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Synthesis of 9-Oxime-11,12-carbamate Ketolides Through a Novel *N*-Deamination Reaction of 11,12-Hydrazonocarbamate Ketolide

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Abstract—A series of 9-oxime-11,12-carbamate ketolides was synthesized for the first time through a key 11,12-hydrazonocarbamate intermediate that was first oximated and further deaminated to give the corresponding carbamate. The N–N bond cleavage was achieved through an original new reaction using glycoaldehyde dimer as deaminating reagent. The new compounds synthesized were shown to display improved antibacterial activities against *Streptococcus pneumoniae* and *S. pyogenes* resistant to erythromycin.

Introduction

Macrolides, including erythromycin, are an old and well-known family of oral antibiotics. Their spectrum of activity covers most relevant bacterial species responsible for upper and lower respiratory tract infections.[1] However, the extensive clinical application of macrolide antibiotics has resulted in an increasing emergence of macrolide MLS_B resistance in respiratory pathogens like *S. pneumoniae*.[2] The ketolides,[3] such as telithromycin[4] or ABT-733,[5] are a new class of semisynthetic erythromycin derivatives recently generated to address the problem of erythromycin resistance. They are very active against erythromycin-resistant and penicillin resistant *S. pneumoniae*, and the most advanced compound of this new class, telithromycin has demonstrated clinical efficacy in human respiratory tract infections.[6] During our initial optimization of the ketolide series,[7] it has been observed that the antibacterial activity of the 11,12 carbamate **I** could be optimized through the introduction of alkyl-aryl or hetero-aryl side chains to give **II** and finally telithromycin (Fig. 1).

Whereas the carbamate **I** is weakly active or inactive (Table 1) against *S. pneumoniae* and *S. pyogenes* resistant to erythromycin (40–2.5 μg/mL), the activity of **II** is greatly improved (20–0.15 μg/mL) and even more, that of telithromycin (5–0.02 μg/mL).

On the other hand, a second series of (*E*)-9-oxime derivatives has been described[7] among which, the (*R*)-3-piperidinyl-oxime **III** displayed interesting activities

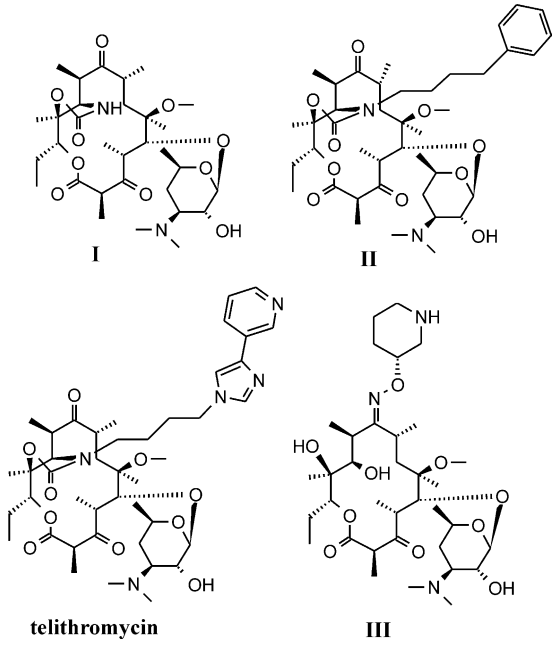

Figure 1. Structure of ketolide series.

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Table 1. In vitro activity of 9-oxime modified ketolides

	MIC 24 h (μg/mL)							
	S. a. EryS	*S. a.* EryRi	*S. a.* EryRc	*S. pyo* EryS	*S. pyo* EryRc	*S. p.* EryS	*S. p.* EryRi	*S. p.* EryRc
CLA	0.3	>40	>40	0.08	>40	0.04	>40	>40
TEL	0.04	0.08	>40	≤0.02	5	≤0.02	≤0.02	≤0.04
I	0.6	0.6	>40	0.04	>40	0.02	2.5	5
II	0.04	0.08	>40	≤0.02	20	≤0.02	0.3	0.15
III	0.3	0.3	>40	0.3	>40	0.08	0.3	2.5
VIII	0.3	0.3	>40	0.3	5	0.6	0.15	1.2
XI	0.6	0.3	>40	0.08	2.5	0.02	0.3	1.2
X	0.3	0.3	>40	0.02	0.6	0.02	0.15	0.6

