Organic Process Research & Development **2010,** *14,* 1393–1401

Initial Scale-Up and Process Improvements for the Preparation of a Lead Antibacterial Macrolone Compound

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Abstract:

Macrolones are a novel class of potent antimicrobial agents that consist of a macrolide scaffold to which a quinolone unit is tethered by various linkers to the 4″-*O*-position of the cladinose sugar. In this paper is described a modified 13-step route to a lead compound in the series. Critical reaction steps in the medicinal chemistry route were modified for an initial scale-up process, and as a result, a synthetic procedure suitable for preparation of multihundred gram quantities of the final product, with 98% purity, has been developed. The new procedure does not require any purification by column chromatography for any of the reaction steps. The overall yield was increased from 5−8% in the medicinal chemistry route to 27% in the improved procedure.

Introduction

Recently our team discovered a new class of antimicrobial compounds which consist of a macrolide scaffold and a quinolone unit, covalently connected by a suitable linker[1−3] which were named "macrolones". The recently prepared analogue **15**, Figure 1, is a key lead for the series, and the combination of a 10-atom bis-ether chain linking the quinolone moiety to an azithromycin core fulfils the medicinal chemistry target product profile.[4]

The initial medicinal chemistry route for the preparation of compound **15** consisted of thirteen reaction steps including several chromatographic purifications, with an overall yield of 5−8%. A more efficient route which avoided expensive and time-consuming chromatography was required to prepare sufficient material to support preclinical *in vivo* safety assessment studies. Given the limited time available it was decided to adapt the existing medicinal chemistry route for scale-up rather than design a completely new approach. This modified synthetic procedure was successfully applied using a laboratory 5 L reactor to prepare an initial 350 g of compound **15**. The material was isolated as the free base, by precipitation in the form of an amorphous solid with purity of 97.7% area by HPLC−UV. The process does not include final crystallization or salt preparation.

Herein we describe the optimized synthesis and present improved reaction conditions that significantly contributed to the scalability, overall yield and final purity of the product **15**.

Results and Discussion

Synthesis of the Quinolone Building Block 6: Steps 1−5. The synthesis of the quinolone moiety was recently described,[4] and only minor modifications in the in the workup, isolation and purification of the final product were required to furnish 2.0 kg of **6** in 66% overall yield with purity of >99.5% area. The major changes involved using compounds **2** and **3**, Scheme 1, without purification. Compound **4** was isolated by crystallization from EtOH rather than *n*-hexane, and compound **5** was crystallized from water rather than THF. In step 5 THF was replaced with EtOH and compound **6** isolated directly from the reaction mixture by adjusting the pH of the solution.

Preparation of iodoquinolone **6** was carried out in five linear steps, starting from 2-fluoro-5-iodo-benzoic acid (**1**) on 500−700 g scales.

Reagents and conditions used in the final optimized synthetic procedure:

Step 1: compound **1**, oxalyl chloride (1.2 equiv), DMF (0.1 equiv), toluene (5 vol), 20 °C, 1.5−2 h, partially concentrated, **2** used in the next step as toluene solution.

Step 2: compound **2**, TEA (1.3 equiv), dimethylaminoacrylate (1.05 equiv), toluene (6 vol), 90 °C, 2 h, insoluble salts filtered off, concentrated, EtOH added, toluene azeotropically removed, **3** used in the next step as a suspension in EtOH.

Step 3: suspension of **3** in EtOH (3 vol), 2 M ethylamine in THF (1.14 equiv), rt, 1.5 h, THF evaporated, **4** crystallized from EtOH. Yield = 67−70% starting from **1**. HPLC−MS: 96.9% area, HPLC−UV: 98.2% area.

Step 4: compound **4**, K_2CO_3 (2 equiv), DMF (3 vol), 120 °C, 1 h, water (3 vol) added, crystals filtered off, aliquot dried. Yield = 97%. HPLC−MS: 99.7% area, HPLC−UV: 99.9% area.

Step 5: compound **5**, NaOH (3 equiv), EtOH/H_2O 1:1 (8 vol), 75 °C, 35−45 min, cooled to 50 °C, 6 M aq HCl (1.3 vol) added (pH = 6), cooled to rt, filtered off, dried. Yield = 96−100%. HPLC−MS 99.5% area, HPLC−UV 99.7% area.

By using these optimized conditions the initial small-scale procedure was significantly improved. In summary, the number

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10.1021/op100199t
Published on Web 09/28/2010

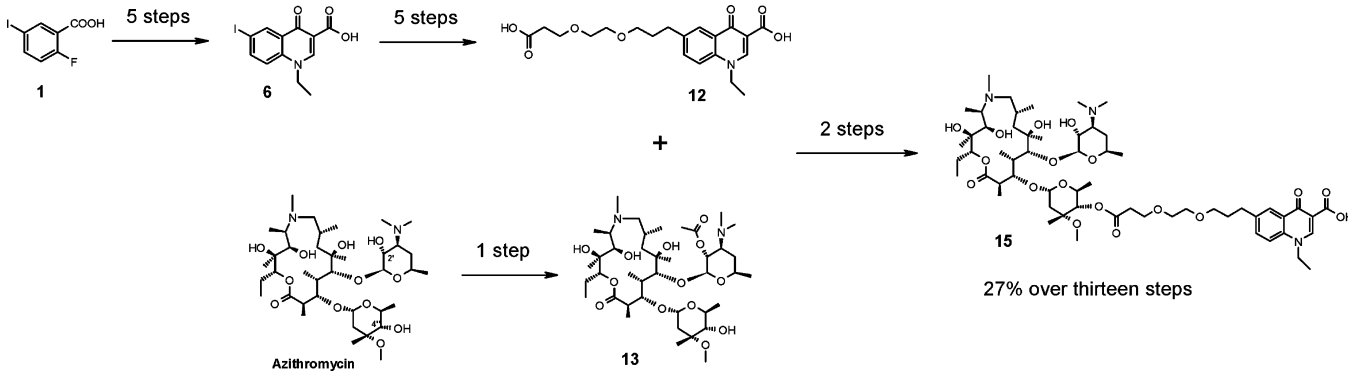
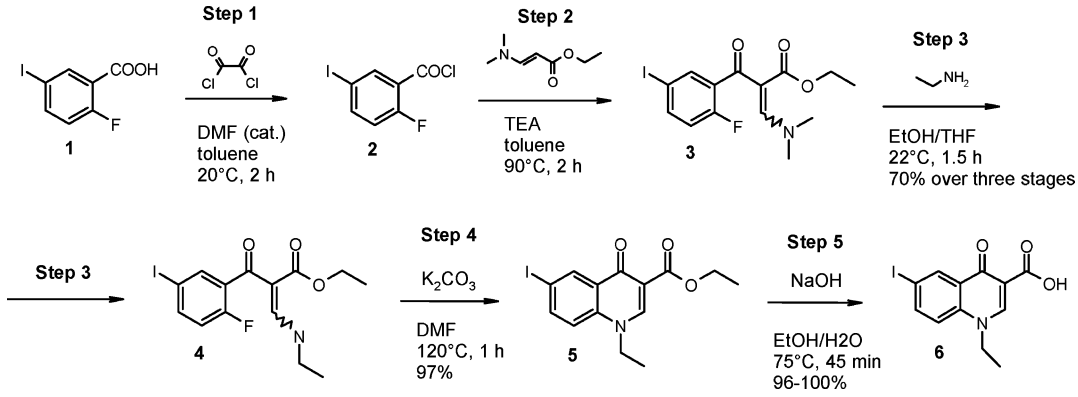


Figure 1. **Outline of the synthetic route to compound 15 and key building blocks.**

Scheme 1. **Synthesis of 1-ethyl-6-iodo-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid (6)**



of organic solvents used in the route decreased from 8 to 4, and evaporation of solutions to dryness was avoided. Intermediates **4** and **5** were isolated by a crystallization from ecologically acceptable solvents and were used in the next steps without drying. Only the final compound needed to be dried. Overall yield on **6** was increased from 37% to 66%.

