EurJOC European Journal of Organic Chemistry

DOI: 10.1002/ejoc.201300266

Regioselective 2-Imino-1,3-thiazolidine vs. 2-Imino-1,3-oxazolidine Formation from the Vicinal *sec*-Amino Alcohol of Desosamine

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Keywords: Medicinal chemistry / Macrocycles / Heterocycles / Amino alcohols / Cyclization

In order to optimize Mukaiyama reagent-induced cyclization of vicinal *sec*-amino alcohols of desosamine origin towards exclusive formation of *N*′-substituted-2-imino-1,3-thiazolidines via a thiocarbamoyl intermediate, the influence of reaction conditions was studied. A novel, mild, one-pot, two-step method was developed, and the formation of *N*′-substituted-2-imino-1,3-oxazolidines as side products was minimized. The inversion of configuration at C-2′ was unambiguously established using NMR-based conformational analysis. A reaction mechanism was proposed. A test series of novel desosamine-modified 14- and 15-membered macrolides, bearing *N*′-alkyl-2-imino-1,3-thiazolidines fused to the desosamine sugar were prepared.

Introduction

In the course of our studies of diverse antibacterial macrolide transformations through the modifications of the desosamine sugar,[1,2] macrolide derivatives that showed potent anti-inflammatory properties but were devoid of antibacterial activity were discovered.[3] These anti-inflammatory macrolides were prepared by an efficient tandem reaction for the fusion of *N*′-substituted-2-imino-1,3-oxazolidine moieties to the desosamine sugar. The tandem reaction involved cyclization of the secondary amine at position 3′-C and the vicinal hydroxy group at position 2′-C of desosamine to form exclusively a 2-imino-1,3-oxazolidine moiety via an intermediate 3′-*N*-thiocarbamoyl. Interestingly, this exclusivity was lost when a polymer-supported Mukaiyama reagent (*N*-methyl-2-chloropyridinium iodide)[4] was used as a thiophilic reagent, providing a 2-imino-1,3-thiazolidine side product in which the configuration at 2′-C was supposed to be inverted (Scheme 1).[1] Such desosamine modification should also diminish antibacterial activity of the parent macrolides, and consequently make them suitable for the treatment of various diseases not connected to bacterial action.[6] Therefore, we were keen to find conditions for the exclusive fusion of *N*′-substituted-2-imino-1,3-thiazolidines with desosamines of 14- and 15-membered antibacterial macrolides. The 2-imino-1,3-thiazolidine moiety can be found as a part of many biologically active compounds, and different approaches to their synthesis via cyclization of *N*-(hydroxyalkyl)thioureas have been studied.[5] However, such approaches usually use harsh conditions and provide a mixture of cyclized products. Here we present a mild one-pot alternative suitable for sensitive macrolide chemistry based on the Mukaiyama reagent-induced cyclization of thiocarbamoyl intermediates to *N*′-substituted-2-imino-1,3-thiazolidines.

Results and Discussion

The conversion of 3′-*N*-demethylated 9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A[1,2] (**1**) to 2′-deoxy-2′-(*S*)-*S*,3′-*N*-(*N*′-benzylcarbonimidoyl)-3′-*N*-demethyl-9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A (**4**) was used as a model reaction (Scheme 1). In order to optimize reaction conditions for the synthesis of mainly *N*′-substituted-2-imino-1,3-thiazolidine compounds and to avoid formation of *N*′-substituted-1,3-oxazolidines, the influence of solvent, base, temperature, and reagent ratios on the course of the Mukaiyama reagent-induced cyclization of *N*′-thiocarbamoyl **2** was studied. Since the Mukaiyama reagent also reacts with secondary amines, although more slowly than with alcohols,[1] the synthesis had to be conducted in two steps (Scheme 1): (1) the formation of 3′-(*N*′-benzyl)-thiocarbamoyl intermediate **2** via reaction of **1** with benzyl isothiocyanate;[1] and (2) subsequent cyclization using the polymer supported Mukaiyama reagent. The ratio of oxazolidine **3**/thiazolidine **4** compounds was determined using LC-MS.

First, the effect of the solvent on the course of the cyclization of thiocarbamoyl intermediate **2** was assessed (Table 1, Entries 1–8). Triethylamine was used as a base in order to avoid cladinose cleavage.[1] It was found that the

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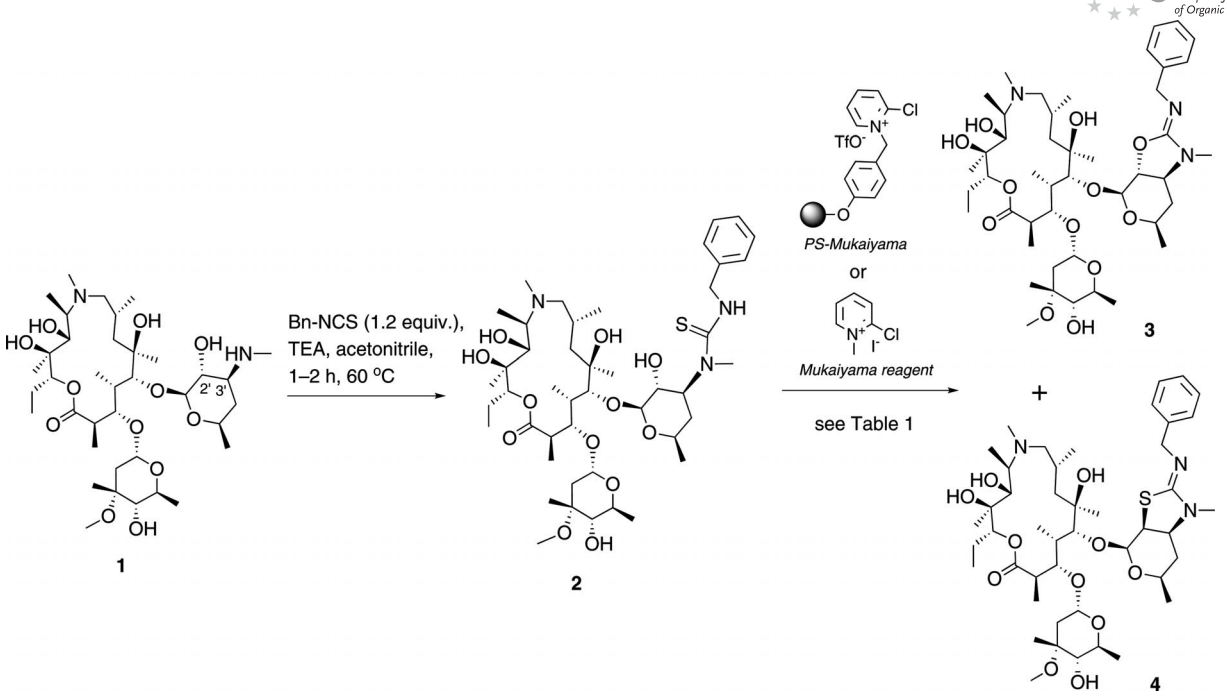
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201300266.



Scheme 1. Model reaction used for optimization of the regioselective synthesis of *N′*-substituted 2-imino-1,3-thiazolidines from the vicinal *sec*-amino alcohol of desosamine.

Table 1. Effects of solvent, base, and polymer support on the cyclization course (Scheme 1.) In all experiments, 1.2 equiv. of benzyl isothiocyanate was used.

Entry	Reagent /equiv.	Base /equiv.	Solvent	Time [h]	Temp. [°C]	Ratio [%]	Conversion [%]
Ref.[1]	EDC/2	–	acetonitrile	24	60	**3/4** = 100:0	100
1	PS-Mukaiyama/3	TEA/6	dimethylformamide	20	60	degradation	
2	PS-Mukaiyama/3	TEA/6	tetrahydrofuran	20	60	**3/4** = 100:0	70
3	PS-Mukaiyama/3	TEA/6	ethyl acetate	20	60	**3/4** = 80:20	80
4	PS-Mukaiyama/3	TEA/6	acetone	20	60	**3/4** = 80:20	70
5	PS-Mukaiyama/3	TEA/6	water	20	60	**3/4** = 80:20	25
6	PS-Mukaiyama/3	TEA/6	toluene	20	60	**3/4** = 90:10	90
7	PS-Mukaiyama/3	TEA/6	chloroform	20	60	**3/4** = 90:10	70
8	PS-Mukaiyama/3	TEA/6	acetonitrile	20	60	**3/4** = 50:50	80
9	PS-Mukaiyama/3	TEA/6	acetonitrile	20	82	**3/4** = 55:45	80
10	PS-Mukaiyama/3	NaH/6	acetonitrile	20	60	degradation	
11	PS-Mukaiyama/3	DMAP/6	acetonitrile	20	60	**3/4** = 100:0	70
12	PS-Mukaiyama/3	DBU/6	acetonitrile	20	60	**3/4** = 20:80	50
13	PS-Mukaiyama/3	–	pyridine	20	60	–	0
14	Mukaiyama/1.3	DBU/6	acetonitrile	1	60	**3/6** = 20:80	90
15	Mukaiyama/1.3	DBU/6	acetonitrile	1	0	**3/6** = 15:85	90
16	Mukaiyama/1.3	DBU/1.3	acetonitrile	1	0	**3/6** = 15:85	90
17	Mukaiyama/1.3	DBU/1.3	acetonitrile	1	–22	**3/6** = 10:90	90
18	Mukaiyama/1.3	DBU/1.3	acetonitrile	1	–41	**3/6** = 5:95	80
19	Mukaiyama/1.3	DBU/1.3	acetonitrile	1 h (–22 °C) + o.n. (60 °C)		**3/4** = 5:95	100

solvent type had a striking effect on the reaction course. The reaction in tetrahydrofuran afforded oxazolidine **3** as the sole product (Entry 2), while in dimethylformamide only degradation occurred (Entry 1). When some other solvents were used, various amounts of thiazolidine **4** were noticed. The best ratio of thiazolidine **4** (50%) was obtained in acetonitrile (Entry 8). The reaction also proceeded in water, albeit with low conversion (Entry 5).

