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Preparation of cyclic 2′,3′-carbamate derivatives of erythromycin macrolide antibiotics

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Abstract—Tricarbonylation of clarithromycin has been effected in a one-pot reaction with phosgene. The 11,12-diol moiety was closed into a cyclic carbonate, while the dimethylamino alcohol of the desosamine sugar was cyclised with loss of a methyl group to form a cyclic 2′,3′-carbamate. The 4″ hydroxyl group in clarithromycin was converted into a chloroformate group and subsequently to an allyl carbonate which on Pd-catalysis furnished a novel *N*-demethylclarithromycin 2′,3′-carbamate-11,12-carbonate. Hydrolytic removal of the cladinose sugar and a subsequent oxidation furnished the corresponding ketolide. The 11,12-cyclic carbonate moiety was cleaved by sodium azide to the 10,11-anhydro-9-ketone. 11-N-Arylated cyclic 11,12:2′,3′-dicarbamate derivatives were prepared in a copper(I) chloride aided reaction between aryl isocyanates and 10,11-anhydro 9-ketones. The products are novel N-arylated-N′-demethylated 11,12:2′,3′-dicarbamate ketolides derived from clarithromycin.

1. Introduction

The cyclic 11,12-carbamate motif is an essential part of the semisynthetic third generation erythromycin drugs because of enhanced antibacterial activity as compared to the natural 11,12-dihydroxy erythromycin macrolide.[1,2] Furthermore, the new drugs are frequently 3-ketolides which become available by hydrolytic removal of the cladinose sugar and oxidation of the alcohol.[3–5] Removal of the cladinose sugar reduces the induction of resistance in bacteria which is linked to the sugar residue. The remaining desosamine sugar in erythromycins seems essential for antibacterial activity.

Transformation of the C-2′ hydroxyl group in the sugar into carbonates, carbamates or ethers has yielded compounds with reduced antibacterial activities.[6] Esters of 2′-hydroxyl derivatives require hydrolysis for activity.[7] The *N*-oxide of the dimethylamine, as well as the product from pyrolysis of the *N*-oxide, had lost the antibacterial activity.[8,9]

Demethylation results in a significant reduction in the antibacterial effect. Alkylation of monomethyl amines with larger alkyl groups (e.g. isopropyl) gave products with reduced biological activity.[10] The antibacterial activity was lost when N-demethylated erythromycin derivatives were N-acylated.[11] X-ray structures of macrolides co-crystallised with the 50S subunit of bacterial ribosomes revealed that the hydroxy functions at C-6, C-11, C-12 and C-2′, as well as the dimethylamino group, participate in hydrogen bond interactions. Modification of the dimethylamino group has been suggested for improving the binding to the ribosome.[12]

We envisioned that introduction of a small group onto the dimethylamino-alcohol motif in the desosamine sugar would reduce interactions when the macrolide was to enter the binding site at the bacterial ribosome. In the phosgene induced cyclic carbamate formation (vide infra), a methyl group is replaced with a carbonyl group. A cyclic 2′,3′-carbamate based on the vicinal amino-hydroxyl groups in the desosamine sugar has not been prepared for biostudies, but has briefly been reported as intermediates.[13,14]

The dimethylamino group in erythromycin derivatives reacts with acid chlorides leading to expulsion of one of the methyl groups and formation of *N*-methylcarbamoyl derivatives. The reaction is exemplified by the

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reaction of benzyl chloroformate providing *N*-benzyloxycarbonyl *N*-demethyl derivatives in good yield.[15] We reasoned that phosgene would react similarly and provide a cyclic product, viz. an oxazolidinone derivative, as loss of alkyl groups from tertiary amines upon treatment with phosgene is well known.[16]

The target molecule was to be a cyclic 2′,3′-carbamate erythromycin to elucidate any modification of antibacterial activity as compared with parent compounds.

The erythromycin target compound **A** in Figure 1 is a ketolide with a cyclic 11,12-carbamate functionality as well as a carbamate functionality over the 2′,3′-position in the desosamine sugar. Clarithromycin (**1**) was the starting material since 6-O-alkylated erythromycins show enhanced biological activity over its parent erythromycin due to reduced degradation in acidic media.[17,18]

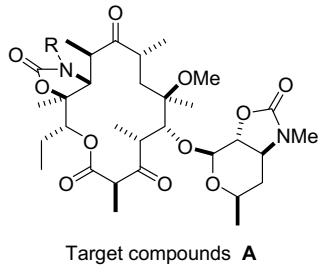
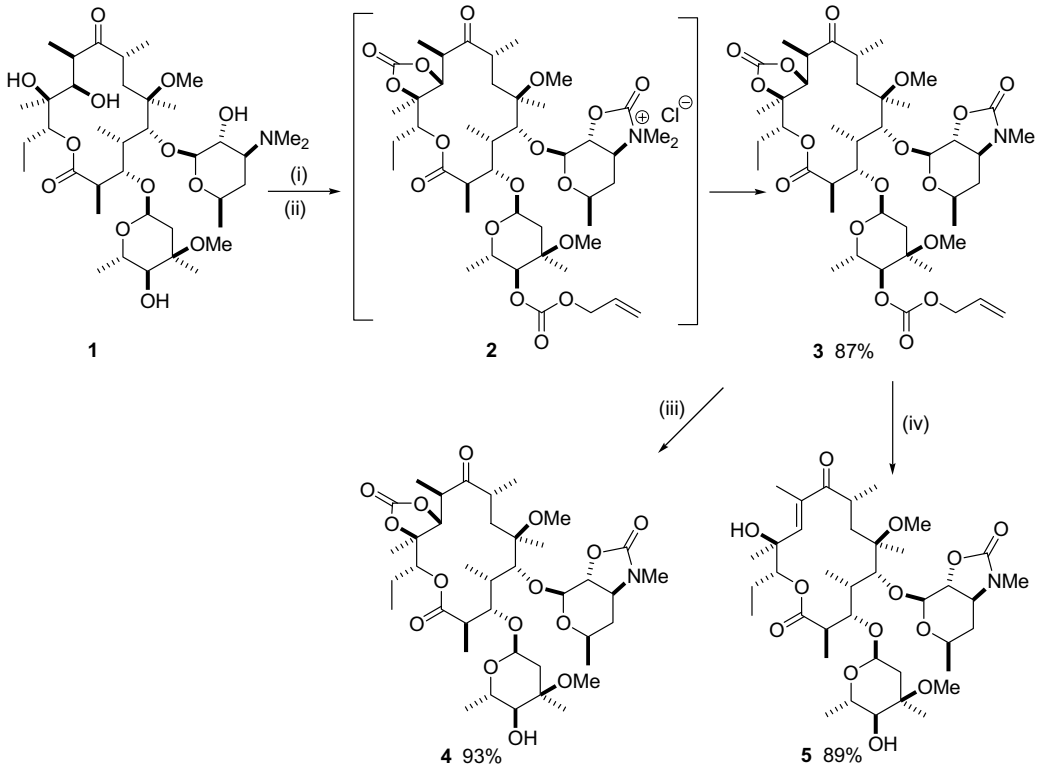


Figure 1.

2. Results and discussion

Treatment of clarithromycin (**1**) with excess phosgene and pyridine as base bridged the hydroxyl groups at C-11 and C-12 into a cyclic carbonate, while the C-2′ hydroxyl function and the 3′-dimethylamino group in the desosamine sugar moiety reacted to provide a cyclic 2′,3′-carbamate intermediate **2** (Scheme 1) as a dimethylammonium salt. Nucleophilic chloride ion attack at one of the methyl groups of the ammonium salt **2** results in N-demethylation. Under the conditions of the reaction, the vicinal 11,12-hydroxyl groups were carbonylated and the free hydroxyl group in the cladinose sugar was chlorocarbonylated. Addition of alcohols, thiols or amines to the carbonyl chloride will provide carbonates, thiocarbonates or carbamates. With allyl alcohol, the allyl carbonate **3** was obtained in high yield. The allyl carbonate function at C-4″ of compound **3** was cleaved by treatment with a catalyst system consisting of palladium diacetate, triphenylphosphine and triethylammonium formate as the reducing agent, in 80% aqueous ethanol under reflux (Scheme 1).[19] The deallylated product **4** was obtained in 93% yield.

Cleavage of the allyl carbonate function of compound **3** was also achieved in 74% yield in DMSO/THF (1:1) under $Pd(dba)_2$/dppb catalysis in the absence of an allyl scavenger. The protocol was developed from a procedure reported by Genêt et al.[20] The original procedure was unsuitable for compound **3** due to its low solubility. The original conditions included $Pd(dba)_2$ and dppe or dppb as catalyst systems and diethylamine or sulfur



Scheme 1. Reagents and conditions: (i) $COCl_2$, pyridine, CH_2Cl_2, rt, 5 h; (ii) CH_2CHCH_2OH, rt, 30 min; (iii) a—$Pd(OAc)_2$, PPh_3, HCO_2H, NEt_3, 80% aq EtOH, reflux, 6 h; or b—$Pd(dba)_2$, dppb, DMSO/THF (1:1), 70 °C; (iv) NaN_3, DMSO, 100 °C, 26 h.

nucleophiles as allyl scavengers. The reaction was performed at room temperature in a THF solution. By changing the solvent to DMSO/THF (1:1) and increasing the temperature to 70 °C, dissolution of compound **3** occurred. The reaction then proceeded smoothly under $Pd(dba)_2$/dppb catalysis with diethylamine as allyl scavenger. Later it was found that the reaction proceeded equally well when diethylamine was left out.

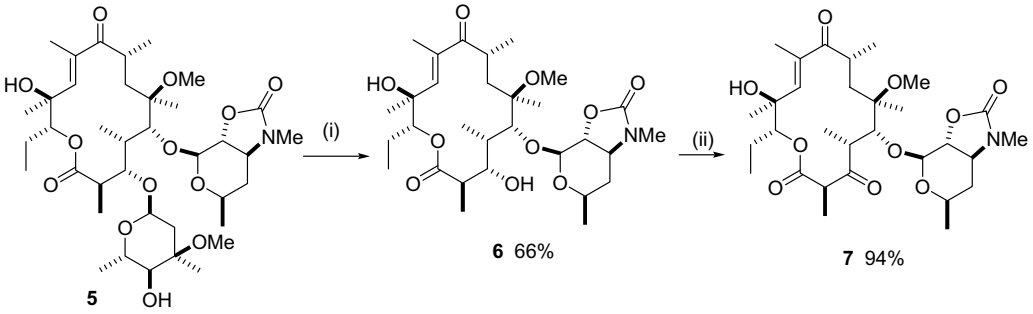
When sodium azide was used to effect removal of the 4″-allyl carbonate group in compound **3**, concurrent cleavage of the cyclic 11,12-carbonate resulted (Scheme 1). The product had a 10,11 C–C double bond in conjugation with the C-9 keto function and was assigned structure **5**. The cyclic 2′,3′-carbamate structure was not affected under these reaction conditions. Normally, the 10,11-double bond in erythromycin derivatives is introduced via base (DBU) mediated elimination of the 11,12-carbonate,[21] analogous to structure **3**, or an 11-mesylate.[3] Recently, NaHMDS mediated elimination of an 11-*O*-acetyl group has been reported.[22] Our method represents an alternative procedure for the preparation of α,β-unsaturated carbonyl intermediates in the synthesis of 3rd generation ketolide antibacterials.

The 3-oxo function in the ketolide was introduced in a two-step procedure including removal of the cladinose sugar and oxidation of the resulting alcohol (Scheme 2). Removal of the cladinose sugar was best effected under mild hydrolytic conditions. Heating substrate **5** in acetic acid/water 1:1 at 70 °C provided the descladinosyl derivative **6** in 66% yield. This procedure was developed because substrate **5** had low solubility in the usual systems with hydrochloric acid in water. A subsequent Dess–Martin periodinane oxidation[23] provided the ketolide **7** in 94% yield.