Synthesis of the Linker−Quinolone Building Block 12: Steps 6−10. An outline of the improved route to compound **12** is given in Scheme 2.

Step 6: Small-Scale Procedure and Reaction Conditions. A synthesis of the intermediate **8**, step 6, started from commercially available benzyloxyethanol (**7**) which was alkylated with propargyl bromide (2 equiv) in THF using NaH (1.2 equiv) as base at room temperature. After removal of the solvent, the product was isolated by EtOAc/H_2O extraction and evaporation of the resultant organic layer to dryness.

Step 6: Optimization of the Reaction Conditions and Improved Procedure. During examination of the reaction's parameters it was found that if toluene was used as the reaction solvent, the quantity of propargyl bromide could be reduced to 1.5 equiv, and the reaction was complete after 1 h compared to 24 h in THF. The purity, assessed by HPLC−UV, was increased from 71% to 83%. Three separate runs were performed starting from 440, 600, and 700 mL of compound **7** all using a modified isolation protocol of azeotropical removal of toluene, from the crude reaction solution, by addition of EtOH. The resulting solution of compound **8** in EtOH was used in the next step without further manipulation, calculating the yield of **8** as 100%.

Step 7: Small-Scale Reaction Conditions and Scale-Up Limitations. The next step was a Sonogashira coupling[5] of quinolone **6** and the linker **8**. The issues in this step were mainly related to usage of large amounts of the catalysts (CuI 15 mol % and $Pd(PPh_3)_2Cl_2$ 10 mol %) and the solvents (TEA 12 vol, MeCN 12 vol), as well as isolation of the product **9** by column chromatography.

Step 7: Modifications of Reaction Conditions and Isolation Procedure. The isolation of compound **9** was modified by diluting the reaction mixture with water (40 vol), washing with *i*-Pr_2O at pH 12, and treatment of the aqueous layer with activated charcoal at 60 °C. Acidification of the aqueous layer to pH 8.5 resulted in a precipitation of the product that was removed by a filtration. Although the yields were acceptable (80−82%) and the purity excellent (>98% area as determined by HPLC−UV), large amounts of solvents and reagents (12 vol MeCN, 12 vol TEA, 40 vol H_2O, 30 vol *i*-Pr_2O) were wasted and limited the amount of starting compound **6** in the 5-L reactor to just 50 g. Attempts to avoid washing with *i*-Pr_2O and to precipitate the product from a mixture MeCN/TEA/H_2O resulted in resinous gum.

Several solvent systems were investigated, and a particular effort was made to find an ecologically acceptable solution.[6] Initial reactions on 1-g scale were performed in toluene, acetone, *i*-PrOAc, and absolute EtOH; in all systems the reaction was complete within 1 h. Simultaneously, the catalyst loading was reduced to 5 mol % each without any detrimental effect on the

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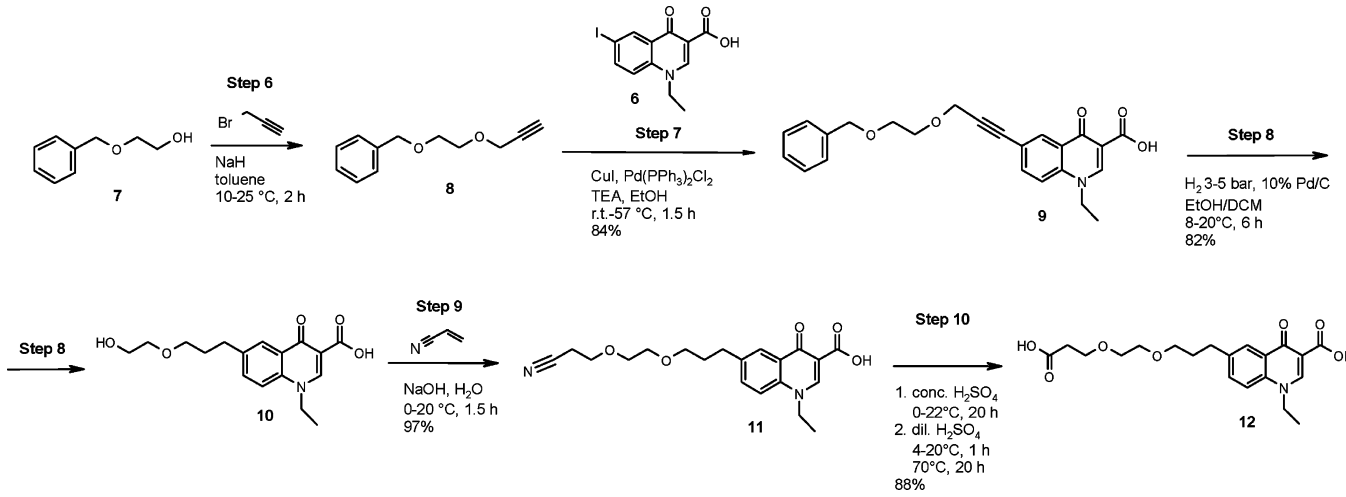
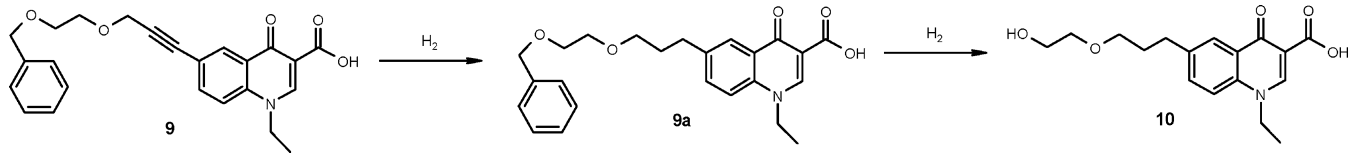
Scheme 2. **Synthetic route and modified reaction conditions for a preparation of intermediate 12**



Scheme 3. **Stepwise hydrogenation of compound 9**



rate of reaction. Toluene was the preferred choice as it was used as the solvent in a previous step and would avoid the necessity of solvent exchange. However, isolation of compound **9** as a tractable solid proved impossible.

Using EtOH as the solvent, on a 5-g scale as described above, the reaction mixture was filtered to remove the catalysts, and the majority of the TEA was evaporated under vacuum. The resultant ethanolic solution of **6** was diluted with water and acidified by addition of 6 M HCl. At pH 7.5 precipitation of the product occurred, but the initial solid residue soon transformed to a sticky gum.

Step 7: Final Modified Procedure. Repeating the above procedure on a 10-g scale, but using only 1 mol % of the catalysts, incurred an increase in reaction time from 1 to 3 h. However, it was found that precipitation from a biphasic mixture EtOH/H_2O/toluene, 1:1:0.8 at pH 8.3−8.5, gave the product **9** in excellent purity as a free-flowing powder that was much easier to filter and dry than the previously isolated gums.

By using this procedure six large-scale batches (300−500 g) were performed, affording the compound **9** in high yield (81−86%) and purity (97.7% area by HPLC−MS, 99.2% area by HPLC−UV). Approximately 2.3 kg of the compound was produced.

NMR analysis of the solid residue was performed in order to investigate possible formation of the TEA salt of the product **9** at relatively high pH 8.4. For the analysis, the material after precipitation and filtration at pH 8.4 was used and compared with an aliquot of the material isolated by precipitation at lower pH 5.0. In the ^{1}H NMR spectra of compound **9** after precipitations at pH 8.4 (wet and dried) and pH 5.0 (dried), no TEA signals were observed, confirming that compound **9** is isolated as a free acid. The only differences observed were higher levels of the residual solvents H_2O and toluene in the wet product.

