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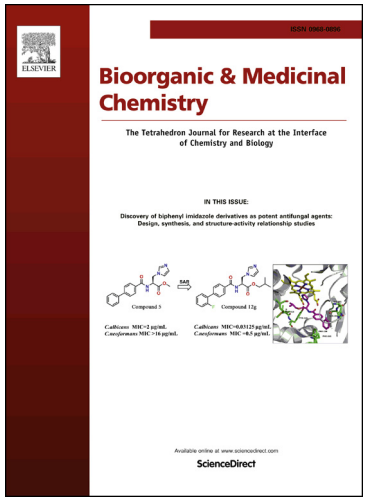

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Synthesis of clarithromycin ketolides chemically modified at the unreactive C10-methyl group

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Abstract: Chemoselective substitutions in the C10-methyl group of erythromycin A ketolides is reported. The C10-methyl group in the clarithromycin derived substrate 10,11-anhydro-O^6-methyl-descladinosylerythromycin was activated by conversion into an allyl acetate and thereafter to the corresponding allylic cyanide. Both the allylic acetate and the cyanide reacted with carbonyldiimidazole and ammonia to afford a C11,C12-cyclic carbamate with concurrent elimination of the allylic function to yield a methylene α,β-unsaturated ketone. Conjugate addition with amines resulted in stereoselective C-N bond formation between the terminal methylene carbon and the amino nitrogen. Carbylation in the methylene group was effected under Stille conditions for cross-coupling with Pd-catalysis. With anion stabilized nucleophiles, such as a sodium salt of a malonate, stereoselectivity was observed in the formation of the 10-substituent. Stereoselective cycloaddition with trimethylsilyldiazomethane afforded a spirane where the C10 carbon of the macrolide skeleton had become a quaternary spirocarbon. Antibacterial *in vitro* data for a selected group of compounds against strains of respiratory pathogens *S. pneumoniae* and *S. aureus* are reported. Most of the compounds tested showed improved activities over CLA as a reference compound against efflux resistant *S. pneumoniae* as well as against efflux and inducibly resistant strains of *S. aureus.*

Keywords: Antibacterials, *in vitro* MIC data, syntheses, C10-aminomethyl-3-ketolides, NCS acetoxylation, allylic substitutions, stereoselectivity.

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1. Introduction

Erythromycin A is a major antibiotic macrolide. The macrolide structure has been subjected to a number of chemical modifications over the years to improve its physicochemical properties and antibacterial profiles. All positions in the macrolactone scaffold, except for the 10-position, had been chemically modified when our work on chemical modifications was started.[1,2] The low chemical reactivity of the C10-methyl group may in part be ascribed to its position in an electronically non-activated site in the macrocyclic ring. Some modifications of the 10-position, however, had been effected by genetic engineering techniques that afforded 10-desmethylerythromycin A, 10-ethyl and 10-hydroxy macrolides.[3,4] Quaternization at C10 had been effected by intramolecular 1,3-dipolar cycloaddition in a C10-C11 unsaturated macrolide, the product being a tricyclic derivative.[5] The generically produced macrolides possessed moderate antibacterial activity including the 10-desmethyl analogue. Recently, considerable efforts have been reported on development of methods for total syntheses of desmethyl macrolide antibiotics including 4,8,10-tridesmethyl telithromycin and 4,10-didesmethyl telithromycin.[6,7,8] In general, it appears that the synthetic 10-desmethyl macrolides were inferior to telithromycin as antibacterial agents.[6] We were interested in structural modifications which could lead to an increase in the size of the 10-substituent. The substrate for the chemical transformation was to be a clarithromycin derivative where the 10-methyl group was to be chemically modified. Part of this work has been presented in preliminary publications.[1,2] The target compounds were 3-ketolides, modified as cyclic 11,12-carbamate 6-methoxyerythromycin derivatives where the 11,12-cyclic carbamate linkage occupies the positions of the two hydroxyl groups in erythromycin A.[9,10]

From work on the development of erythromycin drugs it appears that side-chains in positions other than the macrolide 10-position have variable and significant influence on the activity of the ketolides. A reference is made to the drug telithromycin which has aza-hetaryls spaced from the lactone ring structure via short alkyl or allyl linkages attached to the carbamate nitrogen.[11-13] In our work the emphasis has been on functionalization of the 10-methyl group for making available products which may serve as intermediates for subsequent introduction of pharmacophoric side-chains extending from the 10-position.

In the macrolide scaffold, the 10-position is expected to be only weakly polarized. Consequently, the C10-methyl group may show relatively low reactivity towards chemical transformations. We wanted to increase the polarizability of the C10-methyl group by working with unsaturated intermediates, in particular with C10-C11 double bond structures. In this manner allylic properties will be conferred onto the methyl group.

2. Results and discussion

The target molecules are 3-ketolides with a modified methyl substituent in the C10-position, strucures **A** in Fig. 1. Ketolides are available from erythromycin macrolides by selective removal of the O^3-sugar (L-cladinose moiety) and oxidation of the resultant hydroxyl compound to a corresponding oxo compound. Ketolides in general show relatively good acid stability and antibacterial potency against bacteria which may be resistant to macrolides.[9]

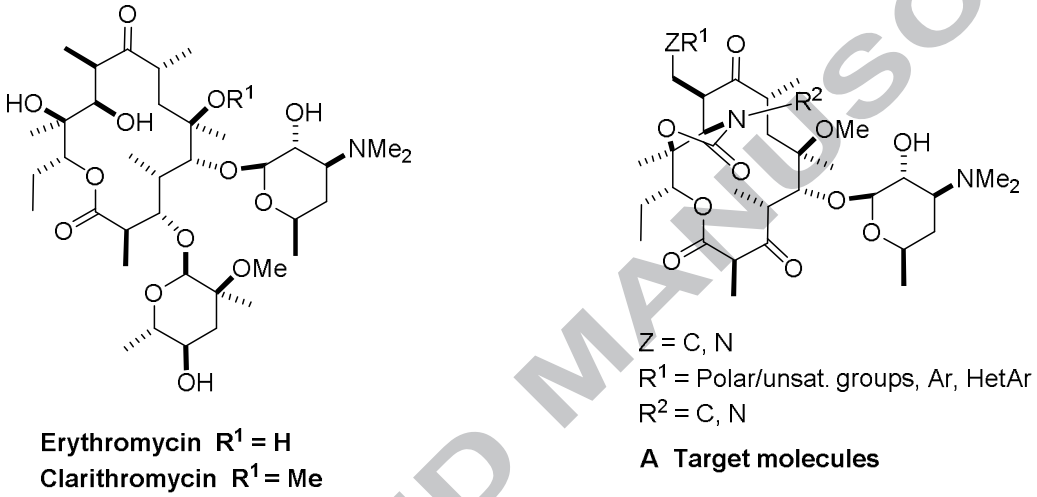
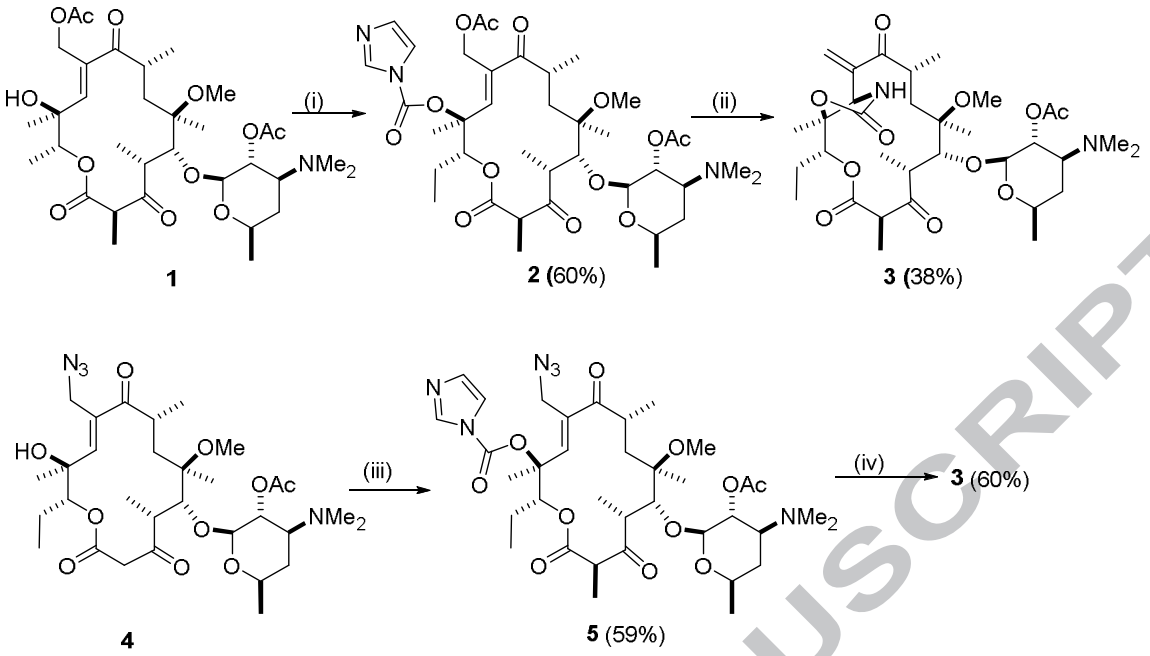


Fig. 1 Structural relationships between clarithromycin and targeted 10-substituted 3-ketolides.

Reactions leading to transformations of the C10-methyl group in the erythromycin scaffold are shown in Scheme 1. In clarithromycin, the O^6-methyl analogue of erythromycin, the methoxy function may be regarded as a protected 6-hydroxy group. Various alkyl, aryl or acyl groups attached to the oxygen would be eligible for the protecting function in general provided these groups can be removed after the synthetic operations have been completed. Protection of the 6-OH group in erythromycin is necessary to avoid chemical interference in the series of transformations to be carried out.

The 9-methylene ketolide **3** was the substrate for most of the chemical transformations (Scheme 1). It is available from clarithromycin after transformations we have in part previously reported.[1]



Scheme 1. Reagents and conditions; (i) CDI, NaH, 0 ^{o}C to rt 17 h; (ii) NH_3(aq), MeCN, THF, rt, 48 h; (iii) (a) NaH, THF, 0 ^{o}C; (b) CDI, rt, 17 h; (iv) NH_3(aq), MeCN, THF, rt, 17 h.

The allylic acetate **1** was reacted with carbonyldiimidazole (CDI) in the presence of sodium hydride (NaH) in THF. The reaction occurs at the 12-hydroxyl group to afford the 12-acylimidazolyl intermediate **2** in 60% yield. Treatment of the latter with aqueous ammonia in acetonitrile led to a two-step transformation, presumably by initial formation of a corresponding urethane followed by cyclization in a stereoselective manner by analogy to the methodology developed by Baker.[14]

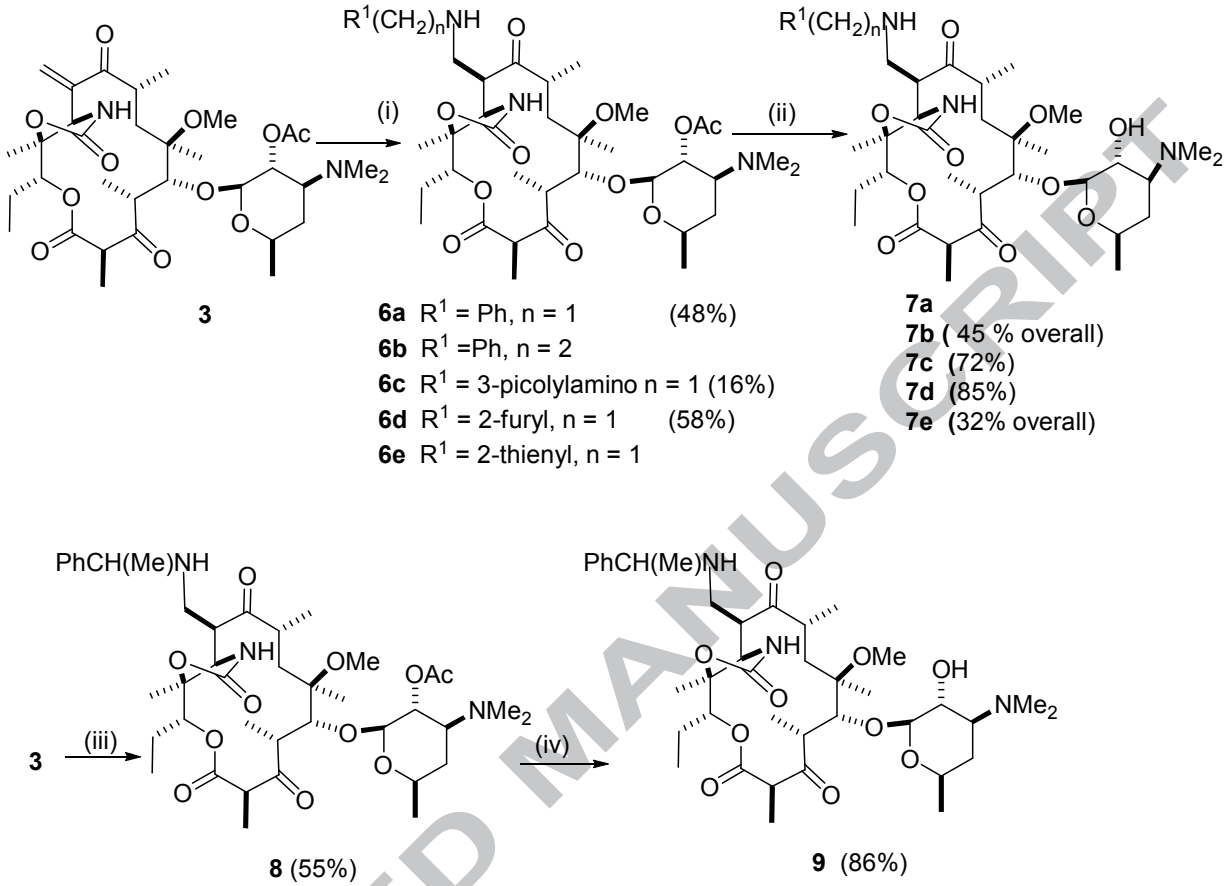
In a similar manner, the allylic azide **4** can be an intermediate in the preparation of compound **3.** We have previously reported a synthesis of the azide **4** involving a cyanide substitution of the allylic acetate function in compound **1**.[1] Treatment of the sodium salt of azide **4** with carbonyldiimidazole afforded the 12-acylimidazolyl azide **5.** The cyanide function was expelled when the cyanide **5** was cyclized in a reaction with ammonia to afford the target compound **3**.

The stereochemistry in the cyclic carbamate formation in the applied protocol was originally established by NMR spectroscopy.[14] Subsequently, this methodology has gained wide application and in some cases the stereochemical outcome has been verified by single crystal X-ray analysis.[6,10, 15] In cyclizations shown in Scheme 1, however, the internal Michael addition reaction resulted in acetate or cyanide eliminations rather than protonation at C-10. The product was a novel 10-methylene derivative **3**.

For comparison, C12-vinyl ketolides have been prepared from the natural C12-methyl group in the erythromycin core. The C12-vinyl macrolides are described as active antibacterial agents against respiratory pathogens.[16]

Dipolar addition between amines and 10-methylene substrates has been used to achieve C-N bond formation. The C10-hinged methylene group in structure **3** is part of an electron deficient α,β-unsaturated carbonyl system which will react with heteroatom nucleophiles. In Scheme 2, amine addition reactions in refluxing THF afford C10-aminomethyl products **6**. Benzylamine was a good nucleophile in the conjugated amine addition to afford **6a**. Phenethylamine reacted in the same manner to yield **6b**. Pyridine-3-amine has a π-deficient system with deactivation of the amino group; the yield of **6c** was 16%. The furyl-2-amine and the thienyl-2-amine are π-excessive systems and afforded the furyl derivative **6d** and the thienyl derivative **6e** in high yields. The ester group in compounds **6** was cleaved by methanolysis at room temperature to provide the corresponding hydroxy compounds **7**. Only one stereoisomer at the epimeric C10-carbon was observed. The product was identified by its diagnostic signal in ^{1}H NMR from H-11 which resonated as a singlet at ca 3.9 ppm (3.82, 3.91 and 3 x 3.93 ppm) and was therefore assigned the (*R*)-configuration) **7**.

