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Novel Tandem Reaction for the Synthesis of *N*′-Substituted 2-Imino-1,3-oxazolidines from Vicinal (*sec*- or *tert*-)Amino Alcohol of Desosamine

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Two one-pot methods, sequential and tandem, for the preparation of *N*′-substituted 2-imino-1,3-oxazolidines from the vicinal (*sec*- or *tert*)-amino alcohol of desosamine via intermediary alkyl-, aryl-, heteroaryl-, and heteroalkyl-thiourea moieties are described. Particularly interesting is the novel one-pot tandem reaction of the vicinal *tert*-amino alcohol that involves dealkylation, thiourea formation, and a final cyclization to yield 2-imino-1,3-oxazolidine structures. The yields of both one-pot methods are comparable to the yield of the sequential reaction. A small library of a new class of desosamine-modified 14- and 15-membered macrolides was prepared to demonstrate the variety of substituents that can be easily introduced and thus enable a huge variation of the physicochemical and hence biological properties of these new molecules.

Introduction

Macrolide antibiotics have been used for the treatment of bacterial infections for more than 50 years.[1] However, it seems that the broad potential of macrolides against other biological agents has still to be fully discovered. For example, 14- and 15-membered macrolide antibiotics are of interest for the treatment of important chronic diseases such as asthma, chronic sinusitis, diffuse panbronchiolitis, and cystic fibrosis,[2] whereas some also have proved to be active in the treatment of malaria[3] and cancer.[4]

To improve the biological properties of standard antibacterial macrolides, bridging of the macrocyclic lactone ring of antibacterial macrolides appeared to be a very promising chemical transformation.[5] However, to the best of our knowledge, only one example of the bridging of desosamine functional groups has been reported that did not allow the possibility for the easy incorporation of various substituents.[6] Because desosamine occurs in diverse natural antibacterial macrolides and is directly involved in the binding of macrolides to ribosome through a network of hydrogen bonds and ionic interactions, new reactions that provide the easy incorporation of the bridge carrying various substituents would be of great significance.

In the course of our studies of macrolide transformations, we recently revealed a novel method for the synthesis of a new class of bicyclic 9a,11-bridged 15-membered azalides. This one-pot procedure involves the cyclization of a secondary amine at the 9a-position and the vicinal hydroxy group at C-11 via intermediate 9a-thiocarbamoyls to afford an *N*′-substituted 2-imino-1,3-oxazolidine moiety condensed to an azalide aglycon.[7] We envisioned that demethylation of the 3′-dimethylamino group of desosamine would provide another vicinal secondary amino alcohol unit suitable for the construction of an *N*′-substituted 2-imino-1,3-oxazolidine moiety between the 2′- and 3′-positions of the desosamine ring of various macrolide scaffolds. However, steric hindrance around the desosamine ring is quite different in comparison to the 9a,11 part of the azalide aglycon in which the secondary amine is a part of the macrocyclic ring and thus the outcome of the reaction would be uncertain.

Results and Discussion

3′-*N*-Demethylation of desosamine is a fairly well-known process that can be achieved by using several reagents,[8] for example, sodium acetate/iodine,[9] sodium acetate/iodine/tris-(hydroxymethyl)aminomethane,[10] diethyl azodicarboxylate,[11] *N*-iodosuccinimide,[12] and benzoyl chloroformate.[13] To test the possibility of forming 2-imino-1,3-oxazolidines on a desosamine sugar, we first chose three different antibacterial macrolide scaffolds and removed one methyl from the 3′-dimethylamino group. The sodium acetate/iodine

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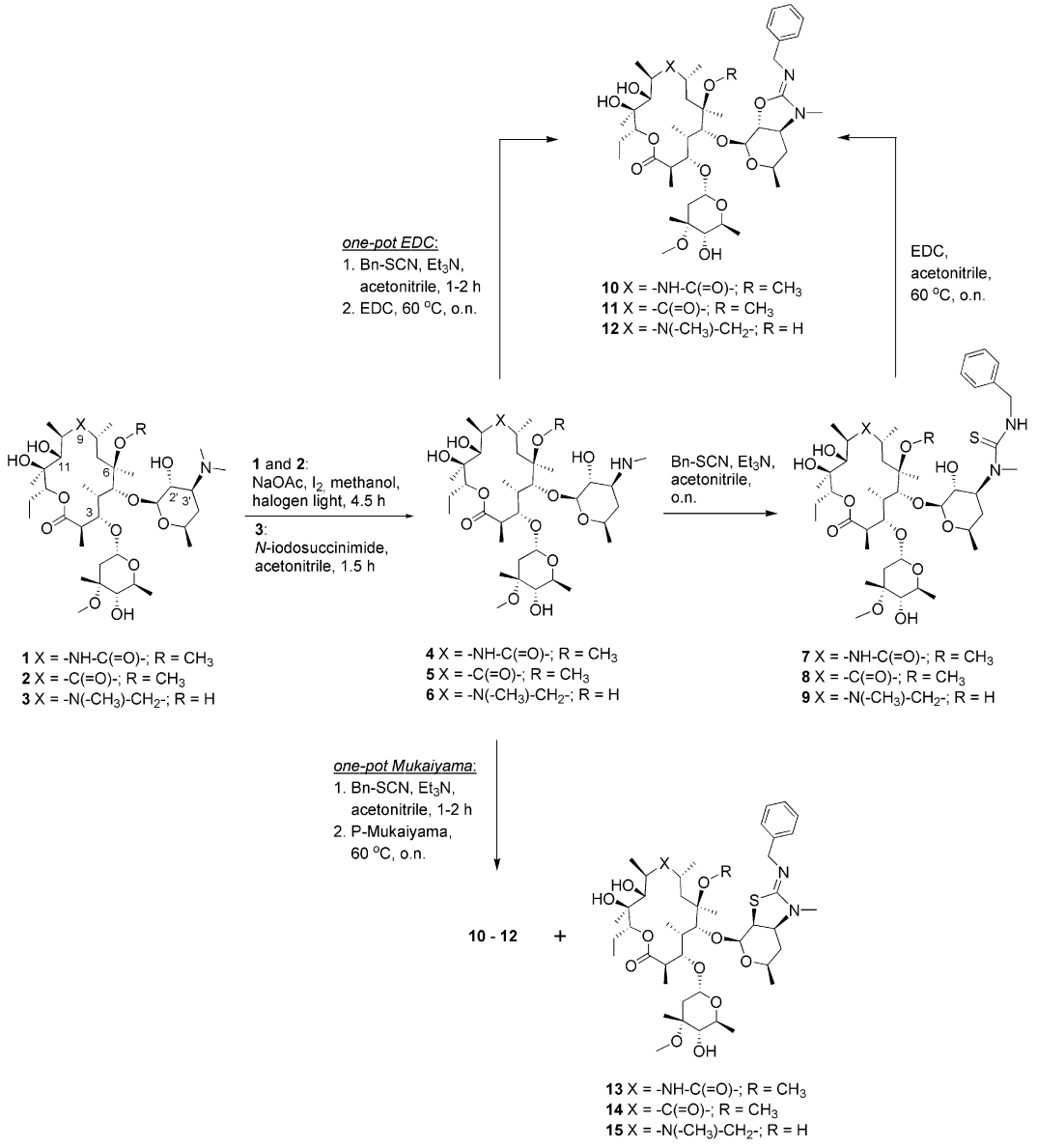


Scheme 1. Stepwise and sequential one-pot synthesis of *N*′-substituted 2-imino-1,3-oxazolidines from the vicinal *sec*-amino alcohol of desosamine.

method using halogen light irradiation proved to be effective for the preparation of 3′-*N*-demethyl-6-*O*-methyl-9a-aza-9a-homoerythromycin A (**4**) and 3′-*N*-demethyl-6-*O*-methylerythromycin A (**5**), whereas *N*-iodosuccinimide was found to be an optimal demethylation reagent for the preparation of 3′-*N*-demethyl-9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A (**6**; Scheme 1).

The use of *N*-iodosuccinimide for the demethylation 3′-amino group of **3** increases the conversion and reduces the amount of side-products (for example, demethylation of the nitrogen at the 9a-position) observed with other methods. Having the desired vicinal amino alcohols **4**–**6** in hand, we first examined whether thioureas formed at the 3′-position of desosamine (3′-thiocarbamoylamino derivatives) would react with the vicinal 2′-hydroxy group to form the desired five-membered 1,3-oxazolidine ring. Therefore, *N*′-benzylthioureas attached to the 3′-position (**7**–**9**) were prepared on demethylated scaffolds **4**–**6** by reaction with benzyl isothiocyanate using a similar procedure to that described earlier for the formation of thioureas at the N-9a position.[7] Cyclization of the *N*′-benzylthiourea derivatives **7**–**9** by using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) in chloroform readily afforded the desired 1,3-oxazolidine compounds **10**–**12** (Scheme 1).

When we had proved that the cyclization of 3′-thiourea derivatives could be easily achieved, the next step was to apply the sequential one-pot procedure[7] for the synthesis of **10**–**12** by using either EDC in solution or polymer-supported Mukaiyama reagent (*N*-methyl-2-chloropyridinium salt). The demethylated compounds **4**–**6** were treated with benzyl isothiocyanate and after 2 h EDC or the Mukaiyama reagent was added to the reaction mixture

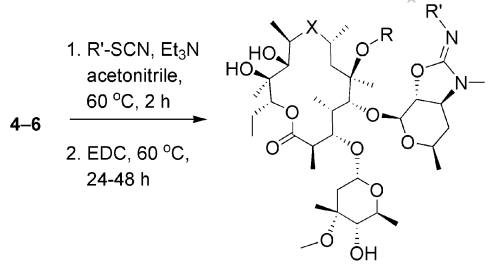
(Scheme 1). The one-pot method using EDC afforded the desired *N*′-benzyl-2-imino-1,3-oxazolidine structures annulated to the desosamine ring (**10**–**12**) in comparable yields to the two-step procedure. Surprisingly, cyclization using the Mukaiyama reagent, either polymer-supported or in solution, proved faster and a better choice for the 9a,11 cyclization of azalides,[7] and in this case resulted in the formation of substantial amounts of side products **13**–**15** (Scheme 1).

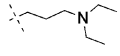
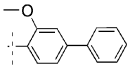
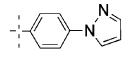
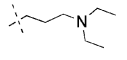
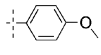
Although side-products **13**–**15** could not be separated by column chromatography, a sufficient amount of **15** was isolated by preparative HPLC and its structure was elucidated. NMR and mass spectrometry data for **15** proved that instead of the oxazolidine moiety, the *N*′-benzyl-2-imino-1,3-thiazolidine ring is condensed onto desosamine. The ^{1}H NMR spectrum shows that the signals of 2′-H and 3′-H of thiazolidine compound **15** are shifted downfield in comparison to those of **12** (4.01 and 3.62 ppm vs. 3.61 and 2.82 ppm, respectively). Also, the ^{13}C NMR spectrum shows a high upfield shift of C-2′ of **15** to 46.2 ppm (δ = 80.4 ppm for **12**). The coupling constant between 2′-H and 1′-H of 2.5 Hz in **15**, compared with 8.0 Hz in **12**, indicates that the configuration at C-2′ is inverted in **15**. Note that the formation of *N*-cyclized products was not observed.[14]

Because the Mukaiyama reagent failed to yield pure products, we used the sequential one-pot procedure with 3 equiv. of the corresponding isothiocyanate and 4 equiv. of EDC to prepare a series of novel 2′,3′-bridged macrolides **16**–**29** with various substituents attached to the *N*′-position of the condensed 2-imino-1,3-oxazolidine moiety (Scheme 2). It has been demonstrated that even bulky substituents like adamantane (**19**) can be easily attached to the desosamine through the 1,3-oxazolidine moiety. All new compounds were identified by NMR and MS spectra.

Our desire to optimize this method for the larger-scale production of 2′,3′-*N*′-substituted 2-imino-1,3-oxazolidines led to the discovery of a very interesting tandem reaction of the vicinal *tert*-amino alcohol of the desosamine. To decrease the EDC excess that is required, we examined the effect of the addition of $CuCl_2$ as co-reagent, the combination of which has previously been used in dehydration reactions,[15] to our model synthesis of **10**–**12**. To our surprise, we found that even 2 equiv. of $CuCl_2$ alone, without EDC, also afforded *N*′-benzyl-2-imino-1,3-oxazolidines **10**–**12** in a one-pot reaction from 3′-demethylamino macrolides **4**–**6**.

