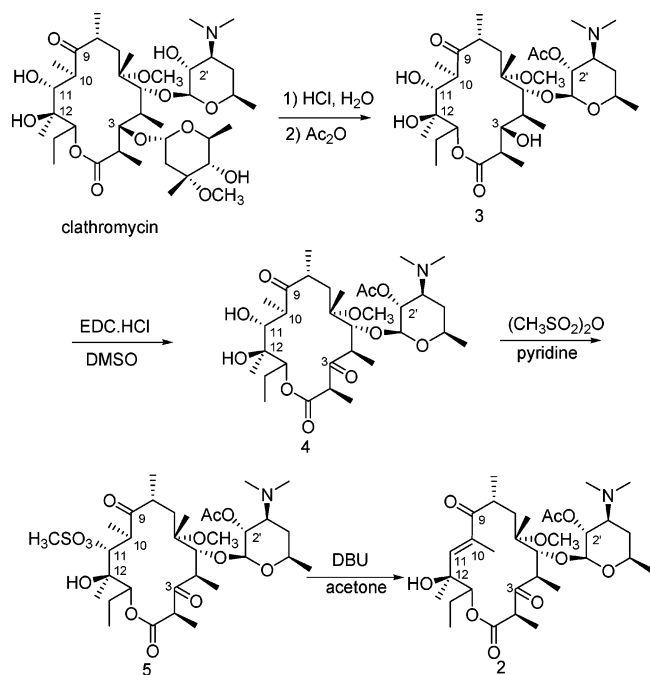
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* To whom correspondence should be addressed. E-mail: youqd@cpu.edu.cn.

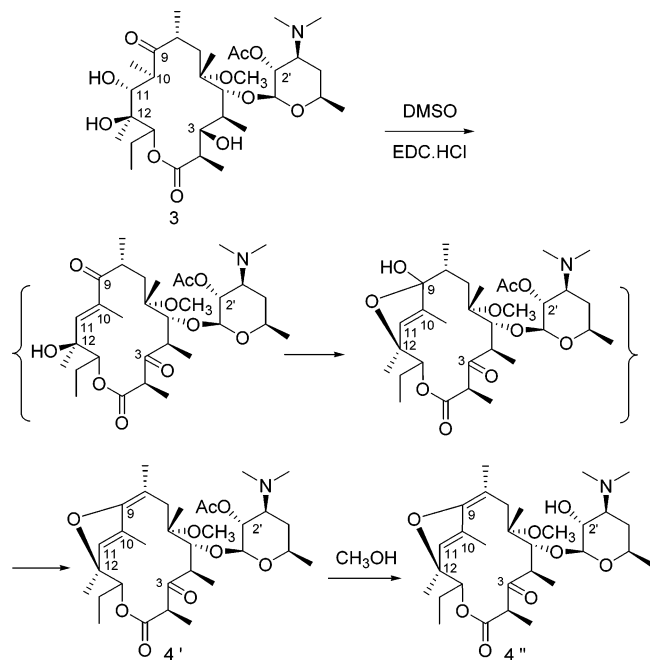
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Scheme 2



Scheme 3



In this process, the selective oxidation of the 3-hydroxy group to the 3-ketone group was very important because there are three hydroxyl groups in compound **3**. This selective oxidation was performed by the EDC·HCl and DMSO system. A large quantity of the expensive reagent EDC·HCl was used for this oxidation. This reagent was not only expensive but also difficult to obtain on commercial scale. However, during the oxidation of **3** to prepare **4** as described in the literature,^{3–6} we found the yield of oxidation was variable. In this procedure, we always got an unexpected byproduct **4'** in addition to the desired product **4**. This new compound **4'** had a molecular ion at m/z 594 with strong

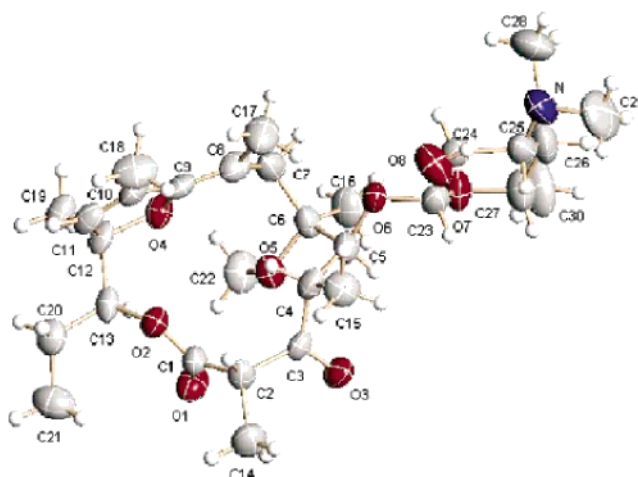


Figure 1. The crystal structure of **4''**.