Step 8: Small-Scale Reaction Conditions and Scale-Up Limitations. The small-scale (0.6−10 g) reactions of hydrogenation of compound **9** were performed at 5−20 bar pressure at rt overnight in a mixture MeOH/DCM, 3:1 (20 vol), in the presence of 10% Pd/C as a catalyst. DCM was added to improve the solubility of **9**. In all batches the reaction stalled at intermediate **9a**, Scheme 3, requiring additional amounts of fresh catalyst to complete the conversion.

After filtration of the catalyst and evaporation of the solvent, in the first experiments compound **10** was isolated by column chromatography. Crystallization of crude residue from EtOH under controlled conditions resulted in compound **10** in 35−78% yields and with 83−93% purity, assessed by HPLC−MS and HPLC−UV.

Step 8: Modifications of Reaction Conditions, Isolation, and Final Improved Procedure. The first step in the optimisation was to replace MeOH as the solvent with EtOH in order to enable direct crystallization of the product **10**. The goal was also to reduce the amount of DCM which is required because of low solubility of starting compound **9** in MeOH. Initial reactions were performed in EtOH/DCM = 4:1 (10 vol) at 5−10 bar pressure, and monitoring of the progress revealed a profile similar to that of small-scale reactions. After removal of the catalyst by filtration, the following three different isolation methods of compound **10** were examined:

Procedure P1. The solution was concentrated, and the product was dissolved in DCM, extracted to water at pH 10, and then precipitated by acidification of the aqueous layer to pH 6.

Procedure P2. After evaporation of DCM into the resulting EtOH solution, water was added, the solution was concentrated to a smaller volume and the precipitation occurred.

Procedure P3. The solution was concentrated, and the product crystallized from EtOH by heating to 60 °C and slowly cooling to 5 °C.

Scheme 4. **Undesired ether bond hydrogenolysis and formation of byproduct 9b at elevated temperature**

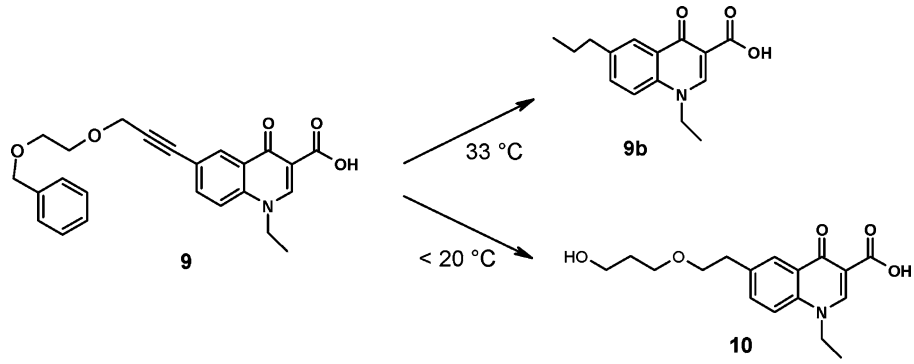


Table 1. **Conditions and results of hydrogenation of compound 9**

batch	**9**/g	Pd cat./g	$T_{min} - T_{max}$/°C	H_2/bar	isolation procedure	yield/%	HPLC−MS/%; HPLC−UV/%
1	173	60.0 + 9.0	20−33	5−10	P1	49.7	67.1/85.8
2	200	29.1 + 3.0	11−27	5	P2	61.3	85.6/96.2
3	**1683**	258.0 + 96.2	8−20	3−5	P3	**82.4**	**94.1/97.6**

Isolation procedure P3 proved to be the best, affording the highest yield and final purity of **10**, as will be shown below.

After initial laboratory reactions the hydrogenation was repeated in a 47-L reactor starting from 173 g of **9**. The first batch showed a highly exothermic reaction as the temperature of the mixture rose from 20 to 33 °C while cooled by water. HPLC−MS analysis revealed that this inadequate temperature control caused ether bond hydrogenolysis resulting in the formation of 33% of 6-propylquinolone **9b** as the only byproduct, Scheme 4.

Although the byproduct **9b** does not take an active part in the next step and can be tolerated in crude product, the goal was to reduce its formation in order to increase the yield of the product **10**. Therefore, additional batches were carried out by controlled addition of hydrogen gas while maintaining the temperature below 20 °C. By using this procedure the amount of **9b** was reduced to 5.9% area, determined by HPLC−MS, and 2.4% by HPLC−UV, batch 3, Table 1.

As mentioned previously and as can be seen in Table 1, isolation procedure P3 gave the highest yields and purities.

Step 9: Small-Scale Reaction Conditions and Scale-Up Limitations. Addition of the final three-atom portion of the linker was achieved by a Michael reaction of compound **9** with acrylonitrile. Initially, acrylonitrile was used as solvent for the reaction with DBU as base at 80 °C for 24 h. This combination required a tedious isolation procedure due to extensive formation of polymers and afforded desired cyano derivative **11** in low yield and purity (66% by HPLC−UV). Furthermore, in two runs exothermic polymerisation of acrylonitrile resulted in a runaway reaction.

Step 9: Modifications of Reaction Conditions and Isolation, and Final Improved Procedure. A definite improvement was achieved when 40% aq NaOH was used as base and methyl isobutyl ketone (MiBK) as solvent, allowing a lower molar ratio of acrylonitrile to be used. The reaction was completed after 2−3 h at 10−20 °C, and cyano derivative **11** was isolated in 70−80% yields. The optimised isolation protocol included extraction of **11** into the aqueous phase at pH 11 and precipitation from aqueous solution at pH 6.0−6.5, affording the desired product in >90% purities, as determined by HPLC. Further improvements of the reaction conditions included complete elimination of the organic solvent and reducing the quantity of NaOH used.

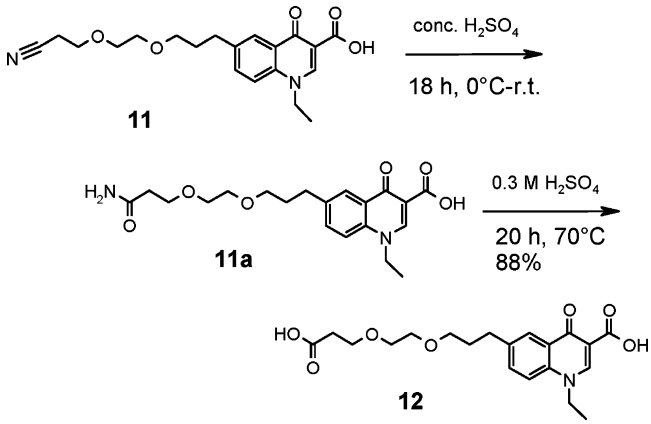
Five batches of compound **11** were successfully prepared on 96−380 g scales, affording the product in high yields and purities. The reactions were carried iout n 10% aq NaOH at room temperature and were completed in only 50 min. The product was isolated by diluting with water and adding conc. HCl until precipitation at pH 6.3 started. Compound **11** was used in the next step as a wet powder, and aliquots weredried in order to calculate the yield. The yields were 92−97% and purities 92−95% by HPLC−MS and 94−95% by HPLC−UV methods.

Step 10: Small-Scale Reaction Conditions and Scale-Up Limitations. In the first experiments a hydrolysis of the nitrile **11** was attempted in ∼60% sulfuric acid, Scheme 2. These conditions afforded quinolone diacid **12** usually contaminated with 20−30% of alcohol **10** formed by retro-Michael reaction. The resulting alcohol **10** is a competitor to 2′-*O*-acetylazithromycin **13** in the esterification step (step 12), and thus formation of this byproduct needs to be suppressed. In the original synthesis compound **12** was isolated by extraction with DCM at pH 3.5 followed by purification by column chromatography.