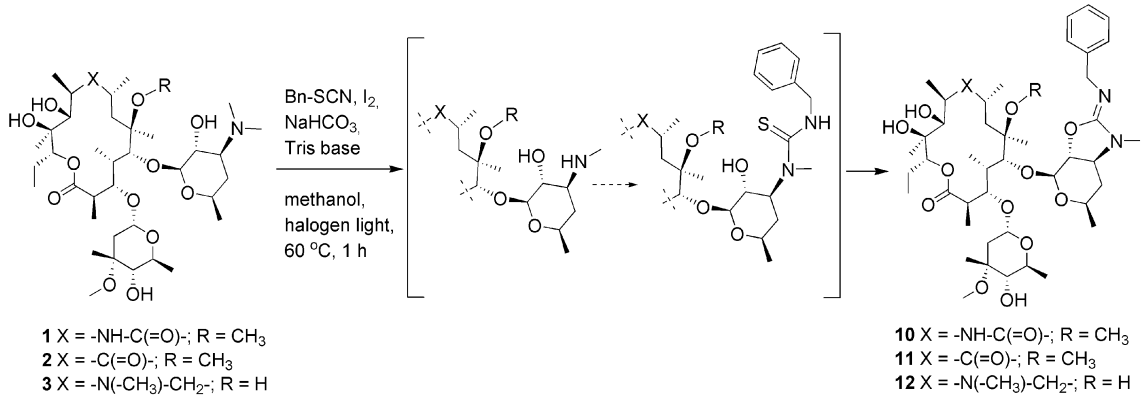
This result led to the conclusion that other simple thiophilic reagents that react with thiourea sulfur[16] could be used in this one-pot synthesis of *N*′-substituted 2-imino-1,3-oxazolidines. The only requirement would be that the reagent should have a very low reactivity towards the secondary amine at the 3′-position. In this sense, a recently published "green" protocol describing carbodiimide preparation from thioureas using only iodine and triethylamine as reagents attracted our attention.[17] Because we used iodine and a base for the 3′-*N*-demethylation of macrolides (see Scheme 1), we reasoned that the formation of *N*′-substituted 2-imino-1,3-oxazolidines on desosamine could also be achieved from non-demethylated 14- and 15-membered antibacterial macrolides **1**–**3**.



	X	R	R'	Yield (%)
16		CH_3		56
17		CH_3		53
18		CH_3		64
19		CH_3		36
20		CH_3		48
21		CH_3		41
22		CH_3		20
23		CH_3		55
24		CH_3		71
25		H		64
26		H		54
27		H		44
28		H		57
29		H		31

Scheme 2. Synthesis of novel 2′,3′-bridged macrolides having various substituents attached to the *N*′-position. Yields were calculated after chromatographic purification.

Indeed, when benzyl isothiocyanate was added to the reaction mixture used for the 3′-*N*-demethylation of **1**–**3**, reasonable amounts of oxazolidines **10**–**12** were obtained. Optimization of the reaction conditions resulted in a novel one-pot tandem reaction for the construction of *N*′-benzyl-2-imino-1,3-oxazolidines condensed onto desosamine (Scheme 3). The reagent mixture includes iodine, sodium hydrogen carbonate as base, tris(hydroxymethyl)aminomethane (Tris base)[9] for quenching the produced formaldehyde, and methanol as solvent.



Scheme 3. Tandem one-pot synthesis of *N*′-substituted 2-imino-1,3-oxazolidines from the vicinal *tert*-amino alcohol of desosamine.

In this tandem reaction macrolides **1**–**3** are first demethylated at the 3′-amino substituent, 3′-thioureas are then readily formed, and finally cyclization to *N*′-benzyl-2-imino-1,3-oxazolidines **10**–**12** occurs. Slightly larger excesses of iodine (6 equiv.) and isothiocyanate (5 equiv.) are needed but the reaction is finished in only 1 h under irradiation with halogen light. The yields of this tandem reaction are also comparable to the overall yields of either the sequential one-pot or stepwise procedures that start from macrolides **1**–**3** (Table 1). The somewhat lower yield obtained in the tandem reaction of **3** can be attributed to non-optimal demethylation conditions. Importantly, the formation of thiazolidine side-products was not observed.

Table 1. Comparison of the overall yields of the three methods of the model reaction for the synthesis of **10**–**12** starting from **1**–**3**.

Starting compound	Overall yields [%] Stepwise	Sequential one-pot	Tandem
1	38	45	60
2	36	64	56
3	49	40	35

To find out which stereoisomer around the imine double bond is formed, the crystal and molecular structure of a hexane/water solvate of the macrolide compound **28** (Figure 1) was determined by single-crystal X-ray diffraction analysis. In the crystallographic asymmetric unit, three macrolide molecules, four water molecules, and one hexane molecule were modeled. The hexane molecule is found in a large hydrophobic void. Its thermal motion is more pronounced, as can be easily seen from its thermal parameters, and is larger than those found in other molecules. This is in agreement with the observation that crystals lose solvent upon exposure to air, which results in the disordered crystal structure.

The molecular structure of **28** is characterized by a 15-membered macrocyclic ring and a desosamine moiety that is constrained by the introduction of a five-membered 2-imino-1,3-oxazolidine ring at the 2′- and 3′-positions. The *Z* configuration of the imine double bond was unambigu-

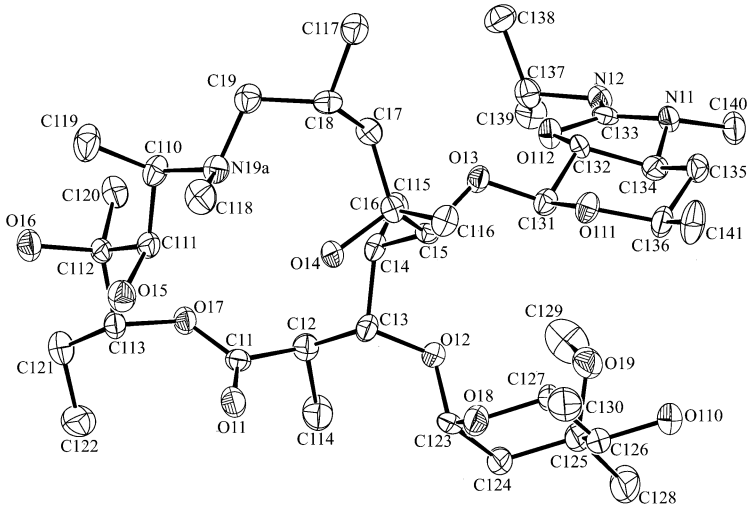


Figure 1. A view of the molecular structure of compound **28**. Displacement ellipsoids are drawn at the 50% probability level and hydrogen atoms have been omitted for clarity. Only one molecule is shown. The other two molecules are essentially identical in appearance and have the same atom-numbering scheme but starting with 2 (e.g., atom C123 in molecule 1 is labeled C223 in molecule 2).

ously confirmed, as it was in the case of the 9a,11 series.[7] Most probably, possible steric influence of the neighboring 3-*N*-methyl group of the oxazolidine ring prevents the formation of the *E* isomer. Because the NMR data for all the new compounds show a similar pattern for the desosamine moiety, we believe that the same orientation is present in all the prepared compounds.

The conformations of the crystallographically independent molecules differ significantly (Figure 2). The main difference in the conformations of the 15-membered macrocycle is the orientation of the substituents (although all macrocycles are found in the folded-in conformation). Other significant differences between the molecular geometries are in the positions of the cladinose and desosamine moieties, and in the conformations of their substituents. The bond lengths are typical of the corresponding chemical groups.[18] Oxygen atoms O1, O4, and O5 (in molecules 1 and 2) point outwards from the ring in the same direction, thereby forming a hydrophilic pocket suitable for the accommodation of a water molecule. Water molecules participate in hydrogen bonding, both "transferring" the hydrogen-bonding interactions throughout the crystal structure and "supporting" the molecular conformation. The intramolecular hydrogen bond between the methylated nitrogen atom (of the 15-membered lactone ring) and the hydroxy oxygen seems to be characteristic of such compounds. The crystal packing is characterized by hydrogen-bonding interactions between the molecules. The hexane molecules are held together by weak van der Waals contacts and relatively close H···H contacts (Figure 3).

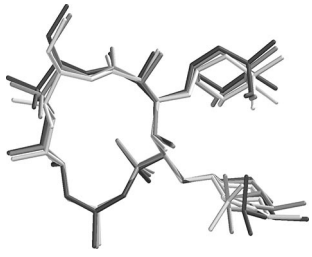


Figure 2. Superposed molecules from the asymmetric unit. Hydrogen atoms have been omitted for clarity.

Conclusions

We have described stepwise, sequential one-pot, and tandem reactions for the preparation of *N′*-substituted 1,3-oxazolidines from the vicinal (*sec*- or *tert*-)amino alcohol of desosamine via alkyl-, aryl-, heteroaryl-, and heteroalkylthiourea intermediates. Particularly interesting is the novel one-pot tandem reaction of the vicinal *tert*-amino alcohol that involves dealkylation, thiourea formation, and a final cyclization to yield 2-imino-1,3-oxazolidine structures. The yields of both the one-pot and tandem methods are comparable to the yields of the stepwise reaction. This reaction provides only the *Z* isomer of the imine double bond, which was proved by X-ray diffraction analysis. The scope and limitations of this reaction is currently being investigated. However, the results presented herein indicate that it can be applied to various vicinal (*sec*- or *tert*-)amino alcohols. A small library of a novel class of desosamine-modified 14- and 15-membered macrolides was prepared to demonstrate the variety of substituents that can be easily introduced and thus enable a huge variation of the physicochemical and hence biological properties of these new molecules.

Experimental Section

General: All solvents and reagents were used as supplied unless noted otherwise. IR spectra were recorded with a Nicolet Magna-IR 760 FT-IR spectrometer (KBr). Mass spectra were recorded with a Varian MAT 311 (FAB) and Platform LCZ or LCQ Deca (ESI) spectrometers. HRMS (ESI) were recorded with a Micromass

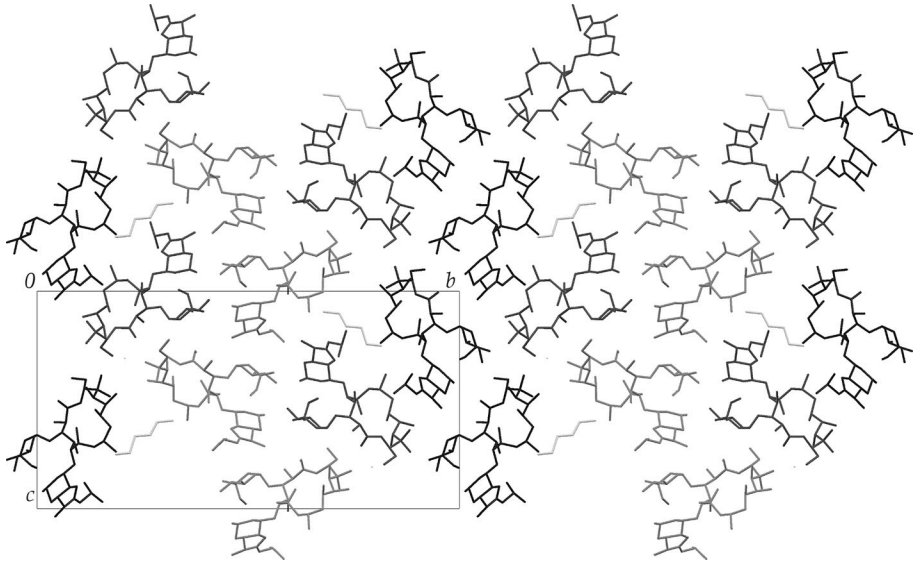


Figure 3. The crystal packing of the hexane/water solvate of the macrolide compound **28** viewed down the crystallographic *a* axis. Hydrogen atoms have been omitted for clarity. Molecules are colored by symmetry equivalence.

Qtof2 spectrometer. NMR spectra were recorded at 25 °C in $CDCl_3$ and [D_6]DMSO with TMS as the internal standard with Bruker Avance DRX500 and Avance III 600 spectrometers equipped with a 5 mm diameter inverse detection probe with a *z*-gradient accessory, as well as with a Bruker Avance DPX300 spectrometer using a dual $^1H/^{13}C$ probe. For characterization of complex organic structures 1D (^1H and APT) and 2D (COSY, HMQC and HMBC) NMR techniques were used.

General Procedure for the Stepwise Synthesis

Step 1: Triethylamine (1 equiv.) and benzyl isothiocyanate (2 equiv.) were added to a solution of 3′-*N*-demethylated macrolides **4**–**6** in acetonitrile (c = 0.03 g/mL). The reaction mixture was stirred at room temperature for 24 h. After evaporation of the solvent the crude product was purified by using Flashmaster II solid-phase extraction techniques using a gradient solvent system [eluent: 1.5% CH_3OH/CH_2Cl_2 to $CH_3OH/CH_2Cl_2/NH_4OH$ (4.5:90:0.25)] to afford products **7**–**9**.

Step 2: EDC (2 equiv.) was added to a solution of **7**–**9** in chloroform (c = 0.03 g/mL). The reaction mixture was stirred at 60 °C for 24 h and then extracted with a saturated aqueous $NaHCO_3$ solution, brine, and water, and then dried with K_2CO_3. After evaporation of the solvent the crude product was purified by using Flashmaster II solid-phase extraction techniques [eluent: 1.5% CH_3OH/CH_2Cl_2 to $CH_3OH/CH_2Cl_2/NH_4OH$ (4.5:90:0.25)] to give products **10**–**12**.

General Procedure for the Sequential One-Pot Synthesis: The corresponding isothiocyanate (3 equiv.) and triethylamine (6 equiv.) were added to a solution of 3′-*N*-demethyl derivatives **4**–**6** in acetonitrile (c = 0.02 g/mL). The reaction was stirred at 60 °C for 2 h and then EDC (4 equiv.) was added. The reaction mixture was further stirred at 60 °C for 24–48 h. Completion of the reaction was checked by LC-MS. The solvent was evaporated and the residue purified by using Flashmaster Personal solid-phase extraction techniques [eluent: 1.5% MeOH/CH_2Cl_2 to MeOH/CH_2Cl_2/NH_4OH (4.5:90:0.25)] to afford the title products.

