Synthesis of a *xylo*-Puromycin Analogue

Benoît Y. Michel, Kollappillil S. Krishnakumar, Peter Strazewski*

Laboratoire de Synthèse de Biomolécules, CNRS, Institut de Chimie et Biochimie Moléculaires et Supramoléculaires (UMR 5246), Université Claude Bernard Lyon 1, F-69622 Villeurbanne Cedex, France
E-mail: strazewski@univ-lyon1.fr

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Abstract: N^6-Bis-demethylated *xylo*-puromycin analogue **2** was synthesized over six steps in 56% yield from adenosine **3**, involving a Mattocks bromoacetylation, a regio- and stereoselective *ribo*-epoxide ring opening with sodium azide and an efficient Staudinger–Vilarrasa reaction to couple the amino acid to an azide precursor.

Key words: coupling, epoxides, nucleosides, amides, malaria

The natural antibiotic nucleoside puromycin (**1**) first isolated from *Streptomyces alboniger*[1] has been used to approach and to clear up the understanding of the mechanism of protein biosynthesis.[2] Its structural similarity to the 3′-terminal 3′-*O*-aminoacyl adenylate moiety of aminoacyl-tRNA explains its activity in the ribosomal A site causing the inhibition of the protein synthesis by transferring the ribosomal nascent polypeptide chain to puromycin's α-amino group.[3]

Besides, it has been demonstrated that some puromycin analogues presented promising antitrypanosomal and antimalarial activities.[4] Numerous syntheses of puromycin analogues[5] and similar nucleosides[6] have been reported that differ from **1**, for example, by the configuration of a substituent, thus, *ara*-puromycin[5a] and L,L-puromycin[5e] analogues were synthesized. However, an inversion of the configuration of the carbon atom carrying the amino acid chain has never been envisaged. Hence, in order to test whether the stereochemistry of the *N*-aminoacyl chain could play a significant role in the antimalarial activity, we decided to synthesize the N^6-bis-demethylated *xylo*-puromycin (**2**; Figure 1).

Target compound **2** has been obtained in six steps from adenosine (**3**; Scheme 1) beginning with the Moffatt methodology[7] for the stereospecific synthesis of the *ribo*-epoxide **5** via vicinal *trans*-bromoacetate intermediates obtained by a Mattocks bromoacetylation reaction.[8] This approach involves, in addition, a regio- and stereoselective epoxide ring opening and finally, as a key step in this reaction sequence, an efficient Staudinger–Vilarrasa amino acid coupling[5x] for which the conditions have been further optimized.

We started with adenosine (**3**) from which *ribo*-epoxide **4** was generated (Scheme 1).[7] The primary alcohol group was protected with a bulky silyl group.[9,5u] Epoxide **5** was regio- and stereoselectively opened with sodium azide under mildly acidic aqueous conditions[5z] to yield the *xylo*-azido alcohol **6** which was coupled to an N-protected L-amino acid oxybenzotriazolyl ester via the Staudinger–Vilarrasa reaction. Various azide reducing conditions using the commercial phosphines PMe_2Ph, $PMePh_2$, PBu_3 and PMe_3 were tested for the efficiency and practicality of the coupling reaction. We justify our preferred use of PMe_3 (1 M in THF) by the weakest steric hindrance of the corresponding in situ formed iminophosphorane and the practical volatility of trimethylphosphine oxide. This alleviated possible co-migration problems upon chromatography over silica and therefore led to the best isolated yields of pure amide.

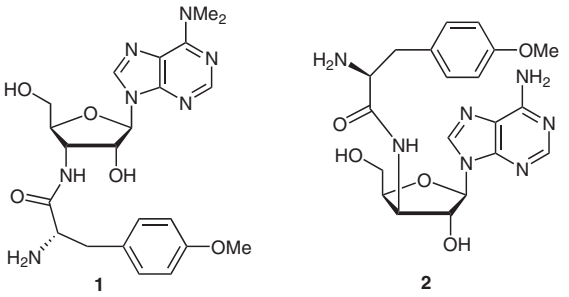

Figure 1 Puromycin (**1**) and N^6-bis-demethylated *xylo*-analogue **2**

A comparative study of the difference in reactivity between this iminophosphorane and the nucleobase's amidine function towards the activated ester is likewise depicted in Scheme 1. The Staudinger–Vilarrasa coupling proved more efficient for the azide **7**, where the N^6-amidine function was protected as a dibutylformamidine (dbf),[10a] than for the less protected azido amidine **9** (83% versus 60% optimized and isolated yields). The main assets of the dbf protection are the facile and efficient preparation and cleavage[10] and, most importantly, it can be used in the presence of numerous groups, such as hydroxyl, azido as well as many usual organic functions, contrary to a number of other common amino protecting groups.[11]