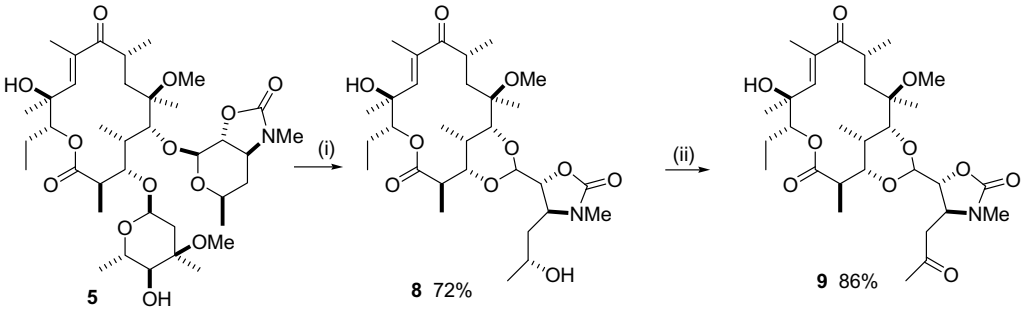
In our first attempt to remove the cladinose sugar, the enone **5** was treated with trifluoroacetic acid in a DMSO/water solution. The product isolated was the species **8** which had arisen from a transacetalisation process. The cladinose sugar had been split off, but the 3-hydroxyl group had entered into acetal formation with the desosamine sugar which was opened up and recyclised to a cyclic acetal over the C-3 hydroxyl function. The spectroscopic data for the product would seem to agree with the 3-hydroxyl target compound **6**. However, when the secondary alcoholic group in the product was oxidised using the Dess–Martin protocol, the NMR spectra of the new product were incompatible with the expected ketolide structure. In particular, one of the expected 3H doublets in ^{1}H NMR was replaced by a 3H singlet corresponding to a methyl ketone. Long range C,H-couplings were missing between C-1′ and C-5′, and new long range signals had appeared around the six-membered 3,5-acetal ring. The ketone was assigned structure **9** (Scheme 3).

To what extent the desosamine carbamate unit is involved in the rearrangement is unknown as the corresponding compound without the cyclic 2′,3′-carbamate was not subjected to the TFA/DMSO/water hydrolysis conditions. For this compound the usual aqueous hydrochloric acid protocol is satisfactory for the removal of the cladinose sugar.[24]

To the best of our knowledge (SciFinder) the opening-reclosing rearrangement of the desosamine sugar has



Scheme 2. Reagents and conditions: (i) AcOH/H_2O 1:1, 70 °C, 1 h; (ii) DMP, CH_2Cl_2, rt, 30 min.



Scheme 3. Reagents and conditions: (i) TFA, DMSO/H_2O (9:1), 110 °C, 2.5 h; (ii) DMP, CH_2Cl_2, rt, 30 min.

not been reported previously for erythromycin compounds. Exposure of macrolide derivatives to strong acidic conditions (hydrogen fluoride–pyridine) results in the complete removal of both sugar moieties.[25] Traditionally the desosamine sugar is regarded as indispensable for macrolide–ribosome binding.[9,26]

However, addition of suitable substituents to the desosamine residue in compound **8** or **9** may lead to inhibition of the bacterial peptidyl transferase activity and improved antibacterial activity. Erythromycin derivatives usually block the peptide exit tunnel in bacterial ribosomes with a binding site close to the peptidyl transferase site. The desosamine sugar protrudes towards the catalytic centre, but the centre is not within reach of the molecule.[27]

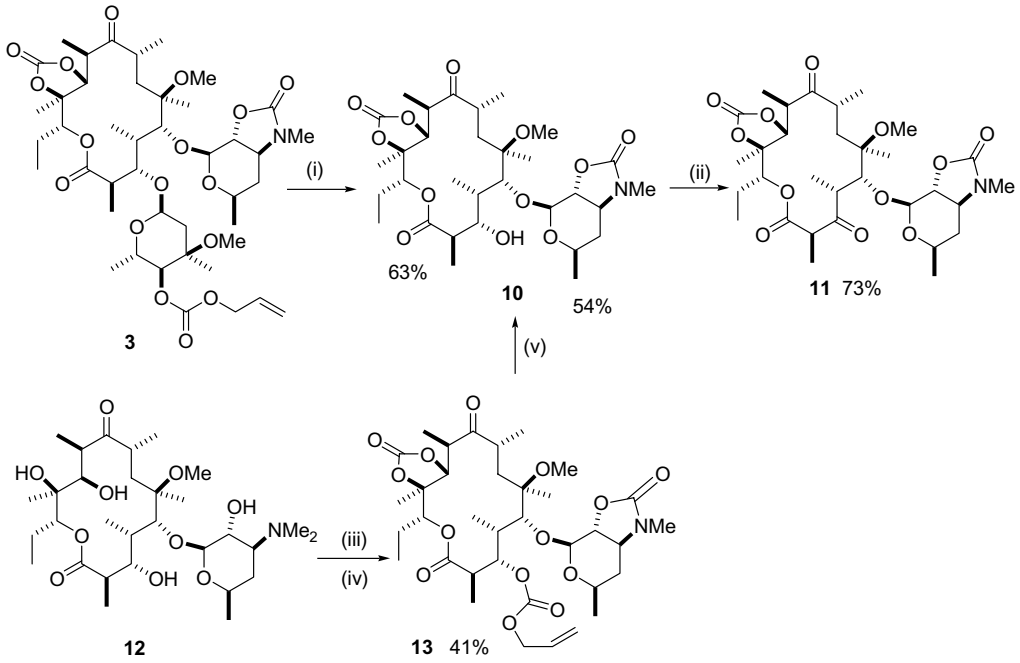
The clarithromycin ketolide **11** was prepared from the allyl carbonate **3** in two steps. When compound **3** was heated in DMSO/H_2O at 110 °C in the presence of TFA, the descladinosyl derivative **10** was obtained without rearrangement and opening of the desosamine sugar. The different reaction patterns between the compounds **3** and **5** must arise from differences in the macrolactone conformations making interactions between the C-3 hydroxyl function and the desosamine sugar possible only in the 10,11-anhydro case. Oxidation of the alcohol **10** under Corey–Kim conditions[28] afforded the ketolide **11** in 73% isolated yield.

In an alternative sequence for the preparation of the intermediate **10**, the descladinosylclarithromycin[3] (**12**) was subjected to phosgene carbonylation with allyl alcohol as quenching agent to provide the allyl carbonate **13** (Scheme 4). The reaction was slower and less clean than for the corresponding macrolide substrate **3** with the cladinose sugar intact. The chemical yield was reduced to 41%. This behaviour may be rationalised by a reduced access to the 3-hydroxyl function in **12** as compared to the hydroxyl function at C-4″ in the cladinose sugar. Formation of the 3-chloroformate structure is therefore slower. Cleavage of the allyl carbonate function of compound **13** was achieved in 54% yield with the nucleophile-free procedure with $Pd(dba)_2$/dppb catalysis in a DMSO/THF solvent system providing the alcohol **10**.

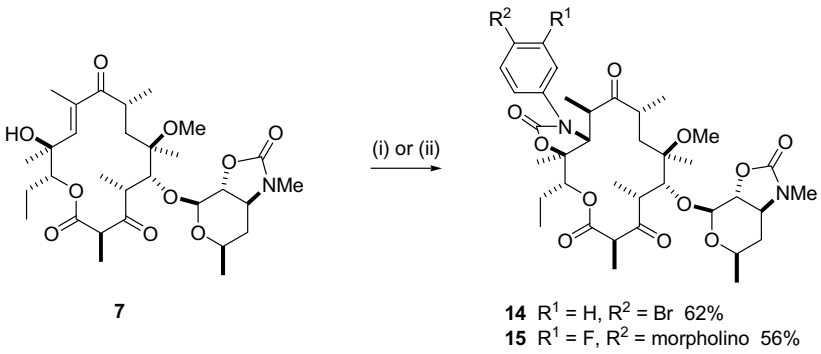
The 11,12-carbamate structural motif is normally synthesised via an enone function as an intermediate, as present in structure **7**. 1,1′-Carbonyldiimidazole (CDI) was reacted with the 12-OH group in the macrolide to form an *O*-acylimidazolyl intermediate. Treatment with a primary amine or ammonia yielded a carbamate where the amido nitrogen adds rapidly onto the C–C double bond to form the cyclic carbamate product.[3,4,21,29]

In a second patent procedure[30] the C-12 alcohol is reacted with an isocyanate under copper(I) chloride activation[31] to form the same carbamate intermediate as described in the previous case. A subsequent spontaneous ring-closing reaction gave the cyclic 11,12-carbamate. The same procedure was recently used in an improved synthesis of tricyclic erythromycin derivatives.[32] However, the intermediate non-cyclic carbamate did not cyclise until treated with *t*-BuOK in a separate step. The isocyanate protocol was adapted in the present work with electronegatively substituted phenylisocyanates and the enone **7** as shown in Scheme 5.

There was no significant antibacterial activity for the compounds hitherto prepared (vide infra). Loss of basicity upon derivatisation of the basic dimethylamine at



Scheme 4. Reagents and conditions: (i) TFA, DMSO/H_2O 9:1, 110 °C, 10 h; (ii) a—NCS, Me_2S, −16 to −10 °C, 1.5 h; b—NEt_3, −5 °C, 1.5 h; (iii) $COCl_2$, pyridine, CH_2Cl_2, rt, 5 h; (iv) CH_2=$CHCH_2OH$, rt, 30 min; (v) $Pd(dba)_2$, dppb, DMSO/THF 1:1, 70 °C, 2 h.



Scheme 5. Reagents and conditions: (i) 4-BrC_6H_4NCO, NaH, CuCl, THF, 50 °C, 42 h; (ii) 4-morpholino-3-F–C_6H_3NCO, NaH, CuCl, THF, 50 °C, 42 h.

C-3′ could be the origin of the activity reduction. Consequently, focus was turned onto reintroduction of a basic nitrogen somewhere else in the molecule. Connection of a basic structure via an aromatic group to a cyclic 11,12-carbamate, in analogy to telithromycin, was investigated via the isocyanate approach and structure **7** as substrate for reaction with bromophenylisocyanate. The cyclic 11,12-carbamate **14** was obtained in 62% yield. TLC analysis indicated full conversion after two hours. NMR analysis showed the product to be a mixture of stereoisomers. Extending the reaction time resulted in isomerisation and transformation to a single stereoisomer. Buchwald–Hartwig[33] type cross-coupling with amines failed to provide aniline derivatives in satisfactory yield because the substrate was labile towards bases. When the amino group was part of an aromatic isocyanate, however, in the form of 3-fluoro-4-morpholinophenylisocyanate, the basic morpholino 11,12-carbamate **15** was isolated in 56% yield. The morpholino group was chosen since basic heteroatom-containing sidechains attached to a cyclic 11,12-carbamate tend to promote antibacterial activity.[6,29]

The clarithromycin configuration at both C-10 and C-11 is lost when the 10,11-double bond is introduced into the macrolide. The subsequent intramolecular Michael addition dictates the stereochemical outcome at the two stereocentres at C-10 and C-11. The single stereoisomers isolated from the isocyanate coupling reactions, **14** and **15**, were both assigned the natural configurations at C-10 and C-11 by comparison with the literature.[21] In particular, no coupling was observed between H-10 and H-11. The stereochemical outcome of C-10 is important since the (10*S*)-11,12-carbamate isomers are almost biologically inactive.[3]

2.1. Antibacterial testing

The antibacterial activity of compounds **3**, **4**, **5**, **10**, **11**, **13** and **15** was measured as the minimum inhibitory concentration (MIC) of bacterial growth against Gram-positive *Staphylococcus aureus* ATCC 25923 and Gram-negative *Escherichia coli* ATCC 25922.[34] Macrolide concentrations were prepared in twofold dilutions with maximum concentrations of 16–64 mg/mL. Low aqueous solubility prevented studies at higher concentrations. All the compounds tested were inactive within the limits of the analyses, suggesting that a basic amino group is required in the 3′-position of the erythromycins. Loss of basicity in this position could not be compensated for by an additional basic nitrogen as in the morpholino product **15**. A dramatic decrease in solubility in common organic solvents as well as water was observed for the carbamates. This would expectedly be accompanied by a disturbance of the distribution and transportation of the compounds in and out of, and within, bacterial cells. Hence, the lack of antibacterial activity could arise from a poor distribution in bacteria rather than from lack of ability to bind to the bacterial ribosome itself.