Since acetonitrile was used for the synthesis of the thiocarbamoyl intermediate **2**, there was an opportunity to perform all other optimization reactions in a one-pot manner: the thiocarbamoyl intermediate **2** was prepared in acetonitrile at 60 °C, and to this solution, which was heated or cooled to the desired temperature, polymer supported Mukaiyama reagent and a base were added, and the reaction continued.

Increasing the temperature of the cyclization reaction from 60 °C to reflux temperature of acetonitrile (82 °C) did not substantially change the ratio of **4** (Entry 9), but rather a small drop from 50% to 45% was noticed.

On the other hand, the use of different bases showed striking influence on the reaction course (Entries 10–13, Table 1).

The reaction conducted with 4-(dimethylamino)pyridine (DMAP) afforded exclusively oxazolidine **3** (Entry 11). There was no cyclization reaction noticed in pyridine (Entry 13) and only degradation occurred if sodium hydride was used (Entry 10). However, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) substantially shifted the ratio of cyclized products to the side of the thiazolidine **4** (**3**/**4** = 20:80%) with moderate conversion (Entry 12).

In an attempt to increase the conversion, we tested non-supported Mukaiyama reagent instead of polymer supported analogue,[7] with DBU as the base (Entry 14). Interestingly, the conversion of the thiocarbamoyl intermediate **2** was finished after only 1 h, providing a minor amount of oxazolidine **3** along with a major unknown product. Attempts to isolate this product were unsuccessful due to its partial conversion to thiazolidine **4** on standing as well as during column chromatography. However, LC-MS and NMR analysis performed on the mixture of this unknown intermediate with thiazolidine **4** indicated covalent binding of Mukaiyama reagent to the hydroxy group at position 2′-C of the thiocarbamoyl intermediate **2** (Figure 1, compound **6**).

This result confirmed the mechanistic routes to both 2-imino-1,3-oxazolidine **3** and 2-imino-1,3-thiazolidine **4** (Figure 1), clearly indicating that the course of the reaction depends on the equilibrium between deprotonated 2′-OH and thiocarbamoyl moieties. In order to form the 2-imino-1,3-oxazolidine product **3**, the Mukaiyama reagent reacts with the thiolate tautomer of the deprotonated thiocarbamoyl moiety to form intermediate **5**, which closes the five-membered oxazolidine ring. On the other hand, reaction of the Mukaiyama reagent with the deprotonated 2′-OH leads to formation of **6**. Subsequently, five-membered thiazolidine ring formation occurs via nucleophilic attack of the thiocarbamoyl sulfur on 2′-C in order to provide the 2-imino-1,3-thiazolidine ring **4**. Since only one stereoisomer of thiazolidine ring (with inverted configuration at 2′-C) was formed, the mechanism of the five-membered thiazolidine ring formation must occur in a concerted manner. The fact that intermediate **5** could not be detected in the reaction mixture indicates that the steady-state concentration of **6** may be a consequence of a relatively slow ring-closure step to the thiazolidine ring in comparison to immediate cyclization of intermediate **5** to the oxazolidine ring.

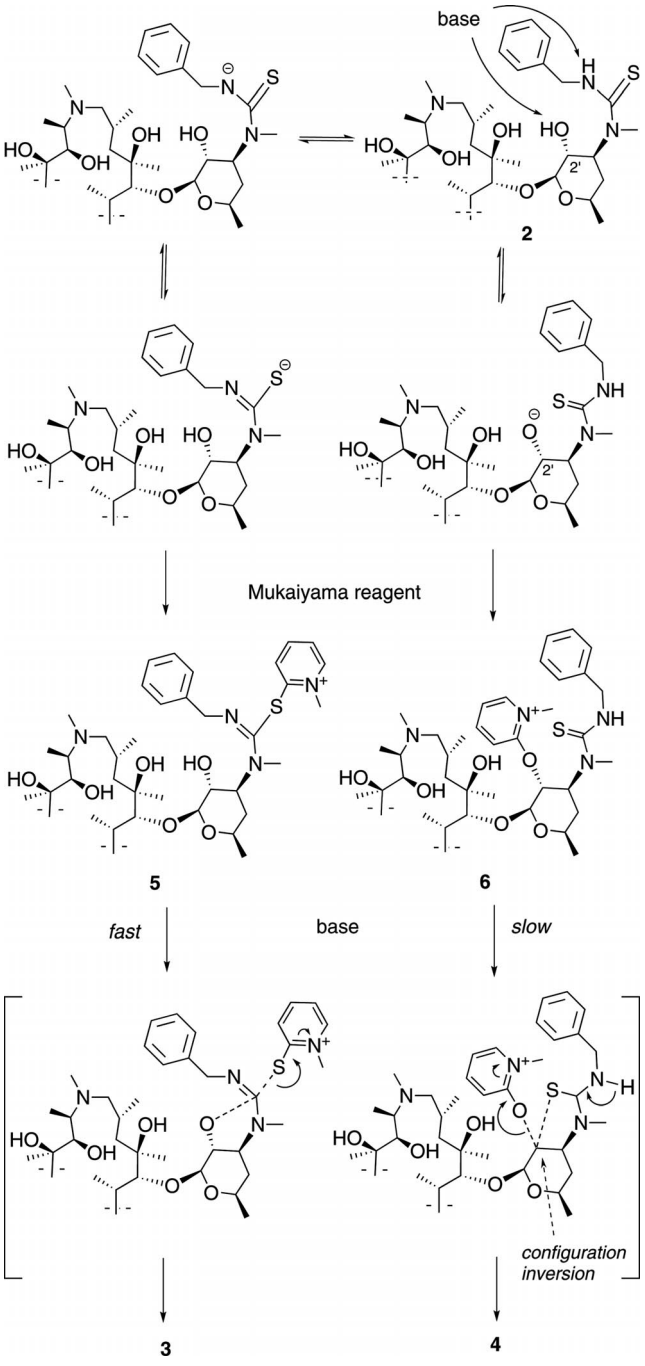
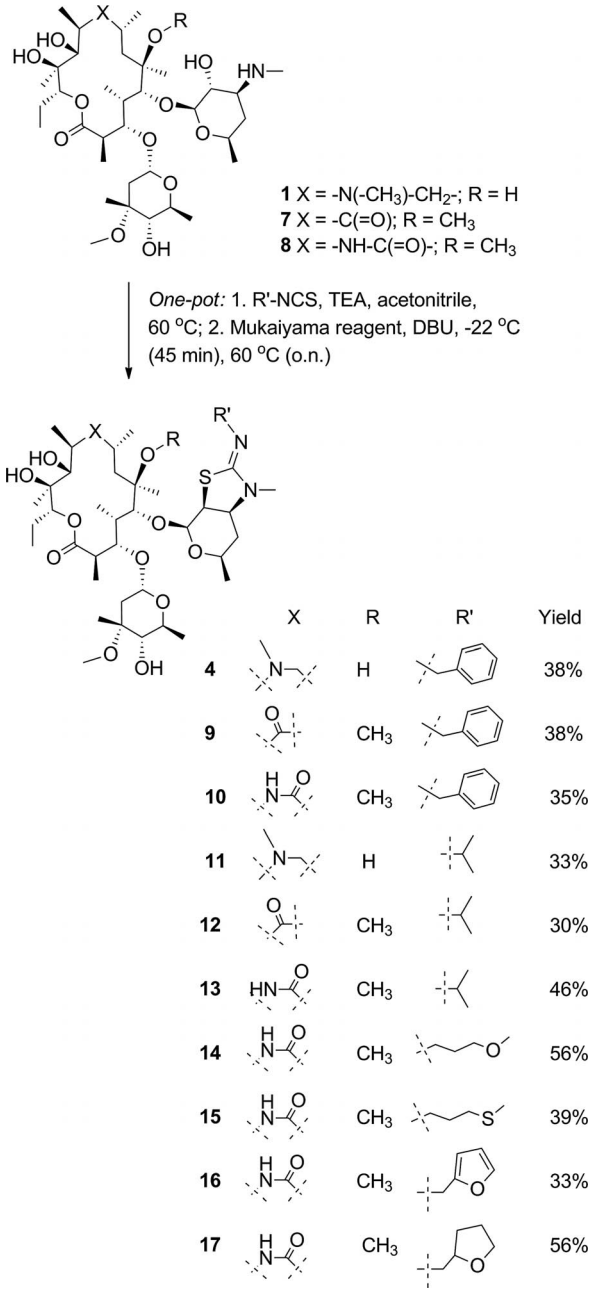


Figure 1. Proposed reaction mechanisms for oxazolidine **3** vs. thiazolidine **4** formation.