MIC, minimum inhibitory concentration; CLA, clarithromycin; TEL, telithromycin; EryS, susceptible; EryRc, constitutive MLS resistance; EryRi, inducible MLS resistance. *S. a., Staphylococcus aureus; S. pyo., Streptococcus pyogenes; S. p., Streptococcus pneumoniae.*

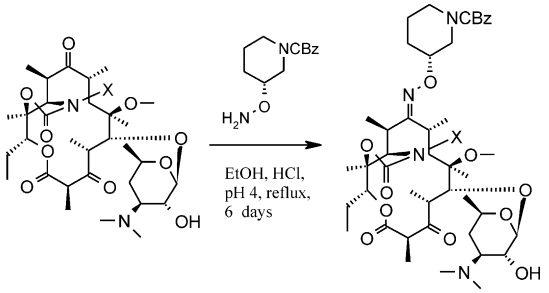
against the inducibly and constitutively resistant *S. pneumoniae* (2.5–0.3 μg/mL). However, **III** is inactive against the constitutively resistant *S. pyogenes* (Table 1).

Whereas the synthesis and the activity of 9-oxime-hydrazonocarbamate ketolides has already been reported,[8] a combination of such chemical features has never been reported in the 11,12 carbamate series. This is why, in continuation of our efforts to further improve the ketolide series, we wondered whether the addition of the (*R*)-3-piperidinyl-oxime feature into the cyclic carbamate skeleton would generate new compounds with improved activity against resistant strains.

Chemistry

The first attempts to introduce an oxime in position 9 of the 11,12 carbamate **I** were all unsuccessful. Whatever the conditions: acidic, basic, temperature, the oximation reaction did not occur. Therefore, we decided to come back to the corrresponding hydrazonocarbamate **IV** as starting material and to react it with an hydroxylamine according to the published conditions.[8] In contrast to **I**, **IV** gave easily the *E*[9] oxime **V** in 77% yield when reacted with the CBz protected (*R*)-3-piperidine-*O*-hydroxylamine in EtOH, HCl (pH 4) at reflux for 6 days (Scheme 1).

We hypothesized that the dramatic change of reactivity of the hydrazonocarbamate series compared to the carbamate, could be explained by an intramolecular activation of the carbonyl group by the NH_2 of the



Scheme 1. Oximation reaction.

hydrazonocarbamate function. The minimized structure of **IV**, built from the crystallized hydrazonocarbamate HMR 3004,[7] revealed that the overall macrocyclic backbone was very rigid and almost identical to crystallized ketolide. Accordingly, the nitrogen of the hydrazonocarbamate and the oxygen of the carbonyl at position 9 were shown to be, as in the parent structure, close enough (2.03 Å) to give an hydrogen bond (Fig. 2). Even if that intramolecular bond is weak (the very long reaction time could reflect this), it could be sufficient to promote the activation of the carbonyl and allow the reaction to occur.

Having now in hand the expected 9-oxime-hydrazonocarbamate ketolide **V**, we decided to use that compound to access the corresponding carbamate through a deamination reaction followed by introduction of the corresponding side chain by nucleophilic alkylation of the free cyclic carbamate.

The deamination was carried out by treating **V** with the dimeric glycolaldehyde in acetic acid. This very unusual reaction was unexpectedly discovered in our labora-

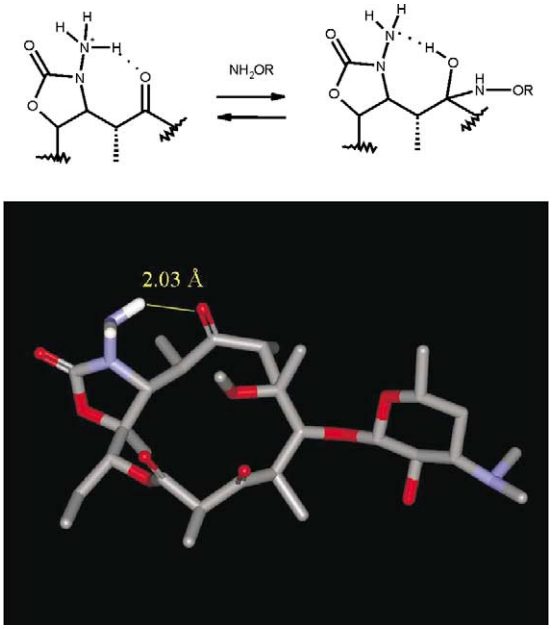
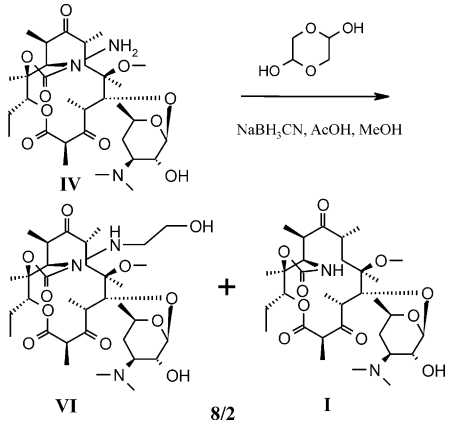