General Procedure for the Tandem One-Pot Synthesis: Benzyl isothiocyanate (5 equiv.), iodine (6 equiv.), tris(hydroxymethyl)aminomethane (1.2 equiv.), and sodium hydrogen carbonate (10 equiv.) were added to a solution of standard macrolide **1**–**3** in acetonitrile (c = 0.025 g/mL). The reaction was stirred and irradiated with a 500 W halogen light for 2 h. The solvent was evaporated and the residue dissolved in dichloromethane (50 mL) and washed with a saturated aqueous $NaHCO_3$ solution. The organic layer was dried with Na_2SO_4, evaporated, and the residue purified by using solid-phase extraction techniques [eluent: 1.5% MeOH/CH_2Cl_2 to MeOH/CH_2Cl_2/NH_4OH (4.5:90:0.25)] to afford the title products.

3′-*N*-Demethyl-6-*O*-methyl-9a-aza-9a-homoerythromycin A (4):[19] Solid iodine (3.9 g, 15.4 mmol) was added to a stirred solution of **1** (10 g, 13.2 mmol) and sodium acetate trihydrate (3.7 g, 27.2 mmol) in methanol (250 mL). The reaction mixture was irradiated with a 500 W halogen light for 5 h and then stirred at room temperature overnight. The solvent was evaporated, the solid residue dissolved in ethyl acetate (250 mL), filtered, and the filtrate washed with saturated aqueous Na_2SO_3 (3 × 100 mL) and NaCl (1 × 100 mL). Ethyl acetate (100 mL) was added to the combined Na_2SO_3 layer (300 mL), the pH was adjusted to 9, the layers were separated, and the aqueous layer extracted again with ethyl acetate (2 × 100 mL). The combined organic layers were dried with Na_2SO_4 and evaporated to afford the crude product (9.7 g), which was crystallized from ethyl acetate/*n*-hexane to afford the title product (7.3 g). ^1H NMR (500 MHz, $CDCl_3$): δ = 6.04 (9a-NH), 4.80 (1′′-H), 4.64 (13-H), 4.39 (1′-H), 4.16 (3-H), 4.13 (10-H), 4.02 (5′′-H), 3.72 (5-H), 3.52 (5′-H), 3.30 (3′′-OCH_3), 3.27 (6-OCH_3), 3.17 (2′-H), 3.17 (11-H), 3.00 (4′′-H), 2.77 (2-H), 2.54 (3′-H), 2.43 (3′-NCH_3), 2.29 (2′′-H_a), 2.17 (8-H), 1.99 (7-H_a), 1.92 (4′-H_a), 1.85 (4-H), 1.84 (14-H_a), 1.52 (2′′-H_b), 1.52 (14-H_b), 1.31 (6-CH_3), 1.28 (5′′-CH_3), 1.24 (7-H_b), 1.22 (3′′-CH_3), 1.20 (2-CH_3), 1.19 (5′-CH_3), 1.17 (4′-H_b), 1.14 (12-CH_3), 1.13 (10-CH_3), 1.06 (8-CH_3), 0.94 (4-CH_3), 0.86 (15-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.8 (C-1), 177.7 (C-9), 102.2 (C-1′), 95.5 (C-1′′), 79.5 (C-6), 79.0 (C-5), 78.5 (C-13), 78.1 (C-4′′), 76.2 (C-3), 74.5 (C-2′), 74.4 (C-12), 73.0 (C-3′′), 72.9 (C-11), 68.4 (C-5′), 66.0 (C-5′′), 60.3 (C-3′), 51.7 (6-OCH_3), 49.6 (3′′-OCH_3), 45.5 (C-10), 44.9 (C-2), 41.6 (C-4), 40.2 (C-7), 37.0 (C-4′), 36.0 (C-8), 34.9 (C-2′′), 32.3 (3′-NCH_3), 21.7 (3′′-CH_3), 21.4 (5′-CH_3), 20.9 (C-14), 20.8 (6-CH_3), 19.8 (8-CH_3), 18.7 (5′′-CH_3), 16.3 (12-CH_3), 15.3 (2-CH_3), 14.0 (10-CH_3), 11.3 (15-CH_3), 9.8 (4-CH_3) ppm. MS (ES^+): m/z = 749.3 $[MH]^+$.

3′-*N*-Demethyl-6-*O*-methylerythromycin A (5):[12] Solid iodine (3.8 g, 15.0 mmol) was added to a stirred solution of **2** (10 g, 13.4 mmol) and sodium acetate trihydrate (5.8 g, 42.6 mmol) in methanol (250 mL). The reaction mixture was irradiated with a 500-W halogen tungsten bulb for 4 h, cooled to room temperature, and the solvent evaporated. The residue was dissolved in ethyl acetate (500 mL), washed with a saturated aqueous $NaHCO_3$ solution (2 × 100 mL), dried with Na_2SO_4, and evaporated to give the crude product (12.4 g), which was purified by column chromatography [$CH_2Cl_2/CH_3OH/NH_4OH$ (90:9:1.5)] to afford the title product (9.35 g). MS (ES^+): m/z = 734.3 $[MH]^+$.

3′-*N*-Demethyl-9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A (6):[20] A solution of **3** (10 g, 13.3 mmol) and *N*-iodosuccinimide (7.5 g, 33.3 mmol) in acetonitrile (250 mL) was stirred at room temperature for 1.5 h. The acetonitrile was evaporated and the solid residue dissolved in CH_2Cl_2 (300 mL), washed with saturated aqueous Na_2SO_3 (5 × 70 mL) and saturated aqueous $NaHCO_3$ (5 × 70 mL) solutions, dried with Na_2SO_4, and evaporated to afford 10.78 g of a yellowish solid. The solid residue was dissolved in a mixture of water (100 mL) and CH_2Cl_2 (50 mL), the pH was adjusted to 4.1, and the layers separated. Extraction at pH 4.1 was repeated twice with CH_2Cl_2 (2 × 50 mL). Fresh CH_2Cl_2 (200 mL) was added to the aqueous layer, the pH was adjusted to 9.3, and the solution extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts at pH 9.3 were dried with Na_2SO_4 and evaporated to afford the title product (8.8 g) as a white solid. MS (ES^+): m/z = 735.2 $[MH]^+$.

3′-*N*-(Benzylthiocarbamoyl)-3′-*N*-demethyl-6-*O*-methyl-9a-aza-9a-homoerythromycin A (7): According to step 1 of the stepwise general procedure, the reaction of **4** (0.33 g, 0.44 mmol) afforded **7** (0.26 g, 66%) as a white foam. ^1H NMR (500 MHz, $CDCl_3$): benzyl: δ = 7.28 (2 CH), 7.23 (2 CH), 7.20 (CH), 4.82 (CH_2) ppm; macrolide: δ = 6.09 (9a-NH), 4.76 (1′′-H), 4.60 (13-H), 4.52 (1′-H), 4.12 (10-H), 4.09 (3-H), 3.99 (5′′-H), 3.73 (5-H), 3.62 (5′-H), 3.27 (2′-H), 3.26 (6-OCH_3), 3.26 (3′′-OCH_3), 3.13 (11-H), 2.98 (4′′-H), 2.75 (2-H), 2.62 (3′-H), 2.27 (2′′-H_a), 2.16 (8-H), 1.95 (7-H_a), 1.82 (4-H), 1.77 (4′-H_a), 1.77 (14-H_a), 1.50 (2′′-H_b), 1.50 (14-H_b), 1.23 (7-H_b), 1.42 (4′-H_b), 1.31 (6-CH_3), 1.20 (3′-NCH_3), 1.18 (2-CH_3), 1.18 (5′′-CH_3), 1.18 (3′′-CH_3), 1.16 (5′-CH_3), 1.10 (10-CH_3), 1.09 (12-CH_3), 1.09 (8-CH_3), 0.91 (4-CH_3), 0.83 (15-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): benzyl: δ = 138.1 (C), 130.0 (2 CH), 128.2 (2 CH), 127.9 (CH), 50.6 (CH_2) ppm; macrolide: δ = 184.5 (C=S), 179.9 (C-1), 177.5 (C-9), 102.9 (C-1′), 95.5 (C-1′′), 79.6 (C-5), 79.4 (C-6), 78.6 (C-13), 78.1 (C-4′′), 76.2 (C-3), 74.4 (C-12), 73.0 (C-3′′), 73.0 (C-2′), 72.9 (C-11), 68.3 (C-5′), 66.2 (C-5′′), 60.8 (C-3′), 51.7 (6-OCH_3), 49.7 (3′′-OCH_3), 45.6 (C-10), 44.8 (C-2),

41.4 (C-4), 40.3 (C-7), 36.5 (C-4′), 35.8 (C-8), 35.0 (C-2′′), 29.9 (3′-NCH_3), 21.8 (3′′-CH_3), 21.8 (6-CH_3), 21.3 (5′-CH_3), 20.9 (C-14), 19.7 (8-CH_3), 18.7 (5′′-CH_3), 16.3 (12-CH_3), 15.4 (2-CH_3), 14.1 (10-CH_3), 11.4 (15-CH_3), 9.9 (4-CH_3) ppm. HRMS (ES): calcd. for $C_{45}H_{76}N_3O_{13}S$ $[M + H]^+$ 898.5099; found 898.5113.

3′-*N*-(Benzylthiocarbamoyl)-3′-*N*-demethyl-6-*O*-methylhomoerythromycin A (8): According to step 1 of the stepwise general procedure, the reaction of **5** (0.36 g, 0.48 mmol) afforded **8** (0.42 g, 65%) as a white foam. ^{1}H NMR (500 MHz, DMSO): benzyl: δ = 7.41 (2 CH), 7.35 (2 CH), 7.19 (CH), 4.83 (CH_2) ppm; macrolide: δ = 8.30 (9a-NH), 4.77 (1′′-H), 5.04 (13-H), 4.42 (1′-H), 2.95 (10-H), 3.61 (3-H), 4.06 (5′′-H), 3.64 (5-H), 3.79 (5′-H), 3.20 (2′-H), 2.96 (6-OCH_3), 3.23 (3′′-OCH_3), 3.64 (11-H), 2.90 (4′′-H), 2.79 (2-H), 2.89 (3′-H), 2.26 (2′′-H_a), 2.54 (8-H), 1.76 (7-H_a), 1.85 (4-H), 1.63 (4′-H_a), 1.81 (14-H_a), 1.53 (2′′-H_b), 1.39 (14-H_b), 1.47 (7-H_b), 1.33 (4′-H_b), 1.30 (6-CH_3), 2.91 (3′-NCH_3), 1.01 (2-CH_3), 1.17 (5′′-CH_3), 1.12 (3′′-CH_3), 1.08 (5′-CH_3), 1.02 (10-CH_3), 1.01 (12-CH_3), 1.04 (8-CH_3), 1.03 (4-CH_3), 0.74 (15-CH_3) ppm. ^{13}C NMR (125 MHz, DMSO): benzyl: δ = 139.9 (C), 128.8 (2 CH), 128.0 (2 CH), 127.1 (CH), 48.3 (CH_2) ppm; macrolide: δ = 184 (C=S), 175 (C-1), 218.5 (C-9), 102.0 (C-1′), 95.7 (C-1′′), 79.1 (C-5), 77.9 (C-6), 75.9 (C-13), 77.2 (C-4′′), 76.9 (C-3), 74.2 (C-12), 72.4 (C-3′′), 71.0 (C-2′), 68.9 (C-11), 66.5 (C-5′), 65.0 (C-5′′), 60 (C-3′), 50.2 (6-OCH_3), 49.0 (3′′-OCH_3), 39.2 (C-10), 44.3 (C-2), 38.5 (C-4), 39.0 (C-7), 35.6 (C-4′), 43.4 (C-8), 34.8 (C-2′′), 30 (3′-NCH_3), 20.8 (3′′-CH_3), 19.9 (6-CH_3), 21.2 (5′-CH_3), 20.9 (C-14), 17.7 (8-CH_3), 18.9 (5′′-CH_3), 17.0 (12-CH_3), 15.7 (2-CH_3), 11.8 (10-CH_3), 10.5 (15-CH_3), 9.0 (4-CH_3) ppm. HRMS (ES): calcd. for $C_{45}H_{75}N_2O_{13}S$ $[M + H]^+$ 883.4990; found 883.4987.