In the 10-methylene substrate **3**, which has no vicinal H-10, the H-11 proton resonated as a singlet at 3.87 ppm. In the analogous methylene compounds **21** and **23** (Scheme 5), H-11 resonated as a singlet at 3.70 ppm and 3.82 ppm, respectively. In closely related clarithromycin derivatives, it has been observed that the vicinal H-11 proton in the (10*S*)-isomer resonated as a doublet, but as a singlet in the (10*R*)-isomer.[14] The stereochemistry at C10 arising from adduct formation of the 10-methylene substrate **3** and the added nucleophile will depend on structural features as well as on experimental conditions. Epimerization changes may favor formation of either the (10*R*)- or the (10*S*)-epimer.[10,15] The natural (10*R*)-isomer is thermodynamically more stable than its (10*S*)-isomer. The same stereochemical course of the reaction is assumed in the formation of the other members in the amine family of adducts **6**. The reactivity will also be affected by the nucleophilicity of the amino nitrogen. Thus aniline failed to form adducts under the conditions used with alkylamines. Non-bonded interactions are also important. With secondary *N*-methylbenzylamine, adduct formation failed. Shifting the methyl group to the α-benzyl carbon, however, gave an active amine for adduct formation affording the product **8** in 55% yield. The target compound **9** was obtained after deprotection of the adduct **8** in methanol in high yield.

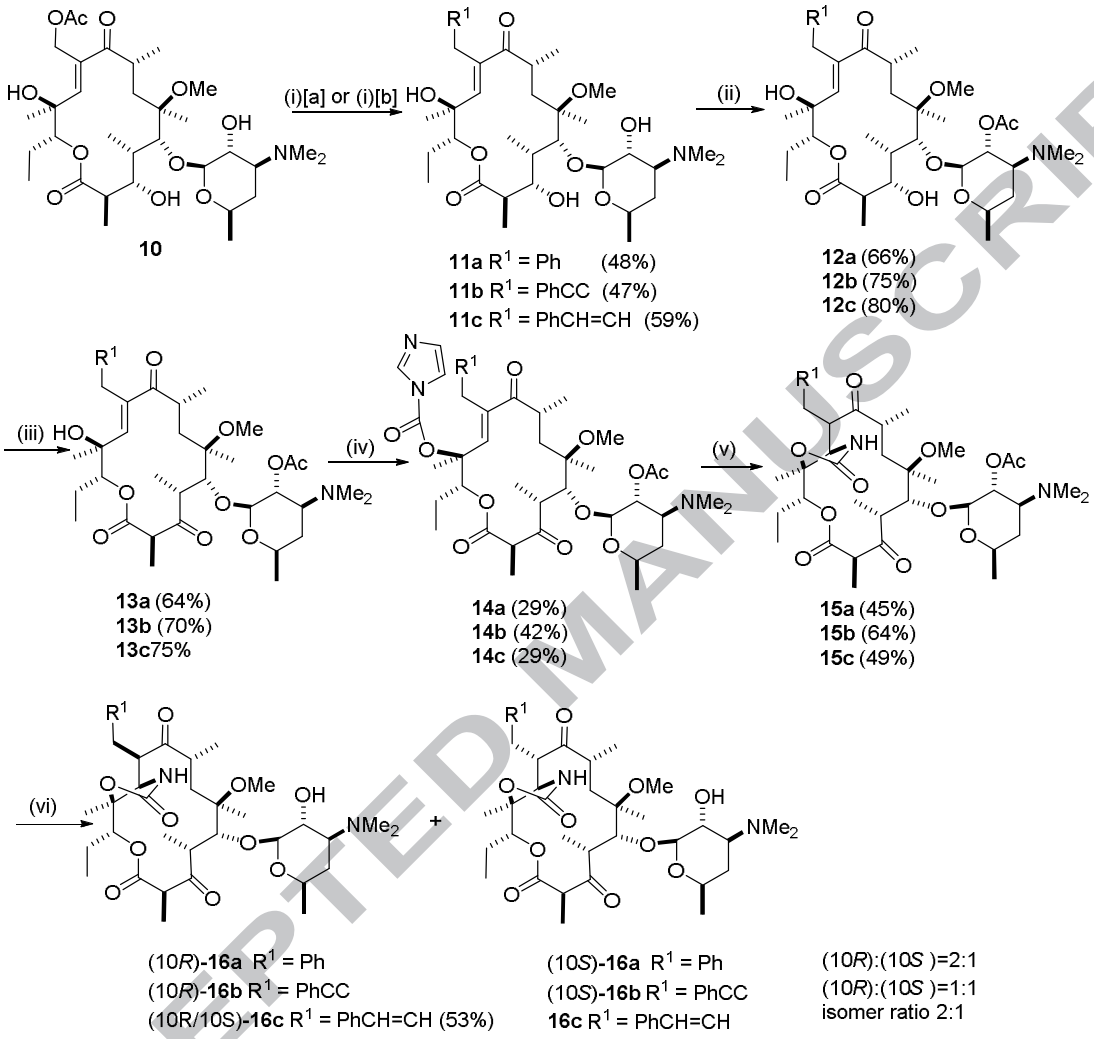


Scheme 2. Reagents and conditions: (i) $R^1(CH_2)_nNH_2$, THF, reflux, 48 h; (ii) MeOH, rt, o.n.; (iii) $PhCH(Me)NH_2$, THF, reflux, 60 h; (iv); MeOH, rt, o.n.

The allylic acetate **10** was the substrate for introduction of unsaturated functions into the C10-methyl group. Palladium mediated transcoupling reactions under Stille conditions with the acetate **10** produced carbylation (Scheme 3). The tin reagent delivered a phenyl, phenylethynyl or a phenylethenyl group. Either *N*-methylpyrrolidone (NMP) or DMF was the solvent. Transfers to the acetoxy carbon afford substitution products **12**. The Stille methodology is highly compatible with our macrolides. If members of the products were to be selected for clinical studies, the methodology for transcoupling may be adapted to the Suzuki conditions because organoboranes are generally considered to be acceptable reagents for compounds prepared for clinical studies.

The 2´-hydroxy group in transcoupled products **11** (Scheme 3) was protected as acetate **12** by reactions with acetic anhydride and trimethylamine. Chemoselective oxidation under the Dess-Martin periodinane (DMP) conditions afforded the 3-ketolides **13**. For cyclic carbamate formation (**15**), carbonyldiimidazole (CDI), was

used under basic conditions. Treatment of the initial product **14** with aqueous ammonia afforded the cyclic carbamates **15**. Subsequent deacetylation of the product in methanol solution at room temperature yielded target compound **16**.

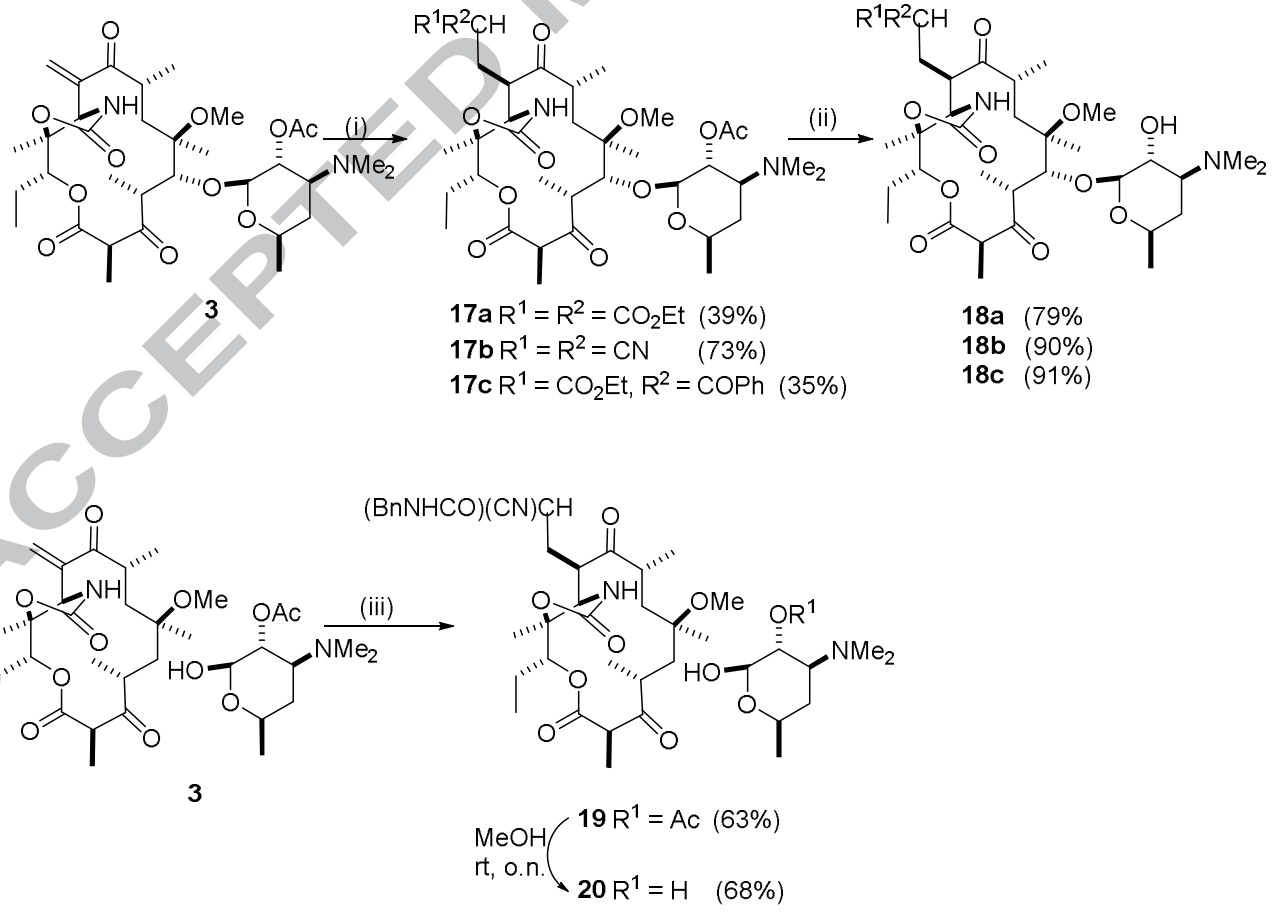


Scheme 3. Reagents and conditions (i) (a) Bu_3SnPh, $Pd_2dba_3.CHCl_3$, NMP, 90 °C, o.n., (b) Bu_3SnR^1, $Pd_2dba_3.CHCl_3$, DMF, 80-90 °C, o.n.; (ii) Ac_2O, NEt_3, CH_2Cl_2, rt, 17 h; (iii) DMP, CH_2Cl_2, rt, 3 h; (iv) CDI, NaH, THF, 0 °C, 20 h; (v) NH_3(aq), MeCN, THF, rt, 48 h; (vi) MeOH, rt, 14 h.

The product **16a** was a mixture of the two C10-epimers. Separation or partial separation could be effected by flash chromatography. The minor isomer in ^{1}H NMR showed H-11 as a doublet at 3.76-3.80 ppm. The ^{1}H NMR signal for H-11 signal for the major isomer was not resolved due to overlap with other signals (3.67-3.74; 3.72-3.78 ppm). Based on the doublet in the minor product this isomer is assigned the (10*S*)-configuration. The major isomer has the (10*R*)-configuration. The isomer distribution in **16b** was close to 1:1. The

first eluted epimer on chromatography showed the H-11 signal as a singlet at 3.97 ppm and therefore this product was assigned the (10*R*)-configuration. The isomer distribution in **16c** was also about 1:1, but separation of the epimers was not achieved.

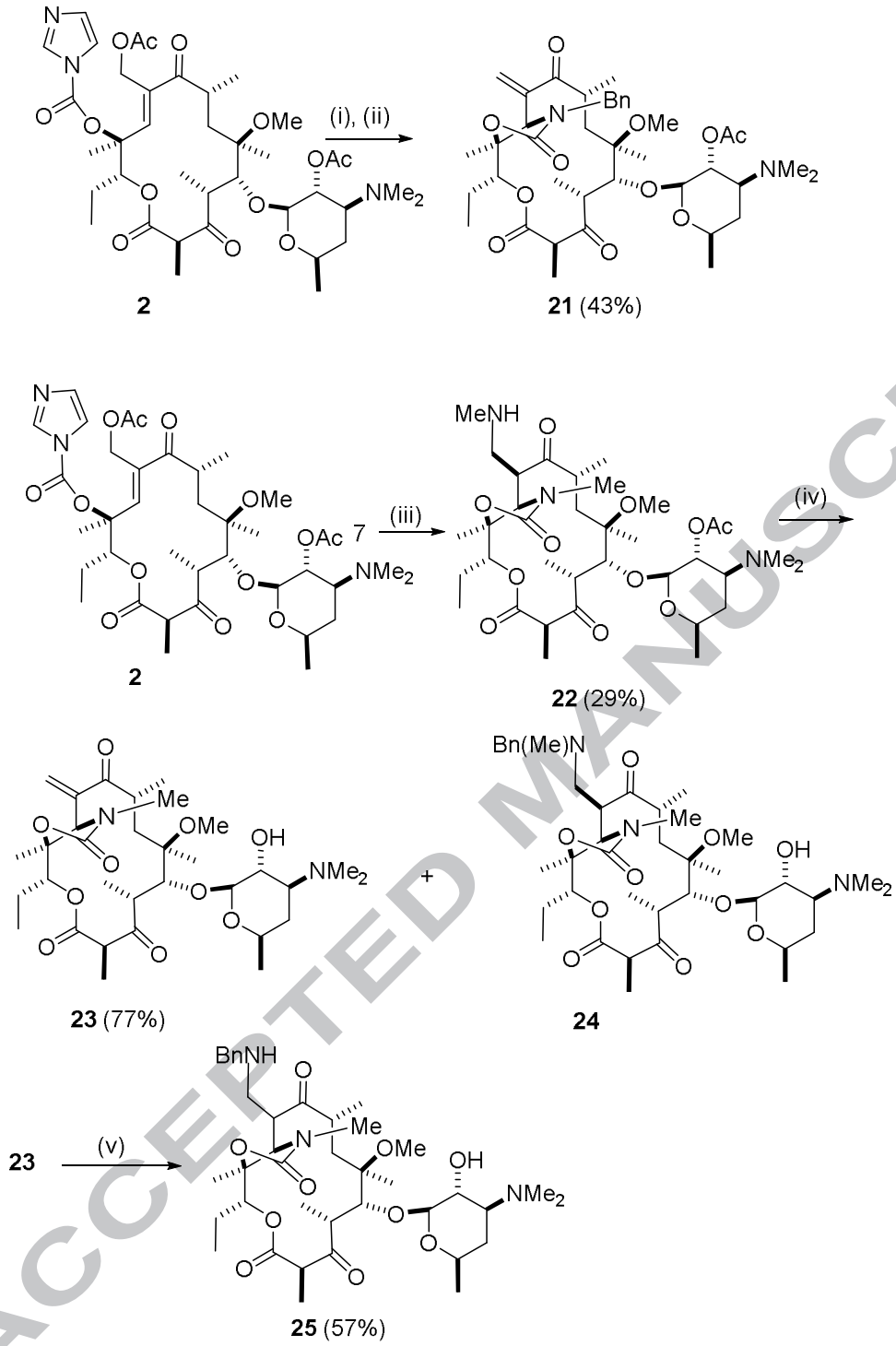
Adduct formation using stabilized carbanion chemistry with sodium salts of diethyl malonate, malononitrile or ethyl 3-oxo-3-phenylpropanoate afforded the products **17** in Scheme 4. The substrate was the cyclic 11,12-carbamate **3**. Acetyl deprotection of the adduct **17** by methanolysis yielded **18**. Adduct formation using *N*-benzyl-2-amino-2-cyanoacetamide proceeded in the same manner to afford adduct **19**. Subsequent methanolysis furnished the target compound **20**. The stereochemistry at the epimeric C10-center is uncertain. The one-proton signal in the region 3.8-4.3 ppm appeared as a doublet with coupling constant close to 7 Hz. The coupling constant is higher than reported for a (10*S*)-isomer. In these reactions strongly basic conditions are used which may well lead to epimerizations in favor of the (10*S*)-epimer. Alternatively, the highly polar substituents may have changed the conformational preferences in the products which may affect the ^{1}H NMR signals. The structures of the products have tentatively been drawn in the (10*R*)-epimeric form.