The decrease of the reaction temperature to 0 °C pushed the equilibrium further towards deprotonation of 2′-OH, slowed down the formation of oxazolidine **3**, and afforded a better ratio of the Mukaiyama adduct **6** (Entry 15). A smaller excess of the DBU base gave the same ratio of products **3** and **6** (Entry 16). By decreasing the reaction temperature further to –22 °C and –41 °C (Entries 17 and 18, respectively), the ratio of intermediate **6** increased in a linear fashion, and in the best case, 95% of thiazolidine **6** could be found in the mixture. Subsequent overnight heating at 60 °C (Entry 19, Table 1) converted intermediate **6** to thiazolidine **4**, without increasing the ratio of oxazolidine side product **3**.

Having in hand an optimized one-pot, two-step procedure for the preparation of *N*′-benzyl-2-imino-1,3-thiazolidine **4** on a small scale, the procedure described in Entry 19 (Table 1) was applied to three 3′-*N*-demethylated antibacterial macrolide scaffolds [9-deoxo-9a-methyl-9a-aza-9a-homo-erythromycin A (**1**), 6-*O*-methyl-erythromycin A (**7**), 6-*O*-methyl-9a-aza-9a-homo-erythromycin A (**8**)][1,2] on a larger scale. This procedure demonstrated similar results on all three scaffolds providing moderate yields of the thiazol-

idine products **4**, **9**, and **10** after purification by column chromatography (Scheme 2).



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

In comparison to their oxazolidine analogues,[1] the ^{1}H NMR spectra of the thiazolidines **4**, **9**, and **10** showed a downfield shift of the 2′-H and 3′-H resonance lines. Equally, a large upfield shift of the 2′-C signal was apparent in the ^{13}C NMR spectra of all thiazolidines, consistent with the insertion of a sulfur in the 2′,3′ bridge. Although observed vicinal coupling constants between 2′-H and 1′-H of ca. 2.5 Hz in thiazolidines (compared to ca. 8.0 Hz in oxazolidines) strongly indicate the inversion of configuration at 2′-C in thiazolidine, it might also be the result of the conformational change of the desosamine sugar. Therefore, with the aim of unambiguously establishing the stereochemistry and 3D structure of desosamine in both the thiazolidine and oxazolidine analogues, NMR analysis of coupling constants (Table 2) and nOe contacts was performed on **3** vs. **4** (Figure 2).

Table 2. Desosamine proton–proton coupling constants (in Hz) for compounds **3** and **4**.

$^{3}J_{n,m}$	**3**	**4**
1′,2′	7.9	2.8
2′,3′	10.6	5.9
3′,4′a	3.5	5.9
3′,4′b	11.7	11.2
4′a,5′	[a]	1.6
4′b,5′	11.0	11.2
5′,5′CH_3	6.1	6.1

[a] Coupling constants not measurable due to the signal overlap.

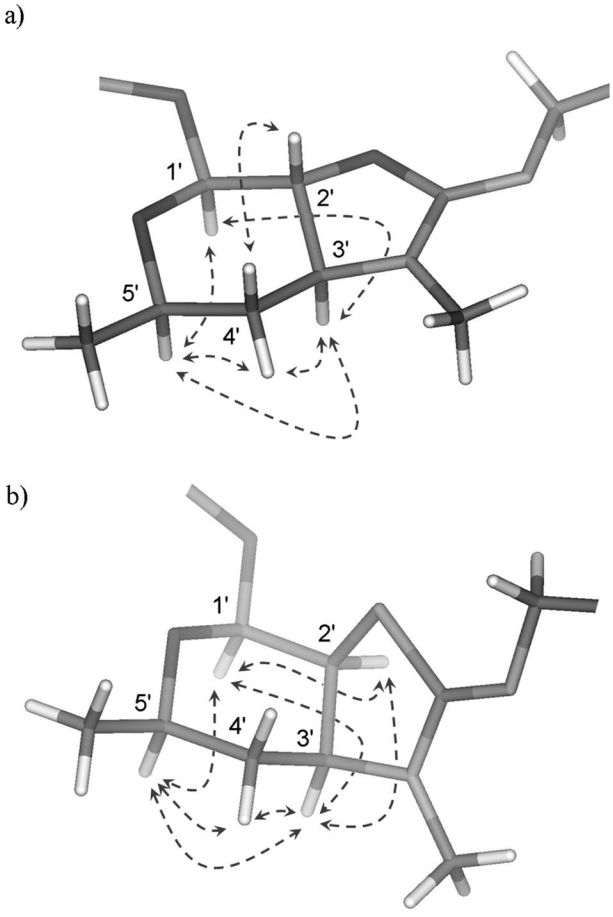
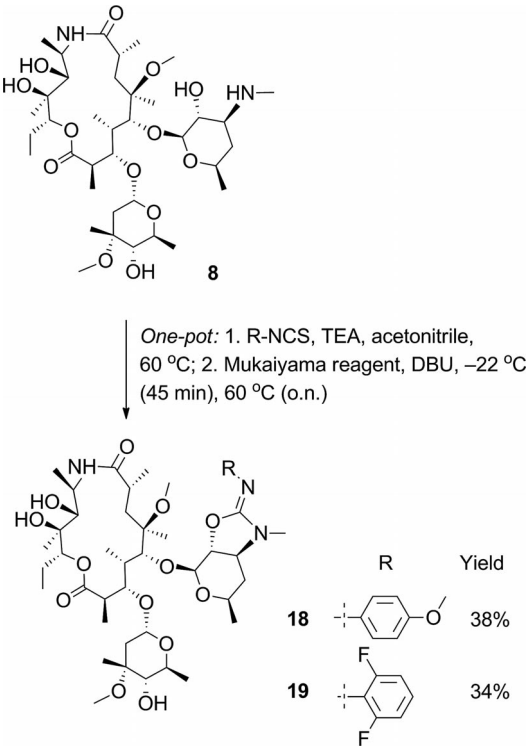


Figure 2. Comparison of the most important nOe contacts observed for oxazolidine **3** (a) and thiazolidine **4** (b).

The system of strong nOe's between the protons 1′-H, 3′-H and 5′-H (visible in both compounds) showed that the desosamine sugar adopted the usual Everett–Tyler chair conformation.[8] The nOe contacts of 4′-H_a with 3′-H, 5′-H and 5′-CH_3 pointed towards the equatorial position of 4′-H_a in both compounds, establishing 4′-H_b as axial. The same was discovered by analysing the coupling constants

between 4′-H_a, 4′-H_b and 5′-H, because they have similar values in both compounds ($^3J_{4'a,5'} \approx 1.5$ Hz; $^3J_{4'b,5'} \approx 11$ Hz). As a result, the presence of an nOe contact between 4′-H_b and 2′-H in **3** reveals the stereochemistry at position 2′ to be *R*. Similarly, the absence of the aforementioned interaction and the presence of two new nOe contacts (1′-H/2′-H and 2′-H/3′-H) establishes the inversion of stereochemistry at position 2′ in **4** (Figure 2). Coupling constants $^3J_{1',2'} = 7.9$ Hz and $^3J_{2',3'} = 10.6$ Hz in **3** vs. $^3J_{1',2'} = 2.7$ Hz and $^3J_{2',3'} = 5.9$ Hz in **4** lead to the same conclusion. In previously described oxazolidines[1] the imine bond stereochemistry was determined to be Z. Analysis of nOe data for compound **3** confirmed that stereochemistry through the absence of nOe contacts between the benzyl CH_2 protons and 3′-NCH_3. Compound **4** showed an identical set of nOe contacts for 3′-NCH_3. as in **3**, suggesting the same stereochemistry (Z) in thiazolidines.

Upon observing the overall conformations of molecules **3** and **4**, it appears that the changes to the desosamine sugar do not affect its usual orientation with respect to the cladinose ring, nor the usual position of either ring relative to the macrocycle.[9] Observed nOe contacts between sugar moieties (like 1′-H/5′′-H and 1′-H/3′′-OCH_3) suggest an up-up orientation of the alpha faces of the two sugars. Furthermore, nOe signals between 1′-H/5-H and 1′-H/4-CH_3 confirm the perpendicular orientation of the desosamine, while 1′-H/5′′-H and 5-H/5′′-H indicate an approximately parallel orientation of the cladinose sugar with respect to the macrocycle.



Scheme 3. Formation of 2-imino-1,3-oxazolidines when aryl-NCS reagents were used, yields were calculated after chromatographic purification.

A test library of novel desosamine modified macrolides **11**–**17**, which have various substituents attached to the *N*′-position of the fused 2-imino-1,3-thiazolidine moiety, was designed, and alkyl derivatives were successfully prepared (Scheme 2). However, when the same reaction conditions were applied to the compounds in which an aromatic ring was bound directly to the thiourea amine, only oxazolidine analogues **18**[3] and **19**[1] were obtained (Scheme 3). According to the proposed reaction mechanisms (Figure 1), this is expected because such aromatic rings stabilize deprotonated thiocarbamoyl moiety by conjugation, pushing the equilibrium towards thiolate tautomer.

Conclusions

In conclusion, a mild and regioselective one-pot method based on the Mukaiyama reagent-induced cyclization of vicinal *sec*-amino alcohols of desosamine origin to *N*′-alkyl-2-imino-1,3-thiazolidines via intermediate thiocarbamoyl moieties was developed. The mechanism of the formation of 2-imino-1,3-thiazolidine vs. 2-imino-1,3-oxazolidine rings was proposed. The applicability of this reaction to various vicinal *sec*-amino alcohols was investigated. The new *N*-alkyl-1,3-thiazolidin-2-ones fused to the desosamine sugars of 14- and 15-membered macrolide derivatives are potential agents for various biological targets.