Finally, both coupled products **8** and **9** were completely deprotected with methyl amine followed in situ by a warm NH_4F treatment in THF.[12] The use of TBAF for desilylation led after chromatography over silica to contamination of the final polar product with the tetrabutylammonium cation.

In view of the shortness of this synthetic route we envisaged synthesizing the N^6-bis-demethylated naturally con-

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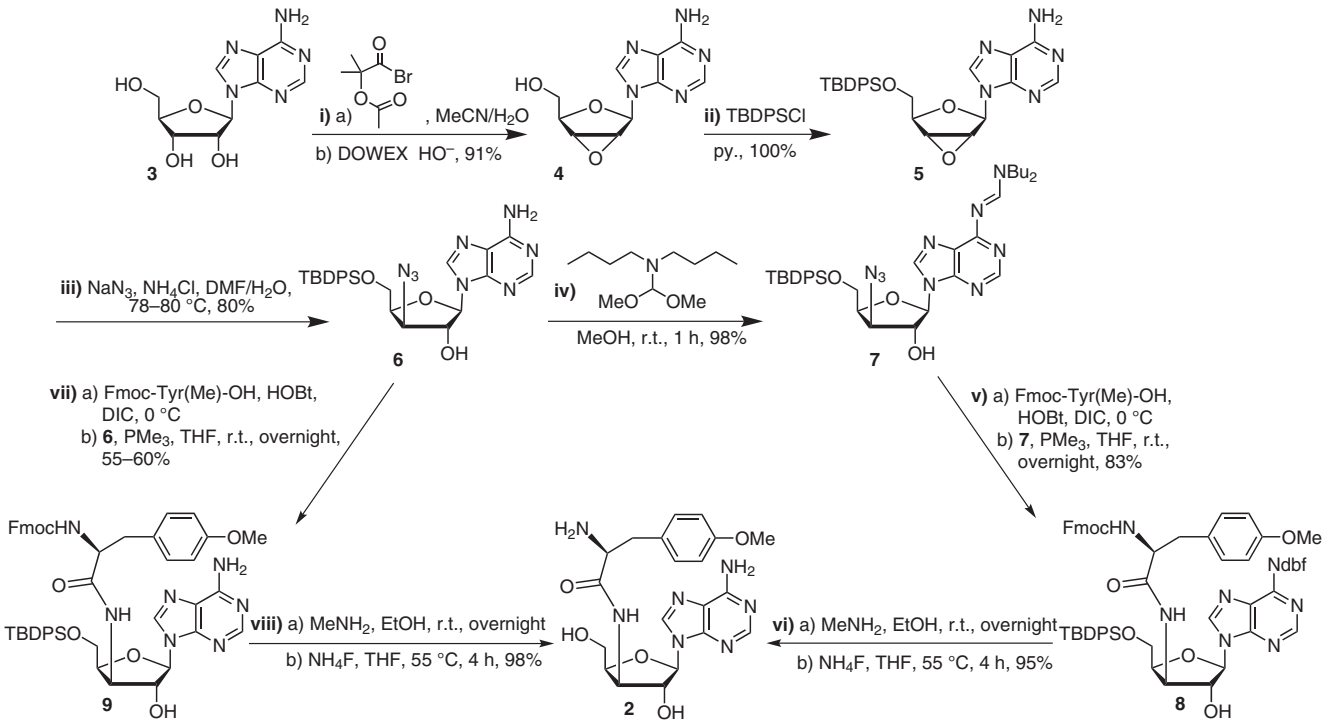
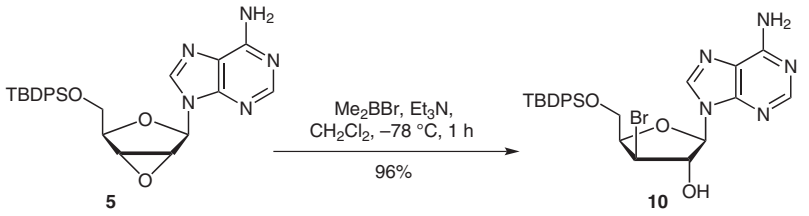


