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Chemoselective synthesis of erythromycin A ketolides substituted in the C10-methyl group

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Abstract—The substrate for selective substitution in the C10-methyl group in erythromycin A derivatives was 10,11-anhydro-6*O*-methyl-descladinosylerythromycin. The latter, as an *N*-oxide, was reacted with NBS in acetic acid to form an allylic acetate. Nucleophilic substitutions and carbylation by Pd-catalysed cross-coupling reactions provided products substituted in the C10-methyl group. Methods for the preparation of 10-methylene derivatives of 11*N*,12*O*-cyclocarbamate 3-ketolides are described. The methylene group is part of an α,β-unsaturated carbonyl system involving the 9-keto group. The products from conjugated addition are substituted in the C10-methyl group.

1. Introduction

Erythromycin A has for a long time been widely used as an important macrolide antibacterial drug. Semisynthetic modifications of the original antibiotic have provided new groups of erythromycin-derived drugs with improved physicochemical properties for the in vivo availability and target selectivity resulting in higher efficacy in the treatment of infectious diseases.[1–3] Most positions in the macrolactone ring and its substituents, except for the 10-position and its methyl substituent, have been chemically modified. Modifications in the 10-position, however, have been effected by genetic engineering techniques as in the preparation of 10-desmethylerythromycin A. 10-Ethyl and 10-hydroxyl macrolides have also been produced by genetic engineering.[4,5] Quarternisation of the C10-carbon has recently been effected in the form of a tricyclic derivative which became available by an intramolecular 1,3-dipolar cycloaddition reaction.[6] We report methodology developed for modification of the C10-methyl group to provide a new series of erythromycin-derived compounds for bioactivity studies. An analysis of the macrolactone ring with its substituents suggested that the 10-position is only weakly polarised and will electronically shield the C10-methyl group towards chemical transformations. We wanted to increase the polarisability of the C10-methyl group by working with unsaturated intermediates, in particular with C10–C11 double bond structures in which case allylic properties should be conferred onto the methyl group. This concept has previously been successfully applied by us to an analogous series originally derived from the same antibiotic.[7]

2. Results and discussion

The reaction sequence leading to transformation of the C10-methyl group is shown in Scheme 1. The 6-hydroxyl group in erythromycin A readily adds to the 9-carbonyl carbon with cyclic hemiketal formation as in the metabolic degradation of erythromycin.[7] The hemiketal formation is prevented when the 6-hydroxyl group is O-carbylated. The substrate in this work was therefore the 6O-methylated analogue, clarithromycin. The latter was converted in a two-step process to 10,11-anhydro-6*O*-methylerythromycin (**1**).[8] In this procedure an intermediate carbonate was prepared over the 11- and 12-hydroxyl groups, and the cladinose sugar attached at the 3-hydroxyl group is removed under acidic conditions.[9]

NBS in acetic acid was chosen as a reagent for functionalisation of the C10-methyl group in the substrate **1**. Interference of the 3′-amino group with the electrophilic NBS reagent in acetic acid was to be expected.[7] The amino group was therefore protected as an *N*-oxide **2**.

Keywords: N-oxidation; NBS acetoxylation; Allylic substitution; Pd-catalysed carbylation; C10-methylamines.
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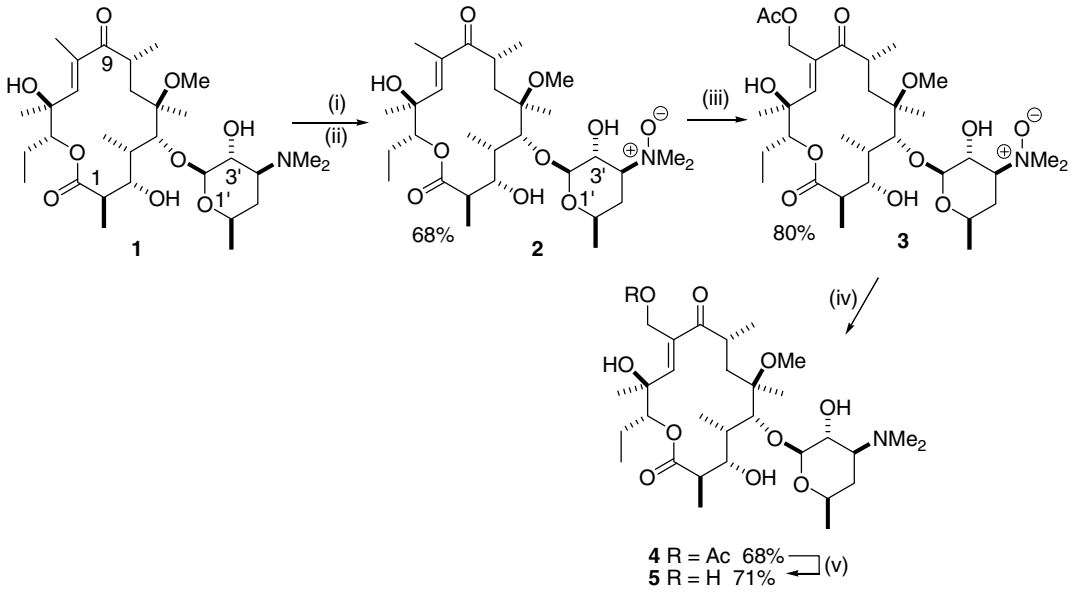


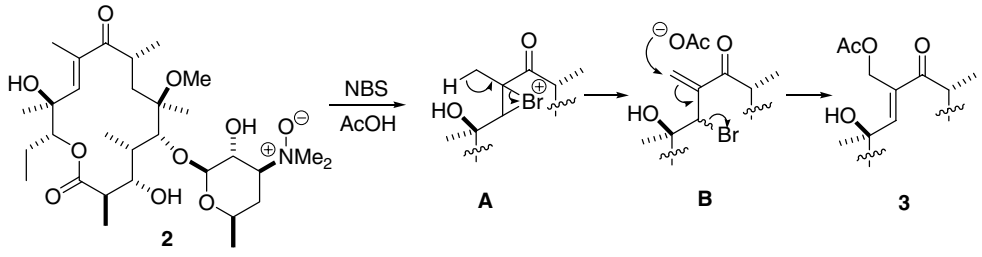
Scheme 1. Reagents and conditions: (i) H_2O_2, MeOH, rt, 5 h; (ii) cyclohexene, rt, 14 h; (iii) NBS, AcOH, rt, 14 h; (iv) PPh_3, THF, reflux, 17 h; (v) MeONa, MeOH, rt, 16 h.

N-Oxide formation was effected in a reaction with an excess of hydrogen peroxide in methanol. Full conversion to the *N*-oxide **2** was observed (crude, NMR) after 4–7 h at room temperature. The *N*-oxide possessed low solubility in common organic solvents. It was therefore difficult to extract the *N*-oxide from a water phase during work-up of the reaction mixture. Extraction operations, however, could be avoided when excess cyclohexene was added to the reaction mixture after completion of the oxidation. The cyclohexene served as a hydrogen peroxide scavenger. The cyclohexene epoxide and the excess cyclohexene were subsequently removed by distillation. The residual material was further purified by flash chromatography, and the pure *N*-oxide **2** was isolated in 68% yield. Two molar equivalents of NBS in acetic acid were used in the bromination reaction, but no bromine-containing products were detected by MS or NMR spectroscopy, not even after short reaction times. The main product was the allylic acetate **3** (Scheme 1) involving participation by the solvent. Since NBS in acetic acid is a source of electrophilic bromine, the course of the reaction may be rationalised by initial formation of a transient bromonium intermediate indicated by structure **A** in Scheme 2. The methyl group in the bromonium intermediate becomes highly activated and is easily deprotonated to provide the brominated α,β-unsaturated ketone **B** (Scheme 2). Conjugate addition to the exocyclic double bond by acetate from the acetic acid, and bromide elimination, provide the final product **3**. NMR analyses of samples withdrawn from the reaction mixture after 5, 10, 15, 20 and 30 min showed only the *N*-oxide **2** and the allylic acetate **3** in the reaction mixture.

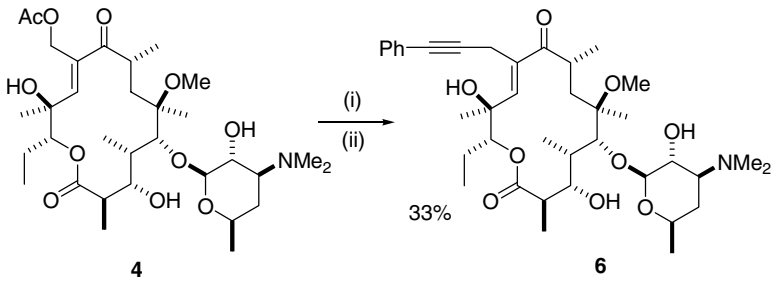
Deoxygenation of the *N*-oxide **3** (Scheme 1) was effected with triphenylphosphine in refluxing THF. The product was the allylic acetate **4**. The ester group in the allylic acetate **4** was cleaved with generation of the allylic alcohol **5** in methanolic sodium methoxide under reflux, yield 71%.

The allylic acetate **4** was expected to undergo carbylation by a palladium-catalysed cross-coupling reaction. This was demonstrated by an alkyne homologation reaction under Stille conditions in the preparation of the 10-phenylpropargyl derivative **6** in Scheme 3. The precatalyst system was composed of the trisdibenzylideneacetone dipalladium chloroform complex ($Pd_2(dba)_3{\cdot}CHCl_3$) and tri(2-furyl)phosphine (TFP) with *N*-methylpyrrolidone (NMP) as solvent.

