Synthesis of Unnatural C-2 Amino Acid Nucleosides Using NIS-Mediated Ring Opening of 1,2-Cyclopropane Carboxylated Sugar Derivatives

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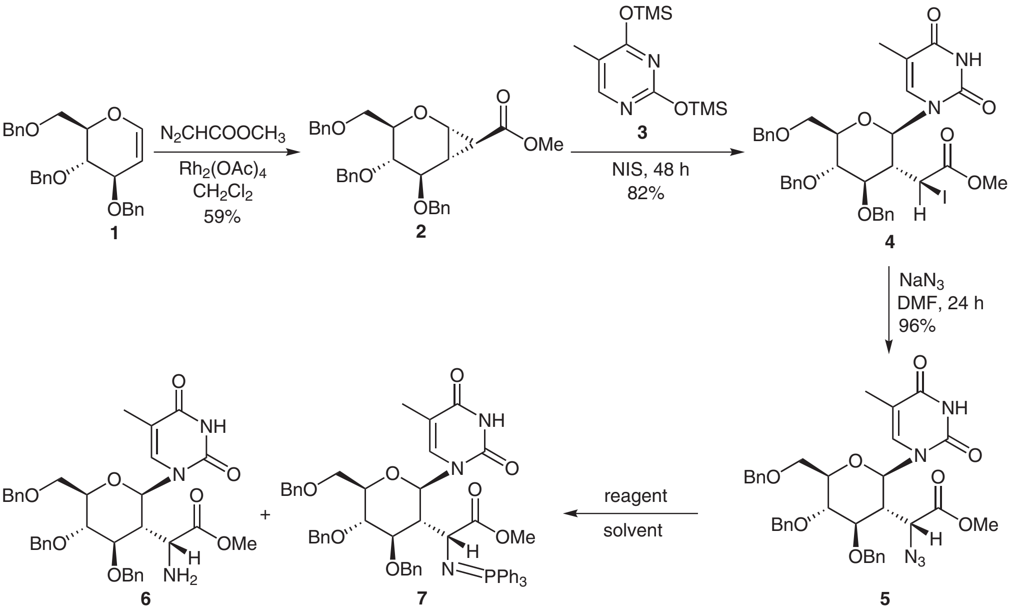
Dedicated to Professor M. V. George on the occasion of his 80th birthday

Abstract: We have developed a general and efficient method for the stereoselective construction of pyrimidine-based pyranosyl C-2 amino acid nucleosides using NIS-mediated ring opening of 1,2-cyclopropanated sugar derivatives. This methodology has been successfully extended to the synthesis of furanosyl nucleosides, which have potential applications in the development of novel, nontoxic antifungal therapeutics.

Key words: amino acid nucleoside, donor–acceptor, polyoxin, purine, pyrimidine

Peptidyl nucleoside antibiotics are a unique class of secondary metabolites[1] that exhibit high antifungal activity against a wide range of pathogenic fungi.[2] For making these molecules, nature uses amino acids and nucleosides as raw materials. Generally total synthesis of these molecules requires some special strategies due to their unique combination of functional groups.[3,4] Diversity of structural arrangement present in these molecules can be used to design new compounds having interesting biological activity.[5] Earlier, we reported from our laboratory an efficient methodology for the synthesis of 2-C-branched glycoamino acids by ring opening of 1,2-cyclopropane carboxylated sugar derivatives[6] and it has been successfully applied to the synthesis of fused perhydrofuro[2,3-*b*]pyrano-γ-butyrolactone derivatives.[7] In this report, we describe the synthesis of a few unnatural C-2 amino acid nucleoside derivatives of the type **6** using NIS-mediated ring opening of 1,2-cyclopropanated sugar derivatives (Scheme 1).