3′-*N*-(Benzylthiocarbamoyl)-3′-*N*-demethyl-6-*O*-methyl-9-deoxo-9a-aza-9a-homoerythromycin A (9): According to step 1 of the stepwise general procedure, the reaction of **6** (0.1 g, 0.14 mmol) afforded **9** (0.11 g, 85%) as a white foam. ^{1}H NMR (500 MHz, DMSO): benzyl: δ = 7.41 (2 CH), 7.36 (2 CH), 7.20 (CH), 4.79 (CH_2) ppm; macrolide: δ = 8.30 (9a-NH), 4.84 (1′′-H), 4.73 (13-H), 4.43 (1′-H), 2.65 (10-H), 4.18 (3-H), 4.11 (5′′-H), 3.54 (5-H), 3.79 (5′-H), 3.22 (2′-H), 3.31 (6-OCH_3), 3.26 (3′′-OCH_3), 3.43 (11-H), 2.91 (4′′-H), 2.65 (2-H), 2.62 (3′-H), 2.24 (2′′-H_a), 1.88 (8-H), 1.54 (7-H_a), 1.88 (4-H), 1.36 (4′-H_a), 1.76 (14-H_a), 1.50 (2′′-H_b), 1.28 (14-H_b), 1.33 (7-H_b), 1.36 (4′-H_b), 1.18 (6-CH_3), 2.20 (3′-NCH_3), 1.07 (2-CH_3), 1.15 (5′′-CH_3), 1.12 (3′′-CH_3), 1.06 (5′-CH_3), 0.94 (10-CH_3), 1.01 (12-CH_3), 0.85 (8-CH_3), 0.94 (4-CH_3), 0.78 (15-CH_3) ppm. ^{13}C NMR (125 MHz, DMSO): benzyl: δ = 139.9 (C), 128.2 (2 CH), 128.0 (2 CH), 127.9 (CH), 48.3 (CH_2) ppm; macrolide: δ = 182 (C=S), 177.1 (C-1), 68.7 (C-9), 102.2 (C-1′), 94.4 (C-1′′), 82.5 (C-5), 73.6 (C-6), 76.3 (C-13), 77.4 (C-4′′), 77.1 (C-3), 72.7 (C-12), 72.5 (C-3′′), 70.9 (C-2′), 74.9 (C-11), 66.5 (C-5′), 64.7 (C-5′′), 60 (C-3′), 48.3 (6-OCH_3), 48.8 (3′′-OCH_3), 61.4 (C-10), 44.6 (C-2), 41.6 (C-4), 41.8 (C-7), 35.7 (C-4′), 26.1 (C-8), 34.7 (C-2′′), 29.9 (3′-NCH_3), 21.0 (3′′-CH_3), 27.4 (6-CH_3), 21.2 (5′-CH_3), 20.9 (C-14), 22.1 (8-CH_3), 18.5 (5′′-CH_3), 17.7 (12-CH_3), 14.7 (2-CH_3), 6.7 (10-CH_3), 11.0 (15-CH_3), 9.1 (4-CH_3) ppm. HRMS (ES): calcd. for $C_{45}H_{78}N_3O_{12}S$ $[M + H]^+$ 884.5306; found 884.5295.

2′-*O*,3′-*N*-(Benzylcarbonimidoyl)-3′-*N*-demethyl-6-*O*-methyl-9a-aza-9a-homoerythromycin A (10): According to step 2 of the stepwise general procedure, the reaction of **7** (0.2 g, 0.22 mmol) afforded **10** (0.14 g, 74%) as a white foam. IR (KBr): $\tilde{\nu}$ = 3448, 2973, 2935, 2879, 1705, 1658, 1526, 1456, 1424, 1379, 1325, 1281, 1237, 1181, 1125, 1079, 1054, 1004, 956, 903, 803, 732, 698, 630 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): benzyl: δ = 7.34 (2 CH), 7.25 (2 CH), 7.18 (CH), 4.44 (CH_2) ppm; macrolide: δ = 6.16 (9a-NH), 4.89 (1′-H), 4.84 (1′′-H), 4.67 (13-H), 4.16 (10-H), 4.12 (3-H), 4.02 (5′′-H), 3.73 (5-H), 3.68 (5′-H), 3.59 (2′-H), 3.31 (6-OCH_3), 3.20 (11-H), 3.12 (3′′-OCH_3), 3.05 (4′′-H), 2.89 (3′-H), 2.85 (3′-NCH_3), 2.83 (2-H), 2.29 (2′′-H_a), 2.22 (8-H), 2.01 (4′-H_a), 1.88 (4-H), 1.88 (7-H_a), 1.87 (14-H_a), 1.58 (2′′-H_b), 1.58 (14-H_b), 1.43 (7-H_b), 1.42 (4′-H_b), 1.35 (6-CH_3), 1.29 (5′′-CH_3), 1.28 (5′-CH_3), 1.23 (2-CH_3), 1.20 (3′′-CH_3), 1.18 (12-CH_3), 1.16 (10-CH_3), 1.10 (8-CH_3), 0.92 (4-CH_3), 0.89 (15-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): benzyl: δ = 138.1 (C), 128.2 (2 CH), 127.7 (2 CH), 126.4 (CH), 49.5 (CH_2) ppm; macrolide: δ = 179.6 (C-1), 177.4 (C-9), 157.4 (C=N), 99.5 (C-1′), 95.8 (C-1′′), 81.0 (C-2′), 80.2 (C-5), 79.1 (C-6), 78.6 (C-13), 77.8 (C-4′′), 77.0 (C-3), 74.3 (C-12), 73.1 (C-3′′), 73.0 (C-11), 70.2 (C-5′), 66.0 (C-5′′), 62.8 (C-3′), 51.6 (6-OCH_3), 49.5 (3′′-OCH_3), 45.5 (C-10), 44.6 (C-2), 40.8 (C-4), 40.0 (C-4′), 36.4 (C-7), 35.6 (C-8), 34.8 (C-2′′), 32.1 (3′-NCH_3), 21.5 (3′′-CH_3), 21.0 (6-CH_3), 20.8 (C-14), 20.6 (5′-CH_3), 19.5 (8-CH_3), 18.3 (5′′-CH_3), 16.2 (12-CH_3), 15.4 (2-CH_3), 14.0 (10-CH_3), 11.2 (15-CH_3), 8.9 (4-CH_3) ppm. HRMS (ES): calcd. for $C_{45}H_{73}N_3O_{13}$ $[M + H]^+$ 864.5184; found 864.5184.

2′-*O*,3′-*N*-(Benzylcarbonimidoyl)-3′-*N*-demethyl-6-*O*-methylerythromycin A (11): According to step 2 of the stepwise general procedure, the reaction of **8** (0.35 g, 0.40 mmol) afforded **11** (0.20 g, 59%) as a white foam. IR (KBr): $\tilde{\nu}$ = 3452, 2972, 2941, 2884, 2826, 2088, 1734, 1704, 1456, 1423, 1377, 1352, 1325, 1287, 1242, 1172, 1127, 1081, 1055, 1000, 903, 854, 751, 700, 628 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): benzyl: δ = 7.33 (2 CH), 7.26 (2 CH), 7.18 (CH), 4.46 (CH_2) ppm; macrolide: δ = 5.07 (13-H), 4.92 (1′′-H), 4.89 (1′-H), 3.97 (5′′-H), 3.74 (11-H), 3.72 (3-H), 3.70 (5′-H), 3.66 (5-H), 3.56 (2′-H), 3.18 (3′′-OCH_3), 3.06 (4′′-H), 3.04 (6-OCH_3), 3.02 (10-H), 2.82 (3′-H), 2.77 (3′-NCH_3), 2.89 (2-H), 2.59 (8-H), 2.35 (2′′-H_a), 1.98 (4′-H_a), 1.93 (14-H_a), 1.91 (4-H), 1.81 (7-H_a), 1.58 (2′′-H_b), 1.77 (14-H_b), 1.61 (7-H_b), 1.43 (4′-H_b), 1.40 (6-CH_3), 1.29 (5′′-CH_3), 1.29 (5′-CH_3), 1.20 (2-CH_3), 1.24 (3′′-CH_3), 1.14 (12-CH_3), 1.12 (10-CH_3), 1.14 (8-CH_3), 1.02 (4-CH_3), 0.85 (15-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): benzyl: δ = 142.2 (C), 128.5 (2 CH), 127.8 (2 CH), 126.6 (CH), 50.4 (CH_2) ppm; macrolide: δ = 221.2 (C-9), 176.0 (C-1), 156.9 (C=N), 100.0 (C-1′), 96.7 (C-1′′), 82.1 (C-5), 80.9 (C-2′), 79.2 (C-3), 78.4 (C-6), 78.2 (C-4′′), 77.1 (C-13), 74.6 (C-12), 73.2 (C-3′′), 70.6 (C-5′), 69.5 (C-11), 66.3 (C-5′′), 63.0 (C-3′), 51.1 (6-OCH_3), 49.8 (3′′-OCH_3), 45.7 (C-8), 45.3 (C-2), 39.4 (C-7), 38.8 (C-4), 37.7 (C-10), 36.8 (C-4′), 35.3 (C-2′′), 32.5 (3′-NCH_3), 21.8 (3′′-CH_3), 21.4 (C-14), 20.0 (6-CH_3), 21.3 (5′-CH_3), 18.7 (5′′-CH_3), 18.4 (8-CH_3), 16.5 (12-CH_3), 16.3 (2-CH_3), 12.7 (10-CH_3), 10.9 (15-CH_3), 9.1 (4-CH_3) ppm. HRMS (ES): calcd. for $C_{45}H_{72}N_2O_{13}$ $[M + H]^+$ 849.5113; found 849.5133.

2′-*O*,3′-*N*-(Benzylcarbonimidoyl)-3′-*N*-demethyl-9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A (12): According to step 2 of the stepwise general procedure, the reaction of **9** (0.10 g, 0.11 mmol) afforded **12** (0.061 g, 66%) as a white foam. IR (KBr): $\tilde{\nu}$ = 3508, 2971, 2935, 2875, 2828, 2645, 2113, 1705, 1462, 1423, 1379, 1345, 1322, 1282, 1255, 1181, 1127, 1080, 1055, 1004, 957, 902, 857, 799, 731, 698 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): benzyl: δ = 7.32 (2 CH), 7.26 (2 CH), 7.18 (CH), 4.45 (CH_2) ppm; macrolide: δ = 5.09 (1′′-H), 4.89 (1′-H), 4.68 (13-H), 4.19 (3-H), 4.02 (5′′-H), 3.68 (5′-H), 3.65 (11-H), 3.61 (5-H), 3.61 (2′-H), 3.17 (3′′-OCH_3), 3.05 (4′′-H), 2.79 (3′-NCH_3), 2.77 (2-H), 2.71 (10-H), 2.54 (9-H_a), 2.42 (3′-H), 2.33 (9a-NCH_3), 2.32 (2′′-H_a), 2.07 (9-H_b), 1.97 (4′-H_a), 1.96 (8-H), 1.95 (4-H), 1.87 (14-H_a), 1.72 (7-H_a), 1.58 (2′′-H_b), 1.48 (14-H_b), 1.42 (4′-H_b), 1.32 (6-CH_3), 1.30 (5′′-CH_3), 1.23 (7-H_b), 1.23 (5′-CH_3), 1.20 (3′′-CH_3), 1.18 (2-CH_3), 1.11 (10-CH_3), 1.08 (12-CH_3), 0.94 (4-CH_3), 0.93 (8-CH_3), 0.89 (15-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): benzyl: δ = 141.6 (C), 128.1 (2 CH), 127.5 (2 CH),126.4 (CH), 49.8 (CH_2) ppm; macrolide: δ = 178.7 (C-1), 157.0 (C=N), 99.8 (C-1′), 95.2 (C-1′′), 84.8

(C-5), 80.6 (C-2′), 78.8 (C-3), 74.1 (C-11), 73.3 (C-6), 78.0 (C-4′′), 77.6 (C-13), 73.1 (C-3′′), 74.2 (C-12), 70.1 (C-5′), 70.0 (C-9), 65.8 (C-5′′), 62.9 (C-3′), 62.4 (C-10), 49.4 (3′′-OCH_3), 45.1 (C-2), 42.0 (C-7), 41.2 (C-4), 36.4 (C-4′), 36.4 (9a-NCH_3), 34.8 (C-2′′), 32.1 (3′-NCH_3), 27.3 (6-CH_3), 26.7 (C-8), 21.9 (8-CH_3), 21.6 (3′′-CH_3), 21.1 (C-14), 20.8 (5′-CH_3), 18.1 (5′′-CH_3), 15.1 (2-CH_3), 16.2 (12-CH_3), 11.2 (15-CH_3), 8.7 (4-CH_3), 7.4 (10-CH_3) ppm. HRMS (ES): calcd. for $C_{45}H_{73}N_3O_{12}$ $[M + H]^+$ 850.5429; found 850.5444.