Recent erythromycin derivatives with improved bioactivity over the parent erythromycin, the third-generation

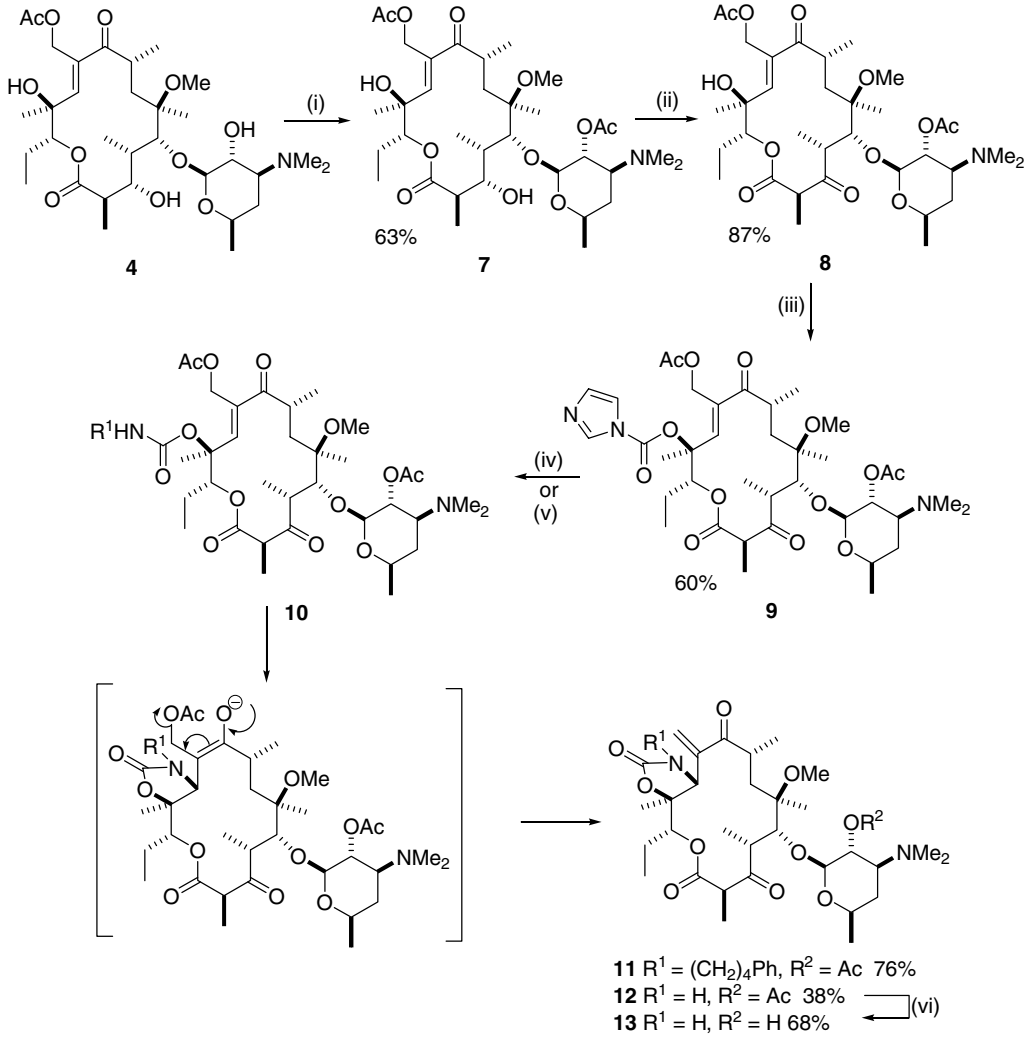


Scheme 2. Mechanistic postulation for the course of the NBS reaction.



Scheme 3. Reagents and conditions: (i) TFP/NMP, 50 °C, 10 min; (ii) $Pd_2(dba)_3{\cdot}CHCl_3$, $PhCCSnBu_3$, 80 °C, 24 h.

macrolides, are characterised by a cyclic carbamate function over the 12-hydroxyl group and an amine substituent in the 11-position. In addition, these drugs carry an oxo group in the macrolactone 3-position and are referred to as ketolides. Carbamate formation at C-11 and C-12 in erythromycin derivatives was first explored by Baker and co-workers in 1988.[10] Following the main published route for the preparation of such derivatives, the C-2′ hydroxyl group was selectively protected as the ester **7** using acetic anhydride with triethylamine as base (Scheme 4). The 3-hydroxyl group was oxidized to an oxo group with the Dess–Martin periodinane reagent providing the 3-ketolide **8** in a very good yield. The 12-acylimidazo derivative **9** was synthesised using carbonyl diimidazole (CDI) with sodium hydride (NaH) as base. The alternative base was sodium bis(trimethylsilyl)amide (NaHMDS). For the subsequent transformation to a cyclic carbamate, the imidazo derivative

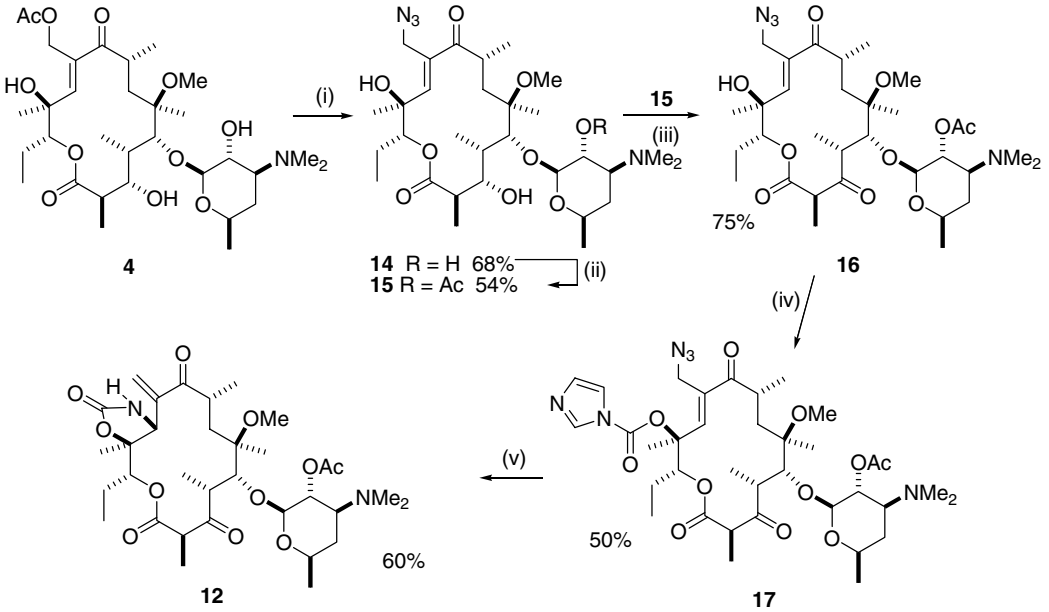


Scheme 4. Reagents and conditions: (i) Ac_2O, NEt_3, CH_2Cl_2, rt, 17 h; (ii) Dess–Martin periodinane reagent, CH_2Cl_2, rt, 2 h; (iii) a—NaHMDS, THF, −40 °C, 75 min, b—CDI, THF, DMF, rt, 20 h; (iv) $Ph(CH_2)_4NH_2$, MeCN, H_2O, 65 °C, 20 h; (v) NH_3(aq), MeCN, THF, rt, 24 h; (vi) MeOH, rt, 14 h.

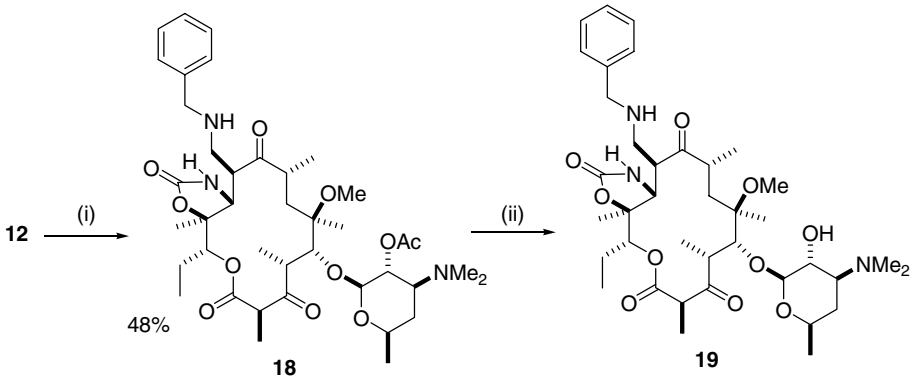
was reacted with 4-phenylbutan-1-amine in a solution of acetonitrile and water at 65 °C for 20 h. The ^{13}C NMR spectrum of the reaction mixture showed a new signal at 120 ppm corresponding to a terminal double bond. The interpretation was confirmed by DEPT-135 experiments. These results indicated that the allylic acetate group was eliminated. The carbamate **11** could be isolated in 76% yield after flash chromatography. The course of the cyclisation starts with addition of the amine to the carbamoyl carbon with replacement of the imidazole. The amino group in the resultant carbamate adds in a Michael fashion to the electrophilic double bond with cyclisation. The allylic acetate elimination can be rationalised by the movement of the negative charge in the cyclisation intermediate as indicated in Scheme 4. A subsequent electronic rearrangement leads to elimination of the acetate group in preference to protonation. The novel 10-methylene product **11** is obtained. Ammonia reacted in the same manner with the imidazocarbamate **9** to provide the methylene cyclic carbamate **12**. The macrolide **13** was obtained by methanolysis of the acetyl function at the 2′-hydroxyl group. The NMR spectra were in accordance with the α,β-unsaturated ketone structure **13**. The geminal protons at the C10 methylene group resonated as singlets at 5.74 and 5.91 ppm in the ^{1}H NMR spectrum. These signals were coupled to the terminal double bond at 119.7 ppm in COSY experiments. Cyclic carbamate formation was supported by a singlet at 3.90 ppm in the ^{1}H NMR spectrum due to the C11 methine proton, and the carbamate signal at 157.9 ppm in the ^{13}C NMR spectrum.

In a second preparation of the 10-methylene compound **12** in Scheme 5, the allylic acetate **4** was subjected to nucleophilic substitution at the allylic carbon using sodium azide. The azidomethyl derivative **14** was readily formed. Before oxidation of the 3-hydroxyl group in product **14**, the 2′-hydroxyl group was protected as an acetate **15**. The 3-hydroxyl group was oxidized by the Dess–Martin periodinane reagent to a keto function, structure **16**, before carbonyl diimidazole was introduced at the 12-OH group. The product was the acyclic carbamate **17**. Ammonia was used to cyclise the carbamate. An NMR analysis of the reaction mixture showed the new product to be formed by elimination of allylic azide to provide the α,β-unsaturated ketone **12** in 60% yield. The allylic azide **16** had thus reacted in the same manner as the allylic acetate **8** in Scheme 4.