Scheme 1 Mattocks–Moffatt bromoacetylation (ia), Moffatt epoxidation (ib), regio- and stereoselective epoxide ring opening with azide (iii) and chemoselective Staudinger–Vilarrasa coupling (v and vii) as the key steps of the synthesis of **2**



Scheme 2 Epoxide ring opening according to Samano and Robins[9]

figured puromycin analogue. Thus, following to the approach of Samano and Robins,[9,5u] *ribo*-epoxide **5** was regio- and stereoselectively opened with Me_2BBr to afford the *xylo*-bromo alcohol **10** (Scheme 2). We then attempted to carry out an S_N2 reaction with sodium azide in position 2′. Not too surprisingly, we obtained, alas, azide **6** in 79% isolated yield which formed from epoxide **5** that was reformed in situ in DMF at 75 °C despite the presence of excess NaN_3.

To conclude, this synthesis is a combination of the Moffatt's approach, to obtain the *ribo*-epoxide, and our own coupling protocol, the Staudinger–Vilarrasa coupling reaction, linked through a regio- and stereoselective epoxide ring opening procedure.[13] It is hitherto the shortest and highest yielding synthesis of a 6-*N*,*N*-bis-demethyl puromycin analogue which was obtained in 56% or 39–43% overall yield over six or five steps, respectively, from adenosine. This route could be used for a series of similar derivatives if **2** were shown to present some interesting biological activity.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(13) **9-(3′-Azido-5′-*O*-*tert*-butyldiphenylsilyl-3′-deoxy-β-D-xylofuranos-1-yl)adenine (6)**: To a stirred solution of **5** (52 mg, 0.11 mmol) in DMF (1 mL), were added NaN_3 (42 mg, 0.69 mmol) and H_2O (0.3 mL). The reaction mixture was precisely warmed to 78–80 °C for 20 h, then quenched with sat. $NaHCO_3$ solution and diluted with EtOAc. The layers were separated and the aqueous portion was washed with EtOAc (3 ×). The combined organic extracts were washed with 10% aq LiCl (3 ×) to remove the residual DMF, washed once with brine, dried over anhyd $MgSO_4$, filtered and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (EtOAc–toluene, 1:1, 3:1, 5:1, 7:1; EtOAc–toluene–MeOH, 7:1:0.5) to afford **6** as a white solid (47 mg, 80%); mp 181 °C (uncorrected); R_f 0.40 (EtOAc–toluene, 4:1). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.99 (s, 9 H, Si-*t*-Bu), 3.88 (dd, 1 H, ^2J = 11.0 Hz, ^3J = 4.5 Hz, H_A5′), 4.00 (dd, 1 H, ^2J = 11.0 Hz, ^3J = 3.9 Hz, H_B5′), 4.46 (m, 1 H, H3′), 4.48 (m, 1 H, H4′), 4.82 (q 'ddd', 1 H, ^3J = 3.9, 4.5 Hz, H2′), 5.91 (d, 1 H, ^3J = 4.5 Hz, H1′), 6.36 (d, 1 H, ^3J = 5.1 Hz, OH), 7.33 (br s, 2 H, NH_2), 7.36–7.46 (m, 6 H, H-*m*-Ar, H-*p*-Ar), 7.61–7.66 (m, 4 H, H-*o*-Ar), 8.13 (s, 1 H, H8), 8.15 (s, 1 H, H2). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 18.8 (Si*C*Me$_3$), 26.6 [3 × C, SiC*Me*$_3$], 63.0 (C5′), 66.0 (C3′), 77.0 (C2′), 79.3 (C4′), 87.6 (C1′), 118.9 (C5), 127.9, 128.0 (4 × C, C-*m*-SiPh), 130.0 (2 × C, C-*p*-SiPh), 132.5, 132.8 (2 × C, C-*i*-SiPh), 135.0, 135.1 (4 × C, C-*o*-SiPh), 138.9 (C8), 149.4 (C4), 152.8 (C2), 156.0 (C6). HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{30}N_8O_3Si$ (530.65): 531.2288; found: 531.2285.