Cyclopropanation of tri-*O*-benzyl-D-glucal (**1**) was carried out using methyl diazoacetate (MDA) in dichloromethane with catalytic rhodium acetate (25 °C, 90 min) to furnish the corresponding 1,2-cyclopropane carboxylated sugar derivative **2** in 59% yield.[8] Treatment of **2** with *N*-iodosuccinimide and trimethylsilyl-activated thymine[9] **3** (1 equiv each, CH_2Cl_2, 25 °C) furnished the iodo compound **4** only in 10% yield after 36 hours, whereas the use of 2.5 equivalent of each reagent (CH_2Cl_2, 25 °C, 48 h) gave the iodide **4** in 82% yield.[10] In the process, we have succeeded in the attachment of the nucleobase as well as



Scheme 1 Synthesis of unnatural C-2 amino acid nucleoside **6**

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the generation of amino acid precursor simultaneously in a single step. The iodide **4** was converted into the corresponding azide **5** using NaN_3 (DMF, r.t., 24 h) in quantitative yield. The crystal structure of compound **5** was in accord with our stereochemical assignment at C1, C2 and C7 (carbohydrate nomenclature) for the ring-opened product.[11] The azide **5** was subjected to the standard Staudinger reduction conditions[12] using PPh_3–THF followed by aqueous hydrolysis. Unfortunately, we got the expected amine **6** only in 30% yield and the corresponding imine **7** was obtained as the major product, even after refluxing for 18 hours. Use of Lindlar's catalyst[13] was also found to be ineffective for the reduction. Benzyltriethylammonium tetrathiomolybdate[14] [$(BnNEt_3)MoS_4$], a versatile alternative reagent to thiols also could not give the expected product in good yield. Finally, zinc-mediated[15] reduction (AcOH–THF, 1:1, 25 °C, 3 h) was found to be the best, which gave the corresponding amine **6** in 80% yield (Table 1).

Table 1 Reduction of Azide **5** with Various Reagents

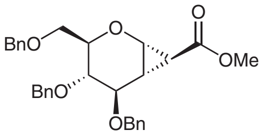
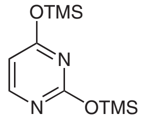
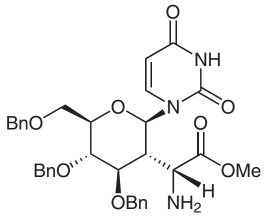
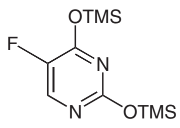
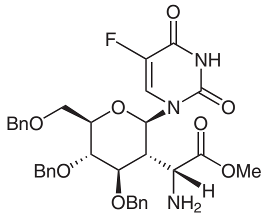
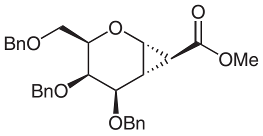
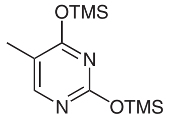
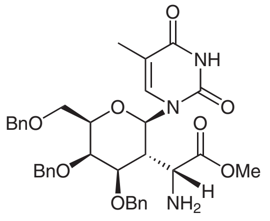
Reagent	Solvent	**6** yield (%)	**7** yield (%)
PPh_3	$THF–H_2O$	30	ca. 50
Lindlar's catalyst	EtOAc	0	0
$(BnNEt_3)MoS_4$	$MeCN–H_2O$	20	0
Zn	AcOH–THF	80	0

After successfully standardizing the reaction protocol, we decided to vary the pyrimidine base. In this regard, cyclopropane ester **2** was treated with the TMS-activated uracil **8** and fluorouracil **12**[9] under the same reaction conditions to get the corresponding iodides **9** and **13**, respectively, in good yields (Table 2). These iodides **9** and **13** were converted into the corresponding azides **10** and **14**, respectively, using NaN_3 under similar conditions as described earlier. The azides **10** and **14** on reduction with Zn (AcOH–THF, 25 °C, 3 h) afforded the corresponding amino acid nucleosides **11** and **15**, respectively in good yields.

Having achieved the synthesis of glucose-derived pyrimidine nucleosides successfully, we next explored the generality of the reaction by changing the carbohydrate part to a galactal derivative. Tribenzyl galactal derived 1,2-cyclopropane carboxylated sugar derivative **16**[8] was treated with NIS and TMS-activated thymine **3**, which gave the corresponding iodide **17** in 80% yield. The iodide **17** was then converted into the corresponding azide **18** (87%). Using the previously established conditions for azide reduction, the galactal-derived C-2 amino acid nucleoside **19** was obtained in good yield (Table 2).