Step 10: Modifications of Reaction Conditions and Isolation, and Final Improved Procedure. Virtually complete suppression of the retro-Michael reaction could be achieved by careful temperature control of the reaction. This resulted in initial formation of the intermediate amide **11a**, Scheme 5, at low temperature and high concentration of acid followed by hydrolysis to the desired product **12** at a higher temperature and lower concentration of acid.

According to this protocol the nitrile **11** was added to conc. H_2SO_4 portionwise with stirring over 1 h, maintaining the temperature at <5 °C. After addition was complete, the solution was then stirred at rt for 18 h, monitoring by HPLC−MS to confirm completion of reaction. The reaction was treated dropwise with water over a 5-h period, keeping the temperature of the mixture below 8 °C until ∼0.3 mol/L concentration of the acid was reached. The temperature was then raised to 70 °C and the mixture stirred overnight. The approach of diluting

Scheme 5. **Two-step hydrolysis of nitrile 11 to diacid 12**



the acid with water was adopted, rather than the dropwise addition of acid to water, because of problems with the high viscosity of the **11a**/H_2SO_4 solution. Isolation included further dilution with water and adjustment of pH to 0.1−0.5 by slow addition of 40% NaOH over 2.5 h, keeping the temperature of the mixture below 8 °C. Dicarboxylic acid **12** was collected by suction filtration in ∼90% yield. HPLC−MS analysis of dried compound **12** revealed less than 5% of retro-Michael product, quinolonic alcohol **10**.

Two batches were carried out starting from 224 and 300 g of compound **11** affording 215 and 281 g of **12**, respectively, with 88.1% purity, assessed by HPLC−UV.

Step 11: Small-Scale Reaction Conditions and Scale-Up Limitations. The second key intermediate in the convergent route to **15**, the 2′-*O*-acetyl derivative **13**, was prepared from the parent azithromycin with slight excess of acetic anhydride (1.1 equiv) in the presence of $NaHCO_3$ (4.5 equiv) in DCM at rt, Scheme 6. Upon completion of the reaction, the mixture was diluted with water, and the product was isolated by extraction with DCM and evaporation to dryness.

By using this procedure compound **13** was always accompanied with 2′,4″-*O,O*-diacetyl byproduct **13a**, Figure 2, in up to 5%, as determined by HPLC−MS.

Exploratory experimentation suggested that reducing the amount of acetic anhydride to 1.0 equiv suppressed formation of the byproduct but also resulted in incomplete conversion of starting azithromycin. Replacement of DCM with environmentally more acceptable EtOAc and reducing the amount of $NaHCO_3$ gave a similar product profile.

Step 11: Modifications of Reaction Conditions and Isolation Procedure. Eventually it was discovered that formation of **13a** could be avoided by using *i*-PrOH as the solvent. Since the reaction rate of the desired acylation at the 2′-OH group is enhanced due to intramolecular catalysis of vicinal dimethylamino group on the C-3′ position,[7,8] the secondary hydroxyl in the solvent is only a competitor to the less reactive 4″-OH group. After applying these modified conditions (*i*-PrOH 3 vol, $NaHCO_3$ 1.5 equiv, Ac_2O 1.1 equiv, 0 °C to rt, 20 h) HPLC−MS analysis revealed less than 0.1% of diacetyl byproduct **13a**. Isolation of the product **13** included dilution of the reaction mixture with water, adjustment to pH 9.3−9.5, and filtration of the resultant crystalline product. Starting from 700 g of azithromycin, 609 g of compound **13** was produced in a single batch. The yield was 88% and the purity 98.0% area, assessed by HPLC−MS.

Synthesis of the Final Compound 15: Steps 12 and 13. To complete site-selective acylation of compound **13** at C4″−OH by dicarboxylic acid **12**, the combination of EDAC × HCl/DMAP was used.[9] After careful comparison of the relative acidity of the two carboxylic groups in diacid **12**[10] it was concluded that a less acidic carboxylic group attached to the quinolone ring would be a much poorer substrate for esterification than the aliphatic acid at the chain terminus. This selectivity is explained by preferred proton transfer from the more acidic carboxylic group to the *N*-atom of carbodiimide, followed by an addition of carboxylate anion to form the *O*-acyl urea active intermediate. Several acylation procedures were investigated, e.g. mixed anhydride of diacid **12** with pivaloyl chloride and DCC, but the most suitable reagent was EDAC × HCl/DMAP. Formation of up to 5% of macrolide byproduct was regularly observed with various molar ratios of acylating agents.

Based on this finding and other exploratory experiments, the final protocol for modified preparation of **14** includes the use of 2.5 equiv of EDAC × HCl and 3 equiv of DMAP. DMF was replaced as the reaction solvent by DCM, which simplified the workup procedure and ensured complete dissolution of reagents and product at low temperatures. In spite of the longer reaction time, the large-scale reactions were conducted and maintained at low temperature, which resulted in reduced levels of byproduct. Furthermore by increasing the concentration of the reactants the reaction rate was accelerated and the level of starting material **13** was kept to <1% in the final product, as monitored by HPLC−MS. The purification method in the final step 13, described below, has allowed almost complete elimination of this byproduct.

The workup included washing the crude reaction mixture with aq $NaHCO_3$ and water to remove the EDAC and the majority of DMAP. Evaporation of the solvent to dryness gave the desired product **14**. Since the required amount of compound **14** had been produced in this single batch, no further optimisation of the isolation procedure was carried out at this stage. Additional experimentation on a 1-g scale showed us that DCM can be easily exchanged with MeOH, and compound **14** was forwarded to the next step as MeOH solution. A total of 1178 g of compound **14** was produced in the form of a syrup with HPLC−MS purity of 91% area. It transpired that intermediate **14**, thus formed, can be used in the next step without any detrimental effect on the course of the next reaction.

Step 13: Modified Extraction Method and Isolation of Solid Amorphous Product 15. Methanolysis of 2′-*O*-acetyl protecting group was performed at 55 °C overnight in two batches starting from 698 and 480 g of crude **14**. After the completion of the reaction, in addition to the product **15**, TLC and HPLC indicated