Compound **12** is an α,β-unsaturated ketone and as such a substrate for conjugated addition reactions. Additions in the 1,4-mode will provide adducts which are macrolactones substituted in the C10-methyl group. The reaction is exemplified in Scheme 6 with the preparation of an amine derivative by heating the 10-methylene substrate **12** together with benzylamine in THF at reflux temperature. The 10-benzylaminomethyl adduct **18** was formed. The 2′-acetyl protecting group can be removed by methanolysis. An NMR analysis of the product mixture from the preparation of the adduct **18** showed mainly one product in addition to some starting material. Hence only one C10-stereoisomer was obtained. The final product **19** was isomer pure. In the ^{13}C NMR spectra, the chemical shift value 207.2 ppm of the 9 keto-carbon in the α,β-unsaturated ketone **12** was increased to 217.3 ppm in the adduct in accordance with saturated ketone formation as in structure **18**. Adduct formation may give rise to formation of either epimer at C10. Only one stereoisomer was obtained (vide supra). Preferential formation of the (10*R*)- or the (10*S*)-epimer is controlled by the synthetic conditions as well as the epimerisation conditions.[9,11,12] The natural (10*R*)-isomer is thermodynamically more stable than its



Scheme 5. Reagents and conditions: (i) NaN_3, THF, DMF, 70 °C, 17 h; (ii) Ac_2O, NEt_3, CH_2Cl_2, rt, 15 h; (iii) Dess–Martin periodinane reagent, CH_2Cl_2, rt, 2 h; (iv) a—NaH, THF, 0 °C, b—CDI, rt, 17 h; (v) NH_3(aq), MeCN, THF, rt, 17 h.



Scheme 6. Reagents and conditions: (i) $BnNH_2$, THF, reflux 17 h; (ii) MeOH, rt, 24 h.

(10*S*)-isomer. In the ^1H NMR spectra in related clarithromycin derivatives, it has been observed that the vicinal H-11 proton in the (10*S*)-isomer resonates as a doublet, but as a singlet in the (10*R*)-isomer.[10] The signal from H-11 in the benzylamine adduct was a singlet at 3.91 ppm. which has led to the assignment to the product of the desired (10*R*)-configuration.

3. Conclusion

Methodology for the preparation of erythromycin A ketolides which are substituted regioselectively in the 10-methyl group has been developed from 10,11-anhydro-6*O* methyl-descladinosylerythromycin as substrate. The natural configuration at the stereogenic centres involved in the reactions was retained. Initially, an *N*-oxide was prepared and reacted with NBS in acetic acid to form an allylic acetate. Nucleophilic substitutions and carbylation by Pd-catalysed cross-coupling reactions provided products substituted in the 10-methyl group. In another series of reactions, the 3-hydroxyl group was converted into an oxo group. The ketolide, as a derivative of 11*N*,12*O*-cyclocarbamate, was converted into a 10-methylene derivative in reactions with amines. The methylene group and the 9-oxo group constitute an α,β-unsaturated carbonyl system. Conjugated addition of nucleophiles provided erythromycin derivatives substituted in the 10-methyl group.

4. Experimental

^1H NMR spectra were recorded in $CDCl_3$ or DMSO at 300, 500 or 600 MHz with Bruker DPX 300, 500 or 600. The ^{13}C NMR spectra were recorded at 75, 100 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 ^1H 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 attenuated total reflectance (ATR). Elemental analyses were performed by Ilse Beetz Mickroanalytisches Laboratorium, Kronach, Germany. Melting points are uncorrected.

All reactions were performed under an inert atmosphere except for the N-oxidations of the macrolides.

THF was distilled from sodium/benzophenone. Dichloromethane and triethylamine were distilled from calcium hydride. NBS was purified by recrystallisation from water and dried. Merck silica gel 60 (230–400 mesh) was used for flash chromatography.

4.1. 10,11-Anhydro-6*O*-methyl-descladinosylerythromycin A (1)

Compound **1** was prepared from erythromycin A as described.[4]

4.2. 10,11-Anhydro-6*O*-methyl-descladinosylerythromycin A *N*-oxide (2)

Hydrogen peroxide (30%; 2.0 mL) was added to a solution of 10,11-anhydro-6*O*-methyl-descladinosylerythromycin A (**1**) (1.60 g, 2.80 mmol) in methanol (20 mL). The reaction mixture was stirred at room temperature for 5 h. Cyclohexene (2 mL) was added to remove excess hydrogen peroxide and the reaction mixture was stirred at room temperature overnight. The solvents were removed under reduced pressure and the crude product was purified by flash chromatography on silica gel using CH_2Cl_2/MeOH/NH_3(aq) 90:20:2; yield 1.11 g (68%) of a white crystalline material, mp 192–193 °C. HRMS [Electrospray, H^+]: 588.3727. Calcd for $C_{30}H_{53}NO_{10}$: 588.3742; ^1H NMR (500 MHz; DMSO); δ 0.79 (3H, t, J = 7.5 Hz, 14-CH_3), 0.86 (3H, d, J = 7.0 Hz, 4-CH_3), 1.03 (3H, d, J = 6.5 Hz, 8-CH_3), 1.13 (6H, m, 5′-CH_3/2-CH_3), 1.17 (3H, s, 6-CH_3), 1.21 (3H, s, 12-CH_3), 1.27–1.34 (1H, m, 4′-H_a), 1.37–1.49 (3H, m, 7-H_a/14-H_a), 1.61–1.62 (1H, m, 4-H), 1.84–1.90 (1H, m, 14-H_b), 1.90 (3H, s, 10-CH_3), 1.94–1.97 (1H, m, 4′-H_b), 2.51–2.56 (1H, m, 2-H), 3.00 (3H, s, 6-OCH_3), 3.04 (6H, s, $N(CH_3)_2$), 3.17–3.19 (1H, m, 8-H), 3.30–3.67 (1H, m, 3′-H), 3.53–3.59 (3H, m, 2′-H/5′-H/3-H), 3.70 (1H, d, J = 2.2 Hz, 5-H), 4.35 (1H, d, J = 7.2 Hz, 1′-H), 4.86 (1H, d, J = 10.5 Hz, 13-H), 5.27 (1H, s, 12-OH), 6.45 (1H, s, 11-H); ^{13}C NMR (75 MHz; DMSO): δ 7.8 (4-CH_3), 10.5 (14-CH_3), 12.4 (10-CH_3),

16.1 (2-CH_3), 16.3 (8-CH_3), 19.7 (12-CH_3), 20.5 (C-14), 20.9 (6-CH_3), 21.2 (5′-CH_3), 33.9 (C-4′), 35.2 (C-8), 37.60 (C-7), 37.9 (C-4), 44.0 (C-2), 48.7 (N-CH_3), 51.7 (6-OCH_3), 58.7 (N-CH_3), 67.5 (C-5′), 71.6 (C-2′), 71.9 (C-12), 74.2 (C-3′), 76.0 (C-3), 78.8 (C-13), 79.3 (C-6), 87.4 (C-5), 104.8 (C-1′), 136.5 (C-10), 143.5 (C-11), 175.9 (C-1), 206.2 (C-9); IR (film) (CH_2Cl_2) ν (cm^{-1}) 3377 (m), 2974 (s), 2937 (s), 2879 (m), 1724 (s), 1663 (m), 1458 (m), 1375 (m), 1353 (w), 1169 (s), 1110 (m), 1081 (s), 1060 (m), 1045 (m), 961 (m), 736 (m).

4.3. 10-Acetoxymethyl-10,11-anhydro-10-desmethyl-6*O*-methyl-descladinosylerythromycin A *N*-oxide (3)

NBS (1.00 g, 5.60 mmol) was added to a solution of 10,11-anhydro-6*O*-methyl-descladinosylerythromycin A *N*-oxide (**2**) (1.11 g, 1.90 mmol) in acetic acid (10 mL) at room temperature and the mixture stirred at this temperature overnight. The solvent was removed under reduced pressure, the residual material dissolved in $CHCl_3$, washed with $NaHCO_3$, dried ($MgSO_4$) and concentrated to afford the crude product as a white solid which was purified by flash chromatography on silica gel using CH_2Cl_2/MeOH/NH_3(aq) 90:10:2, yield 0.995 g (80%); mp 154–157 °C. HRMS [Electrospray, H^+]: 646.3800. Calcd for $C_{32}H_{55}NO_{12}$: 646.3797; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.88 (3H, t, J = 7.4 Hz, 14-CH_3), 1.03 (3H, d, J = 6.9 Hz, 4-CH_3), 1.12 (3H, d, J = 8.2 Hz, 8-CH_3), 1.99 (3H, s, 10-CH_2OCOCH_3), 2.61–2.72 (1H, m, 2-H), 3.07 (3H, s, 6-OCH_3), 3.11 (3H, s, N(CH_3)), 3.14 (3H, s, N(CH_3)), 4.51 (1H, d, J = 7.3 Hz, 1′-H), 4.83–4.87 (1H, m, 13-H), 4.98 (1H, d, J = 11.7 Hz, 10-CH_a), 5.44 (1H, d, J = 11.7 Hz, 10-CH_b), 6.43 (1H, s, 11-H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 7.5 (4-CH_3), 10.4 (14-CH_3), 15.6 (2-CH_3), 16.2 (8-CH_3), 20.3 (6-CH_3), 20.8 (C-14), 21.0/21.1 (12-CH_3/5′-CH_3), 33.8 (C-4′), 36.5 (C-7), 37.3 (C-8), 38.6 (C-4), 44.5 (C-2), 48.0 (N-CH_3), 51.8 (6-OCH_3), 57.9 (10-CH_2), 58.9 (N-CH_3), 67.9 (C-5′), 71.8 (C-2′), 74.4 (C-12), 75.8 (C-3′), 77.2 (C-3), 78.6 (C-13), 81.7 (C-6), 93.2 (C-5), 106.5 (C-1′), 133.7 (C-10), 147.0 (C-11), 172.4 ($OCOCH_3$), 176.8 (C-1), 206.1 (C-9); IR (film) (CH_2Cl_2) ν (cm^{-1}) 3385 (m), 2974 (s), 2937 (s), 2880 (w), 1727 (s), 1673 (m), 1460 (m), 1374 (m), 1352 (w), 1245 (w), 1167 (s), 1109 (m), 1081 (s), 1060 (m), 1043 (s), 1001 (w), 963 (m), 735 (m).