3. Conclusion

A one-pot carbonylation provided novel N-demethylated cyclic 2′,3′-carbamate-11,12-carbonate derivatives of clarithromycin in reactions with phosgene. Hydrolytic removal of the cladinose sugar and a subsequent oxidation furnished corresponding 3-ketolides. 11-N-Arylated cyclic 11,12:2′,3′-dicarbamate derivatives were prepared in a direct reaction between aryl isocyanates and 10,11-anhydroerythromycins.

4. Experimental

^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 at 300, 500 or 600 MHz with Bruker DPX 300, DRX 500 or AV 600. The ^{13}C NMR spectra were recorded at 75, 125 and 150 MHz. Chemical shifts are reported in ppm using $CHCl_3$ (7.24 ppm) and $CDCl_3$ (77 ppm) as references. In DMSO the references were 2.49 ppm for ^{1}H NMR and 39.5 ppm for ^{13}C NMR. Mass spectra were recorded at 70 eV. The spectra are presented as *m*/*z* (% relative intensity). Electrospray spectra were obtained with a Micromass QTOF 2 W spectrometer with electrospray ionisation quadrupole time of flight. IR spectra were recorded on a Nicolet Magna FT-IR 550 spectrometer using ATR (attenuated total reflectance). Elemental analyses were performed by Ilse Beetz Mikroanalytisches laboratorium, Kronach, Germany. Melting points are uncorrected.

All reactions were performed under an inert atmosphere. THF was distilled from sodium/benzophenone. Dichloromethane and triethylamine were distilled from calcium hydride. Merck silica gel 60 (230–400 mesh) was used for flash chromatography.

4.1. 4″-*O*-(Allyloxycarbonyl)-*N*-demethylclarithromycin 2′,3′-carbamate-11,12-carbonate (3)

Clarithromycin (**1**, 5.00 g, 6.69 mmol) was dissolved in dichloromethane (100 mL), and pyridine (6.30 mL, 77.9 mmol) and phosgene (20% in toluene, 20.0 mL, 38.0 mmol) were added. The reaction mixture was stirred at room temperature for 5 h. Allyl alcohol (9.00 mL, 132 mmol) was added, and stirring was continued for 30 min (yellow solution). Aqueous sodium hydroxide was added, and the product was extracted into dichloromethane. The combined organic layers were washed with water and brine, dried ($MgSO_4$), the solvents distilled off and chased with toluene. The product was a pale yellow solid with mp 307–310 °C (toluene); yield: 5.07 g (87%). Found: C, 60.01; H, 7.36. Calcd for $C_{43}H_{67}NO_{17}$: C, 59.36; H, 7.76%; HRMS, ESI pos.: Found: 892.4327. Calcd for $M+Na^+ = C_{43}H_{67}NNaO_{17}$: 892.4301; IR (ATR, cm^{-1}): 3089w, 2976s (C–H), 2941s (C–H), 2885m (C–H), 2835m (C–H), 1815s (C=O), 1770s (C=O), 1749s (C=O), 1713s (C=O), 1456m, 1424w, 1383m, 1368m, 1321m, 1296m, 1258s, 1219w, 1170s, 1128m, 1111m, 1082s, 1044s, 1010s, 986m, 971m, 911m, 789w, 772m, 761w, 733m, 673w, 618m; ^1H NMR (500 MHz, $CDCl_3$): δ 5.89 (1H, ddt, J = 5.8, 10.5, 17.2 Hz, H-2‴), 5.31 (1H, dq, J = 1.4, 17.2 Hz, H-3‴a), 5.25 (1H, dq, J = 1.2, 10.4 Hz, H-3‴b), 5.01 (1H, dd, J = 2.4, 10.6 Hz, H-13), 4.96 (1H, d, J = 7.9 Hz, H-1′), 4.92 (1H, d, J = 4.8 Hz, H-1″), 4.66 (1H, ddt, J = 1.3, 5.8, 13.0 Hz, H-1‴a), 4.59 (1H, ddt, J = 1.5, 5.8, 10.5 Hz, H-1‴b), 4.56 (1H, s, H-11), 4.42 (1H, d, J = 9.8 Hz, H-4″), 4.26 (1H, dq, J = 6.2, 9.8 Hz, H-5″), 3.92–3.87 (1H, m, H-J = 7.8, 11.5 Hz, H-2′), 3.56 (1H, d, J = 6.8 Hz, H-5), 3.25 (1H, dt, J = 3.5, 11.8 Hz, H-3′), 3.22 (3H, s, 3″-OMe), 2.96 (3H, s, 6-OMe), 2.91 (1H, q, J = 6.9 Hz, H-10), 2.84 (1H, dd, J = 7.4, 8.9 Hz, H-2), 2.78 (3H, s, NMe), 2.62–2.57 (1H, m, H-8), 2.39 (1H, d, J = 15.2 Hz, H-2″a), 1.98–1.94 (1H, m, H-4′a), 1.86–1.79 (2H, m, H-4, H-14a), 1.66–1.50 (4H, m, H-7a+b, H-14b, H-2″b), 1.45 (3H, s, Me at C-12), 1.41–1.34 (1H, m, H-4′b), 1.33 (3H, s, Me at C-6), 1.20–1.18 (6H, m, Me at C-2 and C-5′), 1.17 (3H, s, Me at C-3″), 1.16 (3H, d, J = 6.9 Hz, Me at C-10), 1.15 (3H, d, J = 6.1 Hz, Me at C-5″), 1.08 (3H, d, J = 7.1 Hz, Me at C-8), 0.97 (3H, d, J = 7.6 Hz, Me at C-4), 0.84 (3H, t, J = 7.4 Hz, H-15a–c); ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.6 (C-9), 176.1 (C-1), 159.8 (O–(C=O)–N), 155.1 (4″-O–(C=O)–O), 154.0 (11,12-O–(C=O)–O), 131.3 (C-2‴), 119.0 (C-3‴), 98.4 (C-1′), 95.8 (C-1″), 84.8 (C-12), 82.3 (C-4″), 80.6 (C-5/C-11), 80.5 (C-5/C-11), 79.9 (C-2′), 78.1 (C-6), 77.6 (C-3), 75.3 (C-13), 72.6 (C-3″), 69.6 (C-5′), 68.7 (C-1‴), 62.9 (C-5″), 60.7 (C-3′), 50.4 (6-OMe), 49.6 (3″-OMe), 44.8 (C-2), 44.5 (C-8), 38.82 (C-4), 38.78 (C-7), 37.7 (C-10), 36.3 (C-4′), 34.8 (C-2″), 29.9 (NMe), 21.9 (C-14), 20.95 (Me at C-5′/C-3″), 20.9 (Me at C-5′/C-3″), 19.8 (Me at C-6), 18.1 (Me at C-8), 17.9 (Me at C-5″), 15.5 (Me at C-2), 13.1 (Me at C-12), 12.6 (Me at C-10), 10.2 (C-15), 8.6 (Me at C-4); MS, ESI pos. m/z (% rel. int.): 485.9 (5), 517.9 (4), 892.5 (100, $[M+Na^+]$), 908.5 (4, $[M+K^+]$).

4.2. *N*-Demethylclarithromycin 2′,3′-carbamate-11,12-carbonate (4)

Method 1. A suspension of 4″-*O*-(allyloxycarbonyl)-*N*-demethylclarithromycin 2′,3′-carbamate-11,12-carbonate (**3**) (300 mg, 0.35 mmol), triethylamine (0.17 mL, 1.2 mmol), formic acid (0.040 mL, 1.1 mmol), palladium acetate (5 mg, 0.022 mmol, 6 mol%) and triphenylphosphine (22 mg, 0.080 mmol) in 80% aqueous ethanol (6 mL) was heated under reflux for 1.5 h. The yellow mixture was cooled to room temperature, the solvents evaporated, and the residual material subjected to flash chromatography on silica gel (25 g) using ethyl acetate/triethylamine 98:2 as eluent; yield: 251 mg (93%) of a white solid. Recrystallisation from isopropanol removed the last traces of triphenylphosphine.

Method 2. 4″-*O*-(Allyloxycarbonyl)-*N*-demethylclarithromycin 2′,3′-carbamate-11,12-carbonate (**3**) (103 mg, 0.12 mmol) was dissolved in THF/DMSO (1:1, 2.6 mL) at 70 °C. 1,4-Bis(diphenylphosphino)butane (dppb, 8 mg, 0.019 mmol) and bis(dibenzylidene-acetone)palladium ($Pd(dba)_2$, 10 mg, 0.017 mmol, 14 mol%) were added. The reaction mixture was stirred at 70 °C for 4.5 h, cooled to room temperature, aqueous sodium hydroxide added, and the product extracted into dichloromethane. The combined organic layers were washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residual material was subjected to flash chromatography on slica gel (10 g) using hexane/ethyl acetate/triethylamine 23:75:2 as eluent. The product was a white solid with mp 292–295 °C (dec; isopropanol); yield 69 mg (74%). Found: C, 58.91; H, 7.89. Calcd for $C_{39}H_{63}NO_{15}$: C, 59.60; H, 8.08%; HRMS, ESI pos.: Found: 808.4111. Calcd for $M+Na^+ = C_{39}H_{63}NNaO_{15}$: 808.4089; IR (ATR, cm^{-1}): 3518m (br, O–H), 2975s (C–H), 2937s (C–H), 2887m (C–H), 2835w (C–H), 1809s (C=O), 1770s (C=O), 1740s (C=O), 1714m (C=O), 1458m, 1425w, 1381m, 1347w, 1322m, 1287m, 1236m, 1168s, 1128m, 1111m, 1081s, 1044s, 1007s, 972w, 939w, 907w, 772w, 735w, 618m, 602m; ^1H NMR (500 MHz, $CDCl_3$): δ 5.00 (1H, dd, J = 1.4, 10.7 Hz, H-13), 4.85 (1H, d, J = 4.9 Hz, H-1″), 4.83 (1H, d, J = 8.0 Hz, H-1′), 4.55 (1H, s, H-11), 3.90 (1H, dq, J = 6.3, 9.2 Hz, H-5″), 3.65 (1H, d, J = 8.8 Hz, H-3), 3.65–3.59 (1H, m, H-5′), 3.60 (1H, dd, J = 7.9, 11.4 Hz, H-2′), 3.55 (1H, d, J = 7.4 Hz, H-5), 3.25 (3H, s, 3″-OMe), 3.14 (1H, dt, J = 3.2, 11.7 Hz, H-3′), 3.03 (1H, d, J = 8.8 Hz, H-4″), 2.94 (3H, s, 6-OMe), 2.94–2.88 (1H, m, H-10), 2.79 (3H, s, NMe), 2.79–2.73 (1H, m, H-2), 2.62–2.57 (1H, m, H-8), 2.34 (1H, d, J = 15.2 Hz, H-2″a), 1.98–1.95 (1H, m, H-4′a), 1.82 (1H, ddq, J = ~1, 7.5, 12.5 Hz, H-14a), 1.75 (1H, quin, J = 7.5 Hz, H-4), 1.60–1.50 (4H, m, H-7a+b, H-14b, H-2″b), 1.46 (3H, s, Me at C-12), 1.43–1.41 (1H, m, H-4′b), 1.34 (3H, s, Me at C-6), 1.26–1.23 (6H, m, Me at C-5′ and C-5″), 1.22 (3H, s, Me at C-3″), 1.17 (3H, d, J = 6.5 Hz, Me at C-2), 1.15 (3H, d, J = 6.9 Hz, Me at