(2′*S*)-2′-Deoxy-2′-*S*,3′-*N*-(benzylcarbonimidoyl)-3′-*N*-demethyl-9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A (15): Benzyl isothiocyanate (0.22 mL, 1.64 mmol) was added to a solution of 3′-*N*-demethyl derivative **6** (1 g, 1.36 mmol) in acetonitrile (c = 0.02 g/mL). The reaction was stirred at 60 °C for 2 h and then added to a suspension of polymer-supported Mukaiyama reagent (5.4 g, 5.44 mmol) and triethylamine (1.52 mL, 10.9 mmol) in acetonitrile (15 mL) previously stirred at 60 °C for 15 min. The reaction mixture was further stirred at 60 °C overnight. The resin was filtered off and the solvent evaporated. The residue was dissolved in ethyl acetate and washed with water at pH 4.5. The organic layer was evaporated and the residue purified by using Flashmaster Personal solid-phase extraction techniques [eluent: 1.5% MeOH/CH_2Cl_2 to MeOH/CH_2Cl_2/NH_4OH (4.5:90:0.25)] and further by Mass Directed AutoPrep HPLC on an Xterra C18 column using acetonitrile/water with a formic acid modifier. All collected fractions were passed through a SAX column to remove the formic acid and the solvent was freeze-dried to give side-product **15** (7.2 mg). ^{1}H NMR (500 MHz, $CDCl_3$): benzyl: δ = 7.33 (2 CH), 7.28 (2 CH), 7.21 (CH), 4.43 (CH_2) ppm; macrolide: δ = 5.14 (1′′-H), 4.99 (1′-H), 4.71 (13-H), 4.26 (3-H), 4.08 (2′-H), 4.03 (5′′-H), 3.72 (3′-H), 3.69 (5-H), 3.67 (11-H), 3.45 (5′-H), 3.35 (3′′-OCH_3), 3.08 (4′′-H), 2.93 (3′-NCH_3), 2.77 (2-H), 2.71 (10-H), 2.56 (9-H_a), 2.36 (2′′-H_a), 2.34 (9a-NCH_3), 2.07 (9-H_b), 1.80 (4′-H_a), 2.06 (8-H), 1.96 (4-H), 1.91 (14-H_a), 1.69 (7-H_a), 1.62 (2′′-H_b), 1.46 (14-H_b), 1.43 (4′-H_b), 1.36 (6-CH_3), 1.35 (5′′-CH_3), 1.28 (5′-CH_3), 1.26 (3′′-CH_3), 1.22 (7-H_b), 1.21 (2-CH_3), 1.11 (10-CH_3), 1.10 (12-CH_3), 0.92 (4-CH_3), 0.95 (8-CH_3), 0.91 (15-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): benzyl: δ = 141.2 (C), 128.0 (2 CH), 127.3 (2 CH), 126.2 (CH), 58.5 (CH_2) ppm; macrolide: δ = 178.6 (C-1), 158.4 (C=N), 98.1 (C-1′), 94.8 (C-1′′), 84.7 (C-5), 77.9 (C-3), 77.9 (C-4′′), 73.8 (C-11), 73.3 (C-6), 77.5 (C-13), 74.1 (C-12), 73.1 (C-3′′), 67.4 (C-5′), 69.3 (C-9), 65.7 (C-5′′), 62.4 (C-10), 60.7 (C-3′), 49.4 (3′′-OCH_3), 46.5 (C-2′), 45.1 (C-2), 42.0 (C-7), 41.5 (C-4), 36.2 (9a-NCH_3), 34.7 (C-2′′), 31.1 (C-4′), 31.8 (3′-NCH_3), 27.3 (6-CH_3), 26.6 (C-8), 21.9 (8-CH_3), 21.5 (3′′-CH_3), 21.1 (5′-CH_3), 21.0 (C-14), 18.2 (5′′-CH_3), 16.1 (12-CH_3), 14.8 (2-CH_3), 11.1 (15-CH_3), 8.7 (4-CH_3), 7.2 (10-CH_3) ppm. HRMS (ES): calcd. for $C_{45}H_{76}N_3O_{11}S$ $[M + H]^+$ 866.5201; found 866.5196.

2′-*O*,3′-*N*-(Benzylcarbonimidoyl)-3′-*N*-demethyl-6-*O*-methyl-9a-aza-9a-homoerythromycin A (10): According to the general procedure for the sequential one-pot synthesis, the reaction of **4** (0.48 g, 0.64 mmol) and benzyl isothiocyanate afforded **10** (0.34 g, 62%) as a white foam.

2′-*O*,3′-*N*-(Benzylcarbonimidoyl)-3′-*N*-demethyl-6-*O*-methyl-erythromycin A (11): According to the general procedure for the sequential one-pot synthesis, the reaction of **5** (0.47 g, 0.64 mmol) and benzyl isothiocyanate afforded **11** (0.37 g, 68%) as a white foam.

2′-*O*,3′-*N*-(Benzylcarbonimidoyl)-3′-*N*-demethyl-9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A (12): According to the general procedure for the sequential one-pot synthesis, the reaction of **6** (0.47 g, 0.64 mmol) and benzyl isothiocyanate afforded **12** (0.25 g, 46%) as a white foam.

2′-*O*,3′-*N*-(Isopropylcarbonimidoyl)-3′-*N*-demethyl-6-*O*-methyl-9a-aza-9a-homoerythromycin A (16): According to the general procedure for the sequential one-pot synthesis, the reaction of **4** (0.48 g, 0.64 mmol) and isopropyl isothiocyanate afforded **16** (0.29 g, 56%) as a white foam. IR (KBr): $\tilde{\nu}$ = 3487, 2972, 2937, 2880, 2832, 2703, 2376, 1705, 1658, 1640, 1531, 1462, 1424, 1379, 1320, 1289, 1236, 1173, 1126, 1080, 1050, 1005, 957, 903, 866, 723, 629 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): isopropyl: δ = 3.74 (CH), 1.10 (CH_3), 1.03 (CH_3) ppm; macrolide: δ = 6.19 (9a-NH), 4.89 (1′-H), 4.85 (1′′-H), 4.66 (13-H), 4.19 (10-H), 4.14 (3-H), 4.05 (5′′-H), 3.73 (5-H), 3.68 (5′-H), 3.50 (2′-H), 3.30 (6-OCH_3), 3.26 (3′′-OCH_3), 3.19 (11-H), 3.06 (4′′-H), 3.05 (3′-H), 2.69 (3′-NCH_3), 2.86 (2-H), 2.34 (2′′-H_a), 2.23 (8-H), 2.00 (7-H_a), 1.95 (4′-H_a), 1.88 (4-H), 1.89 (14-H_a), 1.57 (14-H_b), 1.56 (2′′-H_b), 1.40 (4′-H_b), 1.36 (6-CH_3), 1.33 (7-H_b), 1.33 (5′′-CH_3), 1.28 (5′-CH_3), 1.26 (3′′-CH_3), 1.25 (2-CH_3), 1.17 (10-CH_3), 1.16 (12-CH_3), 1.11 (8-CH_3), 0.96 (4-CH_3), 0.89 (15-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): isopropyl: δ = 46.3 (CH), 24.1 (2 CH_3) ppm; macrolide: δ = 179.3 (C-1), 177.0 (C-9), 154.6 (C=N), 99.5 (C-1′), 95.4 (C-1′′), 79.6 (C-2′), 79.8 (C-5), 78.8 (C-6), 78.2 (C-13), 77.5 (C-4′′), 76.7 (C-3), 73.8 (C-12), 72.6 (C-3′′), 72.6 (C-11), 69.8 (C-5′), 65.5 (C-5′′), 62.4 (C-3′), 51.2 (6-OCH_3), 49.0 (3′′-OCH_3), 45.0 (C-10), 44.2 (C-2), 40.3 (C-4), 39.6 (C-7), 36.0 (C-4′), 35.1 (C-8), 34.4 (C-2′′), 31.9 (3′-NCH_3), 21.1 (3′′-CH_3), 20.4 (C-14), 20.5 (5′-CH_3), 19.9 (6-CH_3), 19.0 (8-CH_3), 17.8 (5′′-CH_3), 15.7 (12-CH_3), 15.1 (2-CH_3), 13.7 (10-CH_3), 10.8 (15-CH_3), 8.2 (4-CH_3) ppm. HRMS (ES): calcd. for $C_{41}H_{73}N_3O_{13}$ $[M + H]^+$ 816.5222; found 816.5231.

2′-*O*,3′-*N*-[(1-Naphthyl)carbonimidoyl]-3′-*N*-demethyl-6-*O*-methyl-9a-aza-9a-homoerythromycin A (17): According to the general procedure for the sequential one-pot synthesis, the reaction of **4** (0.48 g, 0.64 mmol) and 1-naphthyl isothiocyanate afforded **17** (0.31 g, 53%) as a white foam. IR (KBr): $\tilde{\nu}$ = 3451, 3048, 2973, 2936, 2880, 2832, 2710, 2372, 1688, 1574, 1526, 1509, 1461, 1423, 1325, 1287, 1270, 1227, 1181, 1126, 1078, 1052, 1005, 961, 907, 797, 777, 722, 642 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): naphthyl: δ = 8.30 (CH), 7.78 (CH), 7.52 (CH), 7.42 (CH), 7.38 (2 CH), 7.25 (CH) ppm; macrolide: δ = 6.11 (9a-NH), 4.92 (1′-H), 4.83 (1′′-H), 4.64 (13-H), 4.14 (10-H), 4.09 (3-H), 4.04 (5′′-H), 3.69 (5-H), 3.73 (5′-H), 3.63 (2′-H), 3.28 (6-OCH_3), 3.28 (3′′-OCH_3), 3.16 (11-H), 3.05 (4′′-H), 3.05 (3′-H), 3.02 (3′-NCH_3), 2.78 (2-H), 2.32 (2′′-H_a), 2.17 (8-H), 2.06 (4′-H_a), 1.76 (4-H), 1.91 (7-H_a), 1.86 (14-H_a), 1.58 (2′′-H_b), 1.58 (14-H_b), 1.25 (7-H_b), 1.49 (4′-H_b), 1.32 (5′′-CH_3), 1.32 (5′-CH_3), 1.31 (6-CH_3), 1.25 (3′′-CH_3), 1.20 (2-CH_3), 1.16 (10-CH_3), 1.14 (12-CH_3), 1.04 (8-CH_3), 0.74 (4-CH_3), 0.89 (15-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): naphthyl: δ = 141.8 (C), 133.9 (C), 129.4 (C), 127.3 (CH), 125.4 (CH), 124.9 (CH), 124.3 (CH), 123.7 (CH), 122.3 (CH), 117.8 (CH) ppm; macrolide: δ = 179.4 (C-1), 176.9 (C-9), 154.5 (C=N), 99.4 (C-1′), 95.4 (C-1′′), 80.2 (C-2′), 79.9 (C-5), 78.7 (C-6), 78.2 (C-13), 77.5 (C-4′′), 76.6 (C-3), 73.8 (C-12), 72.7 (C-3′′), 72.5 (C-11), 69.9 (C-5′), 65.5 (C-5′′), 62.0 (C-3′), 51.1 (6-OCH_3), 49.2 (3′′-OCH_3), 44.9 (C-10), 44.2 (C-2), 40.4 (C-4), 39.6 (C-7), 36.1 (C-4′), 35.2 (C-8), 34.4 (C-2′′), 31.5 (3′-NCH_3), 21.2 (3′′-CH_3), 20.4 (C-14), 20.5 (5′-CH_3), 20.0 (6-CH_3), 19.0 (8-CH_3), 17.8 (5′′-CH_3), 15.8 (12-CH_3), 14.9 (2-CH_3), 13.6 (10-CH_3), 10.8 (15-CH_3), 8.1 (4-CH_3) ppm. HRMS (ES): calcd. for $C_{48}H_{73}N_3O_{13}$ $[M + H]^+$ 900.5222; found 900.5248.

2′-*O*,3′-*N*-{[3-(Diethylamino)propyl]carbonimidoyl}-3′-*N*-demethyl-6-*O*-methyl-9a-aza-9a-homoerythromycin A (18): According to the general procedure for the sequential one-pot synthesis, the reaction of **4** (0.48 g, 0.64 mmol) and 3-(diethylamino)propyl isothiocyanate afforded **18** (0.36 g, 64%) as a white foam. IR (KBr): $\tilde{\nu}$ = 3390, 2972, 2936, 2877, 2828, 1706, 1651, 1537, 1463, 1454, 1380, 1324, 1237, 1181, 1126, 1080, 1055, 1005, 958, 903, 869, 804, 757, 725,

627 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): *N*,*N*-diethylaminopropyl: δ = 3.20 (CH_2), 2.52 (2 CH_2), 2.47 (CH_2), 1.63 (CH_2), 1.03 (2 CH_3) ppm; macrolide: δ = 6.16 (9a-NH), 4.86 (1′-H), 4.85 (1′′-H), 4.66 (13-H), 4.17 (10-H), 4.15 (3-H), 4.05 (5′′-H), 3.74 (5-H), 3.67 (5′-H), 3.49 (2′-H), 3.33 (6-OCH_3), 3.26 (3′′-OCH_3), 3.20 (11-H), 3.06 (4′′-H), 2.84 (2-H), 2.72 (3′-H), 2.67 (3′-NCH_3), 2.33 (2′′-H_a), 2.21 (8-H), 2.00 (7-H_a), 1.94 (4′-H_a), 1.87 (4-H), 1.87 (14-H_a), 1.57 (14-H_b), 1.57 (2′′-H_b), 1.39 (4′-H_b), 1.36 (6-CH_3), 1.35 (7-H_b), 1.32 (5′′-CH_3), 1.29 (5′-CH_3), 1.25 (3′′-CH_3), 1.22 (2-CH_3), 1.17 (12-CH_3), 1.16 (10-CH_3), 1.10 (8-CH_3), 0.96 (4-CH_3), 0.89 (15-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): (diethylamino)propyl: δ = 50.5 (CH_2), 46.8 (2 CH_2), 44.8 (CH_2), 28.3 (CH_2), 11.6 (2 CH_3) ppm; macrolide: δ = 179.6 (C-1), 177.3 (C-9), 155.7 (C=N), 99.8 (C-1′), 95.6 (C-1′′), 79.9 (C-2′), 79.8 (C-5), 79.0 (C-6), 78.4 (C-13), 77.8 (C-4′′), 76.7 (C-3), 74.1 (C-12), 72.9 (C-3′′), 72.8 (C-11), 70.0 (C-5′), 65.8 (C-5′′), 62.6 (C-3′), 51.4 (6-OCH_3), 49.4 (3′′-OCH_3), 45.4 (C-10), 44.5 (C-2), 40.7 (C-4), 39.9 (C-7), 36.4 (C-4′), 35.5 (C-8), 34.7 (C-2′′), 32.0 (3′-NCH_3), 21.4 (3′′-CH_3), 20.8 (5′-CH_3), 20.6 (C-14), 20.3 (6-CH_3), 19.3 (8-CH_3), 18.1 (5′′-CH_3), 16.0 (12-CH_3), 15.2 (2-CH_3), 13.9 (10-CH_3), 11.1 (15-CH_3), 8.5 (4-CH_3) ppm. HRMS (ES): calcd. for $C_{45}H_{82}N_4O_{13}$ $[M + H]^+$ 887.5957; found 887.5925.