Figure 2. Minimized conformation of **IV** and proposed activation of 9 carbonyl through intramolecular hydrogen bonding.

tories during the synthesis of a series of hydrazonocarbamate ketolides by reductive amination of different aldehydes. We observed that when **IV** was reacted with the dimeric glycoaldehyde and $NaBH_3CN$ to obtain **VI**, 20% of the deaminated compound **I** was identified as a side product (Scheme 2).

The deamination of a hydrazine with glycoaldehyde has never been reported. Literature methods rather described the use of Zn,[10] $Pb(OAc)_2$,[11] Raney Ni[12] or nitrous deamination[13] to carry out the N–N bond cleavage.

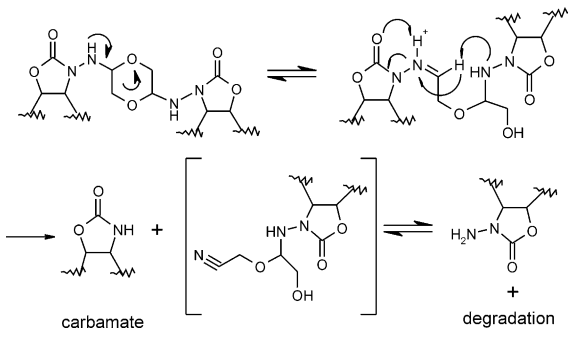
We then decided to react **V** with glycoaldehyde dimer without a hydride to avoid the formation of the 9-oxime analogue of **VI** (Scheme 4).



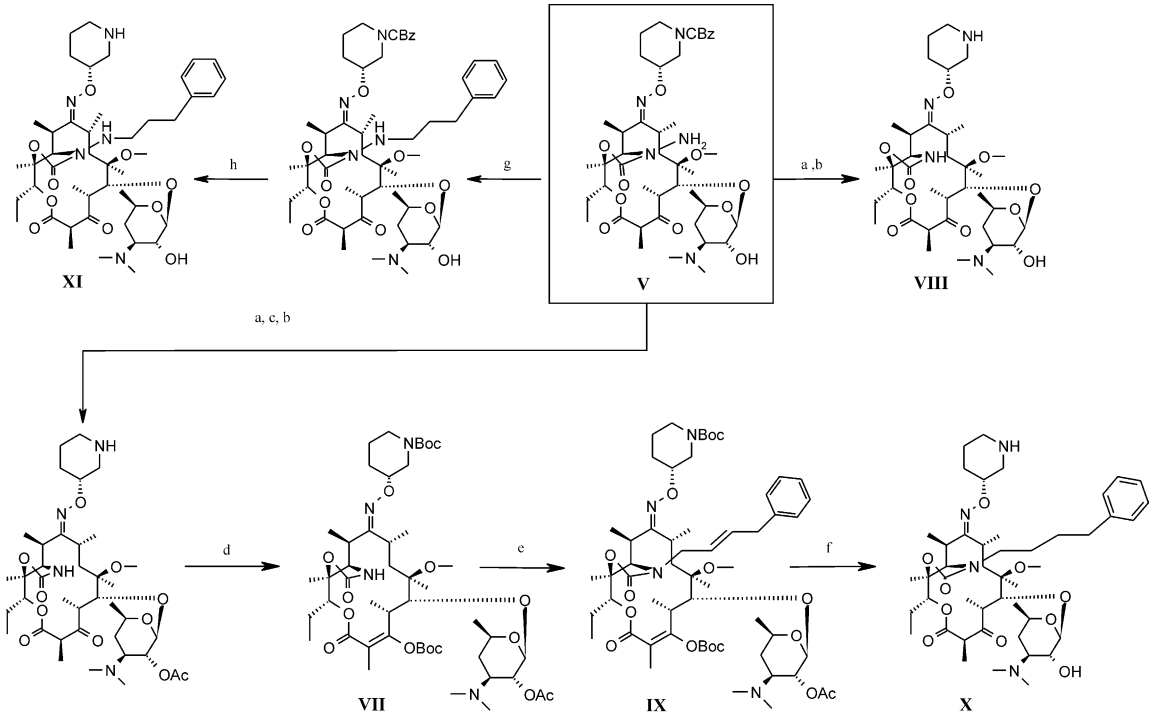
Scheme 2. Unexpected deamination reaction during reductive amination of glycoaldehyde by **IV**.