C-10), 1.09 (3H, d, J = 7.0 Hz, Me at C-8), 0.93 (3H, d, J = 7.5 Hz, Me at C-4), 0.82 (3H, t, J = 7.3 Hz, H-15a–c); ^{13}C NMR (125 MHz, $CDCl_3$): δ 213.2 (C-9), 176.4 (C-1), 159.7 (O–(C=O)–N), 154.1 (O–(C=O)–O), 98.9 (C-1′), 95.9 (C-1″), 84.8 (C-12), 80.7 (C-5), 80.4 (C-11), 79.5 (C-2′), 78.1 (C-3), 77.8 (C-4″), 77.5 (C-6), 75.1 (C-13), 72.7 (C-3″), 70.1 (C-5′), 65.5 (C-5″), 60.8 (C-3′), 50.3 (6-OMe), 49.6 (3″-OMe), 44.9 (C-2), 44.6 (C-8), 39.1 (C-4), 38.7 (C-7), 37.5 (C-10), 35.9 (C-4′), 34.4 (C-2″), 29.9 (NMe), 21.7 (C-14), 21.4 (Me at C-3″), 20.9 (Me at C-5′), 19.8 (Me at C-6), 18.3 (Me at C-8), 18.1 (Me at C-5″), 15.7 (Me at C-2), 13.0 (Me at C-12), 12.7 (Me at C-10), 10.2 (C-15), 8.6 (Me at C-4); MS, ESI pos. m/z (% rel. int.): 517.8 (7), 596.3 (29), 628.3 (27, [M-cladinose+H$^+$]), 650.3 (7), 808.4 (100, [M+Na$^+$]).

4.3. 10,11-Anhydro-*N*-demethylclarithromycin 2′,3′-carbamate (5)

Sodium azide (222 mg, 3.41 mmol) was added to a solution of 4″-*O*-(allyloxycarbonyl)-*N*-demethylclarithromycin 2′,3′-carbamate-11,12-carbonate (**3**) (500 mg, 0.58 mmol) in DMSO (14 mL), and the reaction mixture was stirred at 100 °C for 26 h. The yellow solution was cooled to room temperature, aqueous sodium hydroxide added, and the product extracted into ethyl acetate (PS: dichloromethane and NaN_3 form explosive geminal diazides). The combined organic layers were washed with water and brine, dried ($MgSO_4$) and the solvents evaporated in vacuo. The residual yellow solid (441 mg) was subjected to flash chromatography on silica gel (22 g) using hexane/ethyl acetate/triethylamine 23:75:2 as eluent; yield: 381 mg (89%) of a white solid with mp 157–160 °C (acetone/hexane). Found: C, 60.81; H, 8.26. Calcd for $C_{38}H_{63}NO_{13}$: C, 61.52; H, 8.56%; HRMS, ESI pos.: Found: 764.4215. Calcd for M+Na$^+$ = $C_{38}H_{63}NNaO_{13}$: 764.4191; IR (ATR, cm^{-1}): 3467m (br, O–H), 3056w, 2973s (C–H), 2937s (C–H), 2884m (C–H), 2831m (C–H), 2725w, 1756s (C=O), 1735s (C=O), 1666s (C=C), 1549w, 1458m, 1426m, 1378s, 1346m, 1321m, 1292w, 1269m, 1255w, 1239m, 1167s, 1125m, 1111m, 1076s, 1053m, 1006s, 960w, 941w, 905m, 894w, 860m, 775m, 734s, 702m, 676w, 665w, 619m, 604w; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.55 (1H, s, H-11), 4.98 (1H, dd, J = 2.3, 10.6 Hz, H-13), 4.85 (1H, d, J = 4.6 Hz, H-1″), 4.76 (1H, d, J = 7.8 Hz, H-1′), 3.95 (1H, dq, J = 6.3, 9.3 Hz, H-5″), 3.79 (1H, d, J = 9.4 Hz, H-3), 3.67–3.61 (1H, m, H-5′), 3.63 (1H, d, J = 7.5 Hz, H-5), 3.58 (1H, dd, J = 7.9, 11.5 Hz, H-2′), 3.32–3.27 (1H, m, H-8), 3.25 (3H, s, 3″-OMe), 3.21 (3H, s, 6-OMe), 3.12 (1H, dt, J = 3.5, 11.8 Hz, H-3′), 3.00 (1H, d, J = 9.2 Hz, H-4″), 2.88 (1H, dq, J = 7.1, 9.2 Hz, H-2), 2.76 (3H, s, NMe), 2.35 (1H, d, J = 15.2 Hz, H-2″a), 1.98 (3H, s, Me at C-10), 1.94–1.86 (4H, m, H-4, H-7a, H-14a, H-4′a), 1.56 (1H, dd, J = 4.9, 15.2 Hz, H-2″b), 1.52–1.41 (2H, m, H-14b, H-4′b), 1.38 (3H, s, Me at C-12), 1.36 (3H, s, Me at C-6), 1.28–1.24 (1H, m, H-7b), 1.25 (6H, d, J = 6.1 Hz, Me at C-5′ and C-5″), 1.23–1.18 (3H, m, Me at C-2), 1.21 (3H, s, Me at C-3″), 1.08 (3H, d, J = 6.6 Hz, Me at C-8), 0.97 (3H, d, J = 7.5 Hz, Me at C-4), 0.85 (3H, t, J = 7.4 Hz, H-15a–c); ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.0 (C-9), 174.9 (C-1), 159.7 (O–(C=O)–N), 142.6 (C-11), 138.8 (C-10), 99.5 (C-1′), 96.8 (C-1″), 80.9 (C-5), 79.8 (C-3, C-13), 79.6 (C-2′), 77.7 (C-6, C-4′), 73.2 (C-12), 72.6 (C-3″), 70.2 (C-5′), 65.6 (C-5″), 61.1 (C-3′), 50.9 (6-OMe), 49.6 (3″-OMe), 45.0 (C-2), 40.2 (C-7), 39.4 (C-4), 36.8 (C-8), 36.1 (C-4′), 35.0 (C-2″), 29.9 (NMe), 22.5 (Me at C-6), 21.8 (C-14), 21.4 (Me at C-3″), 20.8 (Me at C-5′), 20.6 (Me at C-12), 18.3 (Me at C-5″), 17.9 (Me at C-8), 15.8 (Me at C-2), 13.2 (Me at C-10), 10.5 (C-15), 9.2 (Me at C-4); MS, ESI pos. m/z (% rel. int.): 453.8 (7), 485.8 (12), 517.8 (8), 618.3 (14), 764.4 (100, [M+Na$^+$]), 780.4 (7, [M+K$^+$].

4.4. 10,11-Anhydro-*N*-demethyl-3-*O*-descladinosylclarithromycin 2′,3′-carbamate (6)

10,11-Anhydro-*N*-demethylclarithromycin 2′,3′-carbamate (**5**) (1.28 g, 1.73 mmol) was dissolved in acetic acid/water (1:1, 18 mL), and the reaction mixture were stirred at 70 °C for 1 h. The mixture was then cooled to room temperature and stirred for another 2 h before the solid precipitate was collected by filtration and dried; yield: 661 mg (66%) of a white solid with mp 282–285 °C (dec). Found: C, 61.63; H, 8.57. Calcd for $C_{30}H_{49}NO_{10}$: C, 61.73; H, 8.46%; HRMS, ESI pos.: Found: 606.3272. Calcd for M+Na$^+$ = $C_{30}H_{49}NNaO_{10}$: 606.3248; IR (ATR, cm^{-1}): 3429s (br, O–H), 2975s (C–H), 2937s (C–H), 2879m (C–H), 2831w (C–H), 1742s (C=O), 1655m (C=C), 1457m, 1428m, 1377m, 1348m, 1328m, 1279w, 1256w, 1239w, 1188m, 1159s, 1076m, 1021m, 985m, 958w, 941w, 906w, 774w; ^{1}H NMR (600 MHz, DMSO-d_6): δ 6.46 (1H, s, H-11), 5.24 (1H, d, J = 6.8 Hz, 3-OH), 5.18 (1H, s, 12-OH), 4.92 (1H, dd, J = 1.9, 10.4 Hz, H-13), 4.83 (1H, d, J = 7.9 Hz, H-1′), 3.69 (1H, d, J = 4.6 Hz, H-5), 3.67–3.64 (1H, m, H-5′), 3.52 (1H, dd, J = 8.0, 11.3 Hz, H-2′), 3.36 (1H, dt, J = 3.5, 11.6 Hz, H-3′), 3.33–3.28 (2H, m, H-3, H-8), 3.09 (3H, s, OMe), 2.65 (3H, s, NMe), 2.52–2.47 (1H, m, H-2), 2.03–2.00 (1H, m, H-4′a), 1.93–1.86 (2H, m, H-4, H-14a), 1.91 (3H, s, Me at C-10), 1.84 (1H, dd, J = 3.6, 14.7 Hz, H-7a), 1.44–1.40 (1H, m, H-14b), 1.33 (1H, q, J = 11.2 Hz, H-4′b), 1.27 (3H, s, Me at C-12), 1.24 (3H, s, Me at C-6), 1.20 (3H, d, J = 6.1 Hz, Me at C-5′), 1.15 (3H, d, J = 6.6 Hz, Me at C-2), 1.06 (1H, dd, J = 9.0, 14.7 Hz, H-7b), 0.97 (3H, d, J = 6.5 Hz, Me at C-8), 0.81–0.73 (6H, m, H-15a–c, Me at C-4); ^{13}C NMR (75 MHz, DMSO-d_6): δ 206.3 (C-9), 174.9 (C-1), 159.2 (O–(C=O)–N), 143.7 (C-11), 137.2 (C-10), 98.7 (C-1′), 80.3 (C-5), 78.8 (C-13, C-2′), 76.7 (C-6), 74.1 (C-3), 71.6 (C-12), 70.2 (C-5′), 60.2 (C-3′), 50.2 (OMe), 44.0 (C-2), 39.3 (C-7), 37.6 (C-4), 35.5 (C-4′), 35.3 (C-8), 29.7 (NMe), 23.4 (Me at C-6), 21.2 (C-14), 20.5 (Me at C-5′), 19.9 (Me at C-12), 18.1 (Me at C-8), 15.8 (Me at C-2), 13.0 (Me at C-10), 10.6 (C-15), 8.5 (Me at C-4); MS, ESI pos. m/z (% rel. int.): 606.3 (100, [M+Na$^+$]), 607.3 (23).