Scheme 4. Reagents and conditions: (i) $R^1CH_2R^2$, NaH, THF, 0 °C to rt; (ii) MeOH, rt, o.n., $BnNHCOCH_2CN$, NaH, THF, 0 °C to rt.

In Scheme 1 it was shown that formation of the urethane ring in compound **3** from the substrate 10-acetoxymethyl-2*O*´-acetyl-12*O*-acylimidazolyl-10,11-anhydro-10-desmethyl-O^6-methyl-3-oxodescladinosylerythromycin **A** was achieved in 38% yield using aqueous ammonia. The corresponding reaction with benzylamine as a nucleophilic primary amine afforded the cyclic urethane **21** in 43% yield (Scheme 5). Another urethane **23** in Scheme 5 has a 10-methylene substituent. Neither compound has a proton at the C10-carbon. Accordingly, H-11 in the ^{1}H NMR resonated as singlets at 3.70 and 3.82 ppm, respectively. In addition reactions with the smaller methylamine molecule, the reaction proceeded largely past cyclization. A second step involved conjugate addition and thereby formation of the diamine **22** as the major product.

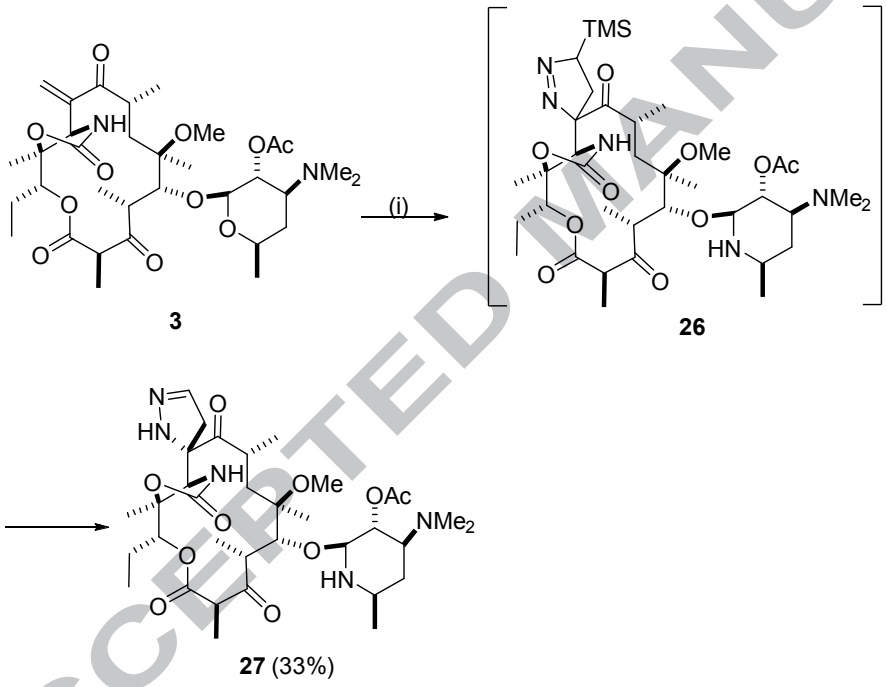
Preparation of the 10-*N*-(methylbenzylamino)methyl amine **23** (Scheme 5) failed in an attempted conjugate addition reaction between the methylene substrate **23** and benzylmethylamine. By a different approach, a synthetic path was developed towards reductive *N*-benzylation using benzaldehyde and sodium tri(acetoxy)borate. The major product from the diamine substrate **22** was formed by elimination of methylamine to afford the 10-methylene derivative **22** (77%). The minor product was the tertiary amine **24** (10%). In the ^{1}H NMR spectra the products **22**, **24** and **25** contained H-11 as a singlet at 3.7 ppm, 2x3.82 ppm, respectively. They have been assigned the (10*R*)-epimer configuration. Conjugated addition of benzylamine to the methylene derivative **23** afforded the diamino adduct **25** in 57% yield after reflux with excess of benzylamine in THF for 60 h. The proton NMR signal for H-11 resonated as a doublet at 4.01 ppm with a coupling constant J = 6.1 Hz. Epimerization to the (10*S*)-configuration may have occurred.



Scheme 5. Reagents and conditions: (i) $BnNH_2$, THF, MeCN, rt, 40 h; (ii) MeOH, rt, 24 h; (iii) $MeNH_2$ (40%), THF, MeCN, rt, 60 h; (iv) PhCHO, $NaB(OAc)_3$, THF, rt, 22 h; (v) (v) $BnNH_2$, THF, reflux, 60 h; (vi) $TMSCHN_2$, CH_2Cl_2, 0 ^oC-rt, 72 h.

The C10-carbon can be transformed into a quaternary spirocarbon by [3+2] by dipolar cycloaddition reactions. In the case presented in Scheme 6 the reagent is trimethylsilyldiazomethane. The reaction with substrate **3** was effected in dichloromethane at 0 ^oC. The reaction was slow. After 48 hours a product with

expected properties was isolated in 33% yield. With electron deficient alkenes the nucleophilic diazoalkene adds to the more electrophilic β-carbon of the alkene. The initially formed 3*H*-4,5-dihydropyrazole is unstable and is isomerized to 1*H*-4,5-dihydropyrazole. The slow cycloaddition reactions may be caused by significant non-bonded interactions from the β-substituents of the macrolide core. Therefore the cycloaddition is postulated to be stereoselective yielding spirane **26** as an intermediate. A subsequent elimination reaction affords the final product **27**. H-11 in **27** has no vicinal protons for coupling and resonates as a singlet at 3.56 ppm. Only one singlet is seen for H-11 in support of an epimerically pure product. Two NH signals are present as singlets at 5.50 ppm and 6.33 ppm in accordance with structure **27**. The product is tentatively assigned structure **27**.

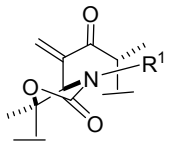


Scheme 6. Reagents and conditions: (i) $TMSCHN_2$, CH_2Cl_2, 0 ^oC-rt, 72 h.

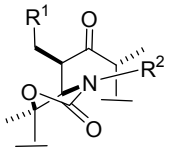
3. Antibacterial activity

Selected ketolides have been tested for *in vitro* activity against strains of respiratory pathogens from *Streptococcus pneumonia* and *Staphylococcus aureus*. Clarithromycin was the reference standard macrolide. The data obtained are shown in Table 1. The compounds tested have been arranged into groups according to their structures and assigned an entry number. Square brackets show the number of these compounds in the synthetic schemes.

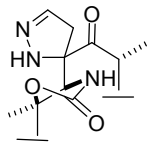
Table 1. In vitro activity of selected C10-substituted ketolides against different strains of the respiratory pathogens *S. pneumoniae* and *S. aureus.* Minimum inhibitory concentration (MIC) value are given in micrograms per milliliter.



Entry
(1) [**3**] R^1 = H
(2) [**21**] R^1 = CH_2Ph



Entry
(3) [**6a**] R^1 = $NHCH_2Ph$, R^2 = H
(4) [**6c**] R^1 = $NHCH_2$(pyridin-3-yl, R^2 = H
(5) [**25**] R^1 = $NHCH_2Ph$, R^2 = Me
(6) [**12a**] R^1 = Ph, R^2 = H
(7) [**17a**] R^1 = $CH(CO_2Et)_2$, R^2 = H



Entry
(8) [**27**]

Entry	*S. pneumoniae*				*S. aureus*			
	ATTC4961	BAA1402	3914	BAA1407	ATCC29213	BAA976	BAA977	ND048910
	M (mef)	MLS	MLS (mef+erm)		M (mef)	iMLS (erm)	cMLS (erm)	
CLA	0.015	2	>16	>8	0.125	64	>64	>64
(1)	1	2	128	>64	32	64	64	>64
(2)	<0.07	0.125	2	64	1	2	2	64
(3)	<0.007	<0.007	2	64	0.25	0.5	1	>64
(4)	0.015	0.06	4	64	1	2	4	>64
(5)	0.25	1	<128	64	16	32	16	>64
(6)	0.25	0.5	64	>64	16	16	32	>64
(7)	0.06	0.125	4	128	0.25	0.5	0.5	>128
(8)	0.06	0.25	16	64	2	2	2	>128

The *in vitro* antibacterial activity values in Table 1 are minimum inhibitory concentrations (MIC) in (μg/mL) as determined by the broth microdilution method.[17] The parent compound in this investigation was the 10-methylene derivative in entry (1). The MIC values show that the parent compound (1) was less active than reference compound clarithromycin. Activity was markedly increased for the more lipophilic *N*-carbamoyl benzylated homologue (2). The entry group (3) – (7) shows compounds where the C10-substituent has been changed from the unsaturation of the methylene group to a saturated and substituted methyl group. The benzylamino derivative in entry (3) was one of the most active compounds. Activity was lower after methylation of its carbamoyl nitrogen, entry (5). Substitution of the benzyl group in (3) with the corresponding basic pyridine moiety,

as in entry (4), had little effect on MIC values. The highly polarized carbonyl derivative, the diester in entry (6) has a similar activity profile as clarithromycin. Even the 10-spiro compound in entry (8), had MIC values which did not differ significantly from the figures for clarithromycin.

In summary, the activity values against *S. pneumoniae* ATTC as well as against *S. aureus* ATCC 29213 are similar or slightly inferior to the values for the reference agent CLA. Most of the compounds, however, showed improved activities against efflux resistant *S. pneumonia* BAA1402 M(mef) as well as against inducibly resistant strains of *S. aureus* BAA976 M(mef), and some improvement towards BAA977 iMLS(erm).

The remaining target compounds in the synthetic schemes have not been tabulated because the MIC values were similar to the values given in the Table 1.

4. Conclusion

In conclusion, we describe synthetic methodology for preparation of ketolides which are substituted regioselectively in the C10-methyl group. In most cases the substituted methyl group is generated with the same stereochemistry as in the original substrate. The clarithromycin derived substrate 10,11-anhydro-O^6-methyl-descladinosylerythromycin was used in the chemical preparations. Both N-C and C-C bond formations are exclusively at the exocyclic methylene carbon in a C11-C12-cyclic carbamate which is generated in reaction with carbonyldiimidazole and ammonia or primary amines. Dipolar conjugate additions were used to achieve stereoselective aminations. Carbon substituents were introduced by Pd-catalyzed cross coupling reactions or by stabilized anionic carbon nucleophiles. Dipolar cycloaddition reactions will afford adducts where the C10-carbon becomes the quaternary carbon in the respective spirane. Highly pharmacophoric functions as described in literature,[11-13] can be introduced at the C10-position by chemical methodology readily adapted from the present work.

The *in vitro* MIC values against strains of the respiratory pathogens *S. pneumoniae* and *S. aureus* showed antibacterial potencies and profiles are close to the values of clarithromycin. Together with improved activities against efflux resistent S. pneumonia BAA1402 M(mef) as well as against inducibly resistant strains of *S. aureus* BAA976 M(mef) and some improvement towards BAA977 iMLS(erm).

5. Experimental

^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO at 300 MHz with Bruker DPX 300. ^{13}C NMR spectra were recorded at 75 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 represented as *m*/*z* (% relative intensity). Electrospray spectra were obtained with a Micromass QTOF 2 W spectrometer with electrospray ionization quadrupole time of flight. Melting points are uncorrected.

The reactions were performed under an inert atmosphere except for the *N*-oxidation of the macrolides. 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.

In vitro antibacterial activities: The *in vitro* minimal inhibitory concentrations (MICs) in μg/mL have been determined by standard broth microdilution methodology.[17]

10-Acetoxymethyl-2´*O*-acetyl-10,11-anhydro-10-desmethyl-*O*^{6}-methyl-3-oxo-descladinosylerythromycin A (1)

10-Acetoxymethyl-2´*O*-acetyl-10,11-anhydro-10-desmethyl-*O*^{6}-methyl-descladinosylerythromycin A[1] (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 3 h before the mixture was concentrated under reduced pressure. The residual material was dissolved in ethyl acetate, the solution washed with dilute KOH (pH adjusted to 10-11), with brine and dried ($MgSO_4$). The crude product was a white solid with mp 172-174 ^{o}C; yield 0.93 g (87%). Spectroscopic and spectrometric data are available.[1]

10-Acetoxymethyl-2´*O*-acetyl-12*O*-acylimidazolyl-10,11-anhydro-10-desmethyl-*O*^{6}-methyl-3-oxodescladinosylerythromycin A (2)

10-Acetoxymethyl-2´*O*-acetyl-10,11-anhydro-10-desmethyl-*O*^{6}-methyl-3-oxodescladinosylerythromycin A (**1**) (0.333 g, 0.496 mmol) was dissolved in THF (4 mL) and the solution cooled to 0 ^{o}C before NaH (0.036 g, 1.49 mmol) was added. A solution of carbonyldiimidazole (0.221 g, 1.4 mmol) in THF (2 mL) was added dropwise over 5 min to the reaction mixture which was stirred for 17 h, cooled to 0 ^{o}C and the reaction quenched with aqueous sodium bicarbonate. The product was extracted into ethyl acetate, washed with water (pH 10-11), with brine and dried (Na_2SO_4). The crude product was a white solid; yield 0.227 g (60%). The crude product was pure according to NMR and was

used as such in the next step without further purification. Spectroscopic and spectrometric data are available.[1]

2´*O*-Acetyl-11*N*,12*O*-cyclocarbamate-11-deshydroxy-10-desmethyl-*O*^{6}-methyl-10-methylene-3-oxodescladinosylerythromycin A (3)

Ammonia(aq) (0.2 mL) was added to a solution of 10-acetoxymethyl-2´*O*-acetyl-12*O*-acylimidazolyl-10,11-anhydro-10-desmethyl-*O*^{6}-methyl-3-oxodescladinosylerythromycin A (**2**) (0.127 g, 0.166 mmol) in acetonitrile (2 mL) and THF (0.2 mL). The reaction mixture was stirred at room temperature for 24 h and concentrated under reduced pressure. The residual material was dissolved in ethyl acetate, the solution washed with dilute 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. Elution was with acetone:hexane, initial ratio 2:1, and then 1:1.The product was a white solid with mp 142-145 ^oC; yield 0.042 g (38%). Spectroscopic and spectrometric data are available.[1]

2´O-Acetyl-12*O*-acylimidazolyl-10,11-anhydro-10-azidomethyl-10-desmethyl-*O*^{6}-methyl-3-oxodescladinosylerythromycin A (5).

NaH (0.006 g, 0.200 mmol) was added to a solution of 2´O-acetyl-10,11-anhydro-10-azidomethyl-10-desmethyl-*O*^{6}-methyl-3-oxodescladinosylerythromycin A (**4**)[1] (0.044 g, 0.067 mmol) in THF (2 mL) at 0 ^oC. A solution of carbonyldiimidazole (CDI) in THF (1 mL) was added dropwise over 5 min. The resultant solution was stirred at room temperature for 17 h, cooled to 0^o C before being quenched with sodium bicarbonate, extracted with ethyl acetate, the organic extracts washed with water (pH 10-11), with brine and dried ($MgSO_4$). The crude product was a white solid, yield 0.050 g (59%). HRMS [Na^+]: M 769.3760. Calc. for $C_{36}H_{54}N_6O_{11}$: 769.3742. The crude product was used in the subsequent step without further purification.