The desired compound was thus obtained with 42% yield only, 25% of starting hydrazonocarbamate being recovered with degradations products. The mechanism of that reaction is unknown, however, the fact that amongst several other aldehydes, dimeric glycoaldehyde was the only one to give that side reaction and that the reaction is incomplete may suggest that the reaction involves two molecules of macrolides for one glycoaldehyde dimer (Scheme 3).

Whereas we do not have experimental data supporting this hypothesis, one can propose that the dimeric intermediate species could undergo a complex rearrangement through intramolecular activation of one nitrogen allowing the formation of the carbamate and an hypothetical hydroxyacetonitrile intermediate which may decompose into the starting hydrazonocarbamate and degradation products. However, this hypothesis



Scheme 3. Proposed mechanism for deamination of hydrazonocarbamate ketolides by dimeric glycoaldehyde.



Scheme 4. Synthesis of 9-oxime-carbamate and hydrazonocarbamate ketolides. Reagents and conditions: (a) 1.1 equiv glycoaldehyde dimer, CH_3CO_2H/CH_2Cl_2 1/1 vol, rt, 12 h, 42%; (b) $Pd(OH)_2$, cyclohexene, dioxane, 80 °C, 24 h, 42–93%; (c) Ac_2O, CH_2Cl_2, rt, 93%; (d) $(Boc)_2O$ 4 equiv, DMAP 0.4 equiv, triethylamine 3.5 equiv, THF, 24 h, rt, 50%; (e) NaH, cinnamyl bromide, DME, 0 °C, 65%; (f) 1-MeOH, 4 h, reflux. 2-CH_2Cl_2, TFA. 3-H_2, Pd/C, dioxane, 4 h, rt, 43% overall yield; (g) 3-phenyl-propionaldehyde, $NaBH_3CN$, AcOH 3 equiv, MeOH, 24 h, rt; (h) H_2, Pd/C, MeOH, 24 h, rt, 36%.

would require further mechanistic studies to be fully assessed.

After further deprotection with $Pd(OH)_2$/cyclohexene the unsubstituted oxime **VIII** was obtained (Scheme 4). The introduction of the phenyl-butyl side chain was carried out in six steps from **V**. After deamination, the 2′OH was protected with Ac_2O, and the Cbz group removed under the same condition than **VIII**. Next, a treatment with an excess of Boc_2O, triethylamine and DMAP in THF allowed the simultaneous protection of the free piperidine nitrogen and of the nucleophilic carbon at position 2 which was now converted into the corresponding *O*-Boc enol ester **VII**.

We had already observed within the ketolide series, that an *O*-alkylation[14] or acylation can easily occur at position 3 with various electrophiles to convert the reactive beta-keto-ester function into the corresponding enol ether or ester. The remaining nitrogen of the cyclic carbamate function was then alkylated with cinnamyl bromide using NaH in DME in 65% yield to give **IX**.

All the protecting groups were then removed without any purification starting first with a treatment with MeOH followed by hydrolysis of the Boc groups with TFA in dichloromethane. Finally, the double bond was hydrogenated with H_2 in the presence of palladium/charcoal to give the desired 9-(*R*)-3-piperidinyl oxime 11,12 carbamate **X** in 43% yield for the three steps. The corresponding hydrazonocarbamate **XI**, was synthesized according to the previous conditions,[7] by reductive amination of 3-phenyl propanaldehyde with $NaBH_3CN$ followed by deprotection of the CBz group by catalytic hydrogenation.