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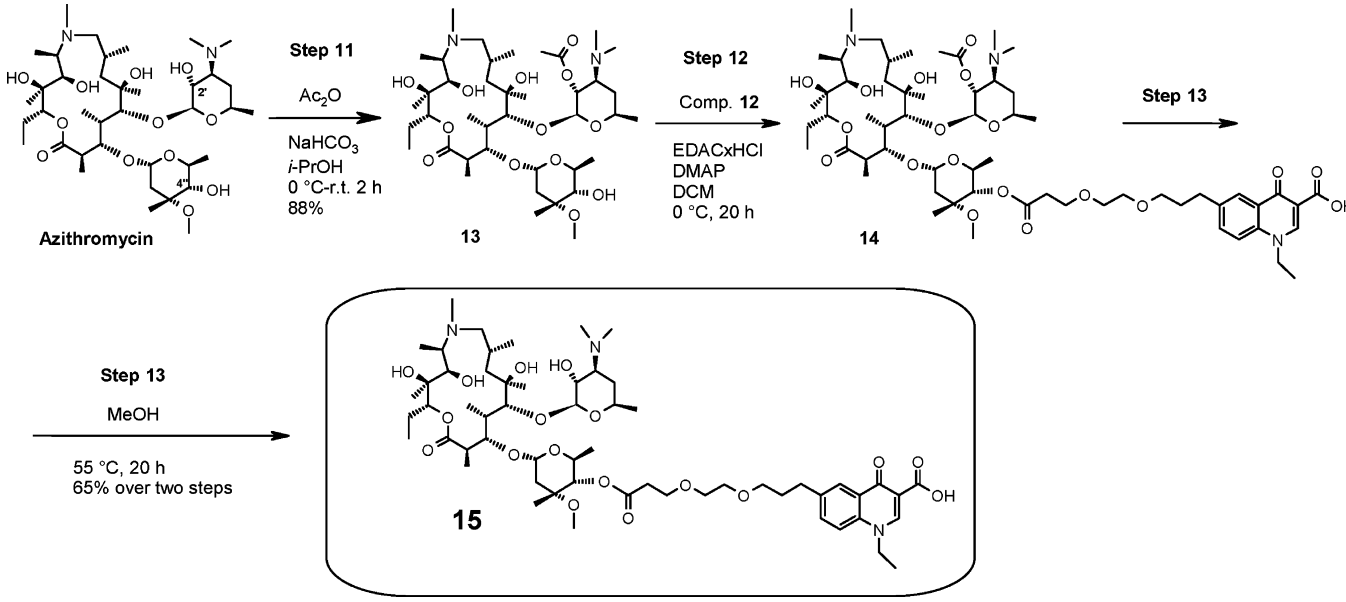
Scheme 6. **Modified reaction conditions for a preparation of the target compound 15**



traces of azithromycin, the quinolone diacid **12**, DMAP, and two macrolide byproduct. Extensive exploration of purification and isolation procedures, in order to avoid column chromatography, resulted in a modified extraction method.

After concentration of the MeOH solution, the reaction mixture was partitioned between *i*-PrOAc and water. Gradient extraction at various pH values resulted in the following: at pH 4.0 *i*-PrOAc extracted quinolone diacid **12** and DMAP; at pH 4.8, 5.0, and 5.3 DCM extracted macrolide byproduct; at pH 5.8 DCM extracted pure product **15** (probably as hydrochloride salt), while unreacted azithromycin remained in the aqueous layer; at pH 8.8 DCM extracted the product **15** as a free base. The organic layer at pH 8.8 was concentrated almost to dryness and DCM exchanged for *i*-PrOAc. The solid product precipitated after slow addition of the *i*-PrOAc solution to a large volume of *i*-Pr_2O. *i*-PrOAc was chosen since it showed encouraging results in initial crystallization experiments. A total of 682 g of the final product **15** was prepared in the form of an amorphous powder with purity of 96.4% area by HPLC−MS and 97.7% area by HPLC−UV, and in 65% yield starting from compound **13**. All impurities were not more than 0.5% area each, as determined by HPLC, and their structures have not been disclosed in this paper.

Conclusions

The initial laboratory 13-step procedure for the preparation of compound **15** was significantly improved, and the new process represents a solid base for further development of a large-scale process. The number of different organic solvents used in the process is reduced, as well as the amount of catalysts. Isolation of intermediates **2**, **3**, **8** and **14** is avoided and other intermediates are obtained by crystallization/precipitation and filtration, preferably from water or EtOH. In all these steps, it is worth to point out that the most significant modification is probably the isolation of compound **9** in Sonogashira reaction step. It was found that it can be isolated by precipitation from a mixture of EtOH/H_2O/toluene at a defined pH value, thereby affording the product in high purity and yield. The most important improvement in the quality of the final product **15** in the modified procedure was achieved by performing extractions at ascending pH values resulting in 97−99% purity, thus avoiding column chromatography. Overall yield from **1** to **15** was increased from 5%, obtained in the laboratory-scale procedure, to 27%.

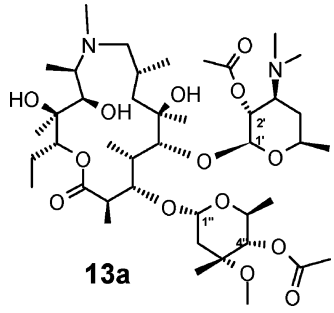


Figure 2. **2′,4″-*O*,*O*-Diacetyl byproduct formed in step 11.**

Experimental Section

All commercial reagents (Merck, Sigma-Aldrich) were used as provided unless otherwise indicated, and all solvents are of the high purity unless otherwise noted.

HPLC−UV and HPLC−MS analyses were carried out on a system comprising an Agilent 1100 HPLC system equipped with diode array detector (Agilent Technologies, Waldbronn, Germany) and a Micromass ZQ 2000 single quadrupole mass spectrometer (Waters, Milford, USA), operating in electrospray ionization (ESI) positive mode. 1D and 2D NMR spectra (^1H, APT, COSY, HSQC, HMBC) were recorded at 25 °C in DMSO-d_6 with TMS as the internal standard on Bruker Avance DRX500 spectrometer using QNI probe and Bruker Avance DPX300 spectrometer using a dual $^1H/^{13}C$ probe. DSC was performed on a Mettler Toledo DSC 822e calorimeter equipped with a refrigerated cooling system. The sample was heated in a pin-holed aluminium pan at heating rate 10 °C/min from 25 to 300 °C. A nitrogen purge at 50 mL/min was maintained over the sample. Reaction flow was monitored by thin layer chromatography (TLC) on Merck Kieselgel 60 (230 −400

mesh) using specifically solvent systems indicated in the protocol. I_2, UV-light (254 nm), and H_2SO_4, followed by heating to >120 °C, were used for detection.

Equipment. The reactions were performed in a 5-L jacketed glass reactor, equipped with a warming−cooling circulation bath, thermostat, electromechanical stirrer, thermometer, distillation condenser, reflux condenser, addition funnel, and Büchner funnel. The whole apparatus can be attached to a vacuum station or be filled with nitrogen.

2-Fluoro-5-iodo-benzoyl Chloride (2). A 5-L reactor was filled with N_2 gas. Toluene (3.5 L) and DMF (42 mL) were introduced, and then 2-fluoro-5-iodo-benzoic acid (**1**) (700 g, 2.63 mol) was added to the mixture. Oxalyl chloride (269.0 mL, 1.2 equiv) was introduced dropwise during 1 h at 22 °C. The reaction mixture was stirred at rt for an additional 1 h and monitored by TLC in a solvent system, EtOAc/*n*-hexane = 1:1. The excess of oxalyl chloride was removed by evaporation under reduced pressure at 50 °C to distill ∼250 mL of toluene/oxalyl chloride mixture. The resulting solution of the title compound **2** was cooled to 20−25 °C and directly forwarded into the next step.

3-Dimethylamino-2-(2-fluoro-5-iodo-benzoyl)acrylic Acid Ethyl Ester (3). Into a toluene solution of compound **2** (2.63 mol) from previous step cooled at 25 °C, was added a mixture of ethyl 3-(dimethylamino)acrylate (414.3 g, 1.1 equiv) and TEA (475 mL, 1.3 equiv) in toluene (700 mL). The resulting solution was stirred at 90 °C for 2 h and the reaction monitored by TLC in a solvent system EtOAc/*n*-hexane = 1:1. The mixture was cooled to 22 °C, and insoluble salts were filtered off through a Büchner funnel. The cake was washed with toluene (400 mL). The mother liquor was concentrated under reduced pressure at 50 °C almost to dryness. To the thick solution was added EtOH (1.2 L) and the mixture evaporated further to remove residual toluene. To the resulting suspension was added EtOH (2.5 L) (total volume of 3.0 L), and the suspension of the title compound **3** was used in next step.