4.5. 10,11-Anhydro-*N*-demethyl-3-*O*-descladinosyl-3-oxoclarithromycin 2′,3′-carbamate (7)

The Dess–Martin periodinane (DMP, 709 mg, 1.67 mmol) reagent was added to a solution of 10,11-anhydro-*N*-demethyl-3-*O*-descladinosylclarithromycin 2′,3′-carbamate

(**6**) (645 mg, 1.11 mmol) in dichloromethane (20 mL), and the reaction mixture stirred at room temperature for 30 min. Aqueous sodium hydroxide was added, the product extracted into dichloromethane, the combined organic layers washed with water and brine, dried ($MgSO_4$), and concentrated. The residual white foam (742 mg) was subjected to flash chromatography on silica (30 g) using dichloromethane/isopropanol/triethylamine 98:1:1 as eluent; yield: 603 mg (94%) of a white solid with mp 231–234 °C (toluene/hexane). Found: C, 61.74; H, 8.31. Calcd for $C_{30}H_{47}NO_{10}$: C, 61.94; H, 8.14%; HRMS, ESI pos.: Found: 604.3121. Calcd for $M+Na^+ = C_{30}H_{47}NNaO_{10}$: 604.3092; IR (ATR, cm^{-1}): 3457m (br, O–H), 2973s (C–H), 2938s (C–H), 2880m (C–H), 2837w (C–H), 1769s (C=O), 1747s (C=O), 1711m (C=O), 1669m (C=C), 1457m, 1426w, 1380m, 1325m, 1293w, 1238w, 1179m, 1111w, 1076m, 1022m, 985m, 898w, 774w, 735w; ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.60 (1H, s, H-11), 4.99 (1H, dd, J = 2.7, 10.0 Hz, H-13), 4.66 (1H, d, J = 7.8 Hz, H-1′), 4.10 (1H, d, J = 9.0 Hz, H-5), 3.74–3.70 (1H, m, H-5′), 3.73 (1H, q, J = 6.9 Hz, H-2), 3.61 (1H, dd, J = 7.9, 11.4 Hz, H-2′), 3.22–3.16 (2H, m, H-8, H-3′), 3.08 (1H, dq, J = 7.6, 8.6 Hz, H-4), 2.86 (3H, s, OMe), 2.76 (3H, s, NMe), 2.00 (3H, d, J = 1.0 Hz, Me at C-10), 1.98–1.92 (2H, m, H-14a, H-4′a), 1.89 (1H, dd, J = 6.3, 14.5 Hz, H-7a), 1.58–1.52 (1H, m, H-14b), 1.49–1.39 (2H, m, H-7b, H-4′b), 1.46 (3H, s, Me at C-12), 1.32 (3H, d, J = 6.9 Hz, Me at C-2), 1.31 (3H, s, Me at C-6), 1.28 (3H, d, J = 6.2 Hz, Me at C-5′), 1.14 (3H, d, J = 7.4 Hz, Me at C-4), 1.12 (3H, d, J = 6.7 Hz, Me at C-8), 0.90 (3H, t, J = 7.4 Hz, H-15a–c); ^{13}C NMR (150 MHz, $CDCl_3$): δ 206.6 (C-9), 203.0 (C-3), 169.8 (C-1), 159.6 (O–(C=O)–N), 142.5 (C-11), 138.6 (C-10), 100.9 (C-1′), 84.0 (C-5), 81.3 (C-13), 79.2 (C-2′), 77.8 (C-6), 73.3 (C-12), 71.0 (C-5′), 61.2 (C-3′), 51.3 (C-2), 50.5 (OMe), 46.7 (C-4), 40.7 (C-7), 37.6 (C-8), 36.1 (C-4′), 30.0 (NMe), 22.3 (C-14), 21.7 (Me at C-12), 21.2 (Me at C-6), 20.6 (Me at C-5′), 18.6 (Me at C-8), 14.7 (Me at C-4), 14.3 (Me at C-2), 13.3 (Me at C-10), 10.8 (C-15); MS, ESI pos. m/z (% rel. int.): 404.8 (12), 449.8 (5), 604.3 (100, [$M+Na^+$]).

4.6. 10,11-Anhydro-3-*O*,5-*O*-{[4-(2-hydroxypropyl)-3- methyloxazolidin-2-one-5-yl]methylene}-6-*O*-methylerythronolide A (8)

10,11-Anhydro-*N*-demethylclarithromycin 2′,3′-carbamate (**5**) (931 mg, 1.26 mmol) and trifluoroacetic acid (0.96 mL, 13 mmol) in DMSO/water (9:1, 30 mL) was stirred at 110 °C for 2.5 h. The mixture was cooled to room temperature, aqueous sodium hydroxide added, and the product was extracted into dichloromethane. The combined organic layers were washed with water and brine, dried ($MgSO_4$) and evaporated to dryness. The residual brown oil (716 mg) was subjected to flash chromatography on silica gel (36 g) using dichloromethane/isopropanol/triethylamine 98:1:1 as eluent; yield: 525 mg (72%) of an off-white foam. Crystallisation from toluene removed the discolouration and left the product as a white solid with mp 187–189 °C (toluene). Found: C, 62.25; H, 8.47. Calcd for $C_{30}H_{49}NO_{10}$: C, 61.73; H, 8.46%; HRMS, ESI pos.: Found: 606.3269. Calcd for $M+Na^+ = C_{30}H_{49}NNaO_{10}$: 606.3248; IR (ATR, cm^{-1}): 3435s (br, O–H), 2974s (C–H), 2939s (C–H), 2879m (C–H), 2835w (C–H), 2360w, 2245w, 1736s (C=O), 1670m (C=C), 1456m, 1439w, 1409w, 1375m, 1363w, 1273w, 1157m, 1072m, 1052w, 1034w, 982w, 958w, 938w, 917w, 899w, 731m; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.21 (1H, s, H-11), 4.99 (1H, dd, J = 1.9, 10.6 Hz, H-13), 4.89 (1H, d, J = 3.7 Hz, H-1′), 4.40 (1H, t, J = 4.1 Hz, H-2′), 3.93–3.89 (1H, m, H-5′), 3.85 (1H, s, H-5), 3.79 (1H, dt, J = 4.0, 8.5 Hz, H-3′), 3.72 (1H, d, J = 10.8 Hz, H-3), 3.13 (3H, s, OMe), 3.04 (1H, dq, J = 6.0, 11.4 Hz, H-8), 2.88 (1H, dq, J = 6.5, 10.8 Hz, H-2), 2.84 (3H, s, NMe), 2.03 (3H, s, Me at C-10), 1.95 (1H, ddq, J = 2.1, 7.5, 14.4 Hz, H-14a), 1.86–1.81 (2H, m, H-4, H-4′a), 1.68 (1H, dt, J = 8.9, 14.2 Hz, H-4′b), 1.55–1.46 (2H, m, H-7a, H-14b), 1.41 (3H, s, Me at C-12), 1.32 (1H, d, J = 14.6 Hz, H-7b), 1.24 (3H, d, J = 6.7 Hz, Me at C-2), 1.22 (3H, d, J = 6.2 Hz, H-6′), 1.18 (3H, d, J = 6.2 Hz, Me at C-8), 1.10 (3H, s, Me at C-6), 1.03 (3H, d, J = 6.6 Hz, Me at C-4), 0.87 (3H, t, J = 7.4 Hz, H-15a–c); ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.0 (C-9), 174.7 (C-1), 157.2 (O–(C=O)–N), 140.7 (C-10), 139.5 (C-11), 101.2 (C-1′), 86.3 (C-5), 84.4 (C-3), 81.1 (C-13), 78.7 (C-6), 77.6 (C-2′), 73.2 (C-12), 65.8 (C-5′), 56.7 (C-3′), 49.8 (OMe), 41.7 (C-4′), 41.4 (C-2), 37.9 (C-7), 37.0 (C-8), 32.6 (C-4), 29.4 (NMe), 23.9 (C-6′), 21.5 (C-14), 20.4 (Me at C-12), 19.6 (Me at C-6), 15.1 (Me at C-8), 14.0 (Me at C-10), 13.8 (Me at C-2), 10.5 (C-15), 8.2 (Me at C-4); MS, ESI pos. m/z (% rel. int.): 345.9 (7), 360.8 (30), 401.8 (35), 419.8 (54), 446.8 (34), 460.8 (62), 464.8 (64), 478.8 (100), 496.8 (33), 505.8 (37), 519.8 (33), 537.8 (11), 606.3 (73, [$M+Na^+$]).

4.7. 10,11-Anhydro-6-*O*-methyl-3-*O*,5-*O*-{[4-(2-oxopropyl)-3-methyloxazolidin-2-one-5-yl]methylene}erythronolide A (9)

10,11-Anhydro-3-*O*,5-*O*-{[4-(2-hydroxypropyl)-3-methyloxazolidin-2-one-5-yl]methylene}-6-*O*-methylerythronolide A (**8**) (500 mg, 0.86 mmol) was dissolved in dichloromethane (10 mL), and Dess–Martin periodinane (DMP, 475 mg, 1.12 mmol) was added. The suspension was stirred at room temperature for 30 min before aqueous sodium hydroxide was added and the product extracted into dichloromethane. The combined organic layers were washed with water and brine, dried ($MgSO_4$), and the solvents removed at reduced pressure. The residual white solid (479 mg) was subjected to flash chromatography on silica gel (10 g) using hexane/ethyl acetate/triethylamine 31:67:2 as eluent; yield: 429 mg (86%) of a white solid with mp 187–189 °C (ethyl acetate). Found: C, 62.01; H, 8.09. Calcd for $C_{30}H_{47}NO_{10}$: C, 61.94; H 8.14%; HRMS, ESI pos.: Found: 604.3080. Calcd for $M+Na^+ = C_{30}H_{47}NNaO_{10}$: 604.3092; IR (ATR, cm^{-1}): 3425s (br, O–H), 2976s (C–H), 2939s (C–H), 2879m (C–H), 2833w (C–H), 1743s (br, C=O), 1670m (C=C), 1456m, 1437m, 1407w, 1362m, 1273w, 1233w, 1155s, 1137m, 1077s, 1052w, 1034w, 959w, 938w, 898w, 735m; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.21 (1H, s, H-11), 4.98 (1H, dd, J = 2.0, 10.7 Hz, H-13), 4.91 (1H, d, J = 2.2 Hz, H-1′), 4.14–4.09 (2H, m, H-2′, H-3′), 3.82 (1H, s, H-5), 3.69

(1H, d, J = 10.8 Hz, H-3), 3.12 (3H, s, OMe), 3.05 (1H, dq, J = 6.1, 11.6 Hz, H-8), 2.90–2.82 (2H, m, H-2, H-4′a), 2.77 (3H, s, NMe), 2.70–2.64 (1H, m, H-4′b), 2.18 (3H, s, H-6′), 2.02 (3H, s, Me at C-10), 1.95 (1H, ddq, J = 2.2, 7.5, 14.4 Hz, H-14a), 1.81 (1H, q, J = 6.7 Hz, H-4), 1.55–1.48 (2H, m, H-7a, H-14b), 1.40 (3H, s, Me at C-12), 1.31 (1H, d, J = 14.6 Hz, H-7b), 1.21 (3H, d, J = 6.5 Hz, Me at C-2), 1.18 (3H, d, J = 6.3 Hz, Me at C-8), 1.10 (3H, s, Me at C-6), 1.01 (3H, d, J = 6.5 Hz, Me at C-4), 0.87 (3H, t, J = 7.4 Hz, H-15a–c); ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.1 (C-9), 204.9 (C-5′), 174.9 (C-1), 157.3 (O–(C=O)–N), 140.6 (C-10), 139.6 (C-11), 100.5 (C-1′), 86.1 (C-5), 83.9 (C-3), 81.0 (C-13), 78.7 (C-6), 77.7 (C-2′), 73.2 (C-12), 53.6 (C-3′), 49.7 (OMe), 46.7 (C-4′), 41.4 (C-2), 37.7 (C-7), 37.0 (C-8), 32.6 (C-4), 30.5 (C-6′), 29.5 (NMe), 21.5 (C-14), 20.4 (Me at C-12), 19.6 (Me at C-6), 15.0 (Me at C-8), 14.0 (Me at C-10), 13.7 (Me at C-2), 10.6 (C-15), 8.0 (Me at C-4); MS, ESI pos. m/z (% rel. int.): 523.9 (15), 537.9 (100), 564.9 (4), 569.9 (10), 578.9 (12), 604.3 (5, [M+Na$^+$]).