Results and Discussion

All the ketolides were tested in vitro by standard agar dilution method against both erythromycin-susceptible and erythromycin-resistant *S. aureus*, *S. pyogenes* and *S. pneumoniae* including constitutive (EryRc) and inducible (EryRi) phenotypes. In addition, one strain of *Haemophilus influenzae* was also tested. As already shown for all the ketolides, the compounds were inactive against the erythromycin-resistant (MLS_B constitutive type) strains of *S. aureus* (MIC >40 μg/mL).

The positive impact of the combination of the piperidinyl-oxime and the carbamate was first observed with the non substituted carbamate **VIII**. The MICs against the *S. pyogenes* and *S. pneumoniae* resistant strains were 2–3 times lower than with the starting analogues **I**. In agreement with the previous observations made in the ketolide series, the addition of a lateral side chain gave the expected increase of activity. Compound **X** was very potent against all the resistant streptococci tested whatever the phenotype (MICs 0.15–0.6 μg/mL). Similar to the non-oxime series, the hydrazonocarbamate analogue **XI** was two times less active than the carbamate **X** against the resistant strains. Compared to telithromycin, the gain of activity obtained with **X** against the constitutively resistant *S. pyogenes* (0.6 μg/mL compared to 5 μg/mL) clearly confirms the interest of this series to further improve the ketolide family against gram positive pathogens. The potential of these oximes remains to be evaluated in vivo.

Conclusion

An original chemical strategy and deamination reaction has allowed us to synthesize for the first time a 9-oxime-11,12 carbamate ketolide. The potential of this new modification in the ketolide series has been confirmed by the very potent activities obtained with compound **X** against the gram-positive respiratory pathogens either constitutively or inducibly resistant to erythromycin. This new series needs to be further optimized and evaluated in vivo.

Experimental

Molecular modelling IV

The calculations were run on a silicon graphics computer using the Accelerys software Insight II with the CVFF forcefield. The initial starting conformation was built from the crystallographic coordinates[7] of the *N*-substituted hydazonocarbamate HMR 3004.

V. A solution of **IV** (1 g, 1.59 mM) and (3*R*)-(aminooxy)-1-(carbobenzyloxy)piperidine (1.19 g, 4.77 mM) in 10 mL of EtOH was adjusted to pH 4 with 5 mL of a 0.5 N HCl/EtOH solution. The mixture was stirred at reflux for 6 days. After evaporation to dryness, the residue was taken up with ethyl acetate, washed with aqueous ammonium hydroxide. After drying over $MgSO_4$ and evaporation of the solvent the residue was purified by column chromatography over silica eluting with 96/4/0.5 CH_2Cl_2/MeOH/ammonium hydroxide to give 1 g (77%) of **V** as a white foam.

Spectral data for V. MS = 860$^+$ (MH^+); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (sl, 3H) **$\underline{CH_3}CH_2$**, 0.97 (d, 3H) **8-CH_3**, 1.13 (s, 3H) **10-CH_3**, 1.23 (3H) **5′-Me**, 1.29 (d, 3H) **4-CH_3**, 1.36 (d, 3H) **2-CH_3**, 1.39–1.44 (6H) **6-CH_3** and **12-CH_3**, 2.27 (s, 6H) **N($\underline{CH_3}$)$_2$**, 2.45 (m, 1H) **H_3′**, 2.61 (s, 1H) **H_{10}**, 2.68 (s, 3H) **6-OCH_3**, 3.07 (m, 1H) **H_4**, 3.18 (m, 1H) **$H_{2'}$**, 3.54 (s, 1H) **H_5′**, 3.66 (m, 1H) **H_8**, 3.86 (q, 1H) **H_2**, 3.89 (s, 1H) **H_{11}**, 4.24 (d, 1H) **H_5**, 4.3 (d, 1H) **H_1′**, 5.1 (m, 3H) **H_{13}** and **OCH_2Ph**, 7.35 (m, 5H) **phenyl**.

VIII-NCbz. To a solution of **V** (9 g, 10.41 mM) in 40 mL of CH_2Cl_2 and 40 mL of acetic acid was added 1.38 g (11.5 mM) of glycoaldehyde dimer (Aldrich). After stirring for one night at room temperature, the reaction was transfered over 350 mL of 2 N sodium hydroxide, washed with water and brine. Drying over $MgSO_4$ and evaporation of the solvent afforded 9.97 g of crude product. The residue was purified by column chromatography over silica eluting with 98/2/0.5 CH_2Cl_2/

MeOH/ammonium hydroxide to give 3.67g (42%) of **VIII–NCbz** as a white foam.