3-Ethylamino-2-(2-fluoro-5-iodo-benzoyl)acrylic Acid Ethyl Ester (4). To the suspension of compound **3** in EtOH (3 L, 2.63 mol) at 10 °C cold was added a solution (4 °C) of ethyl amine in THF (2 M, 1.60 L, 1.22 equiv), and the mixture was stirred at 22 °C for 1.5 h. TLC in the solvent system EtOAc/cyclohexane = 1:1 revealed no starting **3** but one product. THF was evaporated under reduced pressure (450 mbar, temp. of the solution 48 °C) to ∼3 L of solution. The solution was slowly cooled to 10 °C (crystallization occurred at 35 °C), and the resulting suspension was stirred for 15 min. The crystals were filtered off through a Büchner funnel, and the cake was washed with cold EtOH (2 × 300 mL). A quantity of 741.2 g of wet cake was obtained. An aliquot (1.564 g) of the wet cake was dried in a vacuum oven at 50 °C for 4 h, and 1.456 g of dry title compound **4** was obtained. The 741.2 g of wet cake contained 690.0 g of dry title compound **4** (yield = 67% starting from compound **1**). HPLC−MS: 96.9%. HPLC−UV: 98.2%. mp (DSC): 118−122 °C. **^{1}H NMR (300 MHz, DMSO) δ:** 7.77−7.71 (m, 1H), 7.60 (bs, 1H), 7.55 (dd, 1H), 7.02 (dd, 1H), 3.89 (q, 2H), 3.50 (q, 2H), 1.21 (t, 3H), 0.94 (t, 3H). **^{13}C NMR (75 MHz, DMSO) δ:** 186.9, 166.0, 159.8, 159.5, 156.3, 138.7, 138.6, 136.76, 136.3, 136.2, 134.0, 133.8, 117.8, 117.6, 99.4, 87.5, 58.8, 44.5, 15.7, 13.7.

1-Ethyl-6-iodo-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid Ethyl Ester (5). Compound **4** (616.5 g, 1.58 mol) was dissolved in DMF (2.0 L) at 22 °C. K_2CO_3 (431.0 g, 2 equiv) was added, and the suspension was stirred at 125 °C for 1 h (TLC in EtOAc/*n*-hexane = 1:1 revealed no starting material). The mixture was cooled to 25 °C, water (2.0 L) was added, and the suspension was stirred for 15 min. The precipitate was filtered off through a Büchner funnel, and the reactor and the cake were washed with water (2 × 400 mL). An aliquot (1.281 g) of the wet cake (707.7 g wet) was dried in vacuum oven at 70 °C until constant weight, and 1.029 g of dry title compound **5** was obtained. The 707.7 g of wet cake contained 568.5 g of dry title compound **5** (yield = 97%). HPLC−MS: 99.7%, HPLC−UV: 99.9%, mp (DSC): 173−177 °C. **^{1}H NMR (300 MHz, DMSO) δ:** 8.71 (s, 1H), 8.50 (d, 1H), 8.05 (dd, 1H), 7.64 (d, 1H), 4.39 (q, 2H), 4.23 (q, 2H), 1.36 (t, 3H), 1.29 (t, 3H). **^{13}C NMR (75 MHz, DMSO) δ:** 171.3, 164.3, 149.2, 140.6, 138.0, 134.8, 129.9, 119.6, 110.5, 90.0, 59.7, 47.9, 14.2, 14.1.

1-Ethyl-6-iodo-4-oxo-1,4-dihydro-quinoline-3-carboxylic Acid (6). Compound **5** (589.2 g, 1.59 mol) was suspended in water (2.5 L) and EtOH (2.3 L) at 22 °C. NaOH (190.0 g, 3 equiv) was added over 5 min; the mixture was stirred at 78 °C for 35 min. The solution was cooled to 60 °C, and the pH was adjusted from 13.7 to 6.0 using 6 M HCl (820 mL). The resulting suspension was cooled to 5 °C and filtered through a Büchner funnel. The reactor and the cake were washed with a mixture H_2O/EtOH = 4:1 (500 mL). The wet cake (775.6 g) was dried in a vacuum oven at 80 °C until constant weight, yielding 528.1 g of dry title compound **6** (yield = 97%). HPLC−MS: 99.5%. HPLC−UV: 99.7%. mp (DSC): 228−232 °C. **^{1}H NMR (300 MHz, DMSO) δ:** 8.48 (s, 1H), 8.44 (d, 1H), 8.11 (dd, 1H), 7.87 (d, 1H), 4.22 (q, 2H), 3.64 (m, 1H), 1.28 (t, 3H), 1.23 (m, 2H), 1.11 (m, 2H). **^{13}C NMR (75 MHz, DMSO) δ:** 171.4, 164.1, 148.6, 140.6, 139.9, 134.4, 129.2, 120.0, 110.3, 90.3, 59.8, 34.63, 14.2, 7.5.

({[2-(2-Propyn-1-yloxy)ethyl]oxy}methyl)benzene (8). Benzyloxyethanol (**7**) (344 mL, 2.42 mol) was added to toluene (2.4 L) in a 5-L reactor under N_2 at 10 °C. NaH (w = 60% in mineral oil, 116 g, 1.2 equiv) was added portionwise over 1 h while keeping the temperature between 10−20 °C. The mixture was stirred at 10 °C for 45 min. Propargyl bromide (w = 80% in toluene, 404 mL, 1.5 equiv) was added dropwise over 1 h while keeping the temperature below 20 °C. The mixture was stirred at 25 °C for 1 h until TLC in EtOAc/*n*-hexane = 1:4 showed no starting **7**. Water (1.8 L) was added dropwise over 30 min while keeping the temperature below 20 °C. The mixture was stirred for an additional 10 min, the layers were separated, and the organic layer was washed with 10% aq $NaHCO_3$ (450 mL). The organic layer was concentrated under reduced pressure to a smaller volume (∼500 mL) and abs. EtOH (2 L) added. The solution was concentrated to a smaller volume (∼1 L), fresh abs. EtOH (2 L) was added, and the solution of the title compound **8** was used in the next step. HPLC−UV: 82.5%. **^{1}H NMR (300 MHz, DMSO-d_6) δ:** 7.33−7.35 (m, 5H), 4.57 (s, 2H), 4.21 (d, 2H), 3.70−3.74 (m, 2H), 3.63−3.67 (m, 2H),

2,43 (t, 1H). **^{13}C NMR (75 MHz, DMSO) δ:** 138.4, 128.5, 128.4, 127.8, 127.6, 73.3, 69.2, 61.1, 58.4, 19.7.

1-Ethyl-4-oxo-6-[3-({2-[(phenylmethyl)oxy]ethyl}oxy)-1-propyn-1-yl]-1,4-dihydro-3-quinolinecarboxylic Acid (9). Into the solution of compound **8** ($w \approx 82\%$, 501.5 g, 1.36 equiv) in abs. EtOH (2.5 L) from the previous step were added TEA (800 mL, 4 equiv), CuI (2.77 g, 1 mol %), 1-ethyl-6-iodo-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (**6**) (500.0 g, 1.46 mol), and $Pd(PPh_3)_2Cl_2$ (10.2 g, 1 mol %). The suspension was heated to 57 °C and stirred for 80 min. TLC of the solution in DCM/MeOH/NH_4OH = 90:15:1.5 revealed complete conversion of starting **6**. The solution was concentrated under reduced pressure to 2.5 L volume and cooled to 10 °C. Water (2.5 L) and toluene (2.0 L) were added, and the pH was adjusted from 9.4 to 8.3 by dropwise addition of 6 M aq HCl (220 mL). The resulting suspension was stirred at 10 °C for 20 min. The precipitate was filtered off through a Büchner funnel, and the reactor and the cake were washed with toluene (100 mL), then water (500 mL) and EtOH (600 mL), respectively. An aliquot (2.076 g) of wet cake (674.7 g) was dried in a vacuum oven at 65 °C for 5 h, yielding 1.517 g of dry title compound **9**. The 674.7 g of wet cake contained 493.0 g of dry title compound **9** (yield = 83.5%). HPLC−MS: 97.7%; HPLC−UV: 99.2%. **^{1}H NMR (300 MHz, $CDCl_3$) δ:** 8.78 (s, 1H), 8.57 (d, 1H), 7.83 (dd, 1H), 7.57 (d, 1H), 7.38−7.27 (m, 5H), 4.60 (s, 2H), 4.48 (s,2H), 4.39 (q, 2H), 3.82−3.80 (m, 2H), 3.72−3.69 (m, 2H), 1.59 (t, 3H). **^{13}C NMR (75 MHz, $CDCl_3$) δ:** 177.7, 166.7, 148.1, 138.5, 136.6, 130.6, 128.4, 126.5, 121.0, 116.5, 109.3, 87.8, 84.3, 73.4, 69.5, 59.1, 49.8, 14.6.