4.4. 10-Acetoxymethyl-10,11-anhydro-10-desmethyl-6*O*-methyl-descladinosylerythromycin A (4)

10-Acetoxymethyl-10,11-anhydro-10-desmethyl-6*O*-methyl-descladinosylerythromycin A *N*-oxide (**3**) (0.69 g, 0.001 mol) and triphenylphosphine (0.56 g, 0.003 mol) were heated in THF (15 mL) under reflux for 17 h. The cold reaction mixture was extracted with ethyl acetate, the extracts washed with $NaHCO_3$, brine and dried ($MgSO_4$). The crude product was subjected to flash chromatography on silica gel. (A simpler work-up procedure is to remove the THF under reduced pressure and add the crude product onto the silica gel flash column.) The product was a white solid; yield 0.43 g (68%), mp 95–97 °C. HRMS [Electrospray, M^+]: M 652.3674. Calcd for $C_{32}H_{55}NO_{11}$: 652.3667; ^{1}H NMR (500 MHz; $CDCl_3$): δ 0.88 (3H, t, J = 6.8 Hz, 14-CH_3), 1.03 (3H, d, J = 6.5 Hz, 4-CH_3), 1.14 (3H, d, J = 6.5 Hz, 8-CH_3), 1.19 (11H, m, 5′-CH_3/6-CH_3/4′-H_a/7-H_a/12-CH_3), 1.3 (3H, d, J = 6.8 Hz, 2-CH_3), 1.53–1.59 (2H, m, 14-H_a/4-H), 1.71–1.73 (1H, m, 4′-H_b), 2.00 (1H, dd, J = 15.5, 12.3 Hz, 7-H_b), 1.98–1.99 (1H, m, 14-H_b), 2.01 (3H, s, 10-CH_2OCOCH_3), 2.28 (6H, s, N(CH_3)$_2$), 2.54–2.61 (1H, m, 3′-H), 2.66–2.70 (1H, m, 2-H), 3.03–3.07 (1H, m, 8-H), 3.08 (3H, s, 6-OCH_3), 3.24 (1H, dd, J = 10.1, 7.7 Hz, 2′-H), 3.50–3.55 (1H, m, 5′-H), 3.89 (1H, s, 5-H), 4.00 (1H, d, J = 7.3 Hz, 3-H), 4.48 (1H, d, J = 7.6 Hz, 1′-H), 4.86 (1H, dd, J = 11.1, 1.8 Hz, 13-H), 4.96 (1H, d, J = 11.8 Hz, 10-CH_a), 5.48 (1H, d, J = 11.9 Hz, 10-CH_b), 6.39 (1H, s, 11-H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 7.5 (4-CH_3), 10.5 (14-CH_3), 15.9 (8-CH_3), 16.1 (2-CH_3), 20.3 (6-CH_3), 20.9 (C-14), 21.1/21.2/21.3 (12-CH_3/5′-CH_3/$OCOCH_3$), 28.7 (C-4′), 36.7 (C-7), 36.6 (C-8), 38.5 (C-4), 40.3 (N(CH_3)$_2$), 44.4 (C-2), 48.1 (6-OCH_3), 58.1 (10-CH_2), 65.6 (C-3′), 69.6 (C-5′), 70.5 (C-2′), 74.5 (C-12), 77.9 (C-3), 78.8 (C-13), 80.9 (C-6), 92.1 (C-5), 106.7 (C-1′), 134.0 (C-10), 146.3 (C-11), 172.6 ($OCOCH_3$), 176.5 (C-1), 206.1 (C-9); IR (CH_2Cl_2) ν (cm^{-1}): 3417 (m), 2973 (s), 2938 (s), 2879 (w), 2832 (w), 1729 (s), 1675 (m), 1457 (m), 1375 (m), 1243 (w), 1165 (s), 1110 (s), 1095 (s), 1083 (s), 1048 (s), 966 (w), 736 (m).

4.5. 10,11-Anhydro-10-desmethyl-10-hydroxymethyl-6*O*-methyl-descladinosylerythromycin (5)

10-Acetoxymethyl-10,11-anhydro-10-desmethyl-6*O*-methyl-descladinosylerythromycin A (**4**) (0.045 g, 0.071 mmol) was dissolved in methanol (1 mL) and cooled to 0 °C. Sodium methoxide (1 M; 0.09 mL, 0.086 mmol) was added slowly and the reaction mixture was stirred for 16 h. Additional sodium methoxide (2× 0.09 mL of the above solution) was added over the next 2 days. TLC showed full conversion to the product after 3 days when the reaction mixture was quenched with sodium bicarbonate and the methanol removed under reduced pressure. The product was extracted with ethyl acetate and purified by flash chromatography on silica gel using CH_2Cl_2/MeOH/NH_3 90:10:2. The allylic alcohol **5** was obtained as a white solid; yield 0.030 g (71%); mp 205–206 °C. HRMS [Electrospray, Na^+]: M 610.3558. Calcd for $C_{30}H_{53}NO_{10}$: 610.3561; ^{1}H NMR (500 MHz; $CDCl_3$): δ 0.87 (3H, t, J = 6.3 Hz, 14-CH_3), 1.04 (3H, d, J = 8.4 Hz, 4-CH_3), 1.18 (3H, d, J = 6.5 Hz, 8-CH_3), 1.22–1.29 (8H, m, 5′-CH_3/6-CH_3/4′-H_a/7-H_a), 1.31 (3H, d, J = 6.8 Hz, 2-CH_3), 1.33 (3H, s, 12-CH_3), 1.55–1.74 (4H, m, 14-H_a/4-H/4′-H_b/7-H_b), 1.93–1.98 (1H, m, 14-H_b), 2.23 (6H, s, N(CH_3)$_2$), 2.45–2.50 (1H, m, 3′-H), 2.69–2.74 (1H, m, 2-H), 3.07 (3H, s, 6-OCH_3), 3.09–3.12 (1H, m, 8-H), 3.22 (1H, dd, J = 10.3, 7.7 Hz, 2′-H), 3.50–3.54 (1H, m, 5′-H), 3.90 (1H, d, J = 0.7 Hz, 5-H), 3.98 (1H, d, J = 10.5 Hz, 3-H), 4.48 (1H, d, J = 7.6 Hz, 1′-H), 4.55 (2H, dd, J = 18.5, 12.5 Hz, 10-CH_2), 4.91 (1H, dd, J = 11.1, 1.9 Hz, 13-H), 6.52 (1H, s, 11-H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 7.5 (4-CH_3), 10.4 (14-CH_3), 15.5 (8-CH_3), 16.1 (2-CH_3), 20.2 (6-CH_3), 20.7 (C-14), 21.3 (12-CH_3/5′-CH_3), 28.2 (C-4′), 36.9 (C-7), 37.2 (C-8), 38.3 (C-4), 40.2 (N(CH_3)$_2$), 44.3 (C-2), 48.1 (6-OCH_3), 56.9 (10-CH_2), 65.5 (C-3′), 69.7 (C-5′), 70.4 (C-2′), 73.9 (C-12),

78.1 (C-3), 78.8 (C-3), 81.0 (C-6), 91.8 (C-5), 106.7 (C-1′), 138.1 (C-10), 146.3 (C-11), 176.6 (C-1), 207.1 (C-9); IR (CH_2Cl_2) ν (cm^{-1}) 3339 (br, s), 2973 (s), 2938 (s), 2879 (m), 2829 (m), 1727 (s), 1667 (m), 1456 (s), 1368 (s), 1260 (m), 1165 (s), 1081 (s), 1043 (s), 963 (m).

4.6. 10,11-Anhydro-10-desmethyl-6*O*-methyl-10-(3-phenylprop-2-yn-1-yl)descladinosyl-erythromycin A (6)

Tris(2-furyl)phosphine (0.007 g, 0.032 mmol) and $Pd_2(dba)_3{\cdot}CHCl_3$ (0.004 g, 0.004 mmol) were added to a deoxygenated solution of 10-acetoxymethyl-10,11-anhydro-10-desmethyl-6*O*-methyl-descladinosylerythromycin A (**4**) (0.100 g, 0.159 mmol) in NMP (1 mL) under argon and the solution heated at 50 °C for 10 min to generate the catalyst system. Subsequently, a solution of tributyl(phenylethynyl)tin (0.07 mL, 0.191 mmol) was added and the resultant mixture was heated at 80 °C for 24 h. The solvent was removed under reduced pressure, the residue extracted into ethyl acetate, the solution shaken with aqueous sodium hydrogen carbonate, with brine, dried ($MgSO_4$), evaporated and the residual material subjected to flash chromatography on silica gel. The product was a yellow oil; yield 0.035 g (33%). HRMS [Electrospray, H^+]: M 672.4120. Calcd for $C_{38}H_{57}NO_9$: 672.4106; ^{1}H NMR (300 MHz; $CDCl_3$) (selected confirmative signals): δ 2.24 (s, $N(CH_3)_2$), 3.07 (6-OCH_3), 6.47 (1H, s, 11-H), 7.21–7.24 (3H, m, Ar), 7.29–7.31 (2H, m, Ar).