UV absorption. The m/z 594 molecular ion was less 36 mass units than the expected product **4**.

The reason the byproduct **4'** was produced in this step was that EDC·HCl, a strong dehydration agent, removed a mole of H₂O to form 10,11-olifen in the presence of pyridinium trifluoroacetate, and then the hydroxyl group on the 12-position was activated to attack the carbonyl group on the 9-position to afford 9,12-hemiacetal. The byproduct **4'** was treated by methanol to form **4''** (Scheme 3). The structure of **4''** was determined by X-ray analysis in Figure 1.⁷ The stereochemistry for double bond at C10 and C11 was determined as *Z*-configuration by X-ray crystallography.

In the oxidation step by EDC·HCl and DMSO system, the next problem was the purification of the products **4**. The byproduct **4'** could only be removed by silica column chromatography, which increased the costs and limited the output of the products. This uneconomic and inconvenient handling process was less useful for pharmaceutical industry.

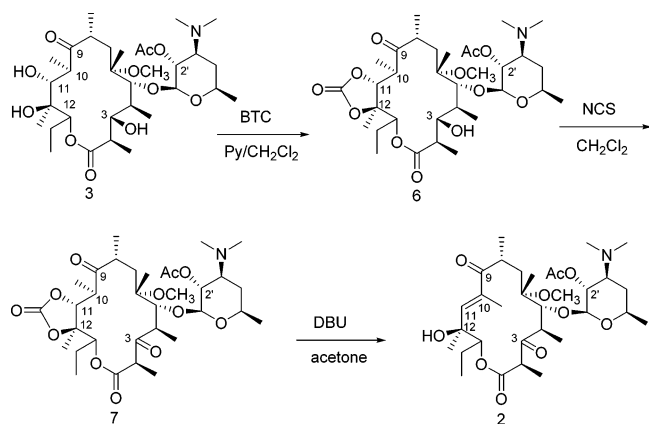
In the above procedure, the selection of EDC·HCl and DMSO as oxidation reagents and the generation of the byproduct **4'** was contributed to by the presence of two hydroxyl groups on the 11,12-positions in the structure of **3**. To avoid using the expensive selective oxidation reagent EDC·HCl and producing the byproduct **4'**, we considered protecting the two hydroxyl groups on the 11,12-positions of **3**. The protective groups should be special to the two hydroxyl groups on the 11,12-positions and should be easily removed after the oxidation of the hydroxyl group on the 3-position. After trying more methods, we found that the carbonate group was a suitable protecting group for the two hydroxyl groups on 11,12-positions of **3**. According to the idea, we designed a novel synthetic process for preparation of the important intermediate **2** for semisynthetic ketolide antibiotics (Scheme 4).

In this process, the **3** was first treated by BTC (bis-(trichloromethanol)carbonate), “Triphosgene”, to produce 11,12-carbonate **6**.⁸ Now **6** only had a free 3-hydroxyl group which could be oxidized by common oxidation agents. In practice, most of the oxidation reagents, such as the NCS,

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Scheme 4



PCC, and so on, used in organic synthesis, could be used for oxidation of **6** to produce **7**. The yield of the oxidation step was very high without any byproducts. The experimental handling for preparing **7** from **6** was more convenient by simple treatment. After getting **7** with the 3-carbonyl group, the next step was to introduce the C–C double bond at the 10,11-positions. From the view of organic synthesis, it was important to change the 11-hydroxyl group to an easily leaving group which could be eliminated in the presence of bases to form a C–C double bond. In the original literature, the 11-hydroxyl group of **4** was converted to 11-methylsulfonate. The methylsulfonate, a more active group, could bring more complex reaction results. In our procedure, the 11,12-carbonate group of **7** was also a moderately active leaving group which was treated by DBU³ to form a C–C double bond on the 10,11-positions to produce the desired product **2** without being further purified by column chromatography (Scheme 4). This new procedure for the preparation of **2** from clathromycin was more efficient and economical since it avoided the use of the expensive and uncommon oxidation agent EDC·HCl and the more active reagent methanesulfonic anhydride.

In summary, we have developed a practical and scaleable process for the synthesis of **2** from commercially available materials. A simple isolation and purification procedure was used in the large-scale preparation of the product without column chromatography. The efficiency and practicality of the process were demonstrated by the synthesis of more than 1 kg of pure **2** with an overall ~74% yield.