2′-*O*,3′-*N*-[(1-Adamantyl)carbonimidoyl]-3′-*N*-demethyl-6-*O*-methyl-9a-aza-9a-homoerythromycin A (19): According to the general procedure for the sequential one-pot synthesis, the reaction of **4** (0.60 g, 0.80 mmol) and 1-adamantyl isothiocyanate afforded **19** (0.26 g, 36%) as a white foam. ^1H NMR (500 MHz, $CDCl_3$): adamantyl: δ = 2.03 (3 CH), 1.85 (3 CH_2), 1.65 (3 CH_2) ppm; macrolide: δ = 6.28 (9a-NH), 4.92 (1′-H), 4.86 (1′′-H), 4.65 (13-H), 4.20 (10-H), 4.14 (3-H), 4.06 (5′′-H), 3.73 (5-H), 3.67 (5′-H), 3.47 (2′-H), 3.34 (6-OCH_3), 3.27 (3′′-OCH_3), 3.18 (11-H), 3.06 (4′′-H), 2.87 (2-H), 2.67 (3′-NCH_3), 2.63 (3′-H), 2.34 (2′′-H_a), 2.25 (8-H), 1.97 (7-H_a), 1.92 (4′-H_a), 1.88 (14-H_a), 1.85 (4-H), 1.58 (2′′-H_b), 1.58 (14-H_b), 1.38 (7-H_b), 1.38 (4′-H_b), 1.36 (6-CH_3), 1.32 (5′′-CH_3), 1.28 (5′-CH_3), 1.26 (2-CH_3), 1.25 (3′′-CH_3), 1.19 (12-CH_3), 1.19 (10-CH_3), 1.13 (8-CH_3), 0.99 (4-CH_3), 0.91 (15-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): adamantyl: δ = 52.5 (C), 43.0 (3 CH), 36.6 (3 CH_2), 29.9 (3 CH_2) ppm; macrolide: δ = 179.6 (C-1), 177.4 (C-9), 152.8 (C=N), 99.8 (C-1′), 95.7 (C-1′′), 80.1 (C-5), 79.7 (C-2′), 79.2 (C-6), 78.6 (C-13), 77.8 (C-4′′), 76.9 (C-3), 74.1 (C-12), 73.0 (C-3′′), 72.9 (C-11), 70.0 (C-5′), 65.8 (C-5′′), 62.1 (C-3′), 51.5 (6-OCH_3), 49.3 (3′′-OCH_3), 45.3 (C-10), 44.5 (C-2), 40.6 (C-4), 39.9 (C-7), 36.3 (C-4′), 35.3 (C-8), 34.7 (C-2′′), 32.7 (3′-NCH_3), 21.4 (3′′-CH_3), 20.8 (5′-CH_3), 20.6 (C-14), 20.1 (6-CH_3), 19.2 (8-CH_3), 18.1 (5′′-CH_3), 16.0 (12-CH_3), 15.5 (2-CH_3), 14.1 (10-CH_3), 11.1 (15-CH_3), 9.3 (4-CH_3) ppm. HRMS (ES): calcd. for $C_{48}H_{82}N_3O_{13}$ $[M + H]^+$ 908.5848; found 908.5833.

2′-*O*,3′-*N*-[(3-Methoxybiphenyl-4-yl)carbonimidoyl]-3′-*N*-demethyl-6-*O*-methyl-9a-aza-9a-homoerythromycin A (20): According to the general procedure for the sequential one-pot synthesis, the reaction of **4** (0.7 g, 0.94 mmol) and 3-methoxybiphenyl-4-yl isothiocyanate afforded **20** (0.43 g, 48%) as a white foam. ^1H NMR (500 MHz, $CDCl_3$): 3-methoxybiphenyl-4-yl: δ = 7.54 (2 CH), 7.42 (CH), 7.38 (2 CH), 7.26 (CH), 7.15 (CH), 6.92 (CH), 3.84 (OCH_3) ppm; macrolide: δ = 6.15 (9a-NH), 4.88 (1′-H), 4.82 (1′′-H), 4.63 (13-H), 4.13 (10-H), 4.04 (3-H), 4.02 (5′′-H), 3.70 (5′-H), 3.65 (5-H), 3.57 (2′-H), 3.34 (6-OCH_3), 3.29 (3′′-OCH_3), 3.11 (11-H), 3.05 (4′′-H), 3.00 (3′-H), 2.94 (3′-NCH_3), 2.56 (2-H), 2.32 (2′′-H_a), 2.17 (8-H), 2.03 (4′-H_a), 1.90 (14-H_a), 1.84 (4-H), 1.80 (7-H_a), 1.58 (2′′-H_b), 1.60 (14-H_b), 1.47 (4′-H_b), 1.21 (7-H_b), 1.30 (6-CH_3), 1.30 (5′′-CH_3), 1.30 (5′-CH_3), 1.27 (3′′-CH_3), 1.26 (2-CH_3), 1.15 (12-CH_3), 1.15 (10-CH_3), 1.06 (8-CH_3), 0.45 (4-CH_3), 0.91 (15-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 3-methoxybiphenyl-4-yl: δ = 151.7 (C), 141.5 (C), 136.3 (C), 133.2 (C), 128.3 (2 CH), 126.8 (2 CH), 126.0 (CH), 123.1 (CH), 121.8 (CH), 111.3 (CH), 55.7 (OCH_3) ppm; macrolide: δ = 179.7 (C-1), 177.1 (C-9), 155.3 (C=N), 99.6 (C-1′), 95.7 (C-1′′), 80.0 (C-5), 80.2 (C-2′), 79.0 (C-6), 78.4 (C-13), 77.0 (C-4′′), 76.9 (C-3), 74.1 (C-12), 73.0 (C-3′′), 72.9 (C-11), 70.1 (C-5′), 65.8 (C-5′′), 62.5 (C-3′), 51.4 (6-OCH_3), 49.5 (3′′-OCH_3), 45.3 (C-10), 44.2 (C-2), 40.4 (C-4), 39.8 (C-7), 36.3 (C-4′), 35.2 (C-8), 34.7 (C-2′′), 31.8 (3′-NCH_3), 21.4 (3′′-CH_3), 20.8 (5′-CH_3), 20.7 (C-14), 20.1 (6-CH_3), 19.2 (8-CH_3), 18.1 (5′′-CH_3), 16.0 (12-CH_3), 15.4 (2-CH_3), 14.0 (10-CH_3), 11.1 (15-CH_3), 8.2 (4-CH_3) ppm. HRMS (ES): calcd. for $C_{51}H_{78}N_3O_{14}$ $[M + H]^+$ 956.5484; found 956.5472.

2′-*O*,3′-*N*-[(2,6-Difluorophenyl)carbonimidoyl]-3′-*N*-demethyl-6-*O*-methyl-9a-aza-9a-homoerythromycin A (21): According to the general procedure for the sequential one-pot synthesis, the reaction of **4** (1.5 g, 2.0 mmol) and 2,6-difluorophenyl isothiocyanate afforded **21** (0.72 g, 41%) as a white foam. ^1H NMR (500 MHz, $CDCl_3$): 2,6-difluorophenyl: δ = 6.89 (CH), 6.80 (2 CH) ppm; macrolide: δ = 6.13 (9a-NH), 4.91 (1′-H), 4.84 (1′′-H), 4.65 (13-H), 4.15 (10-H), 4.10 (3-H), 4.03 (5′′-H), 3.70 (5′-H), 3.67 (5-H), 3.59 (2′-H), 3.30 (6-OCH_3), 3.33 (3′′-OCH_3), 3.14 (11-H), 3.08 (4′′-H), 3.06 (3′-H), 2.91 (3′N-CH_3), 2.81 (2-H), 2.36 (2′′-H_a), 2.18 (8-H), 2.02 (4′-H_a), 1.86 (7-H_a), 1.86 (14-H_a), 1.74 (4-H), 1.57 (2′′-H_b), 1.55 (14-H_b), 1.47 (4′-H_b), 1.22 (7-H_b), 1.32 (6-CH_3), 1.30 (5′′-CH_3), 1.28 (5′-CH_3), 1.24 (2-CH_3), 1.25 (3′′-CH_3), 1.15 (12-CH_3), 1.15 (10-CH_3), 1.05 (8-CH_3), 0.89 (15-CH_3), 0.72 (4-CH_3) ppm. ^{13}C NMR (125 MHz, CDCl3): 2,6-difluorophenyl: δ = 157.0 (CF), 155.1 (CF), 124.8 (C), 122.2 (CH), 110.7 (2 CH) ppm; macrolide: δ = 179.6 (C-1), 177.2 (C-9), 156.8 (C=N), 99.5 (C-1′), 95.7 (C-1′′), 80.5 (C-2′), 80.2 (C-5), 78.9 (C-13), 78.4 (C-6), 77.8 (C-4′′), 77.2 (C-3), 74.1 (C-12), 73.9 (C-3′′), 72.8 (C-11), 70.1 (C-5′), 65.7 (C-5′′), 62.6 (C-3′), 51.4 (6-OCH_3), 49.4 (3′′-OCH_3), 45.2 (C-10), 44.4 (C-2), 40.6 (C-4), 39.8 (C-7), 36.3 (C-4′), 35.5 (C-8), 34.7 (C-2′′), 31.5 (3′N-CH_3), 21.4 (3′′-CH_3), 20.8 (5′-CH_3), 20.6 (C-14), 20.2 (6-CH_3), 19.3 (8-CH_3), 18.1 (5′′-CH_3), 16.0 (12-CH_3), 15.4 (2-CH_3), 13.9 (10-CH_3), 11.1 (15-CH_3), 8.0 (4-CH_3) ppm. HRMS (ES): calcd. for $C_{44}H_{70}N_3O_{13}F_2$ $[M + H]^+$ 886.4877; found 886.4875.

2′-*O*,3′-*N*-[(2-Furylmethyl)carbonimidoyl]-3′-*N*-demethyl-6-*O*-methyl-9a-aza-9a-homoerythromycin A (22): According to the general procedure for the sequential one-pot synthesis, the reaction of **4** (0.7 g, 0.94 mmol) and 2-furyl isothiocyanate afforded **22** (0.16 g, 20%) as a white foam. ^1H NMR (500 MHz, $CDCl_3$): 2-furylmethyl: δ = 7.30 (CH), 6.28 (CH), 6.13 (CH), 4.39 (CH_2) ppm; macrolide: δ = 6.19 (9a-NH), 4.91 (1′-H), 4.87 (1′′-H), 4.67 (13-H), 4.19 (10-H), 4.16 (3-H), 4.06 (5′′-H), 3.76 (5-H), 3.69 (5′-H), 3.56 (2′-H), 3.35 (6-OCH_3), 3.26 (3′′-OCH_3), 3.20 (11-H), 3.08 (4′′-H), 2.89 (2-H), 2.82 (3′-H), 2.73 (3′-NCH_3), 2.34 (2′′-H_a), 2.25 (8-H), 2.04 (7-H_a), 1.99 (4′-H_a), 1.89 (14-H_a), 1.89 (4-H), 1.59 (2′′-H_b), 1.59 (14-H_b), 1.43 (4′-H_b), 1.38 (6-CH_3), 1.32 (5′′-CH_3), 1.31 (5′-CH_3), 1.27 (7-H_b), 1.25 (2-CH_3), 1.25 (3′′-CH_3), 1.19 (12-CH_3), 1.19 (10-CH_3), 1.13 (8-CH_3), 0.99 (4-CH_3), 0.90 (15-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 2-furylmethyl: δ = 155.1 (C), 141.1 (CH), 109.9 (CH), 105.5 (CH), 43.5 (CH_2) ppm; macrolide: δ = 179.6 (C-1), 177.3 (C-9), 156.7 (C=N), 99.7 (C-1′), 95.7 (C-1′′), 80.0 (C-5), 80.1 (C-2′), 79.1 (C-6), 78.5 (C-13), 77.8 (C-4′′), 77.1 (C-3), 74.1 (C-12), 72.9 (C-3′′), 72.9 (C-11), 70.1 (C-5′), 65.8 (C-5′′), 62.6 (C-3′), 51.5 (6-OCH_3), 49.4 (3′′-OCH_3), 45.3 (C-10), 44.5 (C-2), 40.6 (C-4), 39.9 (C-7), 36.3 (C-4′), 35.5 (C-8), 34.7 (C-2′′), 31.8 (3′-NCH_3), 21.4 (3′′-CH_3), 20.8 (5′-CH_3), 20.6 (C-14), 20.3 (6-CH_3), 19.3 (8-CH_3), 18.1 (5′′-CH_3), 16.0 (12-CH_3), 15.4 (2-CH_3), 13.9 (10-CH_3), 11.1 (15-CH_3), 8.6 (4-CH_3) ppm. HRMS (ES): calcd. for $C_{43}H_{72}N_3O_{14}$ $[M + H]^+$ 854.5014; found 854.4996.