4.8. *N*-Demethyl-3-*O*-descladinosylclarithromycin 2′,3′-carbamate-11,12-carbonate (10)

Method (i). Trifluoroacetic acid (0.60 mL, 7.8 mmol) was added to a stirred suspension of 4″-*O*-(allyloxycarbonyl)-*N*-demethylclarithromycin 2′,3′-carbamate-11,12-carbonate (**3**) (1.00 g, 1.15 mmol) in DMSO/water (9:1, 50 mL) at 110 °C. The mixture was heated with stirring for 10 h when TLC showed full conversion. The solution was cooled to room temperature, aqueous sodium hydroxide added, and the product was extracted into dichloromethane. The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered and the filtrate evaporated to dryness. The residual material was subjected to flash chromatography on silica gel (80 g) using dichloromethane/isopropanol/triethylamine 97:1:2 as eluent. The product thus obtained was recrystallised from dichloromethane/toluene; yield: 456 mg (63%) of a white solid with mp 294 °C (dec). Found: C, 58.71; H, 7.64. Calcd for $C_{31}H_{49}NO_{12}$: C, 59.31; H, 7.87%; HRMS, ESI pos.: Found: 628.3347. Calcd for M+H$^+$ = $C_{31}H_{50}NO_{12}$: 628.3327; IR (ATR, cm^{-1}): 3414s (br, O–H), 2974s (C–H), 2936s (C–H), 2880m (C–H), 2837w (C–H), 1810s (C=O), 1747s (C=O), 1718m (C=O), 1457m, 1429w, 1384m, 1362m, 1345w, 1333m, 1284w, 1236m, 1217w, 1192m, 1166m, 1147m, 1139m, 1109m, 1082s, 1050m, 1041m, 1020m, 1004m, 987m, 974m, 946w, 920w, 909w, 775w, 720w, 678w; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.10 (1H, dd, J = 1.9, 10.7 Hz, H-13), 4.97 (1H, d, J = 7.8 Hz, H-1′), 4.70 (1H, s, H-11), 3.72–3.67 (1H, m, H-5′), 3.68 (1H, d, J = 2.1 Hz, H-5), 3.62 (1H, dd, J = 7.9, 11.3 Hz, H-2′), 3.46 (1H, d, J = 10.6 Hz, H-3), 3.23 (1H, dt, J = 3.3, 11.8 Hz, H-3′), 2.93 (1H, q, J = 6.9 Hz, H-10), 2.92 (3H, s, OMe), 2.77 (3H, s, NMe), 2.68 (1H, dq, J = 6.8, 10.6 Hz, H-2), 2.57 (1H, dq, J = 7.0, 11.4 Hz, H-8), 1.97–1.94 (2H, m, H-4, H-4′a), 1.87 (1H, ddq, J = 2.2, 7.5, 14.4 Hz, H-14a), 1.68 (1H, d, J = 12.5 Hz, H-7a), 1.58–1.41 (3H, m, H-7b, H-14b, H-4′b), 1.48 (3H, s, Me at C-12), 1.30–1.27 (3H, m, Me at C-5′), 1.28 (3H, s, Me at C-6), 1.23 (3H, d, J = 6.8 Hz, Me at C-2), 1.17 (3H, d, J = 6.7 Hz, Me at C-10), 1.09 (3H, d, J = 7.1 Hz, Me at C-8), 0.98 (3H, d, J = 7.5 Hz, Me at C-4), 0.84 (3H, t, J = 7.4 Hz, H-15a–c); ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.0 (C-9), 174.9 (C-1), 159.7 (O–(C=O)–N), 154.0 (O–(C=O)–O), 99.3 (C-1′), 84.9 (C-12), 83.6 (C-5), 80.8 (C-11), 79.4 (C-2′), 78.1 (C-3), 77.8 (C-6), 75.3 (C-13), 70.9 (C-5′), 61.2 (C-3′), 49.7 (OMe), 45.3 (C-8), 44.2 (C-2), 38.7 (C-7), 37.4 (C-10), 36.2 (C-4′), 35.8 (C-4), 30.0 (NMe), 22.1 (C-14), 20.8 (Me at C-5′), 19.2 (Me at C-6), 18.3 (Me at C-8), 15.2 (Me at C-2), 13.0 (Me at C-12), 12.9 (Me at C-10), 10.1 (C-15), 7.9 (Me at C-4); MS, ESI pos. m/z (% rel. int.): 409.0 (8), 427.0 (7), 485.6 (8), 517.6 (7), 565.0 (4), 596.0 (100), 609.0 (4), 628.0 (27, [M+H$^+$]), 649.9 (72, [M+Na$^+$]), 665.9 (10, [M+K$^+$]), 687.0 (6).

Method (ii). 3-*O*-(Allyloxycarbonyl)-*N*-demethyl-3-*O*-descladinosylclarithromycin 2′,3′-carbamate-11,12-carbonate (**13**) (377 mg, 0.53 mmol) was dissolved in DMSO/THF (1:1, 12 mL) at 70 °C, and 1,4-bis(diphenylphosphino)butane (dppb, 14 mg, 0.033 mmol) and bis(dibenzylideneacetone)palladium ($Pd(dba)_2$, 17 mg, 0.030 mmol, 6 mol%) were added. The reaction mixture was stirred at this temperature for 2 h, cooled to room temperature, aqueous sodium hydroxide added, and the product extracted into dichloromethane. The combined organic layers were washed with water and brine, dried ($MgSO_4$), filtered and the solvents evaporated. The residual yellow solid (349 mg) was subjected to flash chromatography on silica gel (30 g) using dichloromethane/isopropanol/triethylamine 97:1:2 as eluent followed by recrystallisation from dichloromethane/toluene; yield: 179 mg (54%) of a white solid.

4.9. *N*-Demethyl-3-*O*-descladinosyl-3-oxoclarithromycin 2′,3′-carbamate-11,12-carbonate (11)

A solution of *N*-chlorosuccinimide (NCS, 59 mg, 0.44 mmol) in dichloromethane (3 mL) was cooled to −16 °C. Dimethylsulfide (0.037 mL, 0.50 mmol) was added dropwise over 5 min, and the mixture was stirred for 10 min. A solution of *N*-demethyl-3-*O*-descladinosylclarithromycin 2′,3′-carbamate-11,12-carbonate (**10**) (170 mg, 0.27 mmol) in dichloromethane (20 mL) was added dropwise over 30 min, while the temperature was kept between −16 and −10 °C. The reaction mixture was stirred for 1.5 h, while the temperature was allowed to reach −5 °C. Triethylamine (0.041 mL, 0.29 mmol) was added dropwise over 5 min, the mixture stirred for 1.5 h at −5 °C and allowed to reach room temperature. A colourless solution was formed. Aqueous sodium hydroxide was added, the product extracted into dichloromethane, the combined organic layers were washed with water and brine, dried ($MgSO_4$) and concentrated. The residual white solid (149 mg) was subjected to flash chromatography on silica gel (12 g) using dichloromethane/triethylamine 98.5:1.5 as eluent; yield: 124 mg (73%) of a white solid with mp 283–285 °C (dec; dichloromethane/hexane). Found: C, 58.55; H, 7.45. Calcd for $C_{31}H_{47}NO_{12}$: C, 59.51; H 7.57%; HRMS, ESI pos.: Found: 648.3019. Calcd for M+Na$^+$ = $C_{31}H_{47}NNaO_{12}$: 648.2990; IR (ATR, cm^{-1}): 2974s (C–H), 2938s (C–H), 2881m (C–H), 2845w

(C–H), 1808s (C=O), 1767s (C=O), 1752s (C=O), 1713m (C=O), 1546w, 1457m, 1426m, 1381m, 1361w, 1326m, 1287w, 1235m, 1169m, 1154m, 1111m, 1080m, 1044m, 1016m, 986m, 955w, 906w, 862w, 774m, 735w; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.98 (1H, dd, J = 2.3, 10.1 Hz, H-13), 4.70 (1H, d, J = 7.9 Hz, H-1′), 4.59 (1H, s, H-11), 4.13 (1H, d, J = 8.1 Hz, H-5), 3.79 (1H, q, J = 6.7 Hz, H-2), 3.75–3.72 (1H, m, H-5′), 3.61 (1H, dd, J = 7.9, 11.3 Hz, H-2′), 3.21 (1H, dt, J = 3.4, 11.8 Hz, H-3′), 3.00 (1H, quintett, J = 7.6 Hz, H-4), 2.94 (1H, q, J = 6.9 Hz, H-10), 2.77 (3H, s, NMe), 2.68–2.58 (1H, m, H-8), 2.63 (3H, s, OMe), 1.98–1.95 (1H, m, H-4′a), 1.87 (1H, ddq, J = 2.6, 7.5, 14.4 Hz, H-14a), 1.66–1.55 (3H, m, H-7a+b, H-14b), 1.53 (3H, s, Me at C-12), 1.45 (1H, q, J = 11.8 Hz, H-4′b), 1.36 (3H, d, J = 6.8 Hz, Me at C-2), 1.31 (3H, s, Me at C-6), 1.29 (3H, d, J = 6.2 Hz, Me at C-5′), 1.17 (3H, d, J = 7.2 Hz, Me at C-10), 1.16 (3H, d, J = 8.9 Hz, Me at C-4), 1.12 (3H, d, J = 6.9 Hz, Me at C-8), 0.87 (3H, t, J = 7.4 Hz, H-15a–c); ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.7 (C-9), 204.1 (C-3), 169.0 (C-1), 159.5 (O–(C=O)–N), 153.7 (O–(C=O)–O), 100.5 (C-1′), 84.4 (C-12), 80.8 (C-11), 80.6 (C-5), 79.2 (C-2′), 77.7 (C-6), 76.7 (C-13), 71.0 (C-5′), 61.2 (C-3′), 51.1 (C-2), 49.6 (OMe), 47.5 (C-4), 43.8 (C-8), 39.3 (C-7), 38.0 (C-10), 36.1 (C-4′), 30.0 (NMe), 22.3 (C-14), 20.6 (Me at C-5′), 19.6 (Me at C-6), 17.8 (Me at C-8), 16.2 (Me at C-2), 14.3 (Me at C-4), 13.5 (Me at C-12), 12.4 (Me at C-10), 12.3 (C-15); MS, ESI pos. m/z (% rel. int.): 191.3 (6), 219.2 (4), 399.2 (5), 443.1 (9), 487.1 (7), 537.6 (60), 569.6 (100), 643.0 (44), 647.9 (83, [M+Na$^+$]), 704.9 (85), 1272.8 (11, [2M+Na$^+$]).