4.7. 10-Acetoxymethyl-2′*O*-acetyl-10,11-anhydro-10-desmethyl-6*O*-methyl-descladinosylerythromycin A (7)

A solution of 10-acetoxymethyl-10,11-anhydro-10-desmethyl-6*O*-methyl-descladinosylerythromycin A (**4**) (0.35 g, 0.556 mmol), triethylamine (0.15 mL, 1.11 mmol) and acetic acid anhydride (0.10 mL, 1.11 mmol) in dichloromethane (10 mL) was stirred at room temperature for 17 h. The reaction mixture was concentrated under reduced pressure and the product was extracted into ethyl acetate, the solution washed with $NaHCO_3$, brine and dried ($MgSO_4$). The solution was evaporated and the residual material subjected to flash chromatography on silica gel using acetone/hexane 1:2. The product was a white solid; yield 0.24 g (63%); mp 83–85 °C. HRMS [Electrospray, Na^+]: M 694.3779. Calcd for $C_{34}H_{57}NO_{12}$: 694.3773; ^{1}H NMR (500 MHz; $CDCl_3$): δ 0.87 (3H, t, J = 7.4 Hz, 14-CH_3), 0.91 (3H, d, J = 7.2 Hz, 4-CH_3), 1.11 (3H, d, J = 6.7 Hz, 8-CH_3), 1.23 (3H, d, J = 6.5 Hz, 5′-CH_3), 1.28 (9H, m, 6-CH_3/12-CH_3/2-CH_3), 1.31–1.37 (1H, m, 7-H_a), 1.42–1.46 (1H, m, 4′-H_a), 1.48–1.58 (1H, m, 14-H_a), 1.70–1.76 (3H, m, 4-H/4′-H_b/7-H_b), 1.96–2.00 (1H, m, 14-H_b), 2.00 (3H, s, 10-CH_2OCOCH_3), 2.07 (3H, s, 2′-$OCOCH_3$), 2.24 (6H, s, $N(CH_3)_2$), 2.59–2.66 (2H, m, 3′-H/2-H), 3.00–3.04 (1H, m, 8-H), 3.06 (3H, s, 6-OCH_3), 3.46–3.52 (1H, m, 5′-H), 3.76 (1H, d, J = 10.5 Hz, 3-H), 3.82 (1H, d, J = 2.7 Hz, 5-H), 4.69–4.72 (2H, m, 1′-H/2′-H), 4.90 (1H, dd, J = 10.5, 2.0 Hz, 13-H), 5.09 (1H, d, J = 11.8 Hz, 10-CH_a), 5.35 (1H, d, J = 12.0 Hz, 10-CH_b), 6.36 (1H, s, 11-H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 7.9 (4-CH_3), 10.5 (14-CH_3), 15.5 (2-CH_3), 17.0 (8-CH_3), 20.1 (6-CH_3), 21.0 (10-$OCOCH_3$), 21.2 (2′-$OCOCH_3$), 21.4 (5′-CH_3), 21.5 (C-14), 22.1 (12-CH_3), 30.2 (C-4′), 37.4 (C-7), 37.9 (C-4), 38.6 (C-8), 40.6 ($N(CH_3)_2$), 44.3 (C-2), 48.8 (6-OCH_3), 58.9 (10-CH_2), 64.0 (C-3′), 69.1 (C-5′), 71.8 (C-2′), 74.0 (C-12), 77.2 (C-3), 79.3 (C-13), 79.8 (C-6), 86.1 (C-5), 102.4 (C-1′), 135.7 (C-10), 144.4 (C-11), 170.2 (2′-$OCOCH_3$), 172.3 (10-CH_2OCOCH_3), 175.7 (C-1), 206.3 (C-9); IR (CH_2Cl_2) ν (cm^{-1}) 3583 (m), 3433 (m), 2973 (s), 2938 (s), 2879 (w), 1735 (s), 1674 (m), 1457 (m), 1374 (m), 1240 (s), 1162 (s), 1109 (s), 1053 (s), 988 (w).

4.8. 10-Acetoxymethyl-2′*O*-acetyl-10,11-anhydro-10-desmethyl-6*O*-methyl-3-oxo-descladinosylerythromycin A (8)

10-Acetoxymethyl-2′*O*-acetyl-10,11-anhydro-10-desmethyl-6*O*-methyl-descladinosylerythromycin A (**7**) (1.50 g, 2.30 mmol) was dissolved in dichloromethane (40 mL) and Dess–Martin periodinane reagent (1.40 g, 3.10 mmol) was added. The reaction mixture was stirred at room temperature for 2 h before the reaction mixture was concentrated under reduced pressure. The residual material was dissolved in ethyl acetate, the solution washed with water/KOH (pH adjusted to 10–11), with brine and dried ($MgSO_4$). The crude product was subjected to flash chromatography on silica gel using acetone/hexane 1:1. The product was a white solid with mp 172–174 °C; yield 0.93 g, (87%). HRMS [Electrospray, Na^+]: M 692.3586. Calcd for $C_{34}H_{55}NO_{12}$: 692.3616; ^{1}H NMR (500 MHz; $CDCl_3$): δ 0.87 (3H, t, J = 7.4 Hz, 14-CH_3), 1.06 (3H, d, J = 6.9 Hz, 8-CH_3), 1.10 (3H, d, J = 7.1 Hz, 4-CH_3), 1.21 (3H, d, J = 6.0 Hz, 5′-CH_3), 1.29 (3H, s, 6-CH_3), 1.32 (3H, d, J = 6.9 Hz, 2-CH_3), 1.29–1.33 (1H, m, 4′-H_a), 1.40 (3H, s, 12-CH_3), 1.46–1.54 (1H, m, 14-H_a), 1.65–1.85 (3H, m, 7-H_aH_b/4′-H_b), 1.94–1.99 (1H, m, 14-H_b), 1.99 (3H, s, 10-CH_2OCOCH_3), 2.03 (3H, s, 2′-$OCOCH_3$), 2.24 (6H, s, $N(CH_3)_2$), 2.63–2.69 (1H, m, 3′-H), 2.69 (3H, s, 6-OCH_3), 2.70–3.02 (2H, m, 4-H/8-H), 3.47–3.52 (1H, m, 5′-H), 3.70 (2H, q, J = 6.8 Hz), 4.09 (1H, d, J = 8.6 Hz, 5-H), 4.32 (1H, d, J = 7.6 Hz, 1′-H), 4.71 (1H, dd, J = 10.4, 7.6 Hz, 2′-H), 4.86 (1H, dd, J = 9.8, 2.6 Hz, 13-H), 5.00 (1H, d, J = 11.7 Hz, 10-CH_a), 5.41 (1H, d, J = 12.0 Hz, 10-CH_b), 6.64 (1H, s, 11-H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 10.7 (14-CH_3), 14.0 (4-CH_3), 15.3 (2-CH_3), 18.7 (8-CH_3), 20.2 (6-CH_3), 20.9 (10-$OCOCH_3$), 21.03 (2′-$OCOCH_3$), 21.4 (5′-CH_3), 22.3 (C-14), 23.2 (12-CH_3), 30.4 (C-4′), 40.6 ($N(CH_3)2$), 40.9 (C-8), 41.2 (C-7), 47.5 (C-4), 49.9 (6-OCH_3), 51.2 (C-2), 58.3 (10-CH_2), 63.5 (C-3′), 69.0 (C-5′), 71.4 (C-2′), 73.8 (C-12), 78.2 (C-6), 80.4 (C-5), 80.8 (C-13), 101.7 (C-1′), 134.4 (C-10), 145.5 (C-11), 169.2 (C-1), 169.8 (2′-$OCOCH_3$), 172.5 (10-$OCOCH_3$), 204.0 (C-3), 205.3 (C-9); IR (CH_2Cl_2) ν (cm^{-1}) 3584 (m), 3424 (m), 2972 (s), 2938 (s), 2879 (w), 1744 (s), 1678 (m), 1456 (m), 1374 (m), 1240 (s), 1164 (s), 1109 (s), 1061 (s), 989 (w).

4.9. 10-Acetoxymethyl-2′*O*-acetyl-12*O*-acylimidazolyl-10,11-anhydro-10-desmethyl-6*O*-methyl-3-oxo-descladinosylerythromycin A (9)

4.9.1. Method A. One molar of NaHMDS (1.50 mmol) in THF (1.6 mL) was added dropwise over 30 min to a cold (−40 °C) solution of 10-acetoxymethyl-2′*O*-acetyl-10,11-

anhydro-10-desmethyl-6*O*-methyl-3-oxo-descladinosylerythromycin A (**8**) (0.887 g, 1.30 mmol) in THF (10 mL). The solution was stirred at this temperature for 45 min. A solution of carbonyl diimidazole (CDI) (0.843 g, 5.20 mmol) in THF (10 mL) and DMF (5 mL) was added dropwise over 30 min to the reaction mixture at room temperature. The reaction mixture was stirred at room temperature for 20 h and quenched with sodium bicarbonate at 0 °C. The product was extracted with ethyl acetate, washed with water (pH 10–11), with brine and dried (Na_2SO_4). The crude product was subjected to flash chromatography on silica gel using acetone/hexane 1:1. The product was a white foam; yield 0.37 g (45%).