Spectral data for VIII NCbz. MS = 845$^+$ (MH^+); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H) **CH_3CH_2**, 0.94 (d, 3H) **8-CH_3**, 1.19 (d, 3H) **10-CH_3**, 1.2–1.7 (m, 4H) **CH_2** piperidine, 1.23 (3H) **5′-Me**, 1.22 and 1.66 (2H) **4′-CH_2**, 1.28 (d, 3H) **4-CH_3**, 1.37 (d, 3H) **2-CH_3**, 1.39 and 1.62 (2H) **7-CH_2**, 1.36-1.48 (6H) **6-CH_3** and **12-CH_3**, 2.27 (s, 6H) **N(CH_3)$_2$**, 2.45 (m, 1H) **H_3′**, 2.44 (m, 1H) **H_{10}**, 2.64 (s, 3H) **6-OCH_3**, 3.06 (m, 1H) **H_4**, 3.18 (dd, 1H) **H_2′**, 3.3–3.65 and 3.98 (5H) **CH_2NCO** and **=NOCH**, 3.54 (m, 1H) **H_5′**, 3.64 (m, 1H) **H_8**, 3.85 (q, 1H) **H_2**, 3.87 (s, 1H) **H_{11}**, 4.22 (d, 1H) **H_5**, 4.3 (d, 1H) **H_1′**, 4.83 (dl, 1H) **H_{13}**, 5.12 (mL, 2H) **OCH_2Ph**, 7.35 (m, 5H) **phenyl**.

VIII. To a solution of **VIII-NCbz** (0.6 g, 0.71 mM) in 20 mL of dioxane, were added 0.2 g of Palladium hydroxide and 0.605 mL of cyclohexene (7.36 mM,10 equiv). After stirring 16 h at 80 °C, the reaction was filtered of and evaporated. The residue was purified by column chromatography over silica eluting with 97/3/0.5 CH_2Cl_2/MeOH/ammonium hydroxide to give 0.21g (42%) of **VIII**.

Spectral data for VIII. MS = 711$^+$ (MH^+). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H) **CH_3CH_2**, 0.97 (d, 3H) **8-CH_3**, 1.2 (d, 3H) **10-CH_3,** 1.25 (3H) **5′-Me**, 1.27 (d, 3H) **4-CH_3**, 1.22 and 1.66 (2H) **4′-CH_2**, 1.37 (d, 3H) **2-CH_3**, 1.41 and 1.63 (2H) **7-CH_2**, 1.39–1.43 (6H) **6-CH_3** and **12-CH_3**, 1.47–1.58–1.66 (m, 4H) **=NOCHCH_2CH_2**, 2.24 (s, 6H) **N(CH_3)$_2$**, 2.43 (m, 1H) **H_3′**, 2.44 (m, 1H) **H_{10},** 2.65 (sl, 3H) **6-OCH_3**, 2.65–2.83–3.11 (4H) **=NOCHCH_2NHCH_2**, 3.05 (m, 1H) **H_4,** 3.18 (dd, 1H) **$H_{2'}$**, 3.90 (m, 1H) **=NOCH**, 3.55 (m, 1H) **H_5′**, 3.68 (m, 1H) **H_8**, 3.83 (q, 1H) **H_2**, 3.87 (s, 1H) **H_{11}**, 4.22 (d, 1H) **H_5**, 4.3 (d, 1H) **H_1′**, 5.14 (dd, 1H) **H_{13},** 5.81 m, 1H) **NHCO**. Anal. calcd (%) for $C_{36}H_{62}N_4O_{10}$: C 60.82, H 8.79, N 7.88. Found: C 60.7, H 8.9, N 7.9.