9-(3′-Azido-5′-*O*-*tert*-butyldiphenylsilyl-3′-deoxy-β-D-xylofuranos-1-yl)-6-*N*-(di-*n*-butylamino)methylene-adenine (7): Beforehand co-evaporated with toluene (3 × 2 mL), the azido compound **6** (243 mg, 0.46 mmol) was dissolved in anhyd MeOH (1.2 mL). *N*,*N*-Di-*n*-butylformamide dimethylacetal[5z] (196 mg, 0.96 mmol) was added and the reaction mixture was slightly warmed for a few seconds with a heat gun every 15 min and stirred for 1 h. The volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc–cyclohexanes, 1:1, 2:1, 3:1, 4:1, 5:1) to yield **7** (301 mg, 98%) as a colorless oil; R_f 0.63 (EtOAc–cyclohexanes, 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94–0.97 [m, 6 H, N(CH$_2$CH$_2$CH$_2$C*H*$_3$)$_2$], 0.96 (s, 9 H, Si-*t*-Bu), 1.30–1.46 [m, 4 H, N(CH$_2$CH$_2$C*H*$_2$CH$_3$)$_2$], 1.59–1.72 [m, 4 H, N(CH$_2$C*H*$_2$CH$_2$CH$_3$)$_2$], 3.40 [t, 2 H, ^3J = 7.4 Hz, N(C*H*$_2$CH$_2$CH$_2$CH$_3$)$_2$], 3.61–3.79 [m, 2 H, N(C*H*$_2$CH$_2$CH$_2$CH$_3$)$_2$], 3.87 (dd, 1 H, ^2J = 10.8 Hz, ^3J = 4.8 Hz, H_A5′), 3.94 (dd, 1 H, ^2J = 10.8 Hz, ^3J = 5.4 Hz, H_B5′), 4.37 (dd, 1 H, ^3J = 4.7, 5.1 Hz, H3′), 4.54 (pseudo q 'ddd', 1 H, ^3J = 4.8, 5.1, 5.4 Hz, H4′), 4.81 (pseudo t, 1 H, ^3J = 4.1, 4.7 Hz, H2′), 5.91 (d, 1 H, ^3J = 4.1 Hz, H1′), 6.46 (br s, 1 H, OH), 7.32–7.42 (m, 6 H, H-*m*-Ar, H-*p*-Ar), 7.62–7.65 (m, 4 H, H-*o*-Ar), 8.05 (s, 1 H, H8), 8.41 (s, 1 H, H2), 9.01 (s, 1 H,

N=C*H*NBu$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6, 13.9 [2 × C, N($CH_2CH_2CH_2CH_3$)$_2$], 19.0 (Si*C*Me$_3$), 19.7, 20.1 [2 × C, N(CH_2CH_2*C*H_2CH_3)$_2$], 26.7 (3 × C, SiC*Me*$_3$), 29.2, 30.9 [2 × C, N($CH_2CH_2CH_2CH_3$)$_2$], 45.3, 52.0 [2 × C, N(*C*$H_2CH_2CH_2CH_3$)$_2$], 62.1 (C5′), 66.2 (C3′), 79.5 (C2′), 81.3 (C4′), 90.9 (C1′), 125.8 (C5), 127.7 (4 × C, C-*m*-SiPh), 129.8 (2 × C, C-*p*-SiPh), 132.7 (2 × C, C-*i*-SiPh), 135.5 (4 × C, C-*o*-SiPh), 139.5 (C8), 150.4 (C4), 152.0 (C2), 158.8 (N=*C*HNBu$_2$), 159.9 (C6). HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{35}H_{47}N_9O_3Si$ (669.89): 670.3644; found: 670.3649.