2´O-Acetyl-11*N*,12*O*-cyclocarbamate-11-deshydroxy-10-desmethyl-*O*^{6}-methyl-10-methylen-3-oxodescladinosylerythromycin A (3) available from the azide 4.[1]

Ammonia(aq) (0.2 mL) was added to a solution of 2´*O*-acetyl-12*O*-acylimidazolyl-10,11-anhydro-10-azidomethyl-10-desmethyl-*O*^{6}-methyl-3-oxodescladinosylerythromycin A (**4**)[1] (0.07 mmol) in acetonitrile (2 mL) and THF (0.2 mL). The mixture was 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 [Na^+]: M 653.4. Spectra were the same as spectra for the originally produced compound **8**.[1]

10-Benzylaminometyl-10*N*,12*O*-cyclocarbamate-10-deshydroxy-10-desmethyl-*O*^{6}-methyl-3-oxodescladinosylerythromycin A (7a).[1]

10-(2-Phenylethaneaminomethyl)-10,12-cyclocarbamate-10-deshydroxy-10-desmethyl-*O*^{6}-methyl-3-oxodescladinosylerythromycin A (7b).

A solution of phenethylamine (0.093 mL, 0.73 mmol) and 2'O-acetyl- 11,12-cyclocarbamate-11-deshydroxy-10-desmethyl-*O*^{6}-methyl-10-methylen-3-oxodescladinosylerythromycin A (**3**) (0.12 g, 0.18 mmol) in THF (15 mL) was heated under reflux for 24 h. More phenethylamine (0.090 mL, 0.71 mmol) was added 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, the solution dried ($MgSO_4$) and the solvent distilled off. The residual product **6b** was a yellow oil. The adduct **6b** was dissolved in methanol (5 mL) and the solution stirred at room temperature for 24 h. The solvent was evaporated, and the product subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH:NH_3 90:10:2. Flash chromatography was repeated using CH_2Cl_2:MeOH:NH_3(aq) 92:6:1. The title compound **7b** was a white solid; yield 0.06 g (45%). HRMS (Electrospray, H^+): M 732.4448. Calcd. for $C_{39}H_{62}N_3O_{10}$: M 732.4435. ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.88 (3H, t, J = 7.3 Hz, CH_3), 1.07 (3H, d, J = 7.0 Hz, CH_3), l.21-1.31 (1-OH, m), 1.39 (3H, d, J = 6.8 Hz, CH_3), 1.48 (3H, s, CH_3), 1.51-1.61 (2H, m), 1.61-1.77 (2H, m), 1.86-1.96 (1H, m), 2.28 (6H, s, $N(CH_3)_2$), 2.42-2.52 (1H, m), 2.55-2.62 (1H, m), 2.70 (3H, s, OCH_3), 2.70-2.88 (5H, m), 2.90-2.99 (3H, m), 3.15-3.20 (1H, m), 3.51-3.58 (2H, m), 3.80 (lH, q, J=6.8 Hz), 3.93 (1H, s), 4.17 (lH, d, J=7.8 Hz), 4.34, (1H, d, J = 7.3 Hz), 5.07 (lH, dd, J = 10.0, 2.6 Hz), 5.60 (1H, s, NH), 7.14-7.22 (3H, m, Ar), 7.27-7.31 (2H, m, Ar); ^{13}C NMR (75 MHz; $CDC1_3$): δ 10.6 (CH_3), 13.8 (CH_3), 14.4 (CH_3), 16.2 (CH_3), 17.6 (CH_3), 19.5 (6-CH_3), 21.2 (CH_3), 22.6, 28.2, 36.0, 39.S, 40.2 ($N(CH_3)_2$), 44.3, 44.5, 47.7, 47.8, 49.2, 51.2, 51.S, 57.S, 65.9, 69.S, 70.3, 76.3, 78.0, 78.6, 83.9, 103.6, 126.2, 128.4, l28.7, 139.7(C), 157.8 (C), 169.3(C), 204.6 (C), 217.5 (C).

10-(3-Picolylaminomethyl)-11*N*,12*O*-cyclocarbamate-11-deshydroxy- 10-desmethy1-*O*^{6}- methyl-3-oxodescladinosylerythromycin A (7c)

A solution of 3-picolylamine (0.127 g, 1.17 mmol) and 2'*O*-acetyl- 11,12-cyclocarbamate-11-deshydroxy-10-desmethyl-*O*^{6}-methyl-10-methylen-3-oxo-

descladinosylerythromycin A **(3)** (0.192 g, 0.294 mmol) in THF (18 mL) was heated at reflux for 24 h. Another portion of 3-picolylamine (0.127 g, 1.17 mmol) was added 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 aq. $NaHCO_3$, with brine and dried ($MgSO_4$). The solution was evaporated and the residual material was subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH:NH_3(aq) 90:4:1. The product **6c** was a white solid 0.035 (16%). The product **6c** (0.02 g, 0.026 mmol) was stirred in methanol (1.5 mL) at room temperature for 24 h, the solvent evaporated, and the product subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH:NH_3(aq) 90:5:1. The title compound **7c** was a white solid; yield 0.013 g (72%). HRMS (Electrospray, H^+): M 719.4236. Calcd for $C_{37}H_{58}N_4O_{10}$: M 719.4231. ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.85 (3H, t, *J* = 7.3 Hz, CH_3), 1.15 (3H, d, *J* = 7.0 Hz, CH_3), l.21-1.32 (1OH, m), 1.37 (3H, d, *J* = 6.8 Hz, CH_3), 1.46 (3H, s, CH3), 1.51-1.59 (2H, m), 1.60-1.69 (2H, m), 1.86-1.94 (1H, m), 2.25 (6H, s, $N(CH_3)_2$, 2.30-2.52 (2H, m), 2.61 (3H, s, 6-OCH_3), 2.88-3.03 (SH, m), 3.06-3.19 (2H, m), 3.50-3.56 (2H, m), 3.70 (1H, brs) 3.77 (1H, q, *J* = 6.8 Hz), 3.82 (1H, s), 4.15 (1H, d, *J* = 7.8 Hz), 4.30 (1H, d, *J* = 7.3 Hz), 5.07-5.08 (IH, m), 5.63 (1H, s, NH), 7.19-7.25 (IH, m, Ar), 7.55-7.59 (1H, m, Ar), 8.45-8.49 (2H, m, Ar); ^{13}C NMR (75 MHz; $CDCl_3$): δ 10.5 (CH_3), 13.9 (CH_3), 14.4 (CH_3), 163 (CH_3), 17.8 (CH_3), 19.5 (CH_3), 21.1 (CH_3), 22.6, 28.1, 39.6, 40.2, ($N(CH_3)_2$), 44.4, 47.6, 47.8, 49.2, 51.2, 51.9, 57.5, 65.8, 69.5, 70.2, 76.3, 77.2, 78.0, 78.7, 83.8, 103.6, 123.3, 134.9 (C), 135.7, 148.6, 149.5, 157.7 (C), 169.3(C), 204.5 (C), 216.9 (C).

10-(Furan-2-yl)methylamino)methyl)-11*N*,12*O*-cyclocarbamate-11-deshydroxy-10-desmethyl-*O*^{6}-methyl-3-oxo-descladinosylerythromycin A (7d)

A solution of (furan-2-yl)methanamine (0.09 mL, 0.92 mmol) and 2'*O*-acetyl-11*N*-12*O*- cyclocarbamate-11-deshydroxy-10-desmethyl-*O*^{6}-methyl-10-methylen-3-oxo-descladinosylerythromycin A (**3**) (0.15 g, 0.23 mmol) was heated in THF (12 mL) at reflux for 28 h. More (furan-2-yl)methanamine (0.045 mL, 0.46 mmol) was added and the mixture was heated for another 30 h. The solution was concentrated at reduced pressure, and the residual material was extracted with ethyl acetate (3x15 mL), the organic solution washed with aqueous $NaHCO_3$, with brine and dried over ($MgSO_4$). The solvents were distilled off and the residual solid subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH:NH_3(aq) 100:10:2. The product **6d** was a white solid; yield 0.10 g (58%). The adduct **6d** (50 mg) was dissolved in methanol (2 mL) and stirred at room temperature for 24 h before the solvent was

evaporated, and the residual product was subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH:NH_3 92:8:2. The title compound **7d** was a white solid; yield 0.40 g (85%). HRMS (Electrospray, H^+): M 708.4078. Calcd for $C_{36}H_{58}N_3O_{11}$: M 708.4071. ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.86 (3H, t, *J* = 7.4 Hz, CH_3), 1.18-1.31 (14H, m), 1.37 (3H, d, *J* = 6.8), 1.49 (3H, s, CH_3), 1.57-1.70 (4H, m), 1.72-1.80 (1H, m), 1.85-1.95 (1H, m), 2.27 (6H, s, $N(CH_3)_2$), 2.40-2.50 (1H, m), 2.62 (3H, s), 3.00 (2H, s), 3.03-3.07 (1H, m), 3.17-3.20 (1H, m), 3.52-3.55 (1H, m), 3.79 (1H, q, *J* = 6.8 Hz), 3.87-3.90 (2H, m), 3.93 (1H, s), 4.15 (1H, d, *J* = 7.8 Hz), 4.32 (1H, d, *J* = 7.3 Hz), 5.06 (1H, dd, *J* = 10.0, 2.6 Hz), 5.60 (1H, brs), 6.85-6.83 (2H, m), 7.17 (1H, dd, *J* = 5.1, 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.6 (CH_3) , 13.9, (CH_3) 14.5 , 16.3 , 18.0 , 19.6 (CH_3), 21.2 (CH_3), 22.7, 28.3, 39.7, 40.3 (CH_3)x2, 44.4, 44.6, 47.3, 47.8, 49.1, 49.2, 51.3, 57.6, 66.0, 69.5, 70.3, 76.4, 78.1, 78.8, 84.0, 103.7, 124.5, 125.0, 126.7, 143.5 (C), 157.8 (C), 169.4 (C), 204.7 (C), 217.3 (C).

10-(Thiophen-2-yl)methylaminomethyl-11*N*,12*O*-cyclocarbamate-11-deshydroxy-10-desmethyl-0^6-methyl-3-oxodescladinosylerythromycin A (7e)

A solution of (thiophen-2-yl)methanamine (0.11 g, 0.97 mmol) and 2'*O*-acetyl-11*N*,12*O*- cyclocarbamate-11-deshydroxy-10-desmethyl-*O*^{6}-methyl-10-methylene-3-oxo-descladinosyl- erythromycin A (**3**) (0.16 g, 0.24 mmol) was heated in THF (12 mL) under reflux for 28 h. Another portion of (thiophen-2-yl)methanamine (0.10 g, 0.88 mmol) was added and the mixture was heated for another 30 h. The solution was concentrated at reduced pressure, the residual material extracted with ethyl acetate (3x15 mL), the solution washed with $NaHCO_3$, with brine and then dried over ($MgSO_4$). Finally the solvents were removed *in vacuo*. The residual solid **6e** was subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH:NH_3(aq) 90:10:2 to furnish **6e** as a white solid. The adduct **6e** was dissolved in methanol and the solution stirred (2 mL) for 24 h. The solvent was evaporated, and the product was subjected to flash chromatography on silica gel using actone:hexane 1.5:1. The title product **7e** was a white solid; yield 0.06 g (32%). HRMS: (Electrospray, H^+): M 724.3856. Calcd for $C_{36}H_{58}N_3O_{10}S$: M 724.3842; ^{1}NMR (300 MHz; $CDCl_3$): δ 0.86 (3H, t, *J* = 7.4 Hz, CH_3), 1.18-1.31 (14H, m), 1.37 (3H, d, *J* = 6.8 Hz, CH_3), 1.49 (3H, s, CH_3), 1.57-1.70 (4H, m), 1.72-1.80 (1H, m), 1.85-1.95 (1H, m), 2.27 (6H, s, $N(CH_3)_2$), 2.40-2.50 (1H, m), 2.62 (3H, s), 3.00 (2H, s), 3.03-3.07 (1H, m), 3.17-3.20 (1H, m), 3.52-3.55 (1H, m), 3.79 (1H, q, *J* = 6.8 Hz), 3.87-3.90 (2H, m), 3.93 (1H, s), 4.15 (1H, d, *J* = 7.8 Hz), 4.32 (1H, d, *J* = 7.3 Hz), 5.06 (1H, dd, *J* = 10.0, 2.6 Hz), 5.60 (1H, brs), 6.85-6.83 (2H, m), 7.17 (1H, dd, *J* = 5.1,1.2 Hz). ^{13}C NMR (75

MHz; $CDCl_3$): δ 10.6 (CH_3), 13.9 (CH_3), 14.5 (CH_3), 16.3 (CH_3), 18.0 (CH_3), 19.6 (CH_3), 21.2 (CH_3), 22.7 (CH_3), 28.3(CH_3), 39.7(CH_3), 40.3 (CH_3)x2, 44.4, 44.6, 47.3, 47.8, 49.1, 49.2, 51.3, 57.6, 66.0, 69.5, 70.3, 76.4, 78.1, 78.8, 84.0, 103.7, 124.5, 125.0 126.7, 143.5 (C), 157.8 (C), 169.4 (C), 204.7 (C), 217.3 (C).

10-(*N*-1-Phenylethan-1-yl)aminomethyl-11*N*,12*O*-cyclocarbamate-11-deshydroxy-10-desmethyl-O^6-methyl-3-oxodescladinosylerythromycin A (9)

A solution of 1 phenylethan-1-amine (0.13 mL, 0.96 mmol) and 2'*O*-acetyl-11*N*,12*O*- cyclocarbamate-11-deshydroxy-l0-desmethyl-0^6-methyl-l0-methylen-3-oxo-descladinosylerythromycin A (**3**) (0.15 g, 0.24 mmol) was heated under reflux for 28 h. Another portion of phenylethan-1-amine (0.07 mL, 0.48 mmol) was added and the mixture was heated for an additional 30 h. The solution was concentrated at reduced pressure, and the residual material was extracted with ethyl acetate, the extract washed with $NaHCO_3$, and brine before being dried over ($MgSO_4$). The solvents were removed at reduced pressure. The residual solid was subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH:NH_3(aq) 90:5:1. The product **8** was a white solid; yield 0.1 g (55%). The 2'*O*-acetyl adduct **8** (25 mg) was dissolved in methanol (2 mL) and the solution stirred at room temperature overnight. The solvent was evaporated, and the product was subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH:NH_3(aq) 90: 10:2. The title product **9** was a white solid; yield 0.02 g (86%). HRMS (Electrospray, H^+): M 732.4448. Calcd for $C_{39}H_{62}N_30_{10}$: M 732.4435. ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.85 (3H, t, *J* = 7.3 Hz, CH_3), 1.07 (3H, d, *J* = 7.0 Hz, CH3), 1.15-1.31 (15H, m), 1.32-1.34 (3H, m), 1.50 (3H, s, CH_3), 1.60-1.80 (4H, m), 1.80-1.90 (1H, m), 2.26 (6H, s, $N(CH_3)_2$), 2.61 (1H, d, *J* = 11.9 Hz), 2.70-2.77 (2H, m), 2.88-2.91 (1H, m), 3.04-3.09 (1H, m), 3.14-3.20 (2H, m), 3.46-3.53 (1H, m), 3.54-3.57 (1H, m), 3.79 (1H, t, *J* = 5.7 Hz), 3.88 (1H, d, *J* = 5.7 Hz), 4.16 (1H, d, *J* = 7.7 Hz), 4.32 (1H, d, *J* = 7.3 Hz), 5.04 (1H, m), 5.55 (1H, d, *J* = 16.0 Hz), 7.19-7.25 (3H, m, Ar), 7.27-7.29 (2H, m. Ar).