4.10. 3-*O*-Descladinosylclarithromycin (12)

The title compound was prepared by hydrolysis of clarithromycin (**1**) in aqueous HCl.[3] The crude product was purified by flash chromatography on silica gel using ethyl acetate/triethylamine 96:4 as eluent; yield 81% of a white foam. HRMS, ESI pos.: Found: 590.3914. Calcd for M+H$^+$ = $C_{30}H_{56}NO_{10}$: 590.3898; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.13 (1H, dd, J = 2.4, 11.0 Hz, H-13), 4.34 (1H, d, J = 7.3 Hz, H-1′), 3.81 (1H, d, J = 1.4 Hz, H-11), 3.64 (1H, s, H-5), 3.52 (1H, d, J = 10.5 Hz, H-3), 3.50–3.46 (1H, m, H-5′), 3.19 (1H, dd, J = 7.7, 10.5 Hz, H-2′), 2.96 (1H, q, J = 6.7 Hz, H-10), 2.92 (3H, s, OMe), 2.61 (1H, dq, J = 6.6, 10.4 Hz, H-2), 2.53 (1H, dq, J = 7.1, 10.7 Hz, H-8), 2.42 (1H, ddd, J = 3.8, 10.5, 13.9 Hz, H-3′), 2.21 (6H, s, NMe_2), 2.07 (1H, q, J = 7.3 Hz, H-4), 1.92–1.86 (2H, m, H-7a, H-14a), 1.63–1.61 (1H, m, H-4′a), 1.52 (1H, dd, J = 0.8, 14.3 Hz, H-7b), 1.48–1.38 (1H, m, H-14b), 1.32 (3H, s, Me at C-6), 1.23–1.20 (7H, m, H-4′b, Me at C-2 and C-5′), 1.14 (3H, s, Me at C-12), 1.09–1.07 (9H, m, Me at C-4, C-8 and C-10), 0.8 (3H, t, J = 7.5 Hz, H-15a–c); ^{13}C NMR (125 MHz, $CDCl_3$): δ 220.7 (C-9), 175.0 (C-1), 106.7 (C-1′), 88.4 (C-5), 78.9 (C-3), 78.0 (C-6), 76.5 (C-13), 74.1 (C-12), 70.6 (C-2′), 70.2 (C-5′), 69.7 (C-11), 65.6 (C-3′), 49.5 (OMe), 45.5 (C-8), 44.5 (C-2), 40.2 (NMe_2), 38.7 (C-7), 37.5 (C-10), 35.8 (C-4), 28.0 (C-4′), 21.4 (C-14), 21.2 (Me at C-5′), 18.7 (Me at C-6), 17.7 (Me at C-8), 16.1 (Me at C-12), 15.2 (Me at C-2), 12.6 (Me at C-10), 10.4 (C-15), 8.2 (Me at C-4); MS, ESI pos. m/z (% rel. int.): 558.4 (8), 590.3 (100, [M+H$^+$]), 612.4 (4, [M+Na$^+$]).

4.11. 3-*O*-(Allyloxycarbonyl)-*N*-demethyl-3-*O*-descladinosylclarithromycin 2′,3′-carbamate-11,12-carbonate (13)

A solution of phosgene (20% in toluene, 2.8 mL, 5.4 mmol) was added to a solution of 3-*O*-descladinosylclarithromycin (**12**) (545 mg, 0.92 mmol) and pyridine (0.87 mL, 11 mmol) in dichloromethane (12 mL). The reaction mixture was stirred at room temperature for 7 h. Allyl alcohol (1.5 mL, 22 mmol) was added, and the stirring was continued for 30 min. Aqueous sodium hydroxide was added, and the product was extracted into dichloromethane. The combined organic layers washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residual yellow solid was purified by flash chromatography on silica gel (35 g) using hexane/ethyl acetate/triethylamine 49:49:2 as eluent; yield: 271 mg (41%) of a pale yellow solid. Recrystallisation from chloroform/hexane removed the discolouration and left a white solid with mp 290–295 °C (sublim.). Found: C, 59.75; H, 8.08. Calcd for $C_{35}H_{53}NO_{14}$: C, 59.06; H 7.51%; HRMS, ESI pos.: Found: 734.3349. Calcd for M+Na$^+$ = $C_{35}H_{53}NNaO_{14}$: 734.3358; IR (ATR, cm^{-1}): 3080w, 2975s (C–H), 2939s (C–H), 2905m (C–H), 2882m (C–H), 2839w (C–H), 1808s (C=O), 1770s (C=O), 1746s (C=O), 1706s (C=O), 1650w, 1457m, 1425m, 1376m, 1365m, 1349w, 1324m, 1296w, 1260s, 1215w, 1169s, 1151w, 1131m, 1109m, 1079s, 1043m, 1030m, 1008w, 987w, 965w, 935w, 921w, 863w, 787w, 773w, 736w, 676w; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.91 (1H, ddt, J = 5.8, 10.7, 17.0 Hz, H-2‴), 5.36 (1H, dd, J = 1.0, 16.9 Hz, H-3‴a), 5.27 (1H, d, J = 9.8 Hz, H-3‴b), 5.1 (1H, dd, J = 2.0, 10.8 Hz, H-13), 4.77 (1H, d, J = 11.1 Hz, H-3), 4.67 (1H, dd, J = 5.6, 13.1 Hz, H-1‴a), 4.63 (1H, s, H-11), 4.56 (1H, dd, J = 6.1, 13.1 Hz, H-1‴b), 4.49 (1H, d, J = 7.8 Hz, H-1′), 3.66 (1H, d, J = 3.4 Hz, H-5), 3.56 (1H, dd, J = 7.7, 11.3 Hz, H-2′), 3.53–3.49 (1H, m, H-5′), 3.14 (1H, dt, J = 3.5, 11.8 Hz, H-3′), 2.97 (3H, s, OMe), 2.94–2.87 (2H, m, H-2, H-10), 2.76 (3H, s, NMe), 2.57–2.53 (1H, m, H-8), 2.07 (1H, dq, J = 3.1, 7.6 Hz, H-4), 1.92–1.89 (1H, m, H-4′a), 1.86 (1H, ddq, J = 2.2, 7.5, 14.4 Hz, H-14a), 1.60–1.47 (3H, m, H-7a+b, H-14b), 1.46 (3H, s, Me at C-12), 1.43–1.38 (1H, m, H-4′b), 1.25 (3H, d, J = 6.0 Hz, Me at C-5′), 1.25 (3H, s, Me at C-6), 1.15 (6H, t, J = 6.9 Hz, Me at C-2 and C-10), 1.07 (3H, d, J = 7.1 Hz, Me at C-8), 1.04 (3H, d, J = 7.6 Hz, Me at C-4), 0.83 (3H, t, J = 7.4 Hz, H-15a–c); ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.0 (C-9), 173.8 (C-1), 159.6 (O–(C=O)–N), 155.1 (3-O–(C=O)–O), 153.9 (11,12-O–(C=O)–O), 131.1 (C-2‴), 119.4 (C-3‴), 98.8 (C-1′), 84.8 (C-12), 82.0 (C-3), 80.6 (C-5/C-11), 80.5 (C-5/C-11), 79.2 (C-2′), 77.7 (C-6), 75.6 (C-13), 70.9 (C-5′), 68.8 (C-1‴), 61.1 (C-3′), 50.1 (OMe), 45.0 (C-8), 42.9 (C-2), 38.5 (C-7), 37.4 (C-10), 36.1 (C-4′), 35.8 (C-4), 30.0 (NMe), 21.9 (C-14), 20.6 (Me at C-5′), 19.2 (Me at C-6), 18.3 (Me at C-8), 14.7 (Me at C-2), 13.0 (Me at C-10/C-12), 12.8 (Me at C-10/C-12), 10.0 (C-15), 8.7 (Me at C-4); MS, ESI pos. m/z (% rel. int.): 391.2 (4), 409.2 (5), 449.2 (6),

511.3 (12), 578.3 (9), 680.3 (7), 712.4 (8, [M+H$^+$]), 729.4 (25), 734.3 (100, [M+Na$^+$]), 785.5 (4).

4.12. 11-Amino-*N*-(4-bromophenyl)-*N*′-demethyl-11-deoxy-3-*O*-descladinosyl-3-oxoclarithromycin 11,12:2′,3′-dicarbamate (14)

Sodium hydride (60% in mineral oil, 58 mg, 1.5 mmol) was added to a solution of 10,11-anhydro-*N*-demethyl-3-*O*-descladinosyl-3-oxoclarithromycin 2′,3′-carbamate (**7**) (420 mg, 0.72 mmol) in THF (12 mL). The mixture was stirred at room temperature for 10 min before 4-bromophenyl isocyanate (433 mg, 2.19 mmol) and copper(I) chloride (80 mg, 0.81 mmol) were added. After stirring for 42 h at 50 °C, the mixture was cooled to room temperature and quenched with saturated aq ammonium chloride. Brine was added, and the mixture was extracted with THF. The combined organic layers were washed with brine, dried ($MgSO_4$), and the solvents were removed in vacuo. The residual yellow solid (823 mg) was subjected to flash chromatography on silica (42 g) using toluene/THF 84:16 as eluent; yield: 351 mg (62%) of a white solid with mp 253–256 °C (Et_2O). Found: C, 56.03; H, 6.55. Calcd for $C_{37}H_{51}BrN_2O_{11}$: C, 56.99; H, 6.59%; HRMS, ESI pos.: Found: 801.2595. Calcd for M+Na$^+$ = $C_{37}H_{51}{}^{79}BrN_2NaO_{11}$: 801.2568; IR (ATR, cm^{-1}): 2974 m (C–H), 2938m (C–H), 2880m (C–H), 2841w (C–H), 1767s (C=O), 1716m (C=O), 1493m, 1457w, 1412w, 1394m, 1324m, 1232m, 1176m, 1153m, 1110m, 1078m, 1013m, 985m, 920w, 827w; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (2H, d, J = 8.7 Hz, H-2″a+b), 7.27 (2H, d, J = 8.8 Hz, H-3″a+b), 5.19 (1H, dd, J = 2.1, 10.9 Hz, H-13), 4.67 (1H, d, J = 7.9 Hz, H-1′), 4.21 (1H, d, J = 8.3 Hz, H-5), 4.16 (1H, s, H-11), 3.88 (1H, q, J = 6.8 Hz, H-2), 3.72 (1H, ddq, J = 2.1, 6.2, 10.3 Hz, H-5′), 3.60 (1H, dd, J = 7.9, 11.4 Hz, H-2′), 3.20 (1H, dt, J = 3.6, 11.8 Hz, H-3′), 3.09 (1H, q, J = 6.9 Hz, H-10), 3.03 (1H, quin., J = 7.9 Hz, H-4), 2.76 (3H, s, NMe), 2.65 (3H, s, OMe), 2.40 (1H, hex., J = 6.9 Hz, H-8), 2.03–1.93 (2H, m, H-14a, H-4′a), 1.69–1.58 (1H, m, H-14b), 1.57–1.51 (2H, m, H-7a+b), 1.56 (3H, s, Me at C-12), 1.47–1.40 (1H, m, H-4′b), 1.37 (3H, d, J = 6.8 Hz, Me at C-2), 1.27 (3H, d, J = 6.2 Hz, Me at C-5′), 1.22 (3H, s, Me at C-6), 1.20 (3H, d, J = 7.5 Hz, Me at C-4), 1.17 (3H, d, J = 6.8 Hz, Me at C-10), 1.02 (3H, d, J = 7.0 Hz, Me at C-8), 0.86 (3H, t, J = 7.3 Hz, H-15a–c); ^{13}C NMR (75 MHz, $CDCl_3$): δ 213.7 (C-9), 203.6 (C-3), 170.1 (C-1), 159.5 (2′,3′-O–(C=O)–N), 155.1 (11,12-O–(C=O)–N), 137.1 (C-1″), 131.6 (C-2″a+b), 127.7 (C-3″a+b), 120.0 (C-4″), 100.6 (C-1′), 82.5 (C-12), 81.0 (C-5), 79.2 (C-2′), 77.7 (C-6), 77.4 (C-13), 71.0 (C-5′), 63.2 (C-11), 61.1 (C-3′), 51.1 (C-2), 50.5 (OMe), 46.7 (C-4), 43.8 (C-8), 39.2 (C-10), 38.9 (C-7), 36.0 (C-4′), 30.0 (NMe), 21.9 (C-14), 20.6 (Me at C-5′), 19.9 (Me at C-6), 18.4 (Me at C-8), 15.1 (Me at C-2), 14.5 (Me at C-4/C-12), 14.4 (Me at C-4/C-12), 14.0 (Me at C-10), 10.2 (C-15); MS, ESI pos. *m*/*z* (% rel. int.): 801.3 (95, [M(^{79}Br)+Na$^+$]), 803.3 (100, [M(^{81}Br)+Na$^+$]), 817.2 (7, [M(^{79}Br)+K$^+$]), 819.2 (8, [M(^{81}Br)+K$^+$]).