1-Ethyl-6-{3-[(2-hydroxyethyl)oxy]propyl}-4-oxo-1,4-dihydro-3-quinolinecarboxylic Acid (10). An 8.0-L glass reactor was filled with DCM (4.14 L) and compound **9** (1904.4 g wet, 1683.3 g calculated on dry substance). The suspension was stirred at 20−25 °C for 10 min to dissolve the material. The resulting solution was charged to a 47-L hydrogenator. The glass reactor was washed with EtOH (5.0 L) that was charged to the hydrogenator. The glass reactor was filled with EtOH (5.0 L) to which was added 10% Pd/C (497.2 g wet, 258.0 g dry). The resulting suspension was charged to the hydrogenator. The glass reactor was washed with EtOH (6.5 L) that was charged to the hydrogenator. The reaction mixture was cooled to 8 °C and stirred at 75% of the value of max rpm. The hydrogen pressure was set to 3 bar and kept at that value. The temperature of the mixture was raised to 19.9 °C over 15 min and then started to decrease. Hydrogen pressure was increased to 5 bar, and the mixture was stirred at 15−20 °C for 2 h. Hydrogen consumption was significantly decreased during that period. After 2 h HPLC−MS showed 28.9% of the product **10**, 63.9% of the intermediate **9a**, and 5.3% of a byproduct. Additional amounts of 10% Pd/C (200.0 g wet, 96.2 g dry) were added, and the hydrogenation was continued at 5 bar pressure and 15−20 °C for an additional 4 h until TLC in DCM/MeOH/NH_4OH = 90:15:1.5 revealed complete conversion to the product **10**. Hydrogen was evacuated and the reactor filled with N_2. The reaction mixture was filtered through a sintered glass funnel, and the catalyst was washed with 2 × 2.5 L DCM and 1.0 L EtOH, respectively. The mother liquors were concentrated on a rotavap to a smaller volume (~0.5 L). EtOH (1370 mL) was added, and the suspension was evaporated to dryness. The crude residue was suspended in EtOH (1370 mL) and the suspension charged to a 5-L glass reactor. The suspension was heated to 60 °C and stirred for 30 min until all solid material dissolved. The solution was cooled to 5 °C and the resulting suspension stirred at that temperature for 2 h. The suspension was filtered through a Büchner funnel and the cake washed with EtOH/H_2O = 1:1 mixture (300 mL). Wet cake (1561 g) was dried in a vacuum oven at 40 °C until constant weight, yielding 1093 g of the title compound **10** (yield = 82.4%). HPLC−MS: 94.1%; HPLC−UV: 97.6%; weight loss (105 °C): 0.65%. **^{1}H NMR (300 MHz, DMSO-d_6) δ:** 9.02 (s, 1H), 8.19 (s, 1H), 7.98 (d, 1H), 7.84 (d, 1H), 4.62 (q, 2H), 3.51 (t, 2H), 3.43−3.39 (m, 4H), 2.86 (t, 2H), 1.95−1.85 (m, 2H), 1.43 (t, 3H). **^{13}C NMR (75 MHz, DMSO-d_6) δ:** 177.6, 166.3, 148.7, 140.5, 137.5, 135.1, 125.6, 124.7, 118.2, 108.0, 72.2, 69.4, 60.4, 49.1, 31.2, 30.8, 14.7.

6-[3-({2-[(2-Cyanoethyl)oxy]ethyl}oxy)propyl]-1-ethyl-4-oxo-1,4-dihydro-3-quinolinecarboxylic Acid (11). Water (2.6 L) was added into the reactor followed by the addition of crude NaOH (280 g, 7 equiv). After all NaOH dissolved, compound **10** (320.4 g, 1 mol) was added and the solution cooled to 0 °C. Acrylonitrile (330 mL, 5 equiv) was added dropwise through an addition funnel over 20 min while maintaining temperature at 0 °C. The temperature was alowed to rise to 20 °C over 30 min (a suspension was formed) and the mixture stirred for 50 min until TLC in DCM/MeOH/NH_4OH = 90:15:1.5 revealed no starting **10**. Water (500 mL) and EtOH (300 mL) were added, and the solution was cooled to 0 °C. HCl (conc., 605 mL) was added dropwise through an addition funnel over 50 min to adjust the pH to 6.3 while keeping the temperature at 0−10 °C. The resulting suspension was stirred at 0 °C for 2 h. The precipitate was filtered off through a Büchner funnel and the cake washed with a water (700 mL)/EtOH (300 mL) mixture, yielding 413.2 g of wet title compound **11**. An aliquot (2.935 g) was dried in a vacuum oven at 50 °C until constant weight, yielding 2.582 g of dry title compound **11**. The 413.2 g of wet cake contained 362.1 g of the title compound **11** (yield = 97%). HPLC−MS: 94.7%; HPLC−UV: 94.9%; mp (DSC): 66−74 °C, peak at 71.2 °C. **^{1}H NMR (300 MHz, DMSO-d_6) δ:** 8.57 (s, 1H), 8.09 (d, 1H), 7.68 (d, 1H), 7.59 (dd, 1H), 4.34 (q, 2H), 3.62 (t, 2H), 3.57−3.59 (m, 2H), 3.49−3.51 (m, 2H), 3.42 (t, 2H), 2.76 (t, 2H), 2.75 (t, 2H), 1.34 (t, 3H). **^{13}C NMR (75 MHz, DMSO-d_6) δ:** 175.4, 167.2, 146.7, 137.1, 136.9, 132.6, 128.1, 125.1, 119.2, 116.5, 110.1, 69.5, 69.3, 65.2, 47.3, 31.0, 30.7, 14.4.

6-[3-({2-[(2-Carboxyethyl)oxy]ethyl}oxy)propyl]-1-ethyl-4-oxo-1,4-dihydro-3-quinolinecarboxylic Acid (12). To the reactor was added conc. H_2SO_4 (1.0 L), and the mixture was cooled to 0 °C. Wet compound **11** (300 g dry calculated, 0.81 mol) was added portionwise over 30 min, while keeping the temperature at 0−5 °C. The suspension was stirred at 0 °C for 1 h and then at rt overnight. The solution was cooled to 0 °C, and water (1.6 L) was added dropwise over 5 h while keeping the temperature at 4−8 °C. The solution was stirred at 20 °C for 1 h and at 70 °C overnight. The solution was cooled to 0 °C, and water (1.0 L) was added portionwise over 30 min. NaOH (40% aq 1.10 L) was added portionwise at 4−8 °C over 2.5 h

to adjust the pH to 0.1. The resulting suspension was stirred at 4 °C for 45 min and filtered through a Büchner funnel. The cake was washed with water (1.0 L) and then with a water (700 mL)/EtOH (300 mL) mixture. The cake was dried in a vacuum oven at 70 °C until constant weight, yielding 280.72 g of the title compound **12** (yield = 88.5%). HPLC−MS: 80.1%; HPLC−UV: 88.1%. **^{1}H NMR (300 MHz, DMSO-d_6) δ:** 9.02 (s, 1H), 8.18 (d, 1H), 7.98 (d, 1H), 7.85 (dd, 1H), 4.60 (q, 2H), 3.62 (m, 2H), 3.47−3.53 (ov, 4H), 3.41 (t, 2H), 2.85 (t, 2H), 2.45 (t, 2H), 1.87 (m, 2H), 1.43 (t, 3H). **^{13}C NMR (75 MHz, DMSO-d_6) δ:** 177.4, 172.5, 166.1, 148.4, 140.2, 137.3, 134.9, 125.4, 124.5, 118.0, 107.4, 69.5, 69.3, 69.2, 66.2, 48.9, 34.7, 30.9, 30.5, 14.5.