10,11-Anhydro-10-benzyl-10-desmethyl-O^6-methyldescladinosylerythromycin A (11a)

Tris(2-furyl)phosphine (0.011 g, 0.044 mmol) and Pd_2dba_3.$CHCl_3$ (0.011 mg, 0.011 mmol) were added to a deoxygenated solution of 10-acetoxymethyl-10,11-anhydro-10-desmethyl-O^6-methyldescladinosylerythromycin A (**10**)[1] (0.280 g, 0.44 mmol) in NMP (4 mL) under argon, and the solution heated at 50 °C for 10 min to generate the catalyst system. Subsequently, a solution of tributyl(phenyl)tin (0.28 mL, 0.88 mmol) in NMP (1 mL) was added and the resulting mixture was heated at 90 °C overnight. The solvent was

removed at reduced pressure, the residue extracted into ethyl acetate, the organic solution shaken with aqueous $NaHCO_3$, with brine, dried over $MgSO_4$, evaporated and the residual material subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH:NH_3 (90:10:2). The product was a white solid; 0.140 g (48%). HRMS (Electrospray, H^+): M 648.4107. Calcd for $C_{36}H_{59}N_1O_9$: :M 648.4111; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.88 (t, 3H, 14-CH_3), 1.02 (d, 3H, 4-CH_3), 1.20-2.20 (23H, m, overlapped signals,), 2.23 (6H, s, $N(CH_3)_2$), 2.50-2.68 (1H, m), 2.70-2.81 (1H, m), 3.03 (3H, s, OCH_3), 3.15-3.22 (2H, m), 3.48-3.52 (1H, m), 3.90 (5H, s), 3.98-4.00 (2H, d, C*H*$_2C_6H_5$), 4.06 (1H, brs, 3-H), 4.45-4.49 (1H, d, 1'-H), 4.88-4.94 1H, (dd, 13-H), 6.49 (1H, s, 11-H), 7.07-7.25 (5H, m, H-ar); ^{13}C NMR (75 MHz, $CDCl_3$): 7.6, 10.4, 15.5, 16.2, 20.3, 20.7, 20.8, 21.3, 28.2, 31.5, 36.5, 36.7, 38.5, 44.2, 44.3, 48.0, 65.5, 69.7, 70.5, 74.1, 77.7, 79.1, 80.95, 92.35, 106.8, 125.9, 128.2, 128.5, 140.0, 140.7, 142.3, 176.7 (1-C=O), 207.1 (9-C=O).

10,11-Anhydro-10-desmethyl-*O*^{6}-methyl-10-phenylpropynyldescladinosyl-erythromycin A (11b)

Tris(2-furyl)phosphine (0.047 g, 0.20 mmol) and $Pd_2dba_3.CHCl_3$ (0.048 mg, 0.046 mmol) were added to a deoxygenated solution of 10-acetoxymethyl-10,11-anhydro-10-desmethyl-*O*^{6}-methyldescladinosylerythromycin A (**10**)[1] (1.25 g, 2.0 mmol) in DMF (10 mL) under argon and the solution heated at 50 ^{o}C for 10 min to generate the catalyst system. Subsequently, a solution of tributyl(phenylethynyl)tin (1.17 g, 1.05 mL, 3.0 mmol) in DMF (3 mL) was added and the resulting mixture was heated overnight at 80 ^{o}C. The solvent was removed at reduced pressure, the residue extracted into ethyl acetate, the solution shaken with aqueous $NaHCO_3$, with brine, dried over $MgSO_4$, evaporated and the residual material subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH:NH_3 (aq) 93:7:2 as eluent system. The product was a white solid material 0.630 g (47%). HRMS (Electrospray, H^+): M 672.4128. Calcd for $C_{38}H_{58}N_1O_9$: M 672.4111 ; ^{1}H NMR (300 MHz; $CDCl_3$): 0.82-0.89 (3H, t, 14-CH_3), 0.99-1.02 (3H, d, 4-CH_3), 1.18-2.20 (23H, m, overlapped signals), 2.21[6H, s, $N(CH_3)_2$], 2.50-2.68 (1H, m), 2.70-2.81 (1H, m,), 3.06 (3H, s, OCH_3), 3.09-3.97 (6H, m, overlapped signals), 4.45-4.49 (1H, d), 4.68-4.70 (1H, d, 1'-H), 4.90-4.95 (1H, dd, 13-H), 6.48 (1H, s, 11-H), 7.20-7.33 (5H, m, H-arom).

10,11-Anhydro-10-desmethyl-*O*^{6}-methyl-10-phenylpropenyldescladinosyl-erythromycin A (11c)

Tris(2-furyl)phosphine (0.047g, 0.20 mmol) and $Pd_2dba_3.CHCl_3$ (0.048 mg, 0.046 mmol) were added to a deoxygenated solution of 10-acetoxymethyl-10,11-anhydro-10-desmethyl-*O*^{6}-methyldescladinosylerythromycin A (**10**)[1] (1.25 g, 2.0 mmol) in DMF (10

mL) under argon and the solution heated at 50 °C for 10 min to generate the catalyst system. Subsequently, a solution of tributyl(styryl)tin (1.15 g, 3.0 mmol) in DMF (3 mL) was added and the resulting mixture was heated overnight at 80 °C. The solvent was removed at reduced pressure, the residue extracted into ethyl acetate, the solution shaken with aqueous $NaHCO_3$, with brine, dried over $MgSO_4$, evaporated and the residual material subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH:NH_3 (95:5:2). The product was a white solid 0.800 g (59%). HRMS (Electrospray, H^+): M 674.4262. Calc. for $C_{38}H_{60}N_1O_9$: M 674.4268 ; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.82-1.82 (25H, overlapped signals), 1.88 (1H, s), 1,70-1.73 (1H, m), 2.21 [6H, s, $N(CH_3)_2$], 2.45-2.49 (1H, m), 2.68-2.73 (1H, m), 3.06 (3H, s, OMe), 3.18-3.24 (2H, m), 3.50-3.56 (3H, m, overlapped signals), 3.82 (1H, s), 3.91 (1H, s), 4.00-4.05 (1H, m), 4.46-4.49 (1H, d), 4.66-4.68 (1H, dd), 4.87-4.90 (1H, dd), 6.11-6.18 (1H, m), 6.33-6.38 (1H, d), 6.51 (1H, s), 7.10-7.35 (5H, m, C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$): δ 7.5, 10.4, 15.4, 16.1, 20.3, 20.6, 20.7, 21.3, 28.2, 29.6, 39.6, 36.7, 38.4, 40.2, 44.3, 48.1, 65.5, 69.7, 70.4, 74.1, 77.8, 79.0, 81.0, 92.2, 106,8, 126.0, 127.1, 128.4, 128.5, 130.7, 137.2, 139,7, 142.8, 176.7, 206.6.

2`*O*-Acetyl-10,11-anhydro-10-benzyl -10-desmethyl-*O*^{6}-methyldescladinosyl-erythromycin A (12a)

A solution of 10,11-anhydro-10-benzyl-10-desmethyl-*O*^{6}-methyl-descladinosylerythromycin A (**11a**) (0.455 g, 0.7 mmol), triethylamine (0.196 mL, 1.4 mmol) and acetic acid anhydride (0.132 mL, 1.4 mmol) in dichloromethane (7 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 CH_2Cl_2:MeOH:NEt_3 90:7:2. The product was a white solid; yield 0.32 g, 66%. HRMS (Electrospray, H^+): M 690.4223. Calcd for $C_{38}H_{60}N_1O_{10}$: M 690.4217 ; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.89-0,95 (6H, m), 1.1 (3H, d, 4-CH_3), 1.20-2.20 (19H, m, overlapped signals), 2.02 (3H, s, OAc), 2.22 (6H, s, $N(CH_3)_2$), 2.69-2.72 (1H, m), 2.86 (3H, s, OCH_3), 3.00-3.17 (3H, m), 3.48-3.53 1H, m), 3.70-3.72 (1H, q), 3.85 (1H, d), 4.07-4.13 (2H, m), 4.31 (1H, d), 4.67-4.73 (1H, dd), 4.89-4.93 (1H, dd, 13-H), 6.67 (1H, s, 11-H), 7.07-7.25 (5H, m, H-arom); ^{13}C NMR (75 MHz, $CDCl_3$): 8.1, 10.5, 15.6, 16.3, 20.3, 21.1, 21.2, 21.3, 21.4, 30.0, 32.0, 36.8, 36.9, 38.1, 40.7, 44.3, 48.6, 64.3, 69.3, 71.9, 77.0, 79.5, 79.5, 79.6, 89.1, 103.0, 126.0, 128.2, 128.4, 139.8, 141.7, 142.0, 170.2, 175.9, 207.1 (9-C=O).

2`*O*-Acetyl-10,11-anhydro-10-desmethyl-*O*^{6}-methyl-10-phenylpropynyl-descladinosylerythromycin A (12b)

A solution of 10,11-anhydro-10-desmethyl-*O*^{6}-methyl-10-phenylpropynyl-descladinosylerythromycin A (**11b**) (0.610 g, 0.88 mmol), triethylamine (0.24 mL, 1.76 mmol) and acetic acid anhydride (0.16 mL, 1.76 mmol) in dichloromethane (12 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 CH_2Cl_2:MeOH:TEA 95:5:2. The product was a white solid; yield 0.47 g (75%). HRMS (Electrospray, H^+): M 714.4233. Calcd for $C_{40}H_{60}N_1O_{10}$: M 714.4217 ; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.85-0.94 (6H, m, 6H), 1.18-2.00 (23H, m, overlapped signals), 2.07 (3H, s, OCH_3), 2.20 (6H, s, $N(CH_3)_2$, 2.48-2.61 (2H, m), 3.14 (3H, s, OCH_3), 3.09-3.97 (6H, m, overlapped signals), 4.61-4.71 (3H, m), 5.00-5.03 (1H, dd, 13-H), 6.3 (1H, s11-H), 7.20-7.33 (5H, m, H-ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 7.9, 10.5, 15.5, 16.3, 17.1, 20.1, 21.1, 21.2, 21.2, 21.4, 30.0, 37.1, 37.3, 38.8, 40.7, 44.3, 48.7, 64.2, 69.2, 71.9, 73.9, 77.3, 79.4, 80.2, 87.8, 102.8, 123.3, 127.8, 128.2, 131.5, 138.4, 141.7, 170.2, 175.9, 205.6 (9-C=O).

2`*O*-Acetyl-10,11-anhydro-10-desmethyl-*O*^{6}-methyl-10-phenylpropenyl-descladinosylerythromycin A (12c)

A solution of 10,11-anhydro-10-desmethyl-*O*^{6}-methyl-10-phenylpropenyl-descladinosylerythromycin A (**11c**) (1,00 g, 1.48 mmol), triethylamine (0.416 mL, 2.96 mmol) and acetic acid anhydride (0.28 mL, 2.96 mmol) in dichloromethane (20 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 CH_2Cl_2:MeOH:NEt_3 95:5:2. The product was a white solid; yield 0.850 g (80%). HRMS (Electrospray, H^+): M 716.4379. Calcd for $C_{40}H_{62}N_1O_{10}$: M 716.4373. ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.82-2.03 (27H, overlapped signals), 2.06 (3H, s, OAc), 2.19 (6H, s, $N(CH_3)_2$), 2.59-2.65 (3H, m), 3.06 (3H, s, OCH_3), 3.07-3.11 (1H, m), 3.49-3.54 (3H, m, overlapped signals), 3.83-3.86 1H, (m), 3.87-3.88 (1H, d), 4.63-4.72 (2H, m), 4.90-4.97 (1H, dd), 6.05-6.18 (1H, m), 6.29-6.37 (1H, d), 6.47 (1H, s), 7.16-7.25 (5H, m, C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 7.9, 10.5, 15.6, 16.3, 20.2, 21.0, 21.1, 21.1, 21.4, 29.9, 30.1, 36.9, 37.17, 4.88, 40.7, 44.3, 48.6, 53.4, 64.2, 69.2, 71.9, 73.8, 77.2, 79.3, 80.2, 88.9, 102.9 126.0, 127.1, 128.2, 128.4, 130.8, 137.3, 140.9, 142.3, 170.2, 175.9, 206.6.

2`*O*-Acetyl-10,11-anhydro-10-benzyl -10-desmethyl-*O*^{6}-methyl-3-oxodescladinosyl-erythromycin A (13a)

2`*O*-Acetyl-10,11-anhydro-10-benzyl-10-desmethyl-*O*^{6}-methyl-descladinosylerythromycin A (**12a**) (0.300 g, 0.435 mmol) was dissolved in dichloromethane (4 mL) and Dess–Martin periodinane reagent (0.258 g, 0.60 mmol) was added. The reaction mixture was stirred at room temperature for 3 h before the mixture was concentrated under reduced pressure. The residual material was dissolved in ethyl acetate, the solution washed with aqueous NaOH (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 1.5:1. The product was a white solid; yield 0.200 g (64%). HRMS (Electrospray, H^+): M 688.4066. Calcd for $C_{38}H_{58}N_1O_{10}$: M 688.4060 ; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.89-0.95 (6H, m), 1.1 (3H, d, 4-CH_3), 1.20-2.20 (17H, m, overlapped signals), 2.02 (3H, s, OAc), 2.22 (6H, s, $N(CH_3)_2$), 2.69-2.72 (1H, m), 2.86 (3H, s, OCH_3), 3.00-3.17 (3H, m), 3.48-3.53 (1H, m), 3.70-3.72 (1H, q), 3.85 (1H, d), 4.07-4.14 2H, (m,), 4.30-4.34 (1H, d), 4.67-4.72 (1H, dd), 4.89-4.94 (1H, dd, 13-H), 6.67 (1H, s, 11-H), 7.07-7.24 (5H, m, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.8, 14.0, 15.0, 18.5, 21.0, 21.3, 22.4, 22.6, 30.0, 30.4, 32.3, 38.6, 40.6, 47.4, 50.4, 51.2, 63.4, 69.1, 71.5, 73.9, 78.3, 79.9, 81.4, 101.7, 125.9, 128.2, 128.4, 140.09, 142.5, 169.7, 169.8, 206.8 (9-C=O).

2`*O*-Acetyl-10,11-anhydro-10-desmethyl-*O*^{6}-methyl-3-oxo-10-phenylpropynyl-descladinosylerythromycin A (13b)

2`*O*-Acetyl-10,11-anhydro-10-desmethyl-*O*^{6}-methyl-10-phenylpropynyl-descladinosylerythromycin A (**12b**) (0.43 g, 0.60 mmol) was dissolved in dichloromethane (5 mL) and Dess–Martin periodinane reagent (0.356 g, 0.84 mmol) was added. The reaction mixture was stirred at room temperature for 3 h before the mixture was concentrated under reduced pressure. The residual material was dissolved in ethyl acetate, the solution washed with water/NaOH (pH adjusted to 10–11), with brine and dried ($MgSO_4$). The crude product was subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH:NH_3(aq.) 95:5:1. The product was a white solid; yield 0.300 g (70%). HRMS (Electrospray, H^+): M 712.4081. Calcd for $C_{40}H_{58}N_1O_{10}$: M 712.4060 ; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.83-2.20 (26H, m, overlapped signals), 2.01 (3H, s, OAc), 2.22 (6H, s, $N(CH_3)_2$), 2.69-2.72 (1H, m), 2.78 (3H, s, OCH_3), 3.00-3.17 (2H, m), 3.53-3.89 (4H, m), 4.08-4.13 (2H, m), 4.30-4.34 (1H, d), 4.65-4.71 (1H, dd), 4.96-5.00 (1H, dd, 13-H), 6.60 (1H, s, 11-H), 7.21-7.35 (5H, m, H-arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.8, 14.0, 15.1, 17.3, 18.8, 20.9, 21.3, 22.4, 22.5, 26.9, 30.3, 34.6, 40.6, 40.7, 47.3, 50.1, 51.1, 63.5, 69.1, 71.5, 73.9, 78.3, 80.7, 80.9, 81.2, 88.2, 101.8, 123.2, 127.7, 128.1, 131.5, 142.7, 169.5, 169.7, 205.3 (9-C=O).