4.13. 11-Amino-*N*-(3-fluoro-4-morpholinophenyl)-*N*′-demethyl-11-deoxy-3-*O*-descladinosyl-3-oxoclarithromycin 11,12:2′,3′-dicarbamate (15)

Sodium hydride (60% in mineral oil, 38 mg, 0.95 mmol) was added to a solution of 10,11-anhydro-*N*-demethyl-3-*O*-descladinosyl-3-oxoclarithromycin 2′,3′-carbamate (**7**) (250 mg, 0.43 mmol) in THF (5 mL). The mixture was stirred for 10 min at room temperature, and a freshly prepared solution of 3-fluoro-4-morpholinophenylisocyanate[35,36](1.29 mmol) in THF (3 mL) and copper(I) chloride (52 mg, 0.53 mmol) were added. The reaction mixture was stirred in a sealed tube at 50 °C for 42 h. The mixture was cooled to room temperature, quenched with saturated aq ammonium chloride and stirred for 1 h. Aqueous sodium hydroxide was added, and the product was extracted into ethyl acetate. The combined organic layers were washed with water and brine, dried ($MgSO_4$) and concentrated. The residual pink solid (463 mg) was subjected to flash chromatography on silica gel (30 g) using dichloromethane/isopropanol/triethylamine 98:1:1 as eluent; yield: 193 mg (56%) of an off-white powder with mp 231–235 °C (acetone/Et_2O). Found: C, 62.06; H, 7.24. Calcd for $C_{41}H_{58}FN_3O_{12}$: C, 61.26; H, 7.27%; HRMS, ESI pos.: Found: 804.4103. Calcd for M+H$^+$ = $C_{41}H_{59}FN_3O_{12}$: 804.4077; IR (ATR, cm^{-1}): 2973m (C–H), 2939m (C–H), 2880m (C–H), 2854m (C–H), 1769s (C=O), 1716m (C=O), 1516m, 1456w, 1379m, 1324w, 1230m, 1176m, 1153w, 1111m, 1079m, 1016m, 985w, 917w; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (1H, d, J = 8.6 Hz, H-6″), 7.08 (1H, dd, J = 1.7, 13.3 Hz, H-2″), 6.87 (1H, t, J = 9.0 Hz, H-5″), 5.19 (1H, dd, J = 1.9, 10.7 Hz, H-13), 4.67 (1H, d, J = 7.8 Hz, H-1′), 4.21 (1H, d, J = 8.3 Hz, H-5), 4.15 (1H, s, H-11), 3.87 (1H, q, J = 6.8 Hz, H-2), 3.84–3.81 (4H, m, H-8″a–d), 3.74–3.70 (1H, m, H-5′), 3.59 (1H, dd, J = 7.9, 11.3 Hz, H-2′), 3.20 (1H, dt, J = 3.2, 11.7 Hz, H-3′), 3.12–2.97 (6H, m, H-4, H-10, H-7″a–d), 2.76 (3H, s, NMe), 2.68 (3H, s, OMe), 2.44–2.39 (1H, m, H-8), 2.03–1.92 (2H, m, H-14a, H-4′a), 1.69–1.58 (1H, m, H-14b), 1.57–1.49 (2H, m, H-7a+b), 1.55 (3H, s, Me at C-12), 1.47–1.39 (1H, m, H-4′b), 1.37 (3H, d, J = 6.7 Hz, Me at C-2), 1.27 (3H, d, J = 6.1 Hz, Me at C-5′), 1.22 (3H, s, Me at C-6), 1.19 (3H, d, J = 7.7 Hz, Me at C-4), 1.17 (3H, d, J = 6.9 Hz, Me at C-10), 1.00 (3H, d, J = 6.9 Hz, Me at C-8), 0.86 (3H, t, J = 7.2 Hz, H-15a–c); ^{13}C NMR (75 MHz, $CDCl_3$): δ 213.5 (C-9), 203.6 (C-3), 170.1 (C-1), 159.5 (2′,3′-O–(C=O)–N), 155.3 (11,12-O–(C=O)–N), 154.9 (d, $^1J_{C\text{-}F}$ = 246.0 Hz, C-3″), 138.4 (d, $^2J_{C\text{-}F}$ = 9.8 Hz, C-4″), 132.4 (d, $^3J_{C\text{-}F}$ = 10.2 Hz, C-1″), 122.3 (d, $^4J_{C\text{–}F}$ = 3.3 Hz, C-6″), 117.9 (d, $^3J_{C\text{–}F}$ = 3.9 Hz, C-5″), 114.3 (d, $^2J_{C\text{-}F}$ = 23.3 Hz, C-2″), 100.6 (C-1′), 82.4 (C-12), 81.3 (C-5), 79.2 (C-2′), 77.7 (C-6), 77.4 (C-13), 71.0 (C-5′), 66.9 (C-8″a+b), 63.3 (C-11), 61.2 (C-3′), 51.2 (C-2), 50.8 (C-7″a+b), 50.6 (OMe), 46.6 (C-4), 43.5 (C-8), 39.5 (C-10), 38.9 (C-7), 36.1 (C-4′), 30.0 (NMe), 22.0 (C-14), 20.6 (Me at C-5′), 20.0 (Me at C-6), 18.3 (Me at C-8), 15.0 (Me at C-2), 14.6 (Me at C-4/C-12), 14.4 (Me at C-4/C-12), 13.7 (Me at C-10), 10.2 (C-15); MS, ESI pos. *m*/*z* (% rel. int.): 338.3 (5), 485.8 (6), 494.8 (13), 526.8 (11), 804.4 (100, [M+H$^+$]), 826.4 (39, [M+Na$^+$]), 976.5 (3).

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References and notes

1. Nilius, A. M.; Ma, Z. *Curr. Opin. Pharmacol.* **2002**, *2*, 1–8.
2. Fernandes, P. B.; Baker, W. R.; Freiberg, L. A.; Hardy, D. J.; McDonald, E. J. *Antimicrob. Agents Chemother.* **1989**, *33*, 78–81.
3. Agouridas, C.; Denis, A.; Auger, J.-M.; Benedetti, Y.; Bonnefoy, A.; Bretin, F.; Chantot, J.-F.; Dussarat, A.; Fromentin, C.; D'Ambrières, S. G.; Lachaud, S.; Laurin, P.; Martret, O. L.; Loyau, V.; Tessot, N. *J. Med. Chem.* **1998**, *41*, 4080–4100.
4. Ma, Z.; Clark, R. F.; Brazzale, A.; Wang, S.; Rupp, M. J.; Li, L.; Griesgraber, G.; Zhang, S.; Yong, H.; Phan, L. T.; Nemoto, P. A.; Chu, D. T. W.; Plattner, J. J.; Zhang, X.; Zhong, P.; Cao, Z.; Nilius, A. M.; Shortridge, V. D.; Flamm, R.; Mitten, M.; Meulbroek, J.; Ewing, P.; Alder, J.; Or, Y. S. *J. Med. Chem.* **2001**, *44*, 4137–4156.
5. Bonnefoy, A.; Girard, A. M.; Agouridas, C.; Chantot, J. F. *J. Antimicrob. Chemother.* **1997**, *40*, 85–90.
6. Asaka, T.; Manaka, A.; Sugiyama, H. *Curr. Top. Med. Chem.* **2003**, *3*, 961–989.
7. Tardrew, P. L.; Mao, J. C. H.; Kenney, D. *Appl. Microbiol.* **1969**, *18*, 159–165.
8. Jones, P. H.; Rowley, E. K. *J. Org. Chem.* **1968**, *33*, 665–670.
9. Mao, J. C.-H.; Putterman, M. *J. Mol. Biol.* **1969**, *44*, 347–361.
10. Randolph, J. T.; Sauer, D. R.; Haviv, F.; Nilius, A. M.; Greer, J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1599–1602.
11. Mereu, A.; Moriggi, E.; Napoletano, M.; Regazzoni, C.; Manfredini, S.; Mercurio, T. P.; Pellacini, F. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5801–5804.
12. Schlünzen, F.; Zarivach, R.; Harms, J.; Bashan, A.; Tocilj, A.; Albrecht, R.; Yonath, A.; Franceschi, F. *Nature* **2001**, *413*, 814–821.
13. Hunt, E.; Tyler, J. W. *J. Chem. Soc., Perkin Trans. 2* **1990**, 2157–2162.
14. Martin, S. F.; Yamashita, M. *J. Am. Chem. Soc.* **1991**, *113*, 5478–5480.
15. Flynn, E. H.; Murphy, H. W.; McMahon, R. E. *J. Am. Chem. Soc.* **1955**, *77*, 3104–3106.
16. Babad, H.; Zeiler, A. G. *Chem. Rev.* **1973**, *73*, 75–91.
17. Kurath, P.; Jones, P. H.; Egan, R. S.; Perun, T. J. *Experientia* **1971**, *27*, 362.
18. Adachi, T.; Morimoto, S. *Macrolide Antibiot.* **2002**, 53–72.
19. Yamada, T.; Goto, K.; Mitsuda, Y.; Tsuji, J. *Tetrahedron Lett.* **1987**, *28*, 4557–4560.
20. Genêt, J. P.; Blart, E.; Savignac, M.; Lemeune, S.; Lemaire-Audoire, S.; Bernard, J. M. *Synlett* **1993**, 680–682.
21. Baker, W. R.; Clark, J. D.; Stephens, R. L.; Kim, K. H. *J. Org. Chem.* **1988**, *53*, 2340–2345.
22. Zhu, B.; Marinelli, B. A.; Abbanat, D.; Foleno, B. D.; Henninger, T. C.; Bush, K.; Macielag, M. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1054–1059.
23. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.
24. Elliott, R. L.; Pireh, D.; Griesgraber, G.; Nilius, A. M.; Ewing, P. J.; Bui, M. H.; Raney, P. M.; Flamm, R. K.; Kim, K.; Henry, R. F.; Chu, D. T. W.; Plattner, J. J.; Or, Y. S. *J. Med. Chem.* **1998**, *41*, 1651–1659.
25. LeMahieu, R. A.; Carson, M.; Kierstead, R. W. *J. Antibiot.* **1975**, *28*, 704.
26. Takashima, H. *Curr. Top. Med. Chem.* **2003**, *3*, 991–999.
27. Poulsen, S. M.; Kofoed, C.; Vester, B. *J. Mol. Biol.* **2000**, *304*, 471–481.
28. Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586–7587.
29. Wu, Y.-J.; Su, W.-G. *Curr. Med. Chem.* **2001**, *8*, 1727–1758.
30. Or, Y. S.; Griesgraber, G. W.; Chu, D. T. Patent Applied WO 98/54197, 1998.
31. Duggan, M. E.; Imagire, J. S. *Synthesis* **1989**, 131–132.
32. Keyes, R. F.; Carter, J. J.; Zhang, X.; Ma, Z. *Org. Lett.* **2005**, *7*, 847–849.
33. Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley Inc.: New York, 2002.
34. Vorland, L. H.; Ulvatne, H.; Andersen, J.; Haukland, H. H.; Rekdal, O.; Svendsen, J.; Gutteberg, T. J. *Scand. J. Infect. Dis.* **1998**, *30*, 513–517.
35. Brickner, S. J.; Hutchinson, D. K.; Barbachyn, M. R.; Manninen, P. R.; Ulanowicz, D. A.; Garmon, S. A.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 673–679.
36. Pearlman, B. A. Patent Applied WO 99/24393, 1999.