2′-*O*,3′-*N*-{[4-(1*H*-Pyrazol-1-yl)phenyl]carbonimidoyl}-3′-*N*-demethyl-9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A (23): According to the general procedure for the sequential one-pot synthesis, the reaction of **4** (0.54 g, 0.72 mmol) and 4-(1*H*-pyrazol-1-yl)phenyl isothiocyanate afforded **23** (0.36 g, 55%) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$): 4-(1*H*-pyrazol-1-yl)phenyl: δ = 7.95 (CH), 7.71 (CH), 7.57 (2 CH), 7.24 (2 CH), 6.46 (CH) ppm; macrolide: δ = 6.19 (9a-NH), 4.97 (1′-H), 4.86 (1′′-H), 4.65 (13-H), 4.17 (10-H), 4.16 (3-H), 4.06 (5′′-H), 3.76 (5-H), 3.72 (5′-H), 3.65 (2′-H), 3.34 (6-OCH_3), 3.30 (3′′-OCH_3), 3.18 (11-H), 3.09 (4′′-H), 3.00 (3′-H), 2.89 (3′-NCH_3), 2.85 (2-H), 2.34 (2′′-H_a), 2.22 (8-H), 2.05 (4′-H_a), 1.95 (7-H_a), 1.90 (14-H_a), 1.86 (4-H), 1.60 (2′′-H_b), 1.60 (14-H_b), 1.46 (4′-H_b), 1.27 (7-H_b), 1.37 (6-CH_3), 1.34 (5′′-CH_3), 1.32 (5′-CH_3), 1.27 (3′′-CH_3), 1.25 (2-CH_3), 1.18 (12-CH_3), 1.17 (10-CH_3), 1.09 (8-CH_3), 0.95 (4-CH_3), 0.91 (15-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 4-(1*H*-pyrazol-1-yl)phenyl: δ = 144.9 (C), 140.4 (CH), 135.3 (C), 126.7 (CH), 124.5 (2 CH), 119.4 (2 CH), 106.9 (CH) ppm; macrolide: δ = 179.7 (C-1), 177.2 (C-9), 154.8 (C=N), 99.5 (C-1′), 95.8 (C-1′′), 80.1 (C-5), 80.5 (C-2′), 79.0 (C-6), 78.6 (C-13), 77.7 (C-4′′), 77.0 (C-3), 74.1 (C-12), 73.0 (C-3′′), 72.9 (C-11), 70.1 (C-5′), 65.9 (C-5′′), 62.0 (C-3′), 51.5 (6-OCH_3), 49.5 (3′′-OCH_3), 45.3 (C-10), 44.4 (C-2), 40.6 (C-4), 39.9 (C-7), 36.3 (C-4′), 35.4 (C-8), 34.7 (C-2′′), 31.6 (3′-NCH_3), 21.4 (3′′-CH_3), 20.8 (5′-CH_3), 20.6 (C-14), 20.2 (6-CH_3), 19.3 (8-CH_3), 18.1 (5′′-CH_3), 16.0 (12-CH_3), 15.4 (2-CH_3), 14.0 (10-CH_3), 11.1 (15-CH_3), 8.8 (4-CH_3) ppm. HRMS (ES): calcd. for $C_{47}H_{74}N_5O_{13}$ $[M + H]^+$ 916.5283; found 916.5293.

2′-*O*,3′-*N*-[(1-Naphthyl)carbonimidoyl]-3′-*N*-demethyl-6-*O*-methylerythromycin A (24): According to the general procedure for the sequential one-pot synthesis, the reaction of **5** (0.47 g, 0.64 mmol) and 1-naphthyl isothiocyanate afforded **24** (0.40 g, 71%) as a white foam. IR (KBr): $\tilde{\nu}$ = 3487, 2973, 2937, 2881, 2832, 2706, 1733, 1688, 1575, 1506, 1461, 1423, 1379, 1344, 1287, 1244, 1228, 1171, 1113, 1080, 1052, 1005, 961, 907, 851, 796, 776, 722, 627 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): naphthyl: δ = 8.32 (CH), 7.81 (CH), 7.55 (CH), 7.44 (2 CH), 7.38 (CH), 7.19 (CH) ppm; macrolide: δ = 5.07 (13-H), 4.97 (1′-H), 4.93 (1′′-H), 4.01 (5′′-H), 3.71 (11-H), 3.76 (5′-H), 3.69 (3-H), 3.65 (5-H), 3.61 (2′-H), 3.34 (3′′-OCH_3), 3.12 (3′-H), 3.07 (4′′-H), 3.05 (3′-NCH_3), 3.04 (6-OCH_3), 2.95 (10-H), 2.86 (2-H), 2.53 (8-H), 2.39 (2′′-H_a), 2.09 (4′-H_a), 1.93 (14-H_a), 1.83 (4-H), 1.69 (7-H_a), 1.62 (2′′-H_b), 1.52 (4′-H_b), 1.51 (7-H_b), 1.49 (14-H_b), 1.38 (6-CH_3), 1.32 (5′′-CH_3), 1.31 (5′-CH_3), 1.28 (3′′-CH_3), 1.22 (2-CH_3), 1.10 (12-CH_3), 1.10 (8-CH_3), 1.08 (10-CH_3), 0.88 (4-CH_3), 0.86 (15-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): naphthyl: δ = 142.4 (C), 134.2 (C), 129.7 (C), 127.6 (CH), 125.6 (2 CH), 124.8 (CH), 124.2 (CH), 122.6 (CH), 118.1 (CH) ppm; macrolide: δ = 220.9 (C-9), 175.7 (C-1), 154.8 (C=N), 99.7 (C-1′), 96.4 (C-1′′), 81.9 (C-5), 80.7 (C-2′), 78.9 (C-3), 78.0 (C-6), 77.8 (C-4′′), 76.7 (C-13), 74.2 (C-12), 73.0 (C-3′′), 70.3 (C-5′), 69.1 (C-11), 65.9 (C-5′′), 62.4 (C-3′), 50.6 (6-OCH_3), 49.6 (3′′-OCH_3), 45.3 (C-8), 44.9 (C-2), 39.1 (C-7), 38.5 (C-4), 36.4 (C-10), 36.4 (C-4′), 34.9 (C-2′′), 31.8 (3′-NCH_3), 21.5 (3′′-CH_3), 21.1 (C-14), 20.9 (5′-CH_3), 19.6 (6-CH_3), 18.3 (5′′-CH_3), 17.9 (8-CH_3), 16.0 (12-CH_3), 15.9 (2-CH_3), 12.3 (10-CH_3), 10.6 (15-CH_3), 8.5 (4-CH_3) ppm. HRMS (ES): calcd. for $C_{48}H_{72}N_2O_{13}$ $[M + H]^+$ 885.5113; found 885.5147.

2′-*O*,3′-*N*-(Isopropylcarbonimidoyl)-3′-*N*-demethyl-6-*O*-methylerythromycin A (25): According to the general procedure for the sequential one-pot synthesis, the reaction of **5** (0.47 g, 0.64 mmol) and isopropyl isothiocyanate afforded **25** (0.33 g, 64%) as a white foam. IR (KBr): $\tilde{\nu}$ = 3466, 2971, 2939, 2882, 2834, 1731, 1707, 1462, 1378, 1347, 1318, 1288, 1237, 1171, 1126, 1111, 1079, 1054, 1033, 996, 954, 905, 723, 626 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): isopropyl: δ = 3.85 (CH), 1.20 (CH_3), 1.13 (CH_3) ppm; macrolide: δ = 5.08 (13-H), 4.94 (1′-H), 4.93 (1′′-H), 3.97 (5′′-H), 3.75 (11-H), 3.72 (5′-H), 3.70 (3-H), 3.68 (5-H), 3.58 (2′-H), 3.26 (3′′-OCH_3), 3.07 (4′′-H), 3.04 (6-OCH_3), 3.03 (10-H), 2.92 (3′-H), 2.86 (3′-NCH_3), 2.90 (2-H), 2.58 (8-H), 2.36 (2′′-H_a), 2.01 (4′-H_a), 1.92 (14-H_a), 1.92 (4-H), 1.80 (7-H_a), 1.62 (2′′-H_b), 1.59 (7-H_b), 1.47 (14-H_b), 1.43 (4′-H_b), 1.40 (6-CH_3), 1.30 (5′′-CH_3), 1.28 (5′-CH_3), 1.26 (3′′-CH_3), 1.21 (2-CH_3), 1.14 (12-CH_3), 1.14 (8-CH_3), 1.11 (10-CH_3), 1.02 (4-CH_3), 0.84 (15-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): isopropyl: δ = 46.7 (CH), 23.7 (CH_3), 23.6 (CH_3) ppm; macrolide: δ = 220.4 (C-9), 175.2 (C-1), 155.7 (C=N), 99.2 (C-1′), 96.0 (C-1′′), 81.7 (C-5), 80.6 (C-2′), 78.6 (C-3), 77.6 (C-6), 77.3 (C-4′′), 76.4 (C-13), 73.9 (C-12), 72.6 (C-3′′), 69.96 (C-5′), 68.7 (C-11), 65.7 (C-5′′), 62.3 (C-3′), 50.3 (6-OCH_3), 49.1 (3′′-OCH_3), 44.9 (C-8), 44.5 (C-2), 38.6 (C-7), 38.0 (C-4), 36.9 (C-10), 35.8 (C-4′), 34.6 (C-2′′), 32.1 (3′-NCH_3), 21.1 (3′′-CH_3), 20.7 (C-14), 20.5 (5′-CH_3), 19.2 (6-CH_3),17.9 (5′′-CH_3), 17.6 (8-CH_3), 15.7 (12-CH_3), 15.5 (2-CH_3), 12.7 (10-CH_3), 10.2 (15-CH_3), 8.2 (4-CH_3) ppm. HRMS (ES): calcd. for $C_{41}H_{72}N_2O_{13}$ $[M + H]^+$ 801.5113; found 801.5138.

2′-*O*,3′-*N*-{[3-(Diethylamino)propyl]carbonimidoyl}-3′-*N*-demethyl-6-*O*-methylerythromycin A (26): According to the general procedure for the sequential one-pot synthesis, the reaction of **5** (0.47 g, 0.64 mmol) and 3-(diethylamino)propyl isothiocyanate afforded **26** (0.30 g, 54%) as a white foam. IR (KBr): $\tilde{\nu}$ = 3459, 2972, 2937, 2877, 2831, 1732, 1713, 1633, 1463, 1423, 1378, 1344, 1320, 1287, 1244, 1170, 1127, 1113, 1080, 1055, 1033, 1005, 959, 936, 903, 852, 802, 755, 721, 698, 626 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): diethylaminopropyl: δ = 3.21 (CH_2), 2.53 (2 CH_2), 2.48 (CH_2), 1.65 (CH_2), 1.01 (2 CH_3) ppm; macrolide: δ = 5.08 (13-H), 4.93 (1′′-H), 4.88 (1′-H), 3.98 (5′′-H), 3.75 (11-H), 3.69 (5′-H), 3.72 (3-H), 3.67 (5-H), 3.49 (2′-H), 3.26 (3′′-OCH_3), 3.05 (6-OCH_3), 3.04 (10-H), 3.01 (4′′-H), 2.88 (2-H), 2.74 (3′-H), 2.67 (3′-NCH_3), 2.58 (8-H), 2.37 (2′′-H_a), 1.95 (4′-H_a), 1.92 (14-H_a), 1.93 (4-H), 1.81 (7-H_a), 1.62 (7-H_b), 1.59 (2′′-H_b),1.49 (14-H_b), 1.40 (6-CH_3), 1.38 (4′-H_b), 1.30 (5′′-CH_3), 1.29 (5′-CH_3), 1.26 (3′′-CH_3), 1.20 (2-CH_3), 1.14 (12-CH_3), 1.14 (8-CH_3), 1.12 (10-CH_3), 1.04 (4-CH_3), 0.85 (15-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): diethylaminopropyl: δ = 50.6 (CH_2), 46.8 (2 CH_2), 44.7 (CH_2), 28.4 (CH_2), 11.6 (2 CH_3) ppm; macrolide: δ = 220.8 (C-9), 175.5 (C-1), 155.6 (C=N), 99.7 (C-1′), 96.3 (C-1′′), 81.6 (C-5), 79.9 (C-2′), 78.8 (C-3), 77.9 (C-6), 77.7 (C-4′′), 76.7 (C-13), 74.1 (C-12), 72.8 (C-3′′), 70.1 (C-5′), 69.0 (C-11), 65.8 (C-5′′), 62.6 (C-3′), 50.6 (6-OCH_3), 49.4 (3′′-OCH_3), 45.5 (C-8), 44.7 (C-2), 38.9 (C-7), 38.4 (C-4), 37.1 (C-10), 36.3 (C-4′), 34.8 (C-2′′), 32.0 (3′-NCH_3), 21.4 (3′′-CH_3), 20.9 (C-14), 20.8 (5′-CH_3), 19.5 (6-CH_3), 18.3 (5′′-CH_3), 17.9 (8-CH_3), 15.9 (12-CH_3), 15.8 (2-CH_3), 12.2 (10-CH_3), 10.5 (15-CH_3), 8.5 (4-CH_3) ppm. HRMS (ES): calcd. for $C_{45}H_{81}N3O_{13}$ $[M + H]^+$ 872.5848; found 872.5856.