9-[5′-*O*-*tert*-Butyldiphenylsilyl-3′-*N*-(α-*N*-fluorenylmethoxycarbonyl-*p*-methoxy-L-phenylalanyl)amido-3′-deoxy-β-D-xylofuranos-1-yl]-6-*N*-(di-*n*-butylamino)methyleneadenine (8): *N*-Fmoc-*O*-Me-L-Tyr (114 mg, 0.282 mmol) and HOBt (45 mg, 0.282 mmol) were co-evaporated from anhyd THF (3 × 3 mL). The mixture was dissolved in anhyd THF (2 mL) and the solution was cooled to 0 °C under N_2 for 10 min. Then, DIC (38.3 μL, 0.242 mmol) was added and the reaction mixture was stirred for 10 min at the same temperature. PMe_3 (1 M in THF, 303 μL, 0.303 mmol) was added to a solution of **7** (135 mg, 0.202 mmol) in THF (2 mL), and the mixture was stirred for 1 min at r.t. The amino acid solution was warmed to r.t. during 1 min, and then added to the iminophosphorane solution. The reaction mixture was stirred at r.t. overnight, concentrated under reduced pressure and co-evaporated from $CHCl_3$ (2 × 3 mL), then dissolved in EtOAc (30 mL) and quenched with sat. $NaHCO_3$ (15 mL). The organic layer was extracted with EtOAc (2 ×) and washed with H_2O (2 × 10 mL), dried over anhyd $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc–toluene, 1:3, 1:2, 1:1, 2:1, 3:1, 4:1, EtOAc–toluene–MeOH, 3:1:0.25) to yield **8** (175 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (s, 9 H, Si-*t*-Bu), 0.96 [t, 6 H, ^3J = 6.9 Hz, N($CH_2CH_2CH_2CH_3$)$_2$], 1.31–1.47 [m, 4 H, N($CH_2CH_2CH_2CH_3$)$_2$], 1.60–1.73 [m, 4 H, N($CH_2CH_2CH_2CH_3$)$_2$], 2.81–2.98 (m, 2 H, Hβ), 3.41 [t, 2 H, ^3J = 7.2 Hz, N($CH_2CH_2CH_2CH_3$)$_2$], 3.61 (s, 3 H, OMe), 3.65–3.81 [m, 3 H, N($CH_2CH_2CH_2CH_3$)$_2$, H_A5′], 3.92 (dd, 1 H, ^2J = 11.3 Hz, ^3J = 4.1 Hz, H_B5′), 4.15 (pseudo t, 1 H, ^3J = 6.0, 6.9 Hz, H aliph. Fl.), 4.24–4.30 (m, 2 H, Hα, CH_2Fl.), 4.38–4.47 (m, 3 H, H4′, H2′, CH_2Fl.), 4.71–4.77 (m, 1 H, H3′), 5.43 (d, 1 H, ^3J = 6.9 Hz, NHFmoc), 5.43 (br s, 1 H, OH), 5.74 (d, 1 H, ^3J = 3.6 Hz, H1′), 6.63 [d, 2 H, ^3J = 8.1 Hz, H-*o*-Ph(OMe)], 6.99 [d, 2 H, ^3J = 8.1 Hz, H-*m*-Ph(OMe)], 7.20–7.30 (m, 8 H, H-*m*^{2}-Fl., H-*m*-SiPh, H-*p*-SiPh), 7.32–7.40 (m, 2 H, H-*p*^{3}-Fl.), 7.48–7.55 (m, 6 H, H-*o*^{1}-Fl., H-*o*-SiPh), 7.73 (t '2×d', 2 H, ^3J = 7.2, 7.5 Hz, H-*m*^{4}-Fl.), 7.97 (s, 1 H, H8), 8.46 (s, 1 H, H2), 8.54 (d, 1 H, ^3J = 7.8 Hz, 3′-NH), 9.02 (s, 1 H, N=C*H*NBu$_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 13.9 [2 × C, N($CH_2CH_2CH_2CH_3$)$_2$], 19.0 [Si*C*Me$_3$], 19.7, 20.2 [2 × C, N($CH_2CH_2CH_2CH_3$)$_2$], 26.7 (3 × C, SiC*Me*$_3$), 29.2, 30.9 [2 × C, N($CH_2CH_2CH_2CH_3$)$_2$], 38.4 (Cβ), 45.4 [N($CH_2CH_2CH_2CH_3$)$_2$], 47.1 (*C*H aliph. Fl.), 52.0 [N(*C*$H_2CH_2CH_2CH_3$)$_2$], 55.0 (OMe), 56.7 (C3′), 57.2 (Cα), 62.6 (C5′), 66.9 (*C*H_2Fl.), 80.3 (C2′), 80.3 (C4′), 91.6 (C1′), 113.8 [2 × C, C-*o*-Ph(OMe)], 119.9 (2 × C, C-*m*^{4}-Fl.), 125.0 (2 × C, C-*o*^{1}-Fl.), 126.7 (C5), 127.0 (2 × C, C-*m*^{2}-Fl.), 127.6 (2 × C, C-*p*^{3}-Fl.), 127.7 (4 × C, C-*m*-SiPh), 127.8 [C-*p*-Ph(OMe)], 129.8 (2 × C, C-*p*-SiPh), 130.3 [2 × C, C-*m*-Ph(OMe)], 132.6, 132.7 (2 × C, C-*i*-SiPh), 135.5 (4 × C, C-*o*-SiPh), 141.2 (2 × C, C8), 141.2 (2 × C, C-*o*^{5}-Fl.), 143.7, (2 × C, C-*i*-Fl.), 150.0 (C2), 151.9 (C4), 155.6 (N=*C*HNBu$_2$), 158.4 (C6), 158.5 [C-*i*-Ph(OMe)], 162.3 [R*C*(O)OCH$_2$Fl.], 171.4 [3′-NH*C*(O)R′]. HRMS (ESI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{60}H_{70}N_8O_7Si$ (1043.36): 1043.5215; found: 1043.5211.