Experimental Section

General Remarks. ¹H NMR spectra were recorded on a ACF-300 Bruker instrument. The electrospray ionization (ESI) mass spectra were obtained using a Finnigan FTMS-2000 spectrometer. IR spectra were obtained using a Nicolet Impact 410 (KBr) spectrometer. All melting points were measured on a MEL-TEMP II apparatus and are uncorrected. HPLC analyses for **6** and **7** were performed on a Shimadzu LC-10A system using a Shimadzu VP-ODS column (4.6 mm × 150 mm, 5 μm) run at a flow rate of 1.0 mL/min with CH₃CN and buffer A (0.008 mol/L CH₃COONH₄ in H₂O) (40:60) with Evaporative Light Scattering Detector (Polymer Laboratories PL-ELS2100, evaporator: 110 °C, nebuliser: 45 °C, gas flow: 2.1 L/min). Analytical HPLC for **2** was

performed on a JASCO PU-2080 plus system using a HiQsil C18W column (4.6 mm × 150 mm, 5 μm) run at a flow rate of 1.0 mL/min with CH₃OH and H₂O (80:20), and was detected at UV 254 nm. All chemicals and reagents were purchased and used without further purification unless otherwise mentioned.

3-*O*-De-[(2,6-dideoxy-3-methyl-3-*O*-methyl-α-L-ribohexopyranosyl)oxy]-6-*O*-methyl-cyclic 11,12-carbonate-erythromycin 2'-acetate (6**).** To a stirred solution of 3-*O*-de-[(2,6-dideoxy-3-methyl-3-*O*-methyl-α-L-ribohexopyranosyl)oxy]-6-*O*-methylerythromycin 2'-acetate **3**³ (200 g, 317 mmol) and dry pyridine (140 mL) in dry methylene chloride (1500 mL) at 0 °C was added dropwise a solution of bis-(trichloromethanol)carbonate (BTC) (66.7 g, 224.7 mmol) of dry methylene chloride (800 mL). The mixture was stirred for about 23 h at room temperature and then cooled to 0 °C. The mixture was poured into a saturated solution of sodium chloride (2000 mL) and extracted with methylene chloride (3 × 1000 mL); the extracts were washed with water (3 × 800 mL) and dried over MgSO₄. Evaporation of the solution afforded 198 g (95.1%) of crude **6** as a light-yellow foam, its purity is enough for the next step synthesis.

Compound **6** was purified by column chromatography eluting with 10:4:1 petroleum ether (60–90 °C)/acetone/triethylamine as a white solid for structure analysis, mp 92–93 °C, purity: 98.885% (HPLC). IR (KBr) 3540, 1814, 1741, 1715 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 0.91(t, *J* = 7 Hz, 3H, CH₃CH₂), 1.13 (s, 3H, 6-CH₃), 1.24 (s, 3H, 12-CH₃), 2.09 (s, 3H, 2'-OCOCH₃), 2.26 (s, 6H, N(CH₃)₂), 2.47-(q, *J* = 7 Hz, 1H, 10-CH), 2.97 (s, 3H, 6-O-CH₃), 3.49 (m, 2H, 3-CH and 5'-CH), 3.87 (q, *J* = 6.5 Hz, 1H, 2-CH), 4.20 (d, *J* = 9 Hz, 1H, 5-CH), 4.42 (d, *J* = 7 Hz, 1H, 11-CH), 4.62 (dd, *J* = 2 and 10 Hz, 1H, 13-CH), 4.88 (dd, *J* = 8 and 10 Hz, 1H, 2'-CH), 5.12(d, *J* = 7.5 Hz, 1H, 1'-CH). MS (ESI) *m/e*: 658 (M + H)⁺

3-*O*-De-[(2,6-dideoxy-3-methyl-3-*O*-methyl-α-D-ribohexopyranosyl)oxy]-6-*O*-methyl-3-oxo-cyclic 11,12-carbonate-erythromycin 2'-acetate (7**).** Method I. To a stirred solution of *N*-chlorosuccinimide (60 g, 450 mmol) in dry methylene chloride (1000 mL) at 0 °C, was added dropwise methyl sulfide (44.8 mL, 746 mmol). A white precipitate appeared immediately. The mixture was cooled to –5 °C, and a solution of crude **6** (196 g, 298.4 mmol) in dry methylene chloride (1000 mL) was added dropwise over 30 min. Stirring was continued for 3 h at –5 °C before a solution of triethylamine (44.7 g, 440 mmol) was added dropwise over 20 min. After warming to room temperature, the organic layer was washed with 1% hydrochloric acid (700 mL), and water (2 × 700 mL) and dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded 183.6 g (94%) of the crude **7** as a yellow foam, its purity is enough for the next step synthesis.

The compound **7** was purified by column chromatography eluting with 10:4:1 petroleum ether (60–90 °C)/acetone/triethylamine as a white solid for structure analysis, mp 105–106 °C, purity: 98.844% (HPLC).

Method II. To a stirred solution of crude **6** (196 g, 298.4 mmol) in dry methylene chloride (2000 mL), was added PCC

(396 g, 1835.4 mmol) at room temperature. The mixture was stirred for 24 h at 30 °C. The brown precipitate formed was filtered off and washed with methylene chloride (3 × 400 mL). The organic layer was washed with a saturated solution of sodium bicarbonate (4 × 800 mL) and water (600 mL) and was dried over MgSO₄. After evaporation of the solvent to afford 186.7 g (95.6%) of the crude **7** as a yellow foam, its purity was enough for the next step synthesis.