Experimental Section

General: All solvents and reagents were used as supplied, unless noted otherwise. Mass spectra were recorded with a Varian MAT 311 instrument (FAB), and Platform LCZ or LCQ Deca instruments (ESI). HRMS (ESI) were recorded with a Micromass Qtof2 instrument. The structure confirmations, complete ^1H and ^{13}C assignments, as well as the conformational analysis were made on the basis of one- and two-dimensional NMR spectra (^1H, APT, COSY, NOESY, ROESY, edited HSQC and HMBC). All spectra were recorded with Bruker Avance III 600 and Bruker Avance DRX500 spectrometers equipped with 5 mm inverse-detection probes with a z-gradient accessory. The spectra were acquired using standard Bruker pulse sequences, on compounds dissolved in $CDCl_3$ or [D_6]DMSO, run at 25 °C with TMS as the internal standard. NOESY spectra were obtained with a mixing time of 400 ms.

General One-Pot Procedure: To a solution of 3′-*N*-demethyl derivatives **1**–**3** in acetonitrile (c = 0.065 g/mL), the corresponding isothiocyanate (1.5 equiv.) and triethylamine (2 equiv.) were added. The reaction was stirred at 60 °C until the thiourea intermediate was formed (according to LC-MS around 30 min), and then cooled to –22 °C (dry ice/CCl_4). Mukaiyama reagent (1.3 equiv.) and DBU (1.3 equiv.) were then added. The reaction mixture was stirred at –22 °C for 45 min and then overnight at 60 °C. The solvent was evaporated, and the residue was purified using column chromatography [eluent 1.5% MeOH/CH_2Cl_2 – MeOH/CH_2Cl_2/NH_4OH (4.5:90:0.25)] to afford chromatographically homogeneous fractions of final compounds.

2′-Deoxy-2′-(*S*)-*S*,3′-*N*-(*N*′-benzylcarbonimidoyl)-3′-*N*-demethyl-9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A (4):[1] According to the general procedure, reaction of **1** (0.5 g, 0.68 mmol) afforded **4** (0.23 g, 38%) as a white foam.

2′-Deoxy-2′-(*S*)-*S*,3′-*N*-(*N*′-benzylcarbonimidoyl)-3′-*N*-demethyl-6-*O*-methyl-erythromycin A (9): According to the general procedure, reaction of **7** (0.5 g, 0.68 mmol) afforded **9** (0.18 g, 38%) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$) *benzyl*: δ = 7.44 (d, J = 7.0 Hz, 2 H, 2×CH), 7.35 (t, J = 7.6 Hz, 2 H, 2×CH), 7.32 (t, J = 7.3 Hz, 1 H, CH), 4.67 (d, J = 15.3 Hz, 1 H, CH_2), 4.49 (d, J = 15.3 Hz, 1 H, CH_2) ppm; *macrolide*: δ = 5.08 (dd, J = 11.3, 2.1 Hz, 1 H, 13-H), 5.03 (d, J = 2.7 Hz, 1 H, 1′-H), 4.90 (d, J = 3.7 Hz, 1 H, 1′′-H), 4.38 (dd, J = 6.6, 2.6 Hz, 1 H, 2′-H), 4.19 (dt, J = 1.3, 6.0 Hz, 1 H, 3′-H), 3.90 (dq, J = 8.5, 6.4 Hz, 1 H, 5′′-H), 3.73 (d, J = 7.3 Hz, 1 H, 11-H), 3.71 (br.s, 1 H, 3-H), 3.70 (d, J = 9.8 Hz, 1 H, 5′-H), 3.43–3.51 (m, J = 11.3, 5.5, 5.5, 5.5, 1.2 Hz, 1 H, 5-H), 3.40 (s, 3 H, 3′-NCH_3), 3.31 (s, 3 H, 3′′-OCH_3), 3.19 (s, 1 H, OH), 3.08 (t, J = 8.9 Hz, 1 H, 4′′-H), 3.04 (s, 3 H, 6-OCH_3), 3.00 (q, J = 7.3 Hz, 1 H, 10-H), 2.85 (dq, J = 9.5, 7.3 Hz, 1 H, 2-H), 2.52–2.64 (m, J = 11.6, 7.0, 7.0, 7.0, 1.2 Hz, 1 H, 8-H), 2.31 (dd, J = 15.0, 0.9 Hz, 1 H, 2′′-H_a), 1.97 (d, J = 8.9 Hz, 1 H, 4′-H_a), 1.93 (dd, J = 12.5, 6.1 Hz, 1 H, 14-H_a), 1.91 (quint, J = 7.3 Hz, 1 H, 4-H), 1.76 (dd, J = 13.6, 12.2 Hz, 1 H, 7-H_a), 1.62 (dd, J = 15.0, 14.9 Hz, 1 H 2′′-H_b), 1.48 (ddq, J = 14.0, 11.0, 7.3 Hz, 1 H 14-H_b), 1.42 (d, J = 14.1 Hz, 1 H, 7-H_b), 1.38 (s, 3 H, 6-CH_3), 1.37 (dd, J = 12.0, 11.3 Hz, 1 H, 4′-H_b), 1.30 (d, J = 6.4 Hz, 3 H, 5′′-CH_3), 1.28 (d, J = 7.6 Hz, 3 H, 5′-CH_3), 1.27 (s, 3 H, 3′′-CH_3), 1.21 (d, J = 7.3 Hz, 3 H, 2-CH_3), 1.18 (d, J = 7.0 Hz, 3 H, 8-CH_3), 1.15 (d, J = 7.6 Hz, 3 H, 10-CH_3), 1.15 (s, 3 H, 12-CH_3), 0.93 (d, J = 7.3 Hz, 3 H, 4-CH_3), 0.85 (t, J = 7.3 Hz, 3 H, 15-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) *benzyl*: δ = 136.6 (C), 128.6 (2×CH), 128.1 (2×CH), 127.8 (CH), 52.9 (CH_2) ppm; *macrolide*: δ = 220.5 (9-C), 175.4 (1-C), 166.5 (C=N), 96.6 (1′-C), 96.3 (1′′-C), 83.2 (5-C), 78.6 (3-C), 77.8 (6-C), 77.4 (4′′-C), 77.1 (13-C), 74.1 (12-C), 73.0 (3′′-C), 69.0 (11-C), 67.1 (5′-C), 66.2 (5′′-C), 63.6 (3′-C), 50.7 (6-OCH_3), 49.7 (3′′-OCH_3), 48.4 (2′-C), 45.0 (8-C), 44.8 (2-C), 39.0 (7-C), 38.3 (4-C), 37.2 (10-C), 35.5 (3′-NCH_3), 34.9 (2′′-C), 31.6 (4′-C), 21.3 (3′′-CH_3), 20.9 (5′-CH_3), 20.9 (14-C), 19.5 (6-CH_3), 18.5 (5′′-CH_3), 18.0 (8-CH_3), 16.0 (12-CH_3), 15.8 (2-CH_3), 12.2 (10-CH_3), 10.5 (15-C), 9.1 (4-CH_3) ppm. HRMS (ES): calcd. for $C_{45}H_{73}N_2O_{12}S$ [M + H^+] 865.4884; found 865.4889.