2`*O*-Acetyl-10,11-anhydro-10-desmethyl-*O*^{6}-methyl-3-oxo-10-phenylpropenyl-descladinosylerythromycin A (13c)

2`*O*-Acetyl-10,11-anhydro-10-desmethyl-*O*^{6}-methyl-10-phenylpropenyl-descladinosylerythromycin A (**12c**) (0.800 g, 1.12 mmol) was dissolved in dichloromethane (10 mL) and Dess–Martin periodinane reagent (0.664 g, 1.56 mmol) was added. The reaction mixture was stirred at room temperature for 3 h before the mixture was concentrated under reduced pressure. The residual material was dissolved in ethyl acetate, the solution washed with dilute NaOH (pH), adjusted to pH 10–11 and dried ($MgSO_4$). The crude product was subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH:NH_3 95:5:2. The product was a white solid; yield 0.610 g (75%). HRMS (Electrospray, H^+): M 714.424. Calcd for $C_{40}H_{60}N_1O_{10}$: M 714.4217 ; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.82-2.03 (22H, overlapped signals), 1.99 (3H, s, OAc), 2.00-2.20 (2H, m), 2.21 (6H, s, $N(CH_3)_2$), 2.60-2.63 (3H,m), 2.81 (3H, s, OCH_3), 2.96-3.13 (3H, m), 3.40-3.56 (3H, m), 3.69-3.71 (1H, m), 4.09-4.12 (1H, d), 4.30-4.33 (1H, d), 4.66-4.69 (1H, m), 4.91-4.96 (1H, dd), 6.15-6.21 1H, (m), 6.31-6.37 (1H, d), 6.66 (1H, s), 7.22-7.26 (5H, m, C_6H_5).

2`*O*-Acetyl-12*O*-acylimidazolyl-10,11-anhydro-10-benzyl-10-desmethyl-*O*^{6}-methyl-3-oxodescladinosylerythromycin A (14a)

The ketolide (**13a)** (0.620 g, 0.90 mmol) was dissolved in THF (8 mL) and the solution cooled to 0 ^{o}C before NaH (60%, 0.053 mg, 1.35 mmol) was added. A solution of carbonyl diimidazole (0.364 g, 2.25 mmol) in THF (2 mL) was added dropwise over 5 min to the reaction mixture. The solution was stirred at room temperature for 20 h before the mixture was cooled to 0 ^{o}C, quenched with $NaHCO_3$, extracted with ethyl acetate, the extracts washed with $NaHCO_3$, with brine and dried ($MgSO_4$). The solution was evaporated and the product was purified by flash chromatography on silica gel using acetone/hexane 1.5:1. The product was a white solid; yield 0.210 g (29%). HRMS (Electrospray, H^+): M 782.4236. Calcd for $C_{42}H_{60}N_3O_{11}$: M 782.4227 ; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.89-1.82 (28H, overlapped signals), 1.99 (3H, s, OAc), 2.19 6H, (s, $N(CH_3)_2$), 2.51-2.60 (1H, m), 2.83 (3H, s, OCH_3), 3.01-3.11 (1H, m), 3.20-3.23 (1H, m), 3.31-3.42 (1H, m), 3.67-3.74 (2H, m, overlapped signals), 3.88-3.96 (1H, d), 4.08-4.12 (2H, m), 4.30-4.34 (1H, d), 4.67-4.69 (1H, dd), 5.61-5.66 (1H, dd, 13-H), 6.82-7.23 (7H, m, overlapped signals, H_{ar}, $H_{imid.}$, 11-H), 7.80 (1H, s, $H_{imid.}$).

2`*O*-Acetyl-12*O*-acylimidazolyl-10,11-anhydro-10-desmethyl-*O*^{6}-methyl-3-oxo-10-benzenepropynyldescladinosylerythromycin A (14b)

The ketolide (**13b)** (0.250 g, 0.35 mmol) was dissolved in THF (5 mL) and the solution cooled to 0 °C before NaH (60%, 0.028 mg, 0.7 mmol) was added. A solution of carbonyl-diimidazole (0.170 g, 2.25 mmol) in THF (2 mL) was added dropwise over 5 min to the reaction mixture. The solution was stirred for 20 h at room temperature. The reaction mixture was cooled to 0 °C, quenched with $NaHCO_3$, diluted with ethyl acetate, washed with $NaHCO_3$, with brine and dried ($MgSO_4$). The solution was evaporated and the compound (**14b**) was purified by flash chromatography on silica gel using acetone/hexane 2:1. The product was a white solid; yield 0.120 g (42%). HRMS (Electrospray, H^+): M 806.4241. Calcd for $C_{44}H_{60}N_3O_{11}$: M 806.4227 ; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.89-1.82 (26H, overlapped signals), 1.99 (3H, s, OAc), 2.21 (6H, s, $N(CH_3)_2$), 2.51-2.60 (1H, m), 2.72 (3H, s, OCH_3), 2.97-3.29 (2H, m), 3.53-3.89 (3H, m, overlapped signals), 4.11-4.15 (1H, m), 4.33-4.37 (1H, d), 4.69-4.76 (1H, dd), 5.66-5.71 (1H, dd, 13-H), 6.93-7.19 (7H, m, overlapped signals, H_{ar}, $H_{imid.}$, 11-H), 8.04 (1H, s, H_{imid}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 1.9, 10.4, 13.8, 15.0, 17.9, 18.6, 20.4, 20.9, 21.3, 22.5, 25.6, 30.3, 40.6, 47.5, 50.3, 51.0, 63.6, 68.0, 69.2, 71.5, 78.6, 80.9, 83.8, 85.5, 116.3, 117.0, 123.0, 127.6, 127.8, 130.6, 131.4, 136.8, 137.7, 139.2,146.0, 168.9, 169.7 (9-C=O and 3-C=O, not seen).

2`*O*-Acetyl-12*O*-acylimidazolyl-10,11-anhydro-10-desmethyl-*O*^{6}-methyl-3-oxo-10-phenylpopenyl-descladinosylerythromycin A (14c)

The ketolide (**13c)** (0.600 g, 0.84 mmol) was dissolved in THF (10 mL) and the solution cooled to 0 °C before NaH (60%, 0.050 mg, 1.26 mmol) was added. A solution of carbonyl diimidazole (0.34 g, 2.1 mmol) in THF (3 mL) was added dropwise over 5 min to the reaction mixture. The solution was stirred at room temperature for 20 h. The reaction mixture was cooled to 0 °C, quenched with $NaHCO_3$, diluted with ethyl acetate, washed with $NaHCO_3$, with brine and dried ($MgSO_4$). The solution was evaporated and the product was purified by flash chromatography on silica gel using acetone:hexane 2:1. The product was a white solid; yield 0.200 g (29%). HRMS (Electrospray, H^+): M 808.4393. Calcd for $C_{44}H_{62}N_3O_{11}$: M 808.4384 .

2`*O*-Acetyl-10-benzyl-11*N*,12*O*-cyclocarbamate-11-deshydroxy-10-desmethyl-*O*^{6}-methyl-3-oxo-descladinosylerythromycin A (15a)

Ammonia(aq) (0.3 mL) was added to a solution of 2`*O*-acetyl-12*O*-acylimidazolyl-10,11-anhydro-10-benzyl-10-desmethyl-*O*^{6}-methyl-3-oxo-descladinosylerythromycin A (**14a**) (0.150 g, 0.192 mmol) in acetonitrile (3 mL) and THF (0.3 mL) and the mixture stirred at room temperature for 48 h. The mixture was concentrated under reduced pressure and the residual material was dissolved in ethyl acetate. The solution was washed with dilute NaOH (pH adjusted to 10–11), with brine and the solution dried ($MgSO_4$). The solution

was evaporated and the residual material subjected to flash chromatography on silica gel using acetone:hexane 3:2. The product was a white solid, mixture of 2 diastereomers (2:1). Isolation of pure isomers failed; yield 0.063 g (45%). The product was used in the next reaction step as a mixture of diastereomers. HRMS (Electrospray, H^+): M 731.4132 Calcd for $C_{39}H_{59}N_2O_{11}$: M 731.4118 .

2`*O*-Acetyl-11*N*,12*O*-cyclocarbamate-11-deshydroxy-10-desmethyl-*O*^{6}-methyl-3-oxo-10-benzenepropynyl-descladinosylerythromycin A (15b)

Ammonia(aq) (0.3 mL) was added to a solution of 2`*O*-acetyl-12*O*-acylimidazolyl-10,11-anhydro-10-desmethyl-*O*^{6}-methyl-3-oxo-10-benzenepropynyldescladinosylerythromycin A (**14b**) (0.100 g, 0.124 mmol) in acetonitrile (3 mL) and THF (0.3 mL) and the mixture stirred at room temperature for 48 h. The reaction mixture was concentrated under reduced pressure and the residual material was dissolved in ethyl acetate. The solution was washed with dilute NaOH (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 1.5:1. The product was a white solid, mixture of 2 diastereomers (1:1); isolation of pure isomers failed; yield 0.060 g (64%). The the diastereomeric product was used in the next reaction step. HRMS (Electrospray, H^+): M 755.4138 Calcd for $C_{41}H_{59}N_2O_{11}$: M 755.4118 .

2`*O*-Acetyl-11*N*,12*O*-cyclocarbamate-11-deshydroxy-10-desmethyl-*O*^{6}-methyl-3-oxo-10-benzenepropenyl-descladinosylerythromycin A (15c)

Ammonia(aq) (0.3 mL) was added to a solution of 2`*O*-acetyl-12*O*-acylimidazolyl-10,11-anhydro-10-desmethyl-*O*^{6}-methyl-3-oxo-10-benzenepropenyl-descladinosylerythromycin A (**14c**) (0.200 g, 0.24 mmol) in acetonitrile (3 mL) and THF (0.3 mL) and the mixture stirred at room temperature for 48 h. The reaction mixture was concentrated under reduced pressure and the residual material was dissolved in ethyl acetate. The solution was washed with dilute NaOH (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 2:1. The product was a white solid which was obtained as a mixture of 2 diastereomers (1:1); isolation of pure isomers failed; yield 0.085 g (49%). The product was used in the next reaction as a mixture of diastereomers. HRMS (Electrospray, H^+): M 757.4299. Calcd for $C_{41}H_{61}N_2O_{11}$ 757.4299.

10-Benzyl-11*N*,12*O*-cyclocarbamate-11-deshydroxy-10-desmethyl-*O*^{6}-methyl-3-oxo-descladinosylerythromycin A (16a)

Methanol (2 ml) was added to the cyclic carbamate (**15a**) (0.063 g, 0.086 mmol) 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 90:5:2. Partial separation of pure diastereomers was achieved:

The major isomer: 20 mg. HRMS (Electrospray, H^+): M 689.4026. Calcd for $C_{37}H_{57}N_2O_{10}$: M 689.4013 ; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.45-0.48 (3H, d), 0.82-2.03 (28H, overlapped signals), 2.22 (6H, s, $N(CH_3)_2$), 2.31-2.60 (1H, m), 2.77 (3H, s, OCH_3), 2.81-3.65 (4H, m, overlapped signals), 3.67-3.74 (2H, m, overlapped signals), 3.72-3.78 (2H, m), 4.04-4.08 (1H, d, 5-H), 4.24-4.27 (1H, d, 1'-H), 4.98-5.04 (1H, dd, 13-H), 6.62 (1H, s, NH), 7.02-7.19 (5H, m, H-Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.7, 14.9, 15.9, 17.4, 18.2, 20.4, 21.2, 22.5, 28.3, 31.7, 39.8, 40.3, 41.8, 48.7, 50.3, 51.3, 58.6, 60.6, 65.7, 69.5, 70.2, 77.7, 78.6, 79.5, 86.2, 104.1, 126.5, 128.5 (4 x C_{ar}), 139.8, 158.6, 169.9, 204.9, 214.6.

The minor isomer: 10 mg. HRMS (Electrospray, H^+): M 689.4023. Calcd for $C_{37}H_{57}N_2O_{10}$: M 689.4013 ; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.00-0.03 (3H, d), 0.82-2.03 (28H, overlapped signals), 2.21 (6H, s, $N(CH_3)_2$), 2.31-2.60 (1H, m), 2.63 (3H, s, OCH_3), 2.96-3.07 (4H, m, overlapped signals), 3.40-3.64 (2H, m, overlapped signals), 3.76-3.80 (1H, d), 4.08-4.12 (3H, m), 4.27-4.30 (1H, d, 1'-H), 5.09-5.16 (1H, dd, 13-H), 5.59 (1H, s, NH), 7.02-7.23 (5H, m, H_{ar}).

11*N*,12*O*-Cyclocarbamate-11-deshydroxy-10-desmethyl-*O*^{6}-methyl-3-oxo-10-phenylpropynyl-descladinosylerythromycin A (16b)

Methanol (2 ml) was added to the cyclic carbamate (**15b**) (0.060 g, 0.079 mmol) 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 93:7:2. Pure diastereomers were isolated.

The first isomer: 23 mg. HRMS (Electrospray, H^+): M 713.4019. Calcd for $C_{39}H_{57}N_2O_{10}$ 713.4013 ; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.80-1.75 (25H, overlapped signals), 1.86-2.02 1H, (m,), 2.23 (6H, s, $N(CH_3)_2$), 2.37-2.49 (1H, m), 2.63 (4H, s+m), 2.73-2.77 (2H, d), 2.98-3.19 (3H, m, overlapped signals), 3.40-3.63 (2H, m, overlapped signals), 3.78-3.84 (1H, q), 3.97 (1H, s), 4.14-4.18 (1H, d, 5-H), 4.30-4.34 (1H, d, 1'-H), 5.04-5.09 (1H, dd, 13-H), 5.61 (1H, s, NH), 7.24-7.36 (5H, m, H-Ar);

The second isomer: 20 mg. HRMS (Electrospray, H^+): M 713.4023. Calcd for $C_{39}H_{57}N_2O_{10}$: 713.4013 ; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.80-1.75 (25H, overlapped

signals), 1.86-2.02 (1H, m, 1H), 2.24 (6H, s, $N(CH_3)_2$), 2.39-2.49 (1H, m), 2.78 (3H, s), 2.79-2.85 (3H, m), 3.00-3.07 (2H, m), 3.12-3.18 (1H, m), 3.45-3.56 (2H, m, overlapped signals), 3.61-3.63 (1H, m), 3.76-3.86 (1H, q), 4.14-4.16 (1H, d, 5-H), 4.26-4.30 (1H, d, 1'-H), 4.96-5.02 (1H, dd, 13-H), 5.32 (1H. s, 1H), 7.24-7.36 5H, (m, 5H, H-Ar).

11*N*,12*O*-Cyclocarbamate-11-deshydroxy-10-desmethyl-*O*^{6}-methyl-3-oxo-10-benzenepropenyl-descladinosylerythromycin A (16c)

Methanol (2 ml) was added to the cyclic carbamate (**15c**) (0.073 g, 0.096 mmol) 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) 90:10:2. A mixture of diastereomers was isolated; yield 50 mg (53%).

10-(2,2-Bis(ethoxycarbonyl)ethan-1-yl)-11*N*,12*O*-cyclocarbamate-11-deshydroxy-10 desmethyl-*0*^{6}-methyl-3-oxodescladinosylerythromycin A (18a)

The ketolide **3** (0.12 g, 0.18 mmol)) was dissolved in THF (6 mL) and the solution cooled to 0 °C before NaH (60%, 0.01 g) was added. Diethyl malonate (0.07 mL, 0.45 mmol) was added dropwise over 5 min to the reaction mixture. The solution was stirred at room temperature for 23 h, the reaction mixture cooled to 0 °C, $NaHCO_3$ added, the mixture extracted with ethyl acetate (3x15 mL), the extracts washed with brine, dried ($MgSO_4$) and the solution evaporated. The residual material was subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH:NH_3(aq) 90:10:2. The product **17a** was white solid; yield 0.058 (39%). Compound **17a** (0.04 g) was dissolved in methanol (2 mL) and the solution stirred at room temperature for 24 h. The solvent was distilled off and the residual material was subjected to flash chromatography on silica gel using actone:hexane 3:2. The title compound **18a** was a white solid; yield 0.03 g (79%).