2′-*O*,3′-*N*-[(1-Naphthyl)carbonimidoyl]-3′-*N*-demethyl-9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A (27): According to the general procedure for the sequential one-pot synthesis, the reaction of **6** (0.47 g, 0.64 mmol) and 1-naphthyl isothiocyanate afforded **27** (0.25 g, 44%, after performing SPE chromatography twice) as a white foam. IR (KBr): $\tilde{\nu}$ = 3508, 3048, 2972, 2935, 2877, 2829, 2736, 2643, 2378, 2247, 1688, 1574, 1506, 1461, 1423, 1380, 1343, 1323, 1285, 1227, 1181, 1127, 1079, 1052, 1005, 960, 907, 853, 796, 776, 726, 644 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): naphthyl: δ = 8.28 (CH), 7.77 (CH), 7.49 (CH), 7.42 (CH), 7.38 (CH), 7.33 (CH), 7.19 (CH) ppm; macrolide: δ = 5.10 (1′′-H), 4.93 (1′-H), 4.69 (13-H), 4.17 (3-H), 4.04 (5′′-H), 3.73 (5′-H), 3.59 (11-H), 3.58 (5-H), 3.62 (2′-H), 3.34 (3′′-OCH_3), 3.08 (4′′-H), 3.06 (3′-H), 3.00 (3′-NCH_3), 2.71 (2-H), 2.65 (10-H), 2.50 (9-H_a), 2.30 (9a-NCH_3), 2.37 (2′′-H_a), 2.07 (4′-H_a), 1.96 (9-H_b), 1.96 (8-H), 1.90 (14-H_a), 1.84

(4-H), 1.59 (7-H_a), 1.59 (2′′-H_b), 1.49 (4′-H_b), 1.45 (14-H_b), 1.32 (5′′-CH_3), 1.31 (6-CH_3), 1.31 (5′-CH_3), 1.26 (3′′-CH_3), 1.19 (2-CH_3), 1.15 (7-H_b), 1.07 (10-CH_3), 1.06 (12-CH_3), 0.87 (8-CH_3), 0.76 (4-CH_3), 0.89 (15-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): naphthyl: δ = 143.0 (C), 134.2 (C), 129.6 (C), 127.5 (CH), 125.6 (CH), 125.5 (CH), 124.7 (CH), 124.3 (CH), 122.3 (CH), 117.9 (CH) ppm; macrolide: δ = 178.6 (C-1), 154.8 (C=N), 99.9 (C-1′), 95.2 (C-1′′), 84.8 (C-5), 80.5 (C-2′), 78.5 (C-3), 78.0 (C-4′′), 78.0 (C-13), 74.2 (C-11), 73.2 (C-6), 73.2 (C-3′′), 74.2 (C-12), 70.2 (C-5′), 70.2 (C-9), 65.8 (C-5′′), 62.6 (C-3′), 62.6 (C-10), 49.6 (3′′-OCH_3), 45.1 (C-2), 41.9 (C-7), 41.3 (C-4), 36.5 (C-4′), 36.4 (9a-NCH_3), 34.8 (C-2′′), 31.8 (3′-NCH_3), 27.3 (6-CH_3), 26.6 (C-8), 22.4 (8-CH_3), 21.6 (3′′-CH_3), 21.1 (C-14), 20.8 (5′-CH_3), 18.1 (5′′-CH_3), 15.0 (2-CH_3), 16.2 (12-CH_3), 11.2 (15-CH_3), 8.3 (4-CH_3), 7.1 (10-CH_3) ppm. HRMS (ES): calcd. for $C_{48}H_{75}N_3O_{12}$ [M + H]$^+$ 886.5429; found 884.5451.

2′-*O*,3′-*N*-(Isopropylcarbonimidoyl)-3′-*N*-demethyl-9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A (28): According to the general procedure for the sequential one-pot synthesis, the reaction of **6** (0.47 g, 0.64 mmol) and isopropyl isothiocyanate afforded **28** (0.29 g, 57%) as a white foam. IR (KBr): $\tilde{\nu}$ = 3508, 2970, 2935, 2875, 2829, 2645, 2374, 2124, 1705, 1462, 1423, 1379, 1318, 1284, 1255, 1236, 1177, 1128, 1080, 1039, 1001, 958, 903, 863, 842, 797, 723, 630 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): isopropyl: δ = 3.81 (CH), 1.16 (CH_3), 1.06 (CH_3) ppm; macrolide: δ = 5.09 (1′′-H), 4.92 (1′-H), 4.68 (13-H), 4.19 (3-H), 4.05 (5′′-H), 3.69 (5′-H), 3.64 (11-H), 3.63 (5-H), 3.61 (2′-H), 3.27 (3′′-OCH_3), 3.07 (4′′-H), 2.82 (3′-H), 2.80 (2-H), 2.78 (3′-NCH_3), 2.70 (10-H), 2.54 (9-H_a), 2.39 (2′′-H_a), 2.33 (9a-NCH_3), 2.13 (9-H_b), 2.00 (8-H), 1.98 (4′-H_a), 1.96 (4-H), 1.89 (14-H_a), 1.72 (7-H_a), 1.60 (2′′-H_b), 1.47 (14-H_b), 1.42 (4′-H_b), 1.32 (6-CH_3), 1.30 (5′′-CH_3), 1.28 (5′-CH_3), 1.28 (7-H_b), 1.23 (3′′-CH_3), 1.20 (2-CH_3), 1.11 (12-CH_3), 1.08 (10-CH_3), 0.97 (4-CH_3), 0.94 (8-CH_3), 0.89 (15-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): isopropyl: δ = 46.8 (CH), 24.3 (CH_3), 24.2 (CH_3) ppm; macrolide: δ = 178.7 (C-1), 155.9 (C=N), 99.9 (C-1′), 95.3 (C-1′′), 84.9 (C-5), 80.4 (C-2′), 78.8 (C-3), 77.6 (C-4′′), 77.5 (C-13), 74.3 (C-11), 73.3 (C-6), 73.2 (C-3′′), 74.2 (C-12), 70.2 (C-5′), 70.1 (C-9), 65.8 (C-5′′), 62.9 (C-3′), 62.4 (C-10), 49.4 (3′′-OCH_3), 45.1 (C-2), 41.9 (C-7), 41.0 (C-4), 36.5 (9a-NCH_3), 36.4 (C-4′), 34.8 (C-2′′), 32.3 (3′-NCH_3), 27.3 (6-CH_3), 26.7 (C-8), 21.9 (8-CH_3), 21.6 (3′′-CH_3), 21.1 (C-14), 20.8 (5′-CH_3), 18.1 (5′′-CH_3), 15.2 (2-CH_3), 16.2 (12-CH_3), 11.2 (15-CH_3), 8.5 (4-CH_3), 7.3 (10-CH_3) ppm. HRMS (ES): calcd. for $C_{41}H_{75}N_3O_{12}$ [M + H]$^+$ 802.5429; found 802.5444.

2′-*O*,3′-*N*-[(4-Methoxyphenyl)carbonimidoyl]-3′-*N*-demethyl-9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A (29): According to the general procedure for the sequential one-pot synthesis, the reaction of **6** (1.0 g, 1.36 mmol) and 4-methoxyphenyl isothiocyanate afforded **29** (0.36 g, 31%) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$): 4-methoxyphenyl: δ = 7.09 (2 CH), 6.79 (2 CH), 3.79 (OCH_3) ppm; macrolide: δ = 5.12 (1′′-H), 4.97 (1′-H), 4.71 (13-H), 4.23 (3-H), 4.08 (5′′-H), 3.73 (5′-H), 3.65 (11-H), 3.63 (2′-H), 3.62 (5-H), 3.33 (3′′-OCH_3), 3.09 (4′′-H), 3.00 (3′-H), 2.86 (3′-NCH_3), 2.81 (2-H), 2.70 (10-H), 2.55 (9-H_a), 2.40 (2′′-H_a), 2.33 (9a-NCH_3), 2.05 (9-H_b), 2.03 (8-H), 2.03 (4′-H_a), 1.97 (4-H), 1.92 (14-H_a), 1.69 (7-H_a), 1.62 (2′′-H_b), 1.52 (14-H_b), 1.45 (4′-H_b), 1.34 (5′′-CH_3), 1.32 (6-CH_3), 1.30 (5′-CH_3), 1.19 (7-H_b), 1.28 (3′′-CH_3), 1.23 (2-CH_3), 1.11 (10-CH_3), 1.10 (12-CH_3), 0.99 (4-CH_3), 0.93 (15-CH_3), 0.90 (8-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 4-methoxyphenyl: δ = 155.0 (C), 139.6 (C), 124.6 (2 CH), 113.49 (2 CH), 55.3 (OCH_3) ppm; macrolide: δ = 178.7 (C-1), 154.3 (C=N), 99.7 (C-1′), 95.0 (C-1′′), 84.6 (C-5), 80.4 (C-2′), 78.5 (C-3), 77.9 (C-4′′), 77.5 (C-13), 73.9 (C-11), 73.2 (C-6), 73.1 (C-3′′), 74.1 (C-12), 70.0 (C-5′), 70.0 (C-9), 65.7 (C-5′′), 62.4 (C-3′), 62.3 (C-10), 49.5 (3′′-OCH_3), 45.0 (C-2), 41.9 (C-7), 41.2 (C-4), 36.2 (9a-NCH_3), 36.4 (C-4′), 34.7 (C-2′′), 31.7 (3′-NCH_3), 27.2 (6-CH_3), 26.6 (C-8), 21.8 (8-CH_3), 21.5 (3′′-CH_3), 21.1 (C-14), 20.7 (5′-CH_3), 18.0 (5′′-CH_3), 15.0 (2-CH_3), 16.1 (12-CH_3), 11.1 (15-CH_3), 8.5 (4-CH_3), 7.2 (10-CH_3) ppm. HRMS (ES): calcd. for $C_{45}H_{76}N_3O_{13}$ [M + H]$^+$ 866.5378; found 866.5402.

2′-*O*,3′-*N*-(Benzylcarbonimidoyl)-3′-*N*-demethyl-6-*O*-methyl-9a-aza-9a-homoerythromycin A (10): According to the general procedure for the tandem one-pot synthesis, the reaction of **1** (0.5 g, 0.65 mmol) and benzyl isothiocyanate afforded **10** (0.32 g, 60%) as a white foam.

2′-*O*,3′-*N*-(Benzylcarbonimidoyl)-3′-*N*-demethyl-6-*O*-methylerythromycin A (11): According to the general procedure for the tandem one-pot synthesis, the reaction of **2** (0.5 g, 0.66 mmol) and benzyl isothiocyanate afforded **11** (0.31 g, 56%) as a white foam.

2′-*O*,3′-*N*-(Benzylcarbonimidoyl)-3′-*N*-demethyl-9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A (12): According to the general procedure for the tandem one-pot synthesis, the reaction of **3** (0.5 g, 0.66 mmol) and benzyl isothiocyanate afforded **12** (0.19 g, 35%) as a white foam.

X-ray Analysis of 28: Crystals suitable for X-ray analysis were grown from *n*-hexane solution by slow evaporation at room temperature over 1 week. The single-crystal diffraction data were collected with an Oxford Diffraction Xcalibur CCD diffractometer (with graphite-monochromated Mo-K_α radiation) in a stream of nitrogen vapor stream at 103 K (using ω scans at a crystal-to-detector distance of 70 mm). Details of data collection and crystal structure refinement are given in Table 2. The programs CrysAlis CCD and CrysAlis RED[21] were used for data collection, cell refinement, and data reduction. The structure was solved by direct methods.[22] The refinement procedure by full-matrix least-squares methods based on values of F^2 against all reflections included anisotropic displacement parameters for all non-hydrogen atoms. The positions of hydrogen atoms on carbon atoms were positioned geometrically

Table 2. Crystallographic data, details of data collection and refinement process for **28**.

Formula	$(C_{41}H_{75}N_3O_{12})_3{\cdot}C_6H_{14}{\cdot}4(H_2O)$
M_r	2564.36
Crystal system, space group	monoclinic, $P2_1$
a [Å]	8.86954(2)
b [Å]	20.6034(4)
c [Å]	40.3041(9)
α [°]	90.00
β [°]	94.994(2)
γ [°]	90.00
V [Å^3]	7337.3(3)
Z, Z'	6, 3
$D_{calcd.}$ [g cm^{-3}]	1.162
λ [Å]	0.71073
θ range [°]	3.71–27.00
T [K]	103(2)
Reflections collected	136332
Independent reflections	16379
μ [mm^{-1}]	0.085
Refinement on F^2	
R, wR [$F^2(2\sigma F^2)$][a]	0.0588, 0.1175
R, wR (F^2 all reflections)[b]	0.1035, 0.1325
Goodness-of-fit, S	0.968
Residual electron density [e Å^{-3}]	0.565, –0.282

[a] $R = \Sigma||F_o| - |F_c||/\Sigma F_o$. [b] $w = 1/[\sigma^2(F_o^2) + (g_1P)^2 + g_2P]$, where $P = (F_o^2 + 2F_c^2)/3$, $S = \Sigma[w(F_o^2 - F_c^2)^2/(N_{obs} - N_{param})]^{1/2}$.

and optimized by applying the riding model. The positions of hydroxy and water hydrogen atoms were obtained from the difference Fourier map and were included in the refinement process with isotropic thermal parameters. The refinement was performed with SHELXL-97[23] (both operating within the WinGX[24] program package). The molecular graphics were drawn by using the ORTEP[25] and Mercury[26] software packages.

CCDC-803516 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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