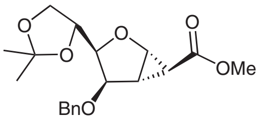
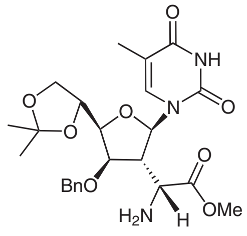
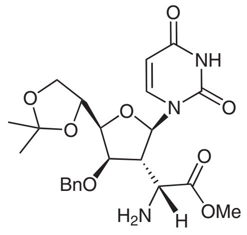
Among the various complex peptidyl nucleosides, polyoxins and nikkomycins are the nucleoamino acids that are well known and the most effective inhibitors of chitin synthase.[16] Polyoxin C constitutes the basic amino acid nucleoside common to the many members of the polyoxin family. Many synthetic routes have been developed for

Table 2 Synthesis of Pyrimidine-Based Unnatural C-2 Amino Acid Nucleosides

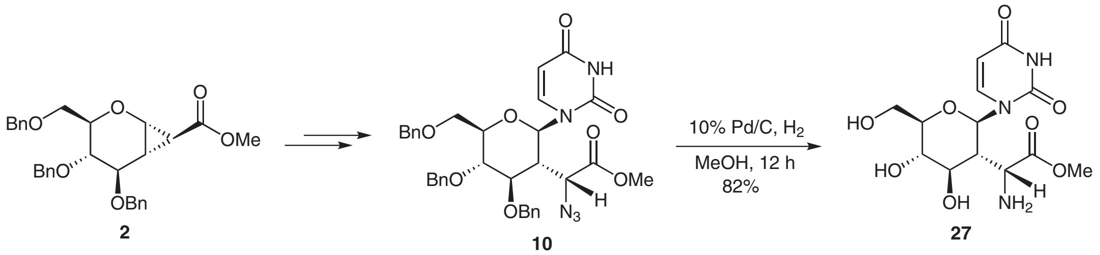
Cyclopropane	Base	Iodide (%)[a]	Azide (%)[a]	Amino acid nucleoside (%)[a]
 **2**	 **8**	**9** (75)	**10** (96)	 O NH N O BnO O O OMe BnO OBn NH2 H **11** (69)
2	 **12**	**13** (75)	**14** (82)	 O F NH N O BnO O O OMe BnO OBn NH2 H **15** (68)
 **16**	 **3**	**17** (80)	**18** (87)	 O NH N O BnO O O OMe BnO OBn NH2 H **19** (69)

[a] Isolated yield after colomn chromatography.

Table 3 Synthesis of Furanosyl Unnatural C-2 Amino Acid Nucleosides **23** and **26** from Mannose-Derived 1,2-Cyclopropane Carboxylate **20**

Cyclopropane	Iodide (%)[a]	Azide (%)[a]	Amino acid nucleoside (%)[a]
 **20**	**21** (71)	**22** (80)	 **23** (70)
20	**24** (68)	**25** (76)	 **26** (65)

[a] Isolated yield after colomn chromatography.



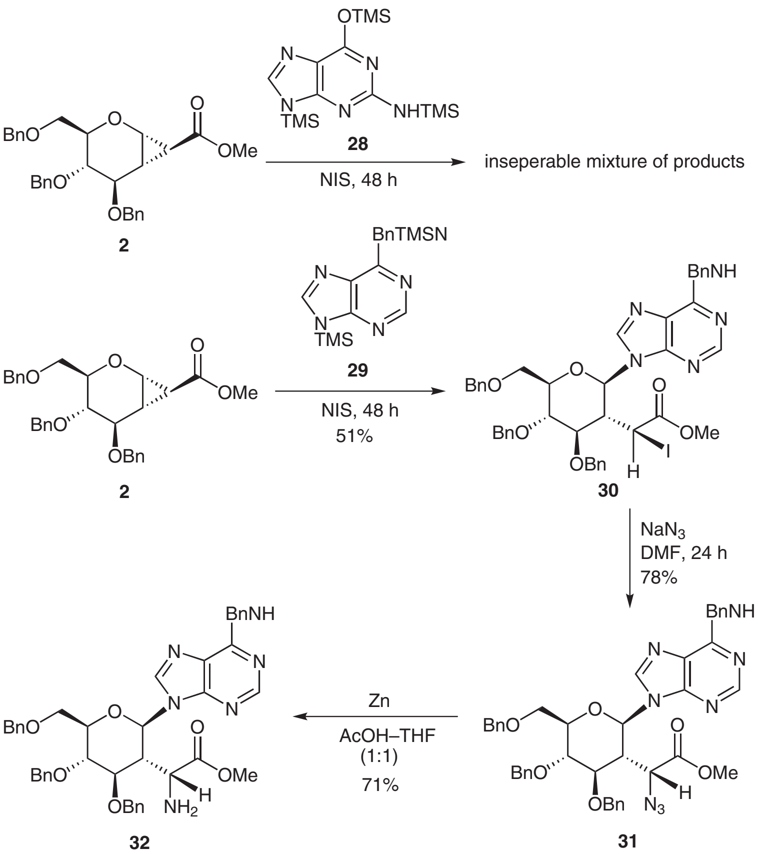
Scheme 2 Synthesis of uracil-substituted pyranosyl C-2 amino acid nucleoside **27**