2′-O-Acetyl-9a-methyl-9-dihydro-9a-aza-9a-homoerythromycin (13). Into a 5-L glass reactor was introduced N_2 gas, and then 2-propanol (2.1 L), azithromycin (700.0 g, 0.875 mol), and $NaHCO_3$ (112.0 g, 1.33 mol) were added. The mixture was cooled to 0−5 °C, and acetic anhydride (99.4 mL, 1.05 mol) was slowly added over 15 min through an addition funnel. The reaction mixture was warmed to rt and stirred for 2 h. To the reaction mixture was added water (1.4 L), and the pH was adjusted to 9.3−9.5 using 10% aq NaOH (300 mL). Additional amounts of water (700 mL) were added, and the mixture was cooled to 5−10 °C. The resulting suspension was stirred for 2 h and then filtered. The cake was washed with a water/2-propanol mixture (500 mL, 1:1) and then with water (2 × 350 mL). The wet cake (929 g) was dried in a vacuum oven at 45−50 °C and then at 75−80 °C until constant weight to provide 609.9 g of the title compound **13** (yield = 88.3%). HPLC−MS: 98.0%; mp (DSC): 180−198 °C.

4″-O-(3-{2-[3-(3-Carboxy-1-ethyl-4-oxo-1,4-dihydro-quinoline-6-yl)propoxy]ethoxy}propionyl)-9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A (15). The reactor was filled with N_2, and DCM (dry, 1.0 L) was added. Compound **12** (280.0 g, 88%, 1.3 equiv) was added and the mixture cooled to 0 °C. EDAC × HCl (241.4 g, 2.6 equiv) was added and the mixture stirred for 5 min. Compound **13** (384.6 g, 0.486 mol) and DMAP (178.2 g, 3 equiv) were added, and the mixture was stirred at 3 °C overnight. $NaHCO_3$ (sat. aq solution, 1.4 L) was added, and the layers were separated. The organic layer was concentrated under reduced pressure at 30 °C to an oily residue. The residue was dissolved in *i*-PrOAc (2.0 L) and the solution concentrated (∼ 600 mL of the solvent was collected in a receiving flask). Water (1.0 L) was added, the pH was adjusted from 9.5 to 6.7 by using AcOH (60 mL), and the layers were separated. The organic layer was concentrated under reduced pressure, resulting in 698 g of oily residue of the compound **14**. The residue (theor. 566 g of **14**) was dissolved in MeOH (5.0 L) and the solution stirred at 55 °C overnight. MeOH was evaporated and the oily residue (620 g) dissolved in *i*-PrOAc (1.2 L). Water (1.5 L) was added, and the pH was adjusted from 7.3 to 4.0 by using 6 M HCl (140 mL). The aqueous layer was separated and washed with *i*-PrOAc (3 × 500 mL). The aqueous layer was separated and washed with DCM (3 × 500 mL) at pH 4.8, 5.0, and 5.3 (40% aq NaOH), respectively. The product was extracted from the aqueous layer with DCM (3 × 500 mL) at pH 5.8. Onto the DCM layer at pH 5.8 was added water (0.5 L), and the pH was adjusted to 8.8 using 10% aq NaOH. The DCM layer was separated and concentrated under reduced pressure to a smaller volume (∼0.5 L). *i*-PrOAc (0.5 L) was added, and the solution was concentrated under reduced pressure to a smaller volume. Fresh *i*-PrOAc (0.4 L) was added and the solution added dropwise over 3.5 h to a stirring *i*-Pr_2O (5.0 L). The resulting suspension was filtered through a Büchner funnel, and the cake was washed with *i*-Pr_2O (1.0 L) and dried in a vacuum oven at 40 °C, yielding 340.8 g of the title compound **15** (yield = 62.4%). HPLC−MS: 96.4%; HPLC−UV: 97.7%. During the filtration a precipitation occurred in the mother liquor. The residue was filtered off through a Büchner funnel, washed with *i*-Pr_2O (100 mL), and dried. The second crop yielded 16.7 g of the title compound **15** (yield = 3.0%). HPLC−MS: 99.0%; HPLC−UV: 99.1%. **^{1}H NMR (300 MHz, DMSO-d_6) δ:** 9.03 (s, 1H), 8.18(d, 1H), 7.98(d, 1H), 7.83 (dd, 1H), 4.91 (d, 1H), 4.73 (dd, 1H), 4.59 (t, 2H), 4.55 (d, 1H), 4.43 (d, 1H), 4.33 (m, 1H), 4.17(dd, 1H), 3.66 (m, 1H), 3.64 (m, 2H), 3.50 (ov, 2H), 3.47 (ov, 1H), 3.45 (ov, 1H), 3.43 (ov, 2H), 3.38(t, 2H), 3.22 (s, 3H), 3.05 (dd, 1H), 2.81(t, 2H), 2.67 (ov, 1H), 2.67 (ov, 1H), 2.59(m, 2H), 2.40 (m, 1H), 2.35 (dd, 1H), 2.31 (d, 1H), 2.21 (s, 3H), 2.18 (s, 3H), 2.11 (t, 1H), 1.88 (ov, 1H), 1.85 (ov, 2H), 1.85 (ov, 1H), 1.78 (m, 1H), 1.66 (dd, 1H), 1.59 (m, 1H), 1.51(d, 1H), 1.42 (t, 3H), 1.37 (m, 1H), 1.27 (dd, 1H), 1.12 (s, 3H), 1.1 (s, 3H), 1.09 (ov, 1H), 1.08 (d, 3H), 1.07 (dd, 3H), 1.03 (d, 3H), 1.01 (s, 3H), 0.96 (d, 3H), 0.94 (d, 3H), 0.84 (d, 3H), 0.79 (t, 3H). **^{13}C NMR (75 MHz, DMSO-d_6) δ:** 177.4, 177.0, 170.9, 166.1, 148.4, 140.2, 137.3, 134.9, 125.5, 124.5, 118.0, 107.4, 102.0, 94.3, 82.6, 78.0, 77.3, 76.3, 74.9, 73.5, 72.4, 72.0, 70.5, 69.3, 69.6, 69.3, 68.6, 66.7, 66.0, 64.8, 62.1, 61.3, 48.8, 44.5, 41.6, 40.2, 35.6, 34.9, 34.2, 31.1, 31.0, 30.6, 27.3, 25.9, 22.0, 21.6, 20.8, 20.5, 17.6, 14.5, 10.8, 8.8, 6.6, 4.9.

Acknowledgment

We thank Biserka Metelko and Gorjana Lazarevski for NMR support, Darko Filić for DSC analysis, and Vitomir Šunjić and John Berge for the discussion and critical reading of the manuscript. A special thanks goes to Đurđica Lugarić for her help and technical expertise.

Received for review July 21, 2010.

OP100199T