9-[3′-Deoxy-3′-*N*-(*p*-methoxy-L-phenylalanyl)amido-β-D-xylofuranos-1-yl]adenine (2): Compound **9** (25 mg, 0.027 mmol) (or **8**) was dissolved in 33% $MeNH_2$–EtOH (5 mL). The reaction mixture was stirred at r.t. overnight in a closed vessel. The solution was concentrated under reduced pressure and co-evaporated from $CHCl_3$ (2 × 4 mL). The oily residue was dissolved in MeOH (1 mL) and then ammonium fluoride (5.2 mg, 0.138 mmol) was added to the solution. The reaction mixture was warmed to 50–55 °C for 4 h, and monitored by TLC. The volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc–MeOH–H_2O, 14:1:0.5, 12:1: 0.5, 10:1:0.5, 8:1:0.5, 6:1:0.5, 4:1:0.5) to yield after evaporation the target compound **2** as a fluffy white solid (12 mg, 98% from **9**). ^{1}H NMR (300 MHz, CD_3OD): δ = 2.90 (dd, 1 H, ^2J = 13.5 Hz, ^3J = 6.3 Hz, Hβ1), 2.97 (dd, 1 H, ^2J = 13.5 Hz, ^3J = 7.5 Hz, Hβ2), 3.53 (dd, 1 H, ^2J = 12.6 Hz, ^3J = 4.2 Hz, H_A5′), 3.64 (s, 3 H, OMe), 3.68–3.70 (m, 1 H, Hα), 3.75 (dd, 1 H, ^2J = 12.6 Hz, ^3J = 3.3 Hz, H_B5′), 4.34 ('ddd', 1 H, ^3J = 3.3, 3.6, 6.9 Hz, H4′), 4.43 (t, 1 H, ^3J = 5.1 Hz, H2′), 4.60 (dd, 1 H, ^3J = 5.4, 5.7 Hz, H3′), 5.79 (d, 1 H, ^3J = 4.8 Hz, H1′), 6.73 [d, 2 H, ^3J = 8.7 Hz, H-*o*-Ph(OMe)], 7.11 [d, 2 H, ^3J = 8.7 Hz, H-*m*-Ph(OMe)], 8.18 (s, 1 H, H8), 8.22 (s, 1 H, H2). ^{13}C NMR (125 MHz, CD_3OD): δ = 40.9 (Cβ), 55.6 (OMe), 57.6 (C3′), 58.6 (Cα), 62.1 (C5′), 79.4 (C2′), 81.4 (C4′), 92.5 (C1′), 115.0 [2 × C, C-*o*-Ph(OMe)], 121.3 (C5), 129.8 [C-*p*-Ph(OMe)], 131.6 [2 × C, C-*m*-Ph(OMe)], 142.5 (C8), 149.4 (C4), 153.6 (C2), 157.7 (C6), 160.2 [C-*i*-Ph(OMe)], 175.2 [3′-NHC(O)R′]. HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{25}N_7O_5$: 466.1815; found: 466.1817.

The supporting information for this article contains protocols and experimental details for the syntheses of **4**, **5**, **9**, and **10**, as well as the ^{1}H NMR, DEPT, ^{13}C NMR, ^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC, and (in part) ^{1}H–^{13}C HMBC spectra of all compounds.