2′-Deoxy-2′-(*S*)-*S*,3′-*N*-(*N*′-benzylcarbonimidoyl)-3′-*N*-demethyl-6-*O*-methyl-9a-aza-9a-homoerythromycin A (10): According to the general procedure, reaction of **8** (0.5 g, 0.67 mmol) afforded **10** (0.15 g, 25%) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$) *benzyl*: δ = 7.35 (d, J = 7.6 Hz, 2 H, 2×CH), 7.28 (t, J = 7.6 Hz, 2 H, 2×CH), 7.21 (d, J = 7.3 Hz, 1 H, CH), 4.35–4.45 (m, 2 H, CH_2) ppm; *macrolide*: δ = 6.09 (d, J = 7.9 Hz, 1 H, 9a-NH), 4.96 (d, J = 2.7 Hz, 1 H, 1′-H), 4.86 (d, J = 4.9 Hz, 1 H, 1′′-H), 4.67 (d, J = 10.1 Hz, 1 H, 13-H), 4.17–4.21 (m, 2 H, 3-H, 10-H), 4.05 (dd, J = 6.0, 2.6 Hz, 1 H, 2′-H), 4.02 (dq, J = 9.2, 6.1 Hz, 1 H, 5′′-H), 3.79 (d, J = 6.7 Hz, 1 H, 5-H), 3.69 (dt, J = 10.9, 5.7 Hz, 1 H, 3′-H), 3.37–3.45 (m, 1 H, 5′-H), 3.33 (s, 6 H, 6-OCH_3, 3′′-OCH_3), 3.30 (br.s, 1 H, OH), 3.21 (d, J = 4.3 Hz, 1 H, 11-H), 3.07 (t, J = 9.3 Hz, 1 H, 4′′-H), 2.91 (s, 3 H, 3′-NCH_3), 2.83 (quint, J = 6.7 Hz, 1 H, 2-H), 2.41 (br.s, 1 H, OH), 2.34 (d, J = 15.0 Hz, 1 H, 2′′-H_a), 2.22 (quint, J = 7.2 Hz, 1 H, 8-H), 2.15 (d, J = 9.8 Hz, 1 H, OH), 1.99 (dd, J = 14.8, 8.1 Hz, 1 H, 7-H_a), 1.81–1.93 (m, 2 H, 4-H, 14-H_a), 1.78 (dd, J = 12.2, 5.5 Hz, 1 H, 4′-H_a), 1.60 (dd, J = 15.1, 5.0 Hz, 1 H, 2′′-H_b), 1.51–1.59 (m, 1 H, 14-H_b), 1.44 (q, J = 11.6 Hz, 1 H,4′-H_b), 1.38 (s, 3 H, 6-CH_3), 1.34 (d, J = 6.4 Hz, 3 H, 5′′-CH_3), 1.29–1.32 (m, 1 H, 7-H_b), 1.27 (d, J = 7.2 Hz, 3 H, 5′-CH_3), 1.26 (s, 3 H, 3′′-CH_3), 1.24 (d, J = 7.6 Hz, 3 H, 2-CH_3), 1.18 (s, 3 H, 12-CH_3), 1.17 (d, J = 7.2 Hz, 3 H, 10-CH_3), 1.13 (d, J = 7.0 Hz, 3 H, 8-CH_3), 0.90 (d, J = 6.2 Hz, 3 H, 15-H), 0.89 (t, J = 7.0 Hz, 3 H, 4-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) *benzyl*: 141.2 (C), 128.0 (2×CH), 127.4 (2×CH), 126.2 (CH), 58.5 (CH_2) ppm; *macrolide*: δ = 179.5 (1-C), 177.4 (9-C), 158.3 (C=N), 98.0 (1′-C), 95.6 (1′′-C), 80.6 (5-C), 79.0 (6-C), 78.4 (13-C), 77.7 (4′′-C), 76.3 (3-C), 74.1 (12-C), 73.0 (3′′-C), 72.8 (11-C), 67.3 (5′-C), 65.8 (5′′-C), 60.5 (3′-C), 51.5 (6-OCH_3), 49.5 (3′′-OCH_3), 46.3 (2′-C), 45.3 (10-C), 44.5 (2-C), 40.9 (4-C), 39.8 (7-C), 35.6 (8-C), 34.7 (2′′-C), 31.8 (3′-NCH_3), 31.1 (4′-C), 21.4 (3′′-CH_3), 21.1 (5′-CH_3), 20.6 (14-C), 20.4 (6-CH_3), 19.4 (8-CH_3), 18.4 (5′′-CH_3), 16.0 (12-CH_3), 15.2 (2-CH_3), 13.9 (10-CH_3), 11.0 (15-C), 8.8 (4-CH_3) ppm. HRMS (ES): calcd. for $C_{45}H_{74}N_3O_{12}S$ [M + H^+] 880.4993; found 880.4991.

2′-Deoxy-2′-(*S*)-*S*,3′-*N*-(*N*′-isopropylcarbonimidoyl)-3′-*N*-demethyl-9-deoxo-9a-methyl-9a-aza-9a-homoerythromycin A (11): According to the general procedure, reaction of **1** (0.5 g, 0.68 mmol) afforded **11** (0.18 g, 33%) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$) *isopropyl*: δ = 3.20 (dt, J = 12.4, 6.3 Hz, 1 H, CH), 1.14 (d, J = 6.2 Hz, 3 H, CH_3), 1.13 (d, J = 6.2 Hz, 3 H, CH_3) ppm; *macrolide*: δ = 5.11 (d, J = 4.6 Hz, 1 H, 1′′-H), 4.96 (d, J = 2.7 Hz, 1 H, 1′-H), 4.69 (dd, J = 10.1, 2.1 Hz, 1 H, 13-H), 4.25 (dd, J = 4.9, 1.5 Hz, 1 H, 3-H), 4.02 (dq, J = 9.5, 6.1 Hz, 1 H, 5′′-H), 4.01 (dd, J = 5.8, 2.7 Hz, 1 H, 2′-H), 3.68 (d, J = 7.3 Hz, 1 H, 5-H), 3.64–3.66 (m, 1 H, 11-H), 3.62 (dt, J = 10.9, 5.7 Hz, 1 H, 3′-H), 3.37–3.46 (m, 1 H, 5′-H), 3.33 (s, 3 H, 3′′-OCH_3), 3.07 (t, J = 9.6 Hz, 1 H, 4′′-H), 2.91 (s, 1 H, OH), 2.84 (s, 3 H, 3′-NCH_3), 2.78 (dq, J = 7.3, 6.0 Hz, 1 H, 2-H), 2.70 (q, J = 6.7 Hz, 1 H, 10-H), 2.55 (d, J = 10.4 Hz, 1 H, 9-H_a), 2.35 (d, J = 14.6 Hz, 1 H, 2′′-H_a), 2.33 (s, 3 H, 9a-NCH_3), 2.07 (dd, J = 16.0, 10.8 Hz, 1 H, 9-H_b), 1.99–2.03 (m, 1 H, 8-H), 1.96 (quint, J = 7.3 Hz, 1 H, 4-H), 1.85–1.94 (m, 1 H, 14-H_a), 1.72 (ddd, J = 13.1, 5.5, 1.2 Hz, 1 H, 4′-H_a), 1.70 (d, J = 14.6 Hz, 1 H, 7-H_a), 1.62 (d, J = 15.3, 4.9 Hz, 1 H, 2′′-H_b), 1.44–1.53 (m, 1 H, 14-H_b), 1.41 (q, J = 13.1 Hz, 1 H, 4′-H_b), 1.35 (s, 3 H, 6-CH_3), 1.33 (d, J = 6.4 Hz, 1 H, 5′′-CH_3), 1.26 (d, J = 7.2 Hz, 3 H, 5′-CH_3), 1.26 (s, 3 H, 3′′-CH_3), 1.20–1.25 (m, 1 H, 7-H_b), 1.20 (d, J = 7.6 Hz, 3 H, 2-CH_3), 1.09 (d, J = 7.0 Hz, 3 H, 10-CH_3), 1.07 (s, 3 H, 12-CH_3), 0.95 (d, J = 6.7 Hz, 3 H, 8-CH_3), 0.91 (d, J = 7.2 Hz, 3 H, 4-CH_3), 0.88 (t, J = 7.3 Hz, 3 H, 15-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) *isopropyl*: δ = 56.5 (CH), 24.8 (CH_3), 24.3 (CH_3) ppm; *macrolide*: δ = 178.5 (1-C), 154.9 (C=N), 98.4 (1′-C), 94.9 (1′′-C), 85.3 (5-C), 78.1 (3-C), 77.9 (4′′-C), 77.5 (13-C), 74.1 (12-C), 73.9 (11-C), 73.3 (3′′-C), 73.1 (6-C), 67.4 (5′-C), 70.9 (9-C), 65.7 (5′′-C), 62.3 (10-C), 60.4 (3′-C), 49.4 (3′′-OCH_3), 46.2 (2′-C), 45.1 (2-C), 41.9 (7-C), 41.3 (4-C), 36.9 (9a-NCH_3), 34.7 (2′′-C), 31.9 (3′-NCH_3), 30.8 (4′-C), 27.3 (6-CH_3), 26.6 (8-C), 21.9 (8-CH_3), 21.5 (3′′-CH_3), 21.1 (14-C), 20.9 (5′-CH_3), 18.1 (5′′-CH_3), 16.1 (12-CH_3), 14.9 (2-CH_3), 11.1 (15-C), 8.7 (4-CH_3), 7.2 (10-CH_3) ppm. HRMS (ES): calcd. for $C_{41}H_{75}N_3O_{11}S$ [M + H^+] 817.5117; found 817.5138.

2′-Deoxy-2′-(*S*)-*S*,3′-*N*-(*N*′-isopropylcarbonimidoyl)-3′-*N*-demethyl-6-*O*-methyl-erythromycin A (12): According to the general procedure, reaction of 0.41 g of **7** (0.55 mmol) afforded **12** (0.067 g, 15%) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$) *isopropyl*: δ = 3.18 (dt, J = 12.7, 6.3 Hz, 1 H, CH), 1.17 (d, J = 6.2 Hz, 3 H, CH_3), 1.16 (d, J = 6.3 Hz, 3 H, CH_3) ppm; *macrolide*: δ = 5.08 (dd, J = 11.0, 2.1 Hz, 1 H, 13-H), 4.97 (d, J = 2.4 Hz, 1 H, 1′-H), 4.93 (d, J = 4.6 Hz, 1 H, 1′′-H), 4.04 (dd, J = 5.6, 2.6 Hz, 1 H, 2′-H), 4.00 (s, 1 H, OH), 3.95 (dq, J = 9.0, 6.2 Hz, 1 H, 5′′-H), 3.75 (s, 1 H, 11-H), 3.75 (d, J = 8.9 Hz, 1 H, 3-H), 3.71 (d, J = 7.0 Hz, 1 H, 5-H), 3.64 (dt, J = 11.0, 5.5 Hz, 1 H, 3′-H), 3.35–3.43 (m, 1 H, 5′-H), 3.32 (s, 3 H, 3′′-OCH_3), 3.19 (s, 1 H, OH), 3.07 (d, J = 9.5 Hz, 3 H, 4′′-H), 3.05 (s, 3 H, 6-OCH_3), 3.01 (q, J = 7.3 Hz, 1 H, 10-H), 2.82–2.88 (m, 1 H, 2-H), 2.85 (s, 3 H, 3′-NCH_3), 2.54–2.64 (m, 1 H, 8-H), 2.37 (d, J = 15.3 Hz, 1 H, 2′′-H_a), 2.11 (d, J = 9.8 Hz, 1 H, OH), 1.90–1.97 (m, 1 H, 14-H_a), 1.91 (quint, J = 7.0 Hz, 1 H, 4-H), 1.80 (dd, J = 14.6, 12.0 Hz, 1 H, 7-H_a), 1.73 (dd, J = 13.1, 5.5 Hz, 1 H, 4′-H_a), 1.68 (br.s, 1 H, OH), 1.62 (dd, J = 15.3, 5.2 Hz,