Method III. To a stirred solution of crude **6** (98 g, 149.2 mmol) in dry methylene chloride (2000 mL) was added PDC (345 g, 917.7 mmol) at room temperature, and the mixture was stirred for 55 h. The brown precipitate that formed was filtered off and washed with methylene chloride (2 × 200 mL). The organic layer was washed with a saturated solution of sodium bicarbonate (4 × 500 mL) and water (400 mL) and was dried over MgSO₄. Evaporation of the solvent afforded 82.8 g (84.8%) of the crude **7** as a yellow foam, its purity was enough for the next step synthesis.

Method IV. To a stirred solution of oxalyl chloride (22 g, 173 mmol) in dry methylene chloride (400 mL) at -78 °C was added dropwise the solution of DMSO (27 g, 345.7 mmol) in dry methylene chloride (100 mL) over 10 min. Then a solution of **6** (75.6 g, 115 mmol) in dry methylene chloride (1000 mL) was added to this solution over 50 min. The mixture was then stirred for 2 h at -60 °C before a solution of triethylamine (67.8 g, 667 mmol) was added dropwise over 20 min. After warming to room temperature, the organic layer was washed with 1% hydrochloric acid (700 mL), a saturated solution of sodium bicarbonate (2 × 500 mL) and water (3 × 700 mL) and was dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded 50.7 g (67.4%) of the crude **7** as a yellow foam, its purity was enough for the next step synthesis.

IR (KBr) 1812, 1748, 1713 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 0.92 (t, *J* = 7 Hz, 3H, CH₃CH₂), 1.15 (s, 3H, 6-CH₃), 1.27 (s, 3H, 12-CH₃), 2.11 (s, 3H, 2'-OCOCH₃), 2.27 (s, 6H, N(CH₃)₂), 2.48 (q, *J* = 7 Hz, 1H, 10-CH), 2.92 (s, 3H, 6-O-CH₃), 3.47 (m, 2H, 3-CH and 5'-CH), 3.85 (q,

J = 6.5 Hz, 1H, 2-CH), 4.21 (d, *J* = 9 Hz, 1H, 5-CH), 4.42 (d, *J* = 7 Hz, 1H, 11-CH), 4.63 (dd, *J* = 2 and 10 Hz, 1H, 13-CH), 4.89 (dd, *J* = 8 and 10 Hz, 1H, 2'-CH), 5.13 (d, *J* = 7.5 Hz, 1H, 1'-CH). MS (ESI) *m/e* 656 (M + H)⁺.

10,11-Didehydro-11-deoxy-3-O-de-[(2,6-dideoxy-3-methyl-3-O-methyl-α-L-ribohexopyranosyl)oxy]-6-O-methyl-3-oxo-erythromycin-2'-acetate (2). To a stirred solution of crude **7** (180 g, 274.8 mmol) in acetone (2000 mL), was added DBU (104 mL, 685.4 mmol). The mixture was refluxed for 14 h and then cooled to room temperature. After evaporation of the acetone, the residue was dissolved in methylene chloride (1000 mL), washed with saturated solution of sodium chloride (5 × 300 mL), and dried over anhydrous magnesium sulfate. After evaporation of the solution, a crude product was afforded as a light-yellow foam. The crude product was added to ethyl acetate (300 mL) and then stirred for 30 min. The white solid that formed was separated by suction filtration, washed with cold ethyl acetate (2 × 50 mL), and dried under vacuum to give 136 g (81%) pure **2** as white solid, mp 218–219 °C, purity: 98.397% (HPLC). IR (KBr) 1747, 1713, 1670 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 0.89 (t, *J* = 7 Hz, 3H, CH₃CH₂), 1.24 (s, 3H, 12-CH₃), 1.45 (s, 3H, 6-CH₃), 2.03 (s, 3H, 10-CH₃), 2.10 (s, 3H, 2'-OCOCH₃), 2.27 (s, 6H, N(CH₃)₂), 2.91 (s, 3H, 6-O-CH₃), 3.49 (m, 2H, 3-CH and 5'-CH), 3.85 (q, *J* = 6.5 Hz, 1H, 2-CH), 4.23 (d, *J* = 9 Hz, 1H, 5-CH), 4.87 (dd, *J* = 8 and 10 Hz, 1H, 2'-CH), 4.98 (dd, *J* = 2 and 10 Hz, 1H, 13-CH), 5.04 (s, 1H, 12-OH), 5.13 (d, *J* = 7.5 Hz, 1H, 1'-CH), 6.68 (s, 1H, 11-CH).

MS (ESI) *m/e* 612 (M + H)⁺

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