18a: HRMS (Electrospray, H^+): M 771.4289. Calcd for $C_{38}H_{64}N_2O_{14}$: M 771.4279. ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.87 (3H, t, *J* = 7.4 Hz, CH_3), 1.02 (3H, d, *J* = 7.0 Hz, CH_3), 1.18-1.32 (16H, m), 1.37 (3H, d, *J* = 6.8 Hz, CH_3), 1.50-1.60 (2H, m), 1.66 (3H, s), 1.67-1.73 (2H, m), 1.89-1.94 (2H, m), 2.22-2.25 (1H, m), 2.26 (6H, s, $N(CH_3)_2$, 2.64 (3H, s), 3.02-3.19 (4H, m), 3.52-3.60 (2H, m), 3.79 (1H, q, *J* = 6.8 Hz), 4.09-4.24 (6H, m), 4.33 (1H, d, *J* = 7.3 Hz), 5.08 (1H, dd, *J* = 9.8, 2.7 Hz), 5.36 (1H, brs). ^{13}C NMR (75 MHz; $CDCl_3$): δ 10.7 (CH_3), 12.8 (CH_3), 13.9 (CH_3), 14.0 (CH_3), 14.5 (CH_3), 16.1 (CH_3), 17.7 (CH_3), 19.6 (CH_3), 21.2 (CH_3), 22.8, 26.0, 28.3, 39.1, 40.2 (CH_3)x2, 41.7, 44.4, 47.5, 49.2, 49.6, 51.4, 57.68, 6.69, 61.9, 65.9, 69.5, 70.2, 76.1,

78.1, 78.2, 84.5, 103.5, 157.9 (C), 168.5 (C), 169.1 (C), 169.4 (C), 204.8 (C), 216.8 (C).

10-(2,2-Biscyanoethan-1-yl)-11*N*,12*O*-cyclocarbamate-11-deshydroxy-10-desmethyl-*0*^{6}-methyl-3-oxodescladinosylerythromycin A (18b)

The ketolide **3** (0.15 g, 0.22 mmol) was dissolved in THF (5 mL) and the solution cooled to 0 °C before NaH (60%, 0.01 g) was added. Malononitrile (0.06 g, 0.90 mmol) was added dropwise over 5 min to the reaction mixture. The solution was stirred at room temperature for 23 h before the reaction mixture was cooled to 0 °C and $NaHCO_3$ added. The mixture was extracted with ethyl acetate (3x15 mL), washed with brine and dried ($MgSO_4$). The solution was evaporated and the residual material was subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH:NH_3(aq) 90:10:2. The product **17b** was a white solid; yield 0.12 g (73%). Compound **17b** was stirred in a methanol solution (2 mL) at room temperature for 24 h. The solvent was evaporated, and the residual material was subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH:NH_3(aq) 90:10:2. The title compound **18b** was a white solid; yield 0.085 g (90%). HRMS (Electrospray, H^+): M 677.3779. Calcd for $C_{34}H_{53}N_4O_{10}$: 677.3761. ^{1}HNMR (300 MHz; $CDCl_3$): δ 0.92 (3H, t, *J* = 7.8 Hz, CH_3), 1.00 (3H, d, *J* = 7.1 Hz, CH_3), 1.18-1.30 (13H, m), 1.44 (3H, d, *J* = 7.1 Hz, CH_3), 1.49 (2H, s), 1.60-1.80 (3H, m), 1.90-2.00 (l H, m), 2.26 [6H, s, $N(CH_3)_2$], 2.40-2.51 (3H, m), 2.74-2.76 (IH, m), 2.85 (3H, s), 2.86-2.96 (l H, m), 3.15-3.21 (l H, m), 3.33-3.38 (1H, m), 3.47-3.50 (1H, m), 3.77-4.02 (3H, m), 4.30 (l H, d, *J* = 7.3 Hz), 4.85-4.99 (1H, m), 5.98 (1H, brs). ^{13}C NMR (75 MHz; $CDCl_3$): δ 10.3 (CH_3), 14.6 (CH_3), 14.5 (CH_3), 16.9 (CH_3), 18.0 (CH_3), 19.7 (CH_3), 20.6 (CH_3), 21.3, 25.5, 28.5, 36.1 (CH_3), 39.2, 40.3 (CH_3)x2, 42.9, 43.9, 49.1, 50.6, 50.9, 58.9, 62.4, 65.6, 69.5, 70.3, 78.8, 79.4, 85.3, 104.1, 119.9, 149.6 (C), 152.1 (C), 170.7 (C), 208.6 (C).

10-(2-Benzoyl-2-ethoxycarbonylethan-1-yl)-11*N*,12*O*-cyclocarbamate-11-deshydroxy- 10-desmethyl-*O*^{6}-methyl-3-oxodescladinosylerythromycin A (18c)

The ketolide **3** (0.20 g, 0.30 mmol) was dissolved in THF (13 mL) and the solution cooled to 0 °C before NaH (60%, 0.02 g) was added. Ethyl 3-oxo-3-phenylpropanoate (0.13 mL, 0.76 mmol) was added dropwise over 5 min to the reaction mixture. The solution was stirred at room temperature for 23 h. The reaction mixture was cooled to 0 °C and $NaHCO_3$ added. The mixture was extracted with ethyl acetate (3x15 mL), the extracts washed with brine and dried ($MgSO_4$). The organic solution was evaporated and the residual material was subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH:NH_3(aq) 90:5:1. The

product **17c** was a white solid; yield 0.09 (35%).

Compound **17c** was dissolved in methanol (2 mL) and the solution stirred at room temperature for 24 h. The solvent was evaporated, and the product was subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH:NH_3(aq) 90:5:1. The title compound **18c** was a white solid; yield 0.06 g (91%). HRMS (Electrospray, H^+): M 803.4324. Calcd for $C_{42}H_{63}N_2O_{13}$: 803.4330. (300 MHz; $CDCl_3$) δ 0.75 (1H,- 0.84-0.89 (3H, m), 1.12-1.38 (19H, m), 1.54-1.65 (2H, m), 1.71 (3H, s), 1.85 (1H, s), 1.87-1.92 (1H, m), 2.24 (2H, s), 2.27 (4H, s), 2.40-2.55 (2H, m), 2.65 (1H, s), 2.67 (2H, s), 2.72-2.80 (1H, m), 3.00-3.20 (2H, m), 3.24-3.29 (1H, m), 3.50-3.60 (1H, m), 3.81 (1H, d, J = 6.7 Hz), 3.92-4.20 (SH, m), 4.28-4.38 (1H, m), 5.06-5.14 (1H, m), 5.22 (1H, brs), 5.38 (1H, brs), 7.42-7.48 (2H, m), 7.57-7.59 (1H, 111), 7.81-7.94 (1H, m). ^{13}C NMR (75 MHz; $CDCl_3$): δ 10.7, 12.8, 12.9, 13.8, 14.5, 15.8, 15.9, 18.0, 19.6, 19.7, 21.2, 22.9, 26.1, 28.3, 39.0, 40.2, 41.8, 42.5, 44.6, 44.8, 47.4, 47.5, 49.2, 51.3 51.5, 52.2, 57.5, 57.9, 61.6, 62.0, 65.9, 69.6, 70.3, 76.1, 76.1, 77.7, 77.9, 78.2, 78.3, 84.6, 84.7, 103.5, 128.4, 128.8, 128.9, 129.0, 133.9, 134.0, 134.5, 135.6, 157.8, 158.10 169.1, 169.5, 169.5, 170.1, 194.0, 194.7, 204.9, 204.9, 216.9, 217.6.

10-(2-Benzylaminocarbonyl-2-cyanoethan-1-yl)-11*N*,12*O*-cyclocarbamate-11 deshydroxy-l0-desmethyl-O^6-methyl-3-oxodescladinosylerythromycin A (20)

The ketolide **3** (0.20 g, 0.3 mmol) was dissolved in THF (15 mL) and the solution cooled to 0 °C before NaH (60%, 0.02 g) was added. *N*-Benzyl-2-cyanoacetamide (0.13 g, 0.76 mmol) was added to the reaction mixture which was stirred at room temperature for 17 h. The mixture was cooled to 0 °C, quenched with $NaHCO_3$ and extracted with ethyl acetate, the extracts washed with brine and dried ($MgSO_4$). The solution was evaporated and the residual material was subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH:NH_3(aq) 90:5:1. The product **23** was a white solid; yield 0.16 g (63%).

The product **19** (0.09 g) was stirred in methanol (2 mL) for 14 h. The solvent was evaporated, and the product was subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH:NH_3(aq) 90:5:1. The product **20** was a white solid; yield 0.04 g (68%). HRMS (Electrospray, H^+): M 785.4324. Calcd for $C_{41}H_{61}N_4O_{11}$: 785.4336 .^{1}H NMR (300 MHz; $CDCl_3$): δ 0.85-0.92 (3H, m), 1.00-1.10 (3H, m), 1.14-1.25 (14H, m), 1.31-1.42 (4H, m), 1.53-1.69 (1H, m), 1.90-1.20 (2H, m), 2.25 (6H, s), 2.30 (3H, s), 2.40-2.50 (2H, m), 2.63-2.72 (1H, m), 2.86 (1H, s), 2.95-3.30 (2H, m), 3.10-3.20 (2H, m), 3.35-3.45 (2H, m), 3.70-3.80 (1H, m), 3.91-3.98 (2H, m), 4.10-4.21 (1H,

m), 4.31 (1H, d, J = 7.3 Hz), 4.50 (1H, d, J = 5.5 Hz), 4.84-4.98 (1H, m), 5.53 (1H, brs, NH), 7.22-7.34 (5H, m, Ar-H), 8.09 (1H, brs, NH). ^{13}C NMR (75 MHz; $CDCl_3$): δ 10.7, 12.8, 14.5, 17.1, 18.3, 19.5, 21.6, 22.8, 26.3, 36.9, 39.9, 40.7, 43.7, 44.0, 49.6, 60.8, 51.4, 62.4, 65.9, 69.8, 70.7, 70.8, 78.5, 78.8, 79.3, 80.1, 104.6, 127.7, 127.9, 129.1, 139.4, 148.2, 152.6, 169.5, 170.6, 207.7, 212.6.

11-*N*-Benzylamino-11*N*,12*O*-cyclocarbamate-11-deshydroxy-10-desmethyl-*O*^{6}-methyl-10-methylen-3-oxodescladinosylerythromycin A (21)

A solution of benzylamine (0.15 mL, 1.3 mmol) and 10-acetoxymethyl-2´O-acetyl-12*O*-acylimidazolyl-10,11-anhydro-10-desmethyl-*O*^{6}-methyl-3-oxodescladinosylerythromycin A (**2**)[1] (0.20 g, 0.26 mmol) in MeCN (2 mL) and THF (0.2 mL) was stirred at room temperature for 40 h. The solution was concentrated under reduced pressure, and the residual material extracted with ethyl acetate. The solution was washed with NaOH (2 M, 2 mL), with brine and dried over $MgSO_4$ before evaporation. The residual material was subjected to ester deprotection by methanolysis by stirring a solution in methanol at room temperature for 24 h. The solvent was distilled off, and the product subjected to flash chromatography on silica gel using CH_2Cl_2: MeOH: NH_3 90:4:1. The title product **21** was a white solid; overall yield 0.08 g (43%). The product was a mixture of diastereomers. The NMR spectra were unresolved and are not included in this report.

10-Methylaminomethyl-11*N*,12*O*-cyclocarbamate-11-deshydroxy-10-desmethyl-*O*^{6}-methyl-*N*-methyl-3-oxodescladinosylerythromycin A (22).

Methylamine (40%, 0.9 mL) was added to a solution of 10-acetoxymethyl-2´O-acetyl-12*O*-acylimidazolyl-10,11-anhydro-10-desmethyl-*O*^{6}-methyl-3-oxodescladinosylerythromycin A (**2**) (0.5 g, 0.65 mmol) in acetonitrile (9 mL) and THF (0.2 mL) and the solution stirred at room temperature for 40 h. The solution was concentrated under reduced pressure, and the residual material extracted with ethyl acetate (3x15 mL). The solution was washed with $NaHCO_3$, with brine, and dried over $MgSO_4$ before evaporation. The residual material was subjected to flash chromatography on silica gel using CH_2Cl_2: MeOH: NH_3(aq) 90:5:1 and then repetition with the system as 90:10.2. The title product **22** was a white solid; yield 0.19 g (29%). HRMS (Electrospray, H^+): M 656.4111. Calcd for $C_{33}H_{58}N_3O_{10}$: 656.4122. ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.81 (3H, 3t,J = 7.4 Hz, CH_3), 1.13-1.25 (12H, m), 1.30-1.34 (6H,m), 1.43 (3H, s, CH_3), 1.48-1.55 (2H, m), 1.55-1.65 (1H, m),1.73-1.78 (1H, m),179-1.90 (1H, m), 1.92 (1H, s), 2.21 (6H, ds, NMe_2), 2.29 (3H, s), 2.39-2.24 (1H,

m), 2.55-2.61 (1H, m), 2.64 (3H, s), 2.65-2.80 (1H, m), 2,94 (3H, s), 2.96-3.00 (1H, m), 3.10-3.17 (2H, m), 3.46-3.51 (8H, m), 3.70 (1H, s), 3.76 (1H, q, *J* = 6.2 Hz), 4.10 (1H, d, *J* = 9.1 Hz), 4.25 (1H, d, *J* = 7.3 Hz), 4.87 (1H, dd, *J* = 10.2, 2.21 Hz); ^{13}C NMR (75 MHz; $CDCl_3$): δ 10.4 (CH_3), 14.2 (CH_3),14.5 (CH_3), 16.3 (CH_3), 18.1 (CH_3) 19.8 (CH_3), 21.0 (CH_3), 22.5, 28.1, 31.9 (CH_3), 37.1 (CH_3), 39.2, 40.1 (CH_3), 40.1 (CH_3) x2, 44.3, 44.9, 47.8, 49.0, 50.3, 51.4, 61.3, 65,7, 69.5, 70.1, 76.5, 78.3, 79.2, 82,4, 103.8, 157.1, 169.6, 203.9, 215.3.

11-*N*-Methylamino-11*N*,12*O*-cyclocarbamate-11-deshydroxy-10-desmethyl-*O*^{6}-methyl-10-methylene-3-oxodescladinosylerythromycin A (23) and **10-*N*-benzyl-*N*-methylaminomethyl-11*N*,12*O*-cyclocarbamate-11-deshydroxy-10-desmethyl-*O*^{6}-methyl-*N*-methyl-3-oxodescladinosylerythromycin A (24)**

10-Methylaminomethyl-11*N*,12*O*-cyclocarbamate-11-deshydroxy-10-desmethyl-*O*^{6}-methyl-*N*-methyl-3-oxodescladinosylerythromycin A (**22**) (0.18 g, 0.26 mmol) and benzaldehyde (0.04 g, 0.26 mmol) were dissolved in THF (10 mL) and tri(acetoxy)borohydride (0.09, 0.42 mmol) added. The reaction mixture was stirred at room temperature under N_2 atmosphere for 22 h before the reaction was quenched by adding a solution of $NaHCO_3$. The mixture was extracted with ethyl acetate, the organic solution shaken with brine and dried ($MgSO_4$). The solvent was removed at reduced pressure and the residual material subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH:NH_3(aq) 250:10:1. Two products were isolated. The minor product **24** (20 mg, 10%) was a white solid. The second product **23** was the white solid; yield 0.125 g (77%).