the synthesis of these polyoxins and their analogues.[17] Keeping this in mind, our methodology was subsequently extended to the reaction of cyclopropanated furan derivatives. The furanosyl cyclopropanated ester **20** was synthesized from mannose as previously reported in the literature.[18]

The ester **20** when treated with NIS (2.5 equiv) and TMS-activated thymine **3** (2.5 equiv, CH_2Cl_2, 25 °C, 48 h) gave the corresponding iodide **21** (71%; Table 3). The iodide **21** was converted into the corresponding azide **22** (80%), followed by the reduction with Zn to get the corresponding furanosyl amino acid nucleoside **23** in 70% yield. Similarly, ester **20** when treated with NIS and TMS-activated uracil **8** gave the corresponding iodide **24** in 68% yield, which was then converted into the azide **25** (76%). Reduction of **25** with Zn (AcOH–THF, 25 °C, 3 h) afforded the uracil-based furanosyl amino acid nucleoside **26** in 65% yield.

There are some recent reports on the synthesis of pyranosyl nucleoside amino acid cores as higher analogues of polyoxin.[19] In light of this, we subjected the nucleoside azide **10** to palladium-mediated hydrogenation and it is noteworthy that we got the corresponding amino triol **27** in 82% yield (Scheme 2). All the above reaction schemes clearly demonstrate the potential utility of NIS-mediated cyclopropane carboxylate ring-opening reaction for the construction of C-2 amino acid nucleoside structural framework of various pyranosyl peptidyl nucleoside antibiotic analogues in a short and efficient way.

While this work was in progress we came across a report on the synthetic studies of amipurimycine.[20] While this group had cleverly synthesized the pyrimidine-based thymine amipurimycine analogue, their attempts failed to attach the purine base to get the amipurimycine. Therefore, we decided to test the generality of our methodology for the synthesis of purine-based C-2 amino acid nucleosides. In the preliminary studies, cyclopropyl ester **2** was treated with the freshly prepared TMS-activated guanosine **28** and NIS (2.5 equiv, CH_2Cl_2, 25 °C, 48 h). Unexpectedly, it gave a mixture of products which could not be separated by column chromatography or by crystallization (Scheme 3). However, when we treated the cyclopropyl ester **2** with the freshly prepared TMS-activated *N*-benzyl purine **29** and NIS (2.5 equiv, CH_2Cl_2, 25 °C, 48 h), it gave the corresponding iodide **30** in moderate yield. The iodide **30** was converted into the corresponding azide **31** followed by Zn-mediated reduction to give the corresponding purine-based amino acid nucleoside **32** in 71% yield.



Scheme 3 Synthesis of unnatural C-2 amino acid nucleoside **32** having a purine base

In conclusion, we have developed a general and efficient method for the stereoselective construction of pyrimidine-based pyranosyl C-2 amino acid nucleosides using NIS-mediated ring-opening reaction of 1,2-cyclopropanated sugar derivatives,[21] which yet again illustrates the utility of donor–acceptor-substituted cyclopropane derivatives in organic synthesis.[22] This methodology has been successfully extended to the synthesis of furanosyl nucleosides, which have potential applications in the development of novel, nontoxic antifungal therapeutics. Partial success has been achieved in the application of this methodology for the synthesis of purine-based pyranosyl amino acid nucleosides. Application of this methodology towards the synthesis of a C-2 analogue of polyoxin C is currently in progress.

Acknowledgment

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(10) Addition of further equivalence of the reagents did not result in any noticeable increase in the yield. The use of excess NIS in the presence of stoichiometric amount of nucleobase was not effective as the reaction was found to be incomplete even after 48 h.