VIII-NCbz-2′OAc. To a solution of **VIII-NCBz** (3.66 g, 4.33 mM) in 60 mL of CH_2Cl_2 was added 0.87 mL (11.5 mM) of acetic anhydride. After stirring 3 h at room temperature, the reaction was washed with ammonium hydroxide and dried over $MgSO_4$ to afford after evaporation 3.59 g (93%) of **VIII-NCbz-2′OAc**. Spectral data for **VIII-NCbz-2′OAc**: MS = 887$^+$ (MH^+); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, 3H) **CH_3CH_2**, 0.95 (d, 3H) **8-CH_3**, 1.13–1.19–1.24–1.37 (12H) **10-CH_3, 5′-Me**, **4-CH_3** and **2-CH_3**, 1.33–1.49 (6H) **6-CH_3** and **12-CH_3**, 2.04 (s, 3H) **$OCOCH_3$**, 2.25 (s, 6H) **N(CH_3)$_2$**, 2.43 (q, 1H) **H_{10},** 2.62 (sl, 3H) **6-OCH_3**, 2.6–2.9 (m, 1H) **H_3′**, 3.01 (m, 1H) **H_4**, 3.35–3.7 (m, 6H) **H_5′**, **CH_2NCO** and **H_8**, 3.98 (1H) **=NOCH**, 3.81 (q, 1H) **H_2**, 4.13 (d, 1H) **H_5**, 4.38 (d, 1H) **H_1′**, 4.74 (dd, 1H) **H_2′**, 4.9–5.2 (2H) **H_{13}** and **OCH_2Ph**, 5.76–6.05 (m, 1H) **NHCO**, 7.35 (m, 5H) **phenyl**.

VIII-2′OAc. To a solution of **VIII-NCbz-2′OAc** (1.5g, 1.69 mM) in 60 mL of dioxane, were added 1.2 g of Palladium hydroxide and 2.7 mL of cyclohexen. After stirring 24 h at 80 °C, the reaction was filtered of and evaporated to give 1.18 g (93%) of crude product. Spectral data for **VIII-2′OAc**: MS = 753$^+$ (MH^+).

VII. To a solution of **VIII-2′OAc** (1.38 g, 1.84 mM) in 50 mL of THF, were added 0.9 mL (3.5 equiv) of triethylamine and 44 mg (0.37 mM, 0.2 equiv) of 4-*N*,*N*-dimethyl-amino-pyridine. The reaction was stirred at room temperature for 24 h and evaporated to dryness. The crude product was purified by column chromatography over silica eluting with 9/1 ethyl acetate/triethylamine to afford 0.866 g (50%) of **VII.**

Spectral data for VII. MS = 953.5$^+$ (MH^+).

IX. To a solution of **VII** (0.82 g, 0.86 mM) in dry dimethoxy-ethane under nitogen were added at 0 °C 55 mg (1.37 mM) of sodium hydride 60% in oil. The reaction was stirred 30 mn at 0 °C and 236 mg (1.11 mM) of cynnamyl bromide diluted in 3 mL of dimethoxy-ethane were added. The reaction was then stirred at room temperature for 3 h and stooped with the addition of a 10% $NaHPO_4$ solution. After extraction with ethyl acetate, drying over $MgSO_4$ and evaporation of the solvent, the residue was purified by column chromatography over silica eluting with 9/1 isopropylic ether/triethylamine to give 0.607 g (65%) of **IX**.

Spectral data for IX. MS = 1083.8 (MH^+).

X. Step A—A solution of **IX** (0.6 g, 0.554 mM) in 20 mL of methanol was stirred at room temperature for 4 h and evaporated to dryness to obtain 0.48 g of crude product. Step B—0.48 g of product of step A were stirred in 5 mL of dichloromethane and 5 mL of trifluoroacetic acid for 2 h at room temperature. The reaction was taken up with ethyl acetate, washed with sodium hydroxide, dried over $MgSO_4$ and evaporated to dryness to afford 0.465 g of crude product. Step C—A solution of 0.465 g of product of step B and 0.2 g of palladium on charcoal in 15 mL of dioxane was stirred under 1.5 atm of hydrogen for 4 h. After filtration and and evaporation to dryness, the residue was purified by column chromatography over silica eluting with 96/4/0.5 $CHCl_3$/MeOH/ammonium hydroxide to give 0.2 g (43%) of **X**.