4.9.2. Method B. The ketolide **8** (0.333 g, 0.496 mmol) was dissolved in THF (4 mL) and the solution cooled to 0 °C before NaH (0.036 g, 1.49 mmol) was added. A solution of carbonyl diimidazole in THF (2 mL) was added dropwise over 5 min to the reaction mixture. The solution was stirred for 17 h and the reaction mixture was cooled to 0 °C again before it was quenched with sodium bicarbonate and extracted with ethyl acetate, washed with water (pH 10–11), with brine and dried (Na_2SO_4). The crude product was a white solid 0.227 g (60%). The crude product was pure according to NMR spectra and was used in the next step without further purification. HRMS [Electrospray, Na^+]: M 786.3778. Calcd for $C_{38}H_{57}N_3O_{13}$: 786.3783; ^1H NMR (500 MHz; $CDCl_3$): δ 0.91 (3H, t, J = 7.5 Hz, 14-CH_3), 1.09 (3H, d, J = 7.4 Hz, 4-CH_3), 1.21–1.23 (7H, m, 8-CH_3/5′-CH_3/4′- H_a), 1.30 (3H, s, 6-CH_3), 1.33 (3H, d, J = 6.8 Hz, 2-CH_3), 1.52 (3H, s, 12-CH_3), 1.61–1.65 (2H, m, 14-H_a/7-H_a), 1.67–1.72 (1H, m, 4′-H_b), 1.74–1.81 (2H, m, 14-H_a/7-H_b), 1.85 (3H, s, 10-CH_2O-COCH_3), 2.02 (3H, s, 2′-OCOCH_3), 2.23 (6H, s, N(CH_3)$_2$), 2.60–2.64 (1H, m, 3′-H), 2.74 (3H, s, 6-OCH_3), 2.95–2.99 (1H, m, 4-H), 3.06–3.10 (1H, m, 8-H), 3.45–3.50 (1H, m, 5′-H), 3.72 (1H, q, J = 6.8 Hz, 2-H), 4.09 (1H, d, J = 8.5 Hz, 5-H), 4.31 (1H, d, J = 7.7 Hz, 1′-H), 4.70 (1H, dd, J = 10.5, 7.8 Hz, 2′-H), 4.81 (2H, dd, J = 19.2, 11.2 Hz, 10-H_aH_b), 5.59 (1H, dd, J = 7.5, 1.5 Hz, 13-H), 7.04 (1H, s, Im), 7.09 (1H, s, 11-H), 7.33 (1H, s, Im), 8.07 (1H, s, Im); ^{13}C NMR (75 MHz; $CDCl_3$): δ 10.4 (14-CH_3), 14.1 (4-CH_3), 15.1 (2-CH_3), 18.4 (8-CH_3), 19.9 (12-CH_3), 20.5 (6-CH_3), 20.9 (5′-CH_3), 21.1 (2′-OCO*C*H$_3$), 21.4 (10-OCO*C*H$_3$), 22.6 (C-14), 30.3 (C-4′), 39.2 (C-8), 40.4 (C-7), 40.6 (N(CH_3)$_2$), 47.5 (C-4), 50.2 (6-OCH_3), 51.0 (C-2), 57.8 (10-CH_2), 63.6 (C-3′), 69.1 (C-5′), 71.4 (C-2′), 77.2 (C-13), 78.6 (C-6), 81.2 (C-5), 83.6 (C-12), 102.0 (C-1′), 117.0 (Im), 131.1 (Im), 135.7 (C-10), 137.0 (Im), 144.4 (C-11), 146.1 (Im-carbonyl), 168.5 (C-1), 169.7 (2′-O*C*OCH$_3$), 170.5 (10-O*C*OCH$_3$), 202.7 (C-9), 203.2 (C-3); IR (CH_2Cl_2) ν (cm^{-1}) 2974 (m), 2939 (m), 1745 (s), 1682 (w), 1457 (m), 1385 (m), 1316 (w), 1292 (m), 1243 (s), 1159 (m), 1104 (m), 1060 (s), 997 (m).

4.10. 2′*O*-Acetyl-11*N*,12*O*-cyclocarbamate-11-deshydroxy-10-desmethyl-6*O*-methyl-10-methylene-*N*-(4-phenylbutan-1-yl)-3-oxo-descladinosylerythromycin A (11)

10-Acetoxymethyl-2′*O*-acetyl-12*O*-acylimidazolyl-10,11-anhydro-10-desmethyl-6*O*-methyl-3-oxo-descladinosylerythromycin A (**9**) (0.100 g, 0.131 mmol) was dissolved in acetonitrile (3 mL) and water (0.3 mL). 4-Phenylbutan-1-amine (0.08 mL, 0.524 mmol) was added and the reaction mixture was stirred at 65 °C for 20 h. The reaction mixture was concentrated under reduced pressure, and the product was extracted into ethyl acetate and the solution washed with water/KOH (pH adusted to 10–11), brine and dried ($MgSO_4$). The crude product was subjected to flash chromatography on silica gel using acetone/hexane initially 2:1, and then 1:1 as eluent. The product was a yellow oil 0.083 g (76%). HRMS [Na^+]: M 807.4.

4.11. 2′*O*-Acetyl-11*N*,12*O*-cyclocarbamate-11-deshydroxy-10-desmethyl-6*O*-methyl-10-methylene-3-oxo-descladinosylerythromycin A (12)

Ammonia (aq) (0.2 mL) was added to a solution of 10-acetoxymethyl-2′*O*-acetyl-12*O*-acylimidazolyl-10,11-anhydro-10-desmethyl-6*O*-methyl-3-oxo-descladinosylerythromycin A (**9**) (0.127 g, 0.166 mmol) in acetonitrile (2 mL) and THF (0.2 mL) and the mixture stirred at room temperature for 24 h. The reaction mixture was concentrated under reduced pressure and the residual material dissolved in ethyl acetate, the solution washed with water/KOH (pH adjusted to 10–11), with brine and dried ($MgSO_4$). The solution was evaporated and the residual material subjected to flash chromatography on silica gel using acetone/hexane initially 2:1, then 1:1. The product was a white solid with mp 142–145 °C; yield 0.042 g (38%). HRMS [Electrospray, H^+]: M 653.3627. Calcd for $C_{33}H_{52}N_2O_{11}$: 653.3643; ^1H NMR (500 MHz; $CDCl_3$): δ 0.88 (3H, t, J = 7.5 Hz, 14-CH_3), 1.11 (3H, d, J = 6.9 Hz, 8-CH_3), 1.14 (3H, d, J = 7.9 Hz, 4-CH_3), 1.19–1.21 (6H, m, 5′-CH_3/6-CH_3), 1.26–1.35 (2H, m, 4′-H_a/7-H_a), 1.40 (3H, s, 12-CH_3), 1.42 (3H, d, J = 7.1 Hz, 2-CH_3), 1.61–1.66 (1H, m, 14-H_a), 1.67–1.72 (1H, m, 4′-H_b), 1.83–1.87 (1H, m, 14-H_b), 2.03 (3H, s, 2′-OCOCH_3), 2.23–2.28 (1H, m, 7-H_b), 2.23 (6H, s, N(CH_3)$_2$), 2.61–2.69 (1H, m, 3′-H), 2.65 (3H, s, 6-OCH_3), 2.82–2.89 (1H, m, 8-H), 3.13–3.19 (1H, m, 4-H), 3.47–3.51 (1H, m, 5′-H), 3.87 (1H, s, 11-H), 3.93 (1H, q, J = 7.0 Hz, 2-H), 4.10 (1H, d, J = 8.5 Hz, 5-H), 4.32 (1H, d, J = 7.2 Hz, 1′-H), 4.70 (1H, dd, J = 10.4, 7.3 Hz, 2′-H), 5.05 (1H, dd, J = 10.8, 2.0 Hz, 13-H), 5.66 (1H, s, NH), 5.74/5.90 (2H, s, 10-CH_2); ^{13}C NMR (75 MHz; $CDCl_3$): δ 10.4 (14-CH_3), 14.3 (4-CH_3), 16.2 (12-CH_3), 18.0 (2-CH_3), 19.8 (8-CH_3), 21.0 (6-CH_3), 21.3 (5′-CH_3/2′-OCO*C*H$_3$), 21.9 (C-14), 30.6 (C-4′), 39.3 (C-8), 40.6 (N(CH_3)$_2$), 40.2 (C-7), 48.7 (C-4), 50.4 (C-2), 50.7 (6-OCH_3), 59.0 (C-11), 63.3 (C-3′), 69.0 (C-5′), 71.5 (C-2′), 77.1 (C-13), 77.2 (C-5), 77.9 (C-6), 86.2 (C-12), 101.7 (C-1′), 119.7 (10-CH_2), 148.4 (C-10), 157.8 (carbamate), 169.8 (2′-O*C*OCH$_3$), 170.7 (C-1), 205.8 (C-3), 207.6 (C-9); IR (CH_2Cl_2) ν (cm^{-1}) 2972 (m), 2938 (m), 1749 (s), 1685 (w), 1457 (m), 1374 (m), 1237 (m), 1159 (m), 1108 (m), 1060 (s), 998 (m).

4.12. 2′*O*-Acetyl-11*N*,12*O*-cyclocarbamate-11-deshydroxy-10-desmethyl-6*O*-methyl-10-methylene-3-oxo-descladinosylerythromycin A (12) from the azide 17

Ammonia (aq) (0.2 mL) was added to a solution of crude 10-azidomethyl-2′*O*-acetyl-12*O*-acylimidazolyl-

10,11-anhydro-10-desmethyl-6*O*-methyl-3-oxo-descladinosylerythromycin A (**17**) (0.07 mmol) in acetonitrile (2 mL) and THF (0.2 mL) and the mixture stirred at room temperature for 17 h. The reaction mixture was concentrated under reduced pressure and the residual material was dissolved in ethyl acetate. The solution was washed with water/KOH (pH adjusted to 10–11), with brine and dried ($MgSO_4$). The solution was evaporated and the residual material subjected to flash chromatography on silica gel using acetone/hexane, initially 2:1, then 1:1. The product was an off white solid, yield 0.026 g (60%); HRMS [H^+]: M 653.4 and ^1H NMR was identical with compound (**12**) as first obtained.