1 H, 2′′-H_b), 1.60 (dd, J = 14.0, 1.5 Hz, 1 H, 7-H_b), 1.45–1.51 (m, 1 H, 14-H_b), 1.45 (s, 3 H, 6-CH_3), 1.35–1.42 (m, 1 H, 4′-H_b), 1.33 (d, J = 6.1 Hz, 3 H, 5′′-CH_3), 1.27 (s, 3 H, 3′′-CH_3), 1.26 (d, J = 6.2 Hz, 3 H, 5′-CH_3), 1.21 (d, J = 7.3 Hz, 3 H, 2-CH_3), 1.14 (br.s, 3 H, 8-CH_3), 1.13 (d, J = 7.0 Hz, 3 H, 10-CH_3), 1.12 (s, 3 H, 12-CH_3), 0.97 (d, J = 7.3 Hz, 3 H, 4-CH_3), 0.86 (t, J = 7.3 Hz, 3 H, 15-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) *isopropyl*: δ = 56.7 (CH), 24.8 (CH_3), 24.3 (CH_3) ppm; *macrolide*: δ = 220.9 (9-C), 175.5 (1-C), 166.5 (C=N), 98.4 (1′-C), 96.3 (1′′-C), 82.8 (5-C), 78.6 (3-C), 78.1 (6-C), 77.7 (4′′-C), 77.1 (13-C), 74.1 (12-C), 72.9 (3′′-C), 69.0 (11-C), 67.5 (5′-C), 65.9 (5′′-C), 60.2 (3′-C), 50.6 (6-OCH_3), 49.5 (3′′-OCH_3), 46.1 (2′-C), 45.2 (8-C), 44.9 (2-C), 38.9 (7-C), 38.7 (4-C), 37.2 (10-C), 34.8 (2′′-C), 32.0 (3′-NCH_3), 30.8 (4′-C), 21.4 (3′′-CH_3), 21.0 (5′-CH_3), 20.9 (14-C), 19.6 (6-CH_3), 18.5 (5′′-CH_3), 18.0 (8-CH_3), 16.0 (12-CH_3), 15.9 (2-CH_3), 12.2 (10-CH_3), 10.5 (15-C), 8.9 (4-CH_3) ppm. HRMS (ES): calcd. for $C_{41}H_{73}N_2O_{12}S$ [M + H^+] 817.4884; found 817.4896.

2′-Deoxy-2′-(*S*)-*S*,3′-*N*-(*N*′-isopropylcarbonimidoyl)-3′-*N*-demethyl-6-*O*-methyl-9a-aza-9a-homoerythromycin A (13): According to the general procedure, reaction of **8** (0.7 g, 0.93 mmol) afforded **13** (0.36 g, 46%) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$) *isopropyl*: 3.16–3.22 (m, 1 H, CH), 1.24 (d, J = 6.2 Hz, 3 H, CH_3), 1.23 (d, J = 6.2 Hz, 3 H, CH_3) ppm; *macrolide*: δ = 6.10 (d, J = 8.2 Hz, 1 H, 9a-NH), 4.94 (d, J = 2.4 Hz, 1 H, 1′-H), 4.86 (d, J = 4.6 Hz, 1 H, 1′′-H), 4.66 (d, J = 10.4 Hz, 1 H, 13-H), 4.13–4.22 (m, 1 H, 10-H), 4.18 (d, J = 6.4 Hz, 1 H, 3-H), 4.01 (dq, J = 8.8, 6.1 Hz, 1 H, 5′′-H), 3.98 (dd, J = 5.6, 2.0 Hz, 1 H, 2′-H), 3.78 (d, J = 6.7 Hz, 1 H, 5-H), 3.60 (dt, J = 11.0, 5.5 Hz, 1 H, 3′-H), 3.39 (dq, J = 11.3, 5.8 Hz, 1 H, 5′-H), 3.33 (s, 3 H, 6-OCH_3), 3.32 (s, 3 H, 3′′-OCH_3), 3.16–3-22 (m, 1 H, 11-H), 3.07 (t, J = 9.6 Hz, 1 H, 4′′-H), 2.79–2.87 (m, 1 H, 2-H), 2.82 (s, 3 H, 3′-NCH_3), 2.39 (s, 1 H, OH), 2.34 (d, J = 15.3 Hz, 1 H, 2′′-H_a), 2.22 (quint, J = 7.1 Hz, 1 H, 8-H), 2.12 (d, J = 9.8 Hz, 1 H, OH), 1.97 (dd, J = 15.0, 7.9 Hz, 1 H, 7-H_a), 1.84–1.92 (m, 2 H, 4-H, 14-H_a), 1.82 (br.s, 1 H, OH), 1.72 (dd, J = 12.5, 5.2 Hz, 3 H, 4′-H_a), 1.60 (dd, J = 15.1, 5.0 Hz, 1 H, 2′′-H_b), 1.56 (m, 1 H, 14-H_b), 1.40 (q, J = 11.6 Hz, 3 H, 4′-H_b), 1.39 (s, 3 H, 6-CH_3), 1.35 (d, J = 7.6 Hz, 3 H, 5′′-CH_3), 1.34 (d, J = 6.1 Hz, 3 H, 5′-CH_3),1.31 (d, J = 15.0 Hz, 1 H, 7-H_b), 1.27 (s, 3 H, 3′′-CH_3), 1.24 (d, J = 7.6 Hz, 3 H, 2-CH_3), 1.18 (s, 3 H, 12-CH_3), 1.16 (d, J = 7.2 Hz, 3 H, 10-CH_3), 1.13 (d, J = 7.2 Hz, 3 H, 8-CH_3), 0.90 (t, J = 6.7 Hz, 3 H, 15-H), 0.89 (d, J = 6.8 Hz, 3 H, 4-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) *isopropyl*: δ = 56.5 (CH), 24.7 (CH_3), 24.2 (CH_3) ppm; *macrolide*: δ = 179.5 (1-C), 177.4 (9-C), 154.9 (C=N), 98.2 (1′-C), 95.5 (1′′-C), 80.6 (5-C), 79.1 (6-C), 78.4 (13-C), 77.7 (4′′-C), 76.4 (3-C), 74.1 (12-C), 73.0 (3′′-C), 72.8 (11-C), 67.4 (5′-C), 65.8 (5′′-C), 60.2 (3′-C), 51.5 (6-OCH_3), 49.5 (3′′-OCH_3), 46.0 (2′-C), 45.3 (10-C), 44.6 (2-C), 40.9 (4-C), 39.8 (7-C), 35.6 (8-C), 34.7 (2′′-C), 31.9 (3′-NCH_3), 30.8 (4′-C), 21.8 (5′-CH_3), 21.4 (3′′-CH_3), 20.6 (14-C), 20.4 (6-CH_3), 19.4 (8-CH_3), 18.4 (5′′-CH_3), 16.0 (12-CH_3), 15.3 (2-CH_3), 13.8 (10-CH_3), 11.1 (15-C), 8.9 (4-CH_3) ppm. HRMS (ES): calcd. for $C_{40}H_{69}N_3O_{12}S$ [M + H^+] 815.4596; found 815.4604.