Spectral data for X. MS = 843$^+$ (MH^+); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, 3H) **CH_3CH_2**, 0.97 (d, 3H) **8-CH_3**, 1.05 (d, 3H) **10-CH_3**, 1.26 (d, 3H) **5′-Me**, 1.28 (d, 3H) **4-CH_3**, 1.35 (d, 3H) **2-CH_3**,1.40–1.46 (s, 6H) **6-CH_3** and **12-CH_3**, 1.23 and 1.68 (m, 2H) **4′-CH_2**, 1.35 and 1.65 (m, 2H) **7-CH_2**, 1.35–1.64 (m, 4H) **=NOCHCH_2CH_2**, 1.63 and 1.82 (m, 4H) **N$CH_2CH_2CH_2CH_2$phenyl**, 2.26 (s, 6H) **N(CH_3)$_2$**, 2.45 (m, 1H) **H_3′**, 2.62 (m, 1H) **H_{10}**, 2.66 (s, 3H) **6-OCH_3**, 2.67–2.78 (m, 2H) **CH_2Ph**, 2.64 and 2.76 (m, 4H) **=NOCHCH_2NHCH_2**, 3.12 (m, 1H) **H_4**, 3.18 (dd, 1H) **$H_{2'}$**, 3.62–3.80 (m, 2H) **CH_2NCO**, 3.97 (m, 1H) **=NOCH**, 3.54 (m, 1H) **H_5′**, 3.73 (m, 1H) **H_8**, 3.87 (q, 1H) **H_2**, 3.76 (s, 1H) **H_{11}**, 4.24 (d, 1H) **H_5**, 4.29 (d, 1H) **H_1′**, 5.02 (dd, 1H) **H_{13}**, 7.16–7.22 (m, 5H) **phenyl**. Anal. calcd (%) for $C_{46}H_{74}N_4O_{10}$: C 65.53, H 8.85, N 6.65. Found: C 65.45, H 8.8, N 6.55.

XI. Step A—A solution of **V** (0.311 mg, 0.367 mM) and 0.099 g (0.734 mM) of 3-phenylpropanaldehyde in 10

mL of methanol and 66 μL of acetic acid was stirred at romm temperature for 24 h. Sodium cyanoborohydride (0.069 g, 1.1 mM) was added and the reaction was stirred for 3 days at room temperature. The reaction was taken up with ethyl acetate, washed with 1 N sodium hydroxide, water and brine and evaporated to dryness to yield 0.4 g of crude product.

Step B—A solution of 0.4 g (0.409 mM) of product of step A and 0.2 g of palladium on charcoal in 10 mL of methanol was stirred under 1.5 atm of hydrogen for 24 h. After filtration and and evaporation to dryness, the residue was purified by column chromatography over silica eluting with 92/8/0.5 CH_2Cl_2/MeOH/ammonium hydroxide to give 0.127 g (36% overall yield for steps A and B) of **XI**.

Spectral data for XI. MS = 844.7$^+$ (MH^+); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, 3H) **$\underline{CH_3}CH_2$**, 1.00 (d, 3H) **8-CH_3**, 1.12 (d, 3H) **10-CH_3**, 1.26 (d, 3H) **5′-Me**, 1.30 (d, 3H) **4-CH_3**, 1.36 (d, 3H) **2-CH_3**, 1.41-1.47 (s, 6H) **6-CH_3** and **12-CH_3**, 1.22 and 1.68 (m, 2H) **4′-CH_2**, 1.38 and 1.7 (m, 2H) **7-CH_2**, 1.5–2 (m, 4H) **=NOCH$\underline{CH_2CH_2}$**, 1.83 (m, 2H) **$NCH_2\underline{CH_2}CH_2$phenyl**, 2.27 (s, 6H) **$\overline{N(\underline{CH_3})_2}$**, 2.45 (m, 1H) **$H_3'$**, 2.67 (m, 1H) **$H_{10}$**, 2.67 (s, 3H) **6-$OCH_3$**, 2.67–2.87–3.04 (m, 8H) **$\underline{CH_2}NHNCO$, =NOCH$\underline{CH_2}$NH$\underline{CH_2}$** and **$\underline{CH_2}$Ph**, 3.10 (m, 1H) **H_4**, 3.18 (dd, 1H) **$\overline{H_{2'}}$**, 3.55 (m, 1H) **$\overline{H_5'}$**, 3.73 (m, 1H) **H_8**, 3.86 (m, 1H) **=NO$\underline{CH}$**, 3.87 (s, 1H) **H_{11}**, 3.88 (q, 1H) **H_2**, 4.27 (d, 1H) **H_5**, 4.29 (d, 1H) **H_1'**, 5.07 (dd, 1H) **H_{13}**, 7.15–7.25 (m, 5H) **phenyl**. Anal. calcd (%) for $C_{45}H_{73}N_5O_{10}$: C 64.03, H 8.72, N 8.03. Foundnbsp;: C 64.49, H 9.55, N 7.49.

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