4.13. 11*N*,12*O*-Cyclocarbamate-11-deshydroxy-10-desmethyl-6*O*-methyl-10-methylene-3-oxo-descladinosylerythromycin A (13)

2′*O*-Acetyl-11*N*,12*O*-cyclocarbamate-11-deshydroxy-10-desmethyl-6*O*-methyl-10-methylene-3-oxo-descladinosylerythromycin A (**12**) (0.072 g, 0.11 mmol) was added to methanol (2 mL) and the mixture stirred at room temperature overnight. The methanol was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel using CH_2Cl_2/MeOH/NH_3(aq) 90:8:2. The product was a white solid with mp 161–163 °C; yield 0.046 g (68%). HRMS [Electrospray, H^+]: M 611.3525. Calcd for $C_{31}H_{50}N_2O_{10}$: 611.3538; ^1H NMR (500 MHz; $CDCl_3$): δ 0.88 (3H, t, J = 7.3 Hz, 14-CH_3), 1.10 (3H, d, J = 6.9 Hz, 8-CH_3), 1.17–1.19 (1H, m, 4′-H_a), 1.19 (3H, d, J = 6.1 Hz, 5′-CH_3), 1.22 (3H,s, 6-CH_3), 1.28 (3H, d, J = 7.5 Hz, 4-CH_3), 1.38–1.40 (1H, m, 7-H_a), 1.39 (3H, s, 12-CH_3), 1.43 (3H, d, J = 7.2 Hz, 2-CH_3), 1.59–1.66 (2H, m, 14-H_a/4′-H_b), 1.81–1.86 (1H, m, 14-H_b), 2.24 (6H, s, $N(CH_3)_2$), 2.41–2.47 (2H, m, 7-H_b/3′-H), 2.66 (3H, s, 6-OCH_3), 2.87–2.93 (1H, m, 8-H), 3.13 (1H, dd, J = 10.1, 7.4 Hz, 2′-H), 3.25–3.24 (1H, m, 4-H), 3.48–3.52 (1H, m, 5′-H), 3.86 (1H, s, 11-H), 3.94 (1H, q, J = 6.7 Hz, 2-H), 4.25 (1H, d, J = 7.0 Hz, 5-H), 4.32 (1H, d, J = 7.5 Hz, 1′-H), 5.05 (1H, dd, J = 11.0, 1.5 Hz, 13-H), 5.75 (1H, s, 10-CH_a), 5.90 (2H, s, 10-CH_b/NH); ^{13}C NMR (75 MHz; $CDCl_3$): δ 10.4 (14-CH_3), 14.7 (4-CH_3), 16.3 (12-CH_3), 18.2 (2-CH_3), 19.8 (8-CH_3), 21.1 (5′-CH_3), 21.3 (6-CH_3), 21.9 (C-14), 28.4 (C-4′), 39.3 (C-8), 40.2 ($N(CH_3)_2$), 42.5 (C-7), 48.9 (C-4), 50.5 (C-2), 50.7 (6-OCH_3), 58.7 (C-11), 65.7 (C-3′), 69.4 (C-5′), 70.4 (C-2′), 77.2 (C-13), 78.0 (C-6), 78.7 (C-5), 86.2 (C-12), 104.1 (C-1′), 119.7 (10-CH_2), 148.4 (C-10), 157.9 (carbamate), 170.8 (C-1), 205.9 (C-3), 207.2 (C-9); IR (CH_2Cl_2) ν (cm^{-1}) 3312 (br, s), 2973 (s), 2938 (s), 2878 (m), 1751 (s), 1687 (m), 1457 (m), 1381 (m), 1274 (m), 1257 (w), 1161 (s), 1109 (s), 1096 (s), 1075 (s), 1048 (s), 991 (m).

4.14. 10,11-Anhydro-10-azidomethyl-10-desmethyl-6*O*-methyl-descladinosylerythromycin A (14)

A solution of 10-acetoxymethyl-10,11-anhydro-10-desmethyl-6*O*-methyl-descladinosylerythromycin A (**4**) (0.048 g, 0.076 mmol) and NaN_3 (0.010 g, 0.152 mmol) in THF (1 mL)/DMF (5 mL) was heated at 70 °C for 17 h. The solution was concentrated at reduced pressure and the residual material extracted with ethyl acetate, the solution washed with $NaHCO_3$, with brine and dried ($MgSO_4$). The solution was evaporated to dryness and the residual material was subjected to flash chromatography on silica gel using CH_2Cl_2/MeOH/NH_3(aq), initially 90:4:2, then 90:8:2. The product was a white solid with mp 98–100 °C; yield 0.022 g (68%). HRMS [M^+]: M 613.3796. Calcd for $C_{30}H_{52}N_4O_9$: 613.3807; ^1H NMR (500 MHz; $CDCl_3$): δ 0.89 (3H, t, J = 7.2 Hz, 14-CH_3), 1.04 (3H, d, J = 6.9 Hz, 4-CH_3), 1.20 (3H, d, J = 6.5 Hz, 8-CH_3), 1.23–1.29 (8H, m, 5′-CH_3/6-CH_3/4′-H_a/7-H_a), 1.31 (3H, d, J = 6.8 Hz, 2-CH_3), 1.34 (3H, s, 12-CH_3), 1.53–1.61 (2H, m, 14-H_a/4-H), 1.67–1.76 (2H, m, 4′-H_b/7-H_b), 1.88–1.95 (1H, m, 14-H_b), 2.26 (6H, s, $N(CH_3)_2$), 2.49–2.55 (1H, m, 3′-H), 2.68–2.75 (1H, m, 2-H), 3.07 (3H, s, 6-OCH_3), 3.11–3.15 (1H, m, 8-H), 3.23 (1H, dd, J = 10.5, 8.0 Hz, 2′-H), 3.49–3.54 (1H, m, 5′-H), 3.91 (1H, s, 5-H), 3.99 (1H, d, J = 8.0 Hz, 3-H), 4.28 (1H, d, J = 12.4 Hz, 10-CH_a), 4.37 (1H, d, J = 12.0 Hz, 10-CH_b), 4.48 (1H, d, J = 8.0 Hz, 1′-H), 4.89 (1H, dd, J = 11.5, 2.0 Hz, 13-H), 6.59 (1H, s, 11-H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 7.5 (4-CH_3), 10.4 (14-CH_3), 15.5 (8-CH_3), 16.1 (2-CH_3), 20.2 (6-CH_3), 20.7 (C-14), 21.3 (5′-CH_3), 21.4 (12-CH_3), 28.4 (C-4′), 36.9 (C-7), 36.9 (C-8), 38.4 (C-4), 40.2 ($N(CH_3)_2$), 44.3 (C-2), 44.9 (10-CH_2), 48.1 (6-OCH_3), 65.5 (C-3′), 69.7 (C-5′), 70.4 (C-2′), 74.3 (C-12), 78.0 (C-3), 78.4 (C-13), 80.0 (C-6), 91.8 (C-5), 106.7 (C-1′), 134.9 (C-10), 146.7 (C-11), 176.6 (C-1), 205.8 (C-9); IR (CH_2Cl_2) ν (cm^{-1}) 3431 (br, s), 2973 (s), 2938 (s), 2879 (m), 2833 (m), 2097 (s), 1728 (s), 1670 (m), 1456 (m), 1379 (m), 1353 (w), 1261 (w), 1165 (m), 1110 (m), 1095 (m), 1083 (s).

4.15. 2′*O*-Acetyl-10,11-anhydro-10-azidomethyl-10-desmethyl-6*O*-methyl-descladinosylerythromycin A (15)

10,11-Anhydro-10-azidomethyl-10-desmethyl-6*O*-methyl-descladinosylerythromycin A (**14**) (0.239 g, 0.390 mmol) was dissolved in dichloromethane (3 mL). Triethylamine (0.11 mL, 0.780 mmol) and acetic acid anhydride (0.07 mL, 0.780 mmol) were added. The reaction mixture was stirred at room temperature for 15 h. The reaction mixture was concentrated under reduced pressure and the product was extracted with ethyl acetate, the organic extracts shaken with $NaHCO_3$, brine and dried ($MgSO_4$). The crude product was subjected to flash chromatography on silica gel using gradient elution with acetone/hexane 1:2–1:1 as eluent. The phases were concentrated to afford the product as a white solid with mp 170–172 °C; yield; 0.136 g (54%); HRMS [H^+]: M 655.3928. Calcd for $C_{32}H_{54}N_4O_{10}$ 655.3912; ^1H NMR (600 MHz; $CDCl_3$): δ 0.89 (3H, t, J = 7.3 Hz, 14-CH_3), 0.92 (3H, d, J = 7.2 Hz, 4-CH_3), 1.20 (3H, d, J = 6.6 Hz, 8-CH_3), 1.24 (3H, d, J = 6.2 Hz, 5′-CH_3), 1.27 (3H, s, 6-CH_3), 1.29 (3H, d, J = 6.7 Hz, 2-CH_3), 1.30–1.36 (1H, m, 4′-H_a), 1.37 (3H, s, 12-CH_3), 1.47–1.57 (2H, m, 7-H_a/14-H_a), 1.63–1.67 (1H, m, 7-H_b), 1.73–1.76 (1H, m, 4′-H_b), 1.77–1.82 (1H, m, 4-H), 1.90–1.94 (1H, m, 14-H_b), 2.09 (3H, s, 2′-OCOCH_3), 2.24 (6H, s, $N(CH_3)_2$), 2.64–2.69 (2H, m, 2-H/3′-H), 3.06 (3H, s, 6-OCH_3), 3.09–3.12 (1H, m, 8-H), 3.48–3.51 (1H, m, 5′-H), 3.74–3.75 (1H, m, 3-H), 3.84 (1H,

d, J = 2.7 Hz, 5-H), 4.27 (1H, d, J = 13.0 Hz, 10-H_a), 4.37 (1H, d, J = 13.0 Hz, 10-H_b), 4.69–4.72 (2H, m, 2′-H/1′-H), 4.96 (1H, dd, J = 10.7, 1.8 Hz, 13-H), 6.58 (1H, s, 11-H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 7.9 (4-CH_3), 10.4 (14-CH_3), 15.5 (2-CH_3), 16.9 (8-CH_3), 20.1 (6-CH_3), 21.2 (5′-CH_3), 21.4 (2′-OCO*C*H_3), 21.4 (C-14), 22.1 (12-CH_3), 30.2 (C-4′), 37.8 (C-7), 37.8 (C-8), 38.1 (C-4), 40.7 (N(CH_3)$_2$), 44.3 (C-2), 45.5 (10-CH_2), 48.8 (6-OCH_3), 64.0 (C-3′), 69.2 (C-5′), 71.8 (C-2′), 73.9 (C-12), 77.2 (C-3), 78.9 (C-13), 79.9 (C-6), 87.3 (C-5), 102.4 (C-1′), 136.3 (C-10), 145.8 (C-11), 170.2 (2′-O*C*OCH$_3$), 175.7 (C-1), 205.6 (C-9); IR (ATR) (CH_2Cl_2) ν (cm^{-1}) 3480 (br, s), 2973 (s), 2939 (s), 2879 (m), 2832 (m), 2097 (s), 1733 (s), 1671 (m), 1457 (m), 1374 (s), 1320 (w), 1239 (s), 1162 (s), 1108 (m), 1097 (m), 1055 (s), 1011 (w), 987 (w).