2′-Deoxy-2′-(*S*)-*S*,3′-*N*-{*N*′-[3-(methyloxy)propyl]carbonimidoyl}-3′-*N*-demethyl-6-*O*-methyl-9a-aza-9a-homoerythromycin A (14): According to the general procedure, reaction of **8** (0.4 g, 0.53 mmol) afforded **14** (0.26 g, 56%) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$) *methoxypropyl*: δ = 3.46 (d, J = 6.7 Hz, 3 H, CH_2), 3.36 (s, 3 H, CH_3), 3.16–3.28 (m, 2 H, CH_2), 1.80–1.93 (m, 2H, CH_2) ppm; *macrolide*: 6.07 (d, J = 7.9 Hz, 1 H, 9a-NH), 4.94 (d, J = 2.7 Hz, 1 H, 1′-H), 4.86 (d, J = 4.6 Hz, 1 H, 1′′-H), 4.67 (d, J = 10.7 Hz, 1 H, 13-H), 4.13–4.21 (m, 2 H, 10-H, 3-H), 4.02 (dq, J = 9.2, 6.1 Hz, 1 H, 5′′-H), 3.99 (d, J = 7.6 Hz, 1 H, 2′-H), 3.78 (d, J = 6.7 Hz, 1 H, 5-H), 3.64 (dt, J = 7.6, 5.5 Hz, 1 H, 3′-H), 3.35–3.43 (m, 1 H, 5′-H), 3.32 (s, 3 H, 6-OCH_3), 3.32 (s, 3 H, 3′′-OCH_3), 3.16–3.28 (m, 1 H, 11-H), 3.07 (t, J = 9.6 Hz, 1 H, 4′′-H), 2.83 (dq, J = 7.9, 6.8 Hz, 1 H, 2-H), 2.82 (s, 3 H, 3′-NCH_3), 2.36 (s, 1 H, OH), 2.33 (d, J = 15.3 Hz, 1 H, 2′′-H_a), 2.22 (quint, J = 7.1 Hz, 1 H, 8-H), 2.10 (d, J = 10.1 Hz, 1 H, OH), 1.99 (dd, J = 15.0, 8.2 Hz, 1 H, 7-H_a), 1.80–1.93 (m, 2 H, 4-H, 14-H_a), 1.74 (dd, J = 12.5, 5.2 Hz, 1 H, 4′-H_a), 1.59 (dd, J = 15.3, 4.9 Hz, 1 H, 2′′-H_b), 1.52–1.62 (m, 1 H, 14-H_b), 1.35–1.43 (m, 1 H, 4′-H_b), 1.39 (s, 3 H, 6-CH_3), 1.34 (d, J = 6.1 Hz, 3 H, 5′′-CH_3), 1.28 (d, J = 15.0 Hz, 1 H, 7-H_b), 1.27 (s, 3 H, 5′-CH_3), 1.27 (d, J = 6.2 Hz, 3 H, 3′′-CH_3), 1.25 (d, J = 7.6 Hz, 3 H, 2-CH_3), 1.18 (s, 3 H, 12-CH_3), 1.16 (d, J = 6.2 Hz, 3 H, 10-CH_3), 1.13 (d, J = 7.0 Hz, 3 H, 8-CH_3), 0.91 (t, J = 7.2 Hz, 3 H, 15-H), 0.89 (d, J = 7.6 Hz, 3 H, 4-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) *methoxypropyl*: δ = 70.9 (CH_2), 58.4 (OCH_3), 51.8 (CH_2), 31.4 (CH_2) ppm; *macrolide*: δ = 179.6 (1-C), 177.5 (9-C), 156.5 (C=N), 98.1 (1′-C), 95.5 (1′′-C), 80.6 (5-C), 79.1 (6-C), 78.5 (13-C), 77.7 (4′′-C), 76.3 (3-C), 74.1 (12-C), 73.0 (3′′-C), 72.7 (11-C), 67.3 (5′-C), 65.8 (5′′-C), 60.4 (3′-C), 51.5 (6-OCH_3), 49.5 (3′′-OCH_3), 46.1 (2′-C), 45.3 (10-C), 44.6 (2-C), 40.9 (4-C), 39.9 (7-C), 35.7 (8-C), 34.7 (2′′-C), 31.8 (3′-NCH_3), 31.0 (4′-C), 21.4 (3′′-CH_3), 21.1 (5′-CH_3), 20.6 (14-C), 20.5 (6-CH_3), 19.5 (8-CH_3), 18.4 (5′′-CH_3), 16.0 (12-CH_3), 15.2 (2-CH_3), 13.8 (10-CH_3), 11.1 (15-C), 8.9 (4-CH_3) ppm. HRMS (ES): calcd. for $C_{42}H_{76}N_3O_{13}S$ [M + H^+] 862.5099; found 862.5109.

2′-Deoxy-2′-(*S*)-*S*,3′-*N*-{*N*′-[3-(methylthio)propyl]carbonimidoyl}-3′-*N*-demethyl-6-*O*-methyl-9a-aza-9a-homoerythromycin A (15): According to the general procedure, reaction of **8** (0.4 g, 0.53 mmol) afforded **15** (0.18 g, 39%) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$) *methylthiopropyl*: δ = 3.25 (td, J = 12.9, 6.3 Hz, 2 H, CH_2), 2.58 (d, J = 7.9 Hz, 2 H, CH_2), 2.13 (s, 3 H, SCH_3), 1.83–1.93 (m, 2 H, CH_2) ppm; *macrolide*: δ = 6.08 (d, J = 8.2 Hz, 1 H, 9a-NH), 4.95 (d, J = 2.7 Hz, 1 H, 1′-H), 4.86 (d, J = 4.6 Hz, 1 H, 1′′-H), 4.67 (d, J = 9.8 Hz, 1 H, 13-H), 4.12–4.23 (m, 2 H, 10-H, 3-H), 4.02 (dd, J = 5.6, 2.6 Hz, 1 H, 5′′-H), 4.00 (dq, J = 9.6, 6.2 Hz, 1 H, 2′-H), 3.78 (d, J = 6.7 Hz, 1 H, 5-H), 3.65 (dt, J = 10.9, 5.7 Hz, 1 H, 3′-H), 3.35–3.43 (m, 1 H, 5′-H), 3.31 (s, 3 H, 6-OCH_3), 3.31 (s, 3 H, 3′′-OCH_3), 3.21 (d, J = 4.0 Hz, 1 H, 11-H), 3.07 (t, J = 9.5 Hz, 1 H, 4′′-H), 2.84 (dq, J = 9.0, 7.0 Hz, 1 H, 2-H), 2.84 (s, 3 H, 3′-NCH_3), 2.36 (s, 1 H, OH), 2.33 (d, J = 15.0 Hz, 1 H, 2′′-H_a), 2.23 (quint, J = 7.0 Hz, 1 H, 8-H), 1.99 (dd, J = 15.0, 7.9 Hz, 1 H, 7-H_a), 1.83–1.93 (m, 2 H, 4-H, 14-H_a), 1.74 (dd, J = 12.1, 5.6 Hz, 1 H, 4′-H_a), 1.58 (dd, J = 15.1, 5.0 Hz, 1 H, 2′′-H_b), 1.52–1.61 (m, 1 H, 14-H_b), 1.35–1.43 (m, 1 H, 4′-H_b), 1.39 (s, 3 H, 6-CH_3), 1.33 (d, J = 6.4 Hz, 3 H, 5′′-CH_3), 1.30 (d, J = 15.0 Hz, 1 H, 7-H_b), 1.27 (d, J = 5.8 Hz, 3 H, 5′-CH_3), 1.27 (s, 3 H, 3′′-CH_3), 1.25 (d, J = 7.6 Hz, 3 H, 2-CH_3), 1.19 (s, 3 H, 12-CH_3), 1.16 (d, J = 7.0 Hz, 3 H, 10-CH_3), 1.13 (d, J = 7.0 Hz, 3 H, 8-CH_3), 0.92 (t, J = 7.6 Hz, 3 H, 15-H), 0.88 (d, J = 7.6 Hz, 3 H, 4-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) *methylthiopropyl*: δ = 54.1 (CH_2), 32.0 (CH_2), 31.1 (CH_2), 15.5 (OCH_3) ppm; *macrolide*: δ = 179.6 (1-C), 177.4 (9-C), 156.5 (C=N), 98.1 (1′-C), 95.5 (1′′-C), 80.6 (5-C), 79.1 (6-C), 78.5 (13-C), 77.7 (4′′-C), 76.3 (3-C), 74.1 (12-C), 73.0 (3′′-C), 72.7 (11-C), 67.3 (5′-C), 65.8 (5′′-C), 60.4 (3′-C), 51.5 (6-OCH_3), 49.5 (3′′-OCH_3), 46.1 (2′-C), 45.3 (10-C), 44.6 (2-C), 40.9 (4-C), 39.9 (7-C), 35.6 (8-C), 34.7 (2′′-C), 31.7 (3′-NCH_3), 31.0 (4′-C), 21.4 (3′′-CH_3), 21.1 (5′-CH_3), 20.6 (14-C), 20.4 (6-CH_3), 19.4 (8-CH_3), 18.4 (5′′-CH_3), 16.0 (12-CH_3), 15.2 (2-CH_3), 13.9 (10-CH_3), 11.1 (15-C), 8.9 (4-CH_3) ppm. HRMS (ES): calcd. for $C_{42}H_{76}N_3O_{12}S_2$ [M + H^+] 878.4870; found 878.4879.