Compound **23**: HRMS (Electrospray, H^+) 625.3695. Calcd for $C_{32}H_{53}N_2O_{10}$: 625.3700. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (3H, t, *J* = 7.4 Hz, CH_3), 1.13-1.27 (14H, m), 1.37 (3H, s, CH_3), 1.44 (3H, d, *J* = 7.1 Hz, CH_3), 1.58-1.70) (2H, m), 1.80-1.90 (1H, m), 2.24 (6H, s, NMe_2), 2.35-2.50 ((2H, m), 2.73 (3H, s), 2.77 (3H, s), 2.85-2.95 (1H, m), 3.11-3.17 (1H, m), 3.30-3,40 (1H, m), 3.45-3.55 (1H, m), 3.82 (1H, s), 3.98 (1H,q, *J* = 7.1 Hz), 4.16 (1H, d, *J* = 9.0 Hz), 4.25 (1H, d, *J* = 7.3 Hz), 4.95 (1H, dd, *J* = 10.8, 2.0 Hz), 5.45 (1H, s), 5.97 (1H, s). ^{13}C NMR (75 MHz; $CDCl_3$): δ 10.3 (CH_3), 14.5 (CH_3), 16.1 (CH_3), 18.6 (CH_3), 20.1 (CH_3), 21.1 (CH_3), 21.3 (CH_3), 21.7, 28.2, 29.8, 39.2, 40.2, (2x CH_3), 41.9, 49.1, 50.4, 51.3, 64.2, 65.7, 69.4, 70.4, 77.2, 77.8, 78.6, 83.1, 104.2, 119.8, 144.5 (C), 157.0 (C), 171,1 (C), 205.9 (C), 206.9 (C).

Compound **24**: HRMS (Electrospray, H^+) M: 746.4598. Calcd for $C_{40}H_{64}N_2O_{10}$: 746.4591. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (3H, t, *J* = 7.4 Hz, CH_3), 1.13-1.27 (14H, m), 1.37 (3H, s, CH_3), 1.44 (3H, d, *J* = 7.1 Hz, CH_3), 1.58-1.70 (2H, m), 1.80-1.90 (1H, m), 2.24 (6H, s, NMe_2, 2.35-2.50 (2H, m), 2.73 (3H, s), 2.77 (3H, s), 2.85-

2.95 (1H, m), 3.11-3.17 (1H, m); 3.30-3.40 (1H, m), 3.45-3.55 (1H, m), 3.82 (1H, s), 3.98 (1H, q, *J* = 7.1 Hz), 4.16 (1H, d, *J* = 9.0 Hz), 4.25 (1H, d, J = 7.3 Hz), 4.95 (1H, (1H, dd, *J* = 10.8, 2.0 Hz), 5.45 (1H, s), 5.97 (1H, s). ^{13}C NMR (75 MHz; $CDCl_3$): δ 10.5 (CH_3), 14.2 (CH_3), 14.6 (CH_3), 16.6 (CH_3), 17.7 (CH_3), 21.2 (CH_3), 22.7, 28.3, 32.1, 39.4, 40.2 (2 CH_3), 42.2, 42.9, 44.8, 48.0, 49.1, 51.6, 57.0, 61.2, 64.4, 65.9, 69.5, 70.3, 76.5, 78.5, 79.0, 82.5, 103.8, 127.0, 128.1, 129.2, 138.6 (C), 157.3 (C), 169.6 (C), 204.1 (C), 215.1 (C).

10-Benzylaminomethyl-11*N*,12*O*-cyclocarbamate-11-deshydroxy-10-desmethyl-*O*^{6}-methyl-*N*-methyl-3-oxodescladinosylerythromycin A (25).

A solution of benzylamine (0.08 g, 0.77 mmol) and the 10-methylene ketolide **23** (0.12 g, 0.19 mmol) in THF (15 mL) was heated under reflux for 30 h. Another portion of benzylamine (0.08 g, 0.77 mmol) was added and the mixture heated for 30 h. The solution was concentrated under reduced pressure, and the residual material extracted with ethyl acetate (3x15 mL). The solution was washed with $NaHCO_3$, with brine, and dried over $MgSO_4$ before evaporation. The residual material was subjected to flash chromatography on silica gel using CH_2Cl_2: MeOH: NH_3(aq) 92:8:2. The title compound **25** was a white solid; yield 0.08 g (57%). HRMS (electrospray, H^+): M 732.4432. Calcd for $C_{39}H_{61}N_3O_{10}$ H^+: 732.4435; ^{1}H NMR(300 MHz; $CDCl_3$): δ 0.85 (3H, t, *J* = 7.3 Hz, CH_3), 1.16-1.29 (12H, m), 1.34-136 (6H, m), 1.46 (3H, s, CH_3), 1.57-1.70 (3H, m), 1.75-1.81 (1H, m), 1.83-1.95 (1H, m), 2.25 (6H, s, $N(CH_3)_2$), 2.39-2.50 (1H, m), 2.67 (3H, s), 2.71-2.87 (2H, m), 2.98 (3H, s), 3.10-3.20 (3H, m), 3.25-3.50 (1H, m), 3.68-3.72 (3H, m), 3.78 (1H, q, *J* = 6.7 Hz), 4.01 (1H, d, *J* = 6.1 Hz), 4.16 (3H, d, *J* = 8.9 Hz), 4.30 (1H, d, *J* = 7.3 Hz), 4.91 (1H, dd, *J* = 10.2, 2.2 Hz), 7.19-7.33 (5H, m); ^{13}C NMR (75 MHz; $CDCl_3$): δ 10.9 (CH_3), 14.8 (CH_3), 14.9 (CH_3), 16.8 (CH_3), 18.8 (CH_3), 20.2 (CH_3), 21.6 (CH_3), 23.0, 25.8, 28.6, 32.5, 39.7, 40.7, (CH_3x2), 45.8, 48.1, 48.3, 49.6, 51.9, 55.0, 61.9, 66.3, 70.0, 70.7, 78.8, 79.7, 82.9, 104.4, 128.3, 128.4, 128.9, 140.3 (C), 157.6 (C), 214.4 (C), 215.7 (C).

1*H*-Spiro[4,5-dihydropyrazol-5,10´-(2´´-*O*-acetyl-11´*N*,12´*O*-cyclocarbamate-11´-deshydroxy-10´-desmethyl-*O*$^{6´}$-methyl-3´-oxodescladinosylerythromycin) (27)

2´*O*-Acetyl-11*N*,12*O*-cyclocarbamate-11-deshydroxy-10-desmethyl-*O*^{6}-methyl-10-methylen-3-oxodescladinosylerythromycin A (**3**) (0.07 g, 0.11 mmol) was dissolved in CH_2Cl_2 (10 mL) and the solution cooled to 0 ^{o}C before trimethylsilyldiazomethane (2.0 M, 0.18 mL), 0.36 mmol) was added. The resultant solution was stirred at room temperature for 72 h. The reaction mixture was quenched with (aq) $NaHCO_3$, and the

mixture extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$), the solvent removed at reduced pressure and the residual material subjected to flash chromatography on silica gel using CH_2Cl_2:MeOH:NH_3(aq) 90:5:1. The desilylated product was a white solid; yield 33%. HRMS (Electrospray, H^+): M 695.3873. Calcd for $C_{34}H_{54}N_4O_{11}$: 695.3867; ^{1}H NMR (300 MHz; $CDCl_3$): δ 0.88 (3H, t, *J* = 7.3 Hz, CH_3), 0.95 (3H, d, *J* = 6.6 Hz, CH_3),1.20-1.32 (11H, m), 1.41 (3H, d, *J* = 6.9 Hz, CH_3), 1.59 (3H, s, CH_3), 1.65-1.72 (4H, m), 1.91-1.99, (2H, m), 2.06 (3H, s), 2.17 (6H, s, $N(CH_3)_2$), 2.78 (3H, s), 2.77-2.80 (2H, m.), 2.90-3.15 (1H, m), 3.56 (1H, s), 3.95 (1H, q, *J* = 7.0 Hz), 4.24 (1H, d, *J* = 6.9 Hz), 4.35 (1H, d, *J* = 7.5 Hz), 4.65-4.75 (1H, m), 5.03-5.08 (1H, m), 5.50 (1H, s, NH), 6.33 (1H, s, NH), 6.78 (1H, s); ^{13}C (75 MHz; $CDCl_3$): δ 10.7 (CH_3), 14.3 (CH_3), 17.8 (CH_3), 21.4 (CH_3), 21.6 (CH_3), 21.7 (CH_3), 22.0 (CH_3), 22.3 (CH_3), 28.1, 39.6, 30.9, 34.7, 39.4, 41.0, 42.3, 48.6, 50.9, 51.5, 62.0, 63.8, 69.5, 75.1, 75.9, 79.0, 79.9, 85.5, 101.9, 143.7, 157.0 (C), 170.2 (C), 171.1 (C), 208.2 (C), 215.3 (C).

6. References

[1] Gunnes, S.; Undheim, K. *Bioorg. Med. Chem.* **2007**, *15*, 119-129.

[2] Gunnes, S.; Rømming, C.; Undheim, K. *Tetrahedron* **2006**, *62*, 6090-6099

[3] Ruan, X.; Pereda, A.; Stassi, D. L.; Zeidner, D.; Summers, R. G.; Jackson, M.; Shivakumar, A.; Kakavas, S.; Staver, M. J.; Donadio, S.; Katz, L. *J. Bacteriol.* **1997**, *179*, 6416-6425.

[4] Katz, L.; Stassi, D. L.; Summers, R. G.; Ruan, X.; Pereda-Lopez, A.; Kakavas, S.; *WO* 98/51695, PCT 1998.

[5] Gu, Y. G.; Zhang, X.; Clark, R. F.; Djuric, S. W.; Ma, Z. *Tetrahedron Lett.* **2004**, 45, 3051-3053.

[6] Andrade, R. B. *Synlett* **2015**, *26*, 2199-2215.

[7] Velvadapu, V.; Paul, T.; Wagh, B., Glassford, I.; DeBrosse, C.; Andrade, R. B. *J. Org. Chem.* **2011**, *76*, 7516-7527.

[8] Velvadapu, V.; Glassford, I.; Lee, M.; Paul, T.; DeBrosse, C.; Klepacki, D.; Small, M. C.; MacKerell, A. D.; Andrade, R. B. *Med. Chem. Lett.* **2012**, *3*, 211-215.

[9] Zhanel, G. C.; Walters, M.; Noreddin, A.; Vercaigne, L. M.; Wierzbowski, A.; Embil, J. M ., Gin, A. S.; Douthwaite, S.; Hoban, D. J. *Drugs* **2002**, *62*, 1771-1804.

[10] Agouridas, C.; Denis, A.; Auger, J.-M.; Benedetti, Y.; Bonnefoy, A.; Bretin, F.; Chantot, J.-F.; Dussarat, A.; Fromentin, C.; D´Ambrires, S. G.; Lachaud, S.; Laurin, P.; Martret, O. L.; Loyau, V.; Tessot, N. *J. Med. Chem*. **1998**, *41*, 4080-4100.

[11] Asaka, T.; Manaka, A.; Sugiyama, H. *Curr. Top. Med. Chem*. **2003**, *3*, 961-989.

[12] Akritopoulou-Zanze, I.; Phelan, K. M. ; Marron, T. G. ; Yong, H. ; Ma, Z. ; Stone, G. G. ; Daly, M. M. ; Hensey, D. M.; Nilius, A. M.; Djuric, S. W. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 3809-3813.

[13] Beebe, X.; Yang, F.; Bui, M. H.; Mitten, M. J.; Ma, Z.; Nilius, A. M.; Djuric, S. W. *Biorg. Med. Chem. Lett.* **2004**, *14*, 2417-2421.

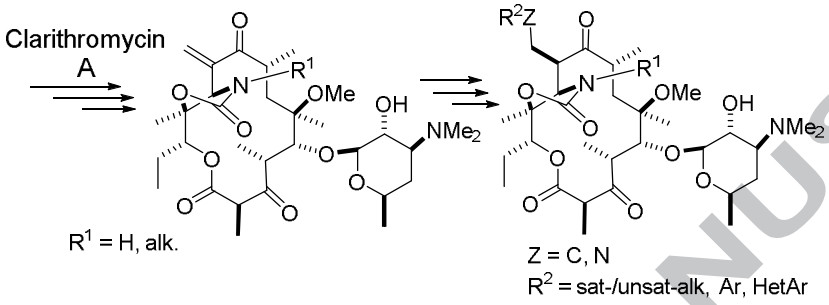
[14] Baker, W. R.; Clark, J. D.; Stephens, R. L.; Kim, K. H. J. *J. Org. Chem.* **1988**, *53*, 2340-2345.

[15] 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.; Muelbroek, J.; Ewing, P.; Alder, J.; Or, Y. S. *J. Med. Chem.* **2001**, *44*, 4137-4156.

[16] Burger, M. T.; Lin, X.; Chu, D. T.; Hiebert, C.; Rico, A. C.; Seid, M.; Caroll, G. L.; Barker, L.; Huh, K.; Langhorne, M.; Shawar, R.; Kidney, J.; Young, K.; Anderson, S.; Desai, M. C.; Plattner, J. J. *J. Med. Chem*. **2006**, *49*, 1730-1743.

[17] Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that grow Aerobically: NCCLS Document M7-A7, **2006**.

Graphical Abstract



CAPTIONS:

Schemes:

Scheme 1. Reagents and conditions: (i) CDI, NaH, 0 ^{o}C to rt 17 h; (ii) NH_3(aq), MeCN, THF, rt, 48 h. (iii) (a) NaH, THF, 0 ^{o}C; (b) CDI, rt, 17 h; (iv) NH_3(aq), MeCN, THF, rt, 17 h.

Scheme 2. Reagents and conditions: (i) $R^1(CH_2)_nNH_2$, THF, reflux, 48 h; (ii) MeOH, rt, o.n.; (iii) $PhCH(Me)NH_2$, THF, reflux, 60 h; (iv); MeOH, rt, o.n.

Scheme 3. Reagents and conditions (i) (a) Bu_3SnPh, $Pd_2dba_3.CHCl_3$, NMP, 90 ^{o}C, o.n., (b) Bu_3SnR^1, $Pd_2dba_3.CHCl_3$, DMF, 80-90 ^{o}C, o.n.; (ii) Ac_2O, NEt_3, CH_2Cl_2, rt, 17 h; (iii) DMP, CH_2Cl_2, rt, 3 h; (iv) CDI, NaH, THF, 0 ^{o}C, 20 h; (v) NH_3(aq), MeCN, THF, rt, 48 h; (vi) MeOH, rt, 14 h.

Scheme 4. Reagents and conditions: (i) $R^1CH_2R^2$, NaH, THF, 0 ^{o}C to rt; (ii) MeOH, rt, o.n., $BnNHCOCH_2CN$, NaH, THF, 0 ^{o}C to rt.

Scheme 5. Reagents and conditions: (i) $BnNH_2$, THF, MeCN, rt, 40 h; (ii) MeOH, rt, 24 h; (iii) $MeNH_2$ (40%), THF, MeCN, rt, 60 h; (iv) PhCHO, $NaB(OAc)_3$, THF, rt, 22 h; (v) (v) $BnNH_2$, THF, reflux, 60 h; (vi) $TMSCHN_2$, CH_2Cl_2, 0 ^{o}C-rt, 72 h.

Scheme 6. Reagents and conditions: (i) $TMSCHN_2$, CH_2Cl_2, 0 ^{o}C-rt, 72 h.

Figures:

Fig. 1 Structure relationships between clarithromycin and targeted 10-substituted 3-ketolides.

Fig. in Table 1. Structures of selected compounds tested for *in vitro* activity against *S. pneumoniae and S. aureus.*

Table:

Table 1. In vitro activity of selected C10-substituted ketolides against selected strains of the respiratory pathogens *S. pneumoniae* and *S.aureus.* Minimum inhibitory concentration (MIC) values are given in micrograms per milliliter.