4.16. 2′*O*-Acetyl-10,11-anhydro-10-azidomethyl-10-desmethyl-6*O*-methyl-3-oxo-descladinosylerythromycin A (16)

The Dess–Martin periodinane reagent (0.140 g, 0.324 mmol) was added to a solution of 2′*O*-acetyl-10,11-anhydro-10-azidomethyl-10-desmethyl-6*O*-methyl-descladinosylerythromycin A (**15**) (0.106 g, 0.162 mmol) in dichloromethane (2 mL). The reaction mixture was stirred at room temperature for 2 h, concentrated under reduced pressure, the residual material dissolved in ethyl acetate, the solution washed with water/KOH (pH adjusted to 10–11), with brine and dried ($MgSO_4$) before evaporation. The product was isolated after flash chromatography of the residual material on silica gel using acetone/hexane 2:1–1:1. The product was a white solid which was recrystallised from diethyl ether and hexane with mp 110–115 °C; yield 0.079 g (75%); HRMS [Na^+]: M 675.3608. Calcd for $C_{32}H_{52}N_4O_{10}$: 675.3575; ^{1}H NMR (600 MHz; $CDCl_3$): δ 0.89 (3H, t, J = 7.8 Hz, 14-CH_3), 1.10 (3H, d, J = 7.3 Hz, 4-CH_3), 1.17 (3H, d, J = 6.9 Hz, 8-CH_3), 1.21 (3H, d, J = 6.1 Hz, 5′-CH_3), 1.24–1.29 (1H, m, 4′-H_a), 1.30 (3H, s, 6-CH_3), 1.32 (3H, d, J = 6.8 Hz, 2-CH_3), 1.45 (3H, s, 12-CH_3), 1.51–1.55 (1H, m, 14-H_a), 1.66–1.72 (2H, m, 7-H_a/4′-H), 1.80–1.84 (1H, m, 7-H_b), 1.91–1.98 (1H, m, 14-H_b), 2.02 (3H, s, 2′-OCOC*H*$_3$), 2.22 (6H, s, N(CH_3)$_2$), 2.60–2.68 (1H, m, 3′-H), 2.68 (3H, s, 6-OCH_3), 2.96–3.02 (2H, m, 4-H/8-H), 3.46–3.51 (1H, m, 5′-H), 3.70 (1H, q, J = 6.6 Hz, 2-H), 4.08 (1H, d, J = 2 Hz, 5-H), 4.17 (1H, d, J = 12.4 Hz, 10-H_a), 4.31 (1H, d, J = 7.6 Hz, 1′-H), 4.40 (1H, d, J = 12.4 Hz, 10-H_b), 4.70 (1H, dd, J = 10.8, 7.8 Hz, 2′-H), 4.92 (1H, dd, J = 10.2, 2.7 Hz, 13-H), 6.76 (1H, s, 11-H); ^{13}C NMR (75 MHz; $CDCl_3$): δ 10.7 (14-CH_3), 14.2 (4-CH_3), 15.3 (2-CH_3), 19.0 (8-CH_3), 20.1 (6-CH_3), 20.2 (5′-CH_3), 21.4 (2′-OCO*C*H_3), 22.4 (C-14), 23.2 (12-CH_3), 30.3 (C-4′), 40.6 (N(CH_3)$_2$), 40.8 (C-8), 41.1 (C-7), 45.8 (10-CH_2), 47.3 (C-4), 50.0 (6-OCH_3), 51.2 (C-2), 63.5 (C-3′), 69.1 (C-5′), 71.5 (C-2′), 73.6 (C-12), 78.3 (C-6), 80.6 (C-13), 81.1 (C-5), 101.9 (C-1′), 135.3 (C-10), 146.8 (C-11), 169.3 (C-1), 169.7 (2′-O*C*OCH$_3$), 202.0 (C-3), 204.9 (C-9); IR (ATR) (CH_2Cl_2) ν (cm^{-1}) 3480 (br, s), 3469 (br, s), 2973 (s), 2938 (s), 2878 (m), 2836 (m), 2783 (m), 2097 (s), 1744 (s), 1716 (s), 1671 (m), 1456 (m), 1374 (s), 1339 (w), 1237 (s), 1163 (s), 1106 (s), 1061 (s), 988 (m), 965 (w), 900 (w).

4.17. 2′*O*-Acetyl-12*O*-acylimidazolyl-10,11-anhydro-10-azidomethyl-10-desmethyl-6*O*-methyl-3-oxo-descladinosylerythromycin A (17)

NaH (0.006 g, 0.200 mmol) was added to a solution of 2′*O*-acetyl-10,11-anhydro-10-azidomethyl-10-desmethyl-6*O*-methyl-3-oxo-descladinosylerythromycin A (**16**) (0.044 g, 0.067 mmol) in THF (2 mL) at 0 °C. Subsequently, a solution of carbonyl diimidazole in THF (1 mL) was added dropwise over 5 min. The resultant solution was stirred at room temperature for 17 h, cooled to 0 °C before it was quenched with sodium bicarbonate, extracted with ethyl acetate, the organic extracts washed with water (pH 10–11), with brine and dried (Na_2SO_4). The crude product was a white solid 0.050 g (98%); HRMS [Na^+]: M 769.3760. Calcd for $C_{36}H_{54}N_6O_{11}$ 769.3742. The crude product was used in the next step without further purification due to instability of the carbamate.

4.18. 10-Benzylaminomethyl-11*N*,12*O*-cyclocarbamate-11-deshydroxy-10-desmethyl-6*O*-methyl-3-oxo-descladinosylerythromycin A (19)

A solution of benzylamine (0.13 mL, 1.18 mmol) and 2′*O*-acetyl-11*N*,12*O*-cyclocarbamate-11-deshydroxy-10-desmethyl-6*O*-methyl-10-methylene-3-oxo-descladinosylerythromycin A (**12**) (0.257 g, 3.39 mmol) in THF (4 mL) was heated at reflux for 17 h. Another portion of benzylamine (0.13 mL, 1.18 mmol) was added to the warm solution and the mixture heated for another 24 h. The solution was concentrated at reduced pressure, and the residual material extracted with ethyl acetate, the solution washed with $NaHCO_3$, with brine and dried ($MgSO_4$). The solution was evaporated and the residual material was subjected to flash chromatography on silica gel using acetone/hexane 1:1. The product **18**, which is the 2′*O*-acetyl derivative, was a white solid 0.150 g (48%); HRMS [M^+]: M 760.4401. Calcd for $C_{40}H_{61}N_3O_{11}$: 760.4378.

A small portion (0.060 g) of this product was stirred in methanol (1 mL) for 24 h. The solvent was evaporated off, and the product subjected to flash chromatography on silica gel using CH_2Cl_2/MeOH/NH_3 90:10:2. The title product **19** was a white solid with mp 185–187 °C; HRMS [H^+]: M 618.4273. Calcd for $C_{38}H_{59}N_3O_{10}$: 718.4273. ^{1}H NMR (600 MHz; $CDCl_3$): δ 0.84 (3H, t, J = 7.3 Hz, 14-CH_3), 1.16 (3H, d, J = 7.0 Hz, 8-CH_3), 1.22 (3H, d, J = 6.2 Hz, 5′-CH_3), 1.21–1.23 (1H, m, 4′-H_a), 1.26 (3H, d, J = 7.5 Hz, 4-CH_3), 1.30 (3H, s, 6-CH_3), 1.37 (3H, d, J = 6.8 Hz, 2-CH_3), 1.45 (3H, s, 12-CH_3), 1.51–1.54 (1H, m, 14-H_a), 1.54–1.66 (2H, m, 7-H_a/4′-H_b), 1.74 (1H, dd, J = 14.1, 2.3 Hz, 7-H_b), 1.87–1.91 (1H, m, 14-H_b), 2.24 (6H, s, N(CH_3)$_2$), 2.40–2.45 (1H, m, 3′-H), 2.57–2.62 (1H, m, 8-H), 2.60 (3H, s, 6-OCH_3), 2.89–2.97 (3H, m, 10-CH_aH_b/10-H), 3.00–3.06 (1H, m, 4-H), 3.15 (1H, dd, J = 9.8, 7.4 Hz, 2′-H), 3.50–3.54 (1H, m, 5′-H), 3.68 (2H, dd, J = 17.9, 13.1 Hz, aromat-CH_2), 3.78 (1H, q, J = 6.9 Hz, 2-H),

3.91 (1H, s, 11-H), 4.14 (1H, d, $J = 7.9$ Hz, 5-H), 4.30 (1H, d, $J = 7.3$ Hz, 1′-H), 5.04 (1H, dd, $J = 10.1$, 2.5 Hz, 13-H), 5.60 (1H, s, carbamate-N*H*), 7.20–7.22 (3H, m, Ar), 7.26–7.29 (2H, m, Ar); ^{13}C NMR (150 MHz; $CDCl_3$): δ 10.6 (14-CH_3), 13.8 (12-CH_3), 14.4 (4-CH_3), 16.3 (2-CH_3), 17.8 (8-CH_3), 19.6 (6-CH_3), 21.2 (5′-CH_3), 22.6 (C-14), 28.2 (C-4′), 36.7 (C-7), 40.2 ($N(CH_3)_2$), 44.3 (C-8), 44.6 (C-10), 47.7 (10-CH_2), 47.8 (C-4), 49.2 (6-OCH_3), 51.23 (C-2), 54.6 (aromat-*C*H_2), 57.7 (C-11), 65.9 (C-3′), 69.6 (C-5′), 70.3 (C-2′), 76.4 (C-13), 78.1 (C-6), 78.8 (C-5), 83.9 (C-12), 103.7 (C-1′), 127.07 (Ar), 127.9 (Ar), 128.4 (Ar), 139.7 (Ar), 157.8 (carbamate), 169.4 (C-1), 204.6 (C-3), 217.3 (C-9); IR (ATR plate) ν (cm^{-1}) 3343 (m), 3351 (m), 2971 (s), 2938 (s), 2878 (m), 2841 (m), 1759 (s), 1694 (m), 1456 (s), 1380 (m), 1325 (w), 1256 (w), 1162 (s), 1108 (s), 1078 (s), 1051 (s), 992 (m).

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