2′-Deoxy-2′-(*S*)-*S*,3′-*N*-[*N*′-(2-furanylmethyl)carbonimidoyl]-3′-*N*-demethyl-6-*O*-methyl-9a-aza-9a-homoerythromycin A (16): According to the general procedure, reaction of **8** (0.4 g, 0.53 mmol) afforded **16** (0.16 g, 33%) as a white foam. ^{1}H NMR (500 MHz,

$CDCl_3$) *2-furanylmethyl*: δ = 7.36 (s, 1 H, CH), 6.31 (t, J = 1.8 Hz, 1 H, CH), 6.20 (d, J = 2.7 Hz, 1 H, CH), 4.38 and 4.33 (d, J = 15.3 Hz, 1 H, CH_2) ppm; *macrolide*: δ = 6.08 (d, J = 8.2 Hz, 1 H, 9a-NH), 4.96 (d, J = 2.7 Hz, 1 H, 1′-H), 4.87 (d, J = 4.6 Hz, 1 H, 1′′-H), 4.67 (d, J = 10.4 Hz, 1 H, 13-H), 4.13–4.22 (m, 2 H, 10-H, 3-H), 4.06 (dd, J = 5.8, 2.1 Hz, 1 H, 2′-H), 4.02 (dq, J = 9.2, 6.4 Hz, 1 H, 5′′-H), 3.79 (d, J = 6.7 Hz, 1 H, 5-H), 3.68 (dt, J = 10.9, 5.7 Hz, 1 H, 3′-H), 3.36–3.44 (m, 1 H, 5′-H), 3.33 (s, 3 H, 6-OCH_3), 3.33 (s, 3 H, 3′′-OCH_3), 3.21 (d, J = 4.3 Hz, 1 H, 11-H), 3.07 (d, J = 8.5 Hz, 1 H, 4′′-H), 2.89 (s, 3 H, 3′-NCH_3), 2.83 (quint, J = 7.6 Hz, 1 H, 2-H), 2.37 (br.s, 1 H, OH), 2.33 (d, J = 15.3 Hz, 1 H, 2′′-H_a), 2.22 (quint, J = 7.1 Hz, 1 H, 8-H), 2.00 (dd, J = 14.8, 8.1 Hz, 1 H, 7-H_a), 1.85–1.95 (m, 2 H, 4-H, 14-H_a), 1.77 (dd, J = 12.4, 5.3 Hz, 1 H, 4′-H_a), 1.59 (dd, J = 15.0, 4.9 Hz, 1 H, 2′′-H_b), 1.50–1.60 (m, 1 H, 14-H_b), 1.45 (q, J = 12.8 Hz, 1 H, 4′-H_b), 1.38 (s, 3 H, 6-CH_3), 1.35 (d, J = 6.1 Hz, 3 H, 5′′-CH_3), 1.29 (br.s, 1 H, 7-H_b), 1.26 (d, J = 7.2 Hz, 3 H, 5′-CH_3), 1.26 (s, 3 H, 3′′-CH_3), 1.25 (d, J = 7.9 Hz, 3 H, 2-CH_3), 1.18 (s, 3 H, 12-CH_3), 1.18 (d, J = 7.2 Hz, 3 H, 10-CH_3), 1.13 (d, J = 7.0 Hz, 3 H, 8-CH_3), 0.91 (t, J = 7.0 Hz, 3 H, 15-H), 0.89 (d, J = 7.0 Hz, 3 H, 4-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) *2-furanylmethyl*: δ = 154.4 (C), 141.4 (CH), 110.0 (CH), 106.0 (CH), 51.7 (CH_2); *macrolide*: δ = 179.5 (1-C), 177.4 (9-C), 159.3 (C=N), 98.0 (1′-C), 95.5 (1′′-C), 80.6 (5-C), 79.1 (6-C), 78.5 (13-C), 77.7 (4′′-C), 76.4 (3-C), 74.1 (12-C), 73.0 (3′′-C), 72.7 (11-C), 67.4 (5′-C), 65.8 (5′′-C), 60.7 (3′-C), 51.5 (6-OCH_3), 49.5 (3′′-OCH_3), 46.4 (2′-C), 45.3 (10-C), 44.6 (2-C), 40.9 (4-C), 39.9 (7-C), 35.7 (8-C), 34.7 (2′′-C), 31.8 (3′-NCH_3), 31.2 (4′-C), 21.4 (3′′-CH_3), 21.1 (5′-CH_3), 20.6 (14-C), 20.5 (6-CH_3), 19.5 (8-CH_3), 18.4 (5′′-CH_3), 16.0 (12-CH_3), 15.2 (2-CH_3), 13.8 (10-CH_3), 11.1 (15-C), 8.9 (4-CH_3) ppm. HRMS (ES): calcd. for $C_{43}H_{72}N_3O_{13}S$ [M + H^+] 870.4786; found 870.4788.

2′-Deoxy-2′-(*S*)-*S*,3′-*N*-[*N*′-(tetrahydro-2-furanylmethyl)carbonimidoyl]-3′-*N*-demethyl-6-*O*-methyl-9a-aza-9a-homoerythromycin A (17): According to the general procedure, reaction of **8** (0.4 g, 0.53 mmol) afforded **17** (0.26 g, 56%) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$) *tetrahydro-2-furanylmethyl*: δ = 4.10 (quint, J = 6.3 Hz, 1 H, CH), 3.95–4.04 (m, 1 H, CH_2), 3.73–3.81 (m, 1 H, CH_2), 3.25 (d, J = 6.1 Hz, 1 H, CH_2), 3.19 (br.s, 1 H, CH_2), 1.93–2.02 (m, 2 H, CH_2), 1.69–1.82 (m, 1 H, CH_2), 1.83–1.93 (m, 1 H, CH_2) ppm; *macrolide*: δ = 6.08 (d, J = 8.2 Hz, 1 H, 9a-NH), 4.94 (s, 1 H, 1′-H), 4.86 (d, J = 4.6 Hz, 1 H, 1′′-H), 4.67 (d, J = 10.4 Hz, 1 H, 13-H), 4.13–4.23 (m, 2 H, 10-H, 3-H), 3.95–4.04 (m, 2 H, 5′′-H, 2′-H), 3.73–3.81 (m, 1 H, 5-H), 3.64 (dt, J = 11.0, 5.5 Hz, 1 H, 3′-H), 3.35–3.43 (m, 1 H, 5′-H), 3.33 (s, 6 H, 6-OCH_3, 3′′-OCH_3), 3.18 (dd, J = 14.0, 5.8 Hz, 1 H, 11-H), 3.07 (d, J = 8.9 Hz, 1 H, 4′′-H), 2.83 (q, J = 6.7 Hz, 1 H, 2-H), 2.83 (s, 3 H, 3′-NCH_3), 2.37 (br.s, 1 H, OH), 2.33 (d, J = 15.3 Hz, 1 H, 2′′-H_a), 2.22 (quint, J = 6.9 Hz, 1 H, 8-H), 2.10 (br.s, 1 H, OH), 1.93–2.02 (m, 3 H, 7-H_a, CH_2), 1.83–1.93 (m, 4 H, 4-H, 14-H_a, CH_2), 1.69–1.82 (m, 3 H, 4′-H_a, CH_2), 1.58 (dd, J = 15.3, 4.9 Hz, 1 H, 2′′-H_b), 1.52–1.61 (m, 1 H, 14-H_b), 1.38–1.46 (m, 1 H, 4′-H_b), 1.39 (s, 3 H, 6-CH_3), 1.34 (d, J = 6.1 Hz, 3 H, 5′′-CH_3), 1.30 (s, 1 H, 7-H_b), 1.27 (s, 3 H, 3′′-CH_3), 1.26 (br.s, 3 H, 5′-CH_3), 1.25 (d, J = 7.6 Hz, 3 H, 2-CH_3), 1.18 (s, 3 H, 12-CH_3), 1.18 (br.s, 3 H, 10-CH_3), 1.13 (d, J = 7.0 Hz, 3 H, 8-CH_3), 0.91 (t, J = 7.3 Hz, 3 H, 15-H), 0.89 (br.s, 3 H, 4-CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): *tetrahydro-2-furanylmethyl*: δ = 79.5 (CH), 68.2 (CH_2), 29.3 (CH_2), 25.6 (CH_2) ppm; *macrolide*: δ = 179.5 (1-C), 177.4 (9-C), 159.3 (C=N), 98.1 (1′-C), 95.5 (1′′-C), 80.6 (5-C), 79.1 (6-C), 78.5 (13-C), 77.8 (4′′-C), 76.4 (3-C), 74.1 (12-C), 73.0 (11-C), 72.8 (3′′-C), 67.4 (5′-C), 65.8 (5′′-C), 60.5 (3′-C), 51.5 (6-OCH_3), 49.5 (3′′-OCH_3), 46.1 (2′-C), 45.3 (10-C), 44.6 (2-C), 40.9 (4-C), 39.9 (7-C), 35.7 (8-C), 34.7 (2′′-C), 31.7 (3′-NCH_3), 31.1 (4′-C), 21.4 (3′′-CH_3), 21.0 (5′-CH_3), 20.6 (14-C), 20.5 (6-CH_3), 19.5 (8-CH_3), 18.4 (5′′-CH_3), 16.0 (12-CH_3), 15.2 (2-CH_3), 13.8 (10-CH_3), 11.1 (15-C), 8.9 (4-CH_3) ppm. HRMS (ES): calcd. for $C_{43}H_{76}N_3O_{13}S$ [M + H^+] 874.5099; found 874.5094.

2′-*O*,3′-*N*-{*N*′-[1-(4-Methoxyphenyl)]carbonimidoyl}-3′-*N*-demethyl-6-*O*-methyl-9a-aza-9a-homoerythromycin A (18):[3] According to the general procedure, reaction of **8** (0.4 g, 0.53 mmol) afforded **18** (0.18 g, 38%) as a white foam.

2′-*O*,3′-*N*-[*N*′-1-(2,6-Difluorophenyl)carbonimidoyl]-3′-*N*-demethyl-6-*O*-methyl-9a-aza-9a-homoerythromycin A (19):[1] According to the general procedure, reaction of **8** (0.4 g, 0.53 mmol) afforded **19** (0.16 g, 34%) as a white foam.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H NMR and ^{13}C NMR spectra of final products, as well as NOESY spectra for compounds **3** and **4** are provided.

Acknowledgments

The authors would like to thank Bill Leavens for providing HRMS data, Željko Osman for the purity and Mark Vine for valuable comments and productive discussions.

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Received: February 20, 2013
Published Online: June 7, 2013