(11) CCDC 706702 contains the supplementary crystallographic data for the azide **5**.

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(21) **General Procedure for the NIS-Mediated Ring Opening of Cyclopropyl Carboxylates; Synthesis of Iodide 4**: To a solution of cyclopropyl carboxylate **2** (0.488 g, 1 mmol) in CH_2Cl_2 (10 mL), freshly prepared TMS-activated thymine **3** (0.675 g, 2.5 mmol) and NIS (0.562 g, 2.5 mmol) were added under an argon atmosphere at r.t. (25 °C). After 48 h the reaction mixture was diluted with $CHCl_3$ (10 mL) and then neutralized with dilute $Na_2S_2O_3$ solution. Insoluble material was removed by filtration. The organic layer was separated and dried over anhyd Na_2SO_4.The filtrate was concentrated and the crude product was purified by flash chromatography on silica gel (230–400 mesh) using 40% EtOAc–PE, which gave the corresponding iodide **4** as a gummy solid (0.606 g, 82%).

Compound **4**: R_f (EtOAc–PE, 2:3) 0.35; $[\alpha]_D$ +31.0 (c = 2, $CHCl_3$). IR (neat): 3214, 3064, 3032, 1721, 1714, 1694, 1454, 1368, 1267, 1027, 736, 698 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.05 (s, 1 H), 7.10–7.34 (m, 18 H), 5.97 (d, J = 9.9 Hz, 1 H), 5.00 (d, AB type, J = 10.5 Hz, 1 H), 4.74 (d, AB type, J = 10.5, 1 H), 4.31 (d, AB type, J = 10.2 Hz, 1 H), 4.46–4.63 (m, 3 H), 3.98 (q, J = 7.8 Hz, 2 H), 3.81 (dd, J_1 = 3.6 Hz, J_2 = 11.1 Hz, 1 H), 3.62–3.71 (m, 2 H), 3.84 (s, 3 H), 1.94 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 163.1, 150.2, 137.9, 137.7, 137.4, 134.9, 128.4, 127.7, 127.5, 112.3, 82.0, 78.9, 77.4, 74.7, 74.6, 73.4, 68.3, 53.6, 48.8, 23.3, 12.5. HRMS: *m/z* [M + Na] calcd for $C_{35}H_{37}IN_2O_8$: 763.1492; found: 763.1559.

General Procedure for the Preparation of Azides; Synthesis of Azide 5: To a stirred solution of iodide **4** (0.236 g, 0.31 mmol) in anhyd DMF (2 mL) was added sodium azide (0.040 g, 0.62 mmol) and the reaction was stirred for 24 h at r.t. (25 °C). Most of the DMF was removed under vacuum followed by dilution with $CHCl_3$ (10 mL), which was washed with H_2O. The organic layer was separated and dried over anhyd Na_2SO_4. The filtrate was concentrated and the crude product was purified by flash chromatography on silica gel (230–400 mesh) using 40% EtOAc–PE to obtain the corresponding azide **5** as a pale yellow solid (0.200 g, 96%).

Compound **5**: mp 182 °C; R_f (EtOAc–PE, 2:3) 0.3; $[\alpha]_D$ +42.22 (c = 1.8, $CHCl_3$). IR (neat): 2114, 1744, 1713, 1693, 1496, 1265, 737, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (s, 1 H), 7.22–7.37 (m, 15 H), 6.99 (s, 1 H), 5.77 (d, J = 7.1 Hz, 1 H), 5.00 (d, J = 11.6 Hz, 1 H), 4.32 (d, J = 10.4 Hz, 1 H), 4.66 (dd, J = 4.8 Hz, J_2 = 17.2 Hz, 2 H), 4.57 (d, J = 12.4 Hz, 1 H), 4.49 (d, J = 12.4 Hz, 1 H), 4.39 (d, J = 1.8 Hz, 1 H), 3.83–3.72 (m, 3 H), 3.64–3.66 (m, 1 H), 3.55 (m, 4 H), 2.51 (br s, 1 H), 1.91 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4, 163.0, 149.4, 137.6, 137.5, 137.4, 128.6, 128.5, 128.4, 128.3, 128.1, 127.9, 110.8, 79.0, 78.4, 77.3, 75.2, 74.8, 73.4, 68.0, 57.9, 52.7, 47.3, 22.5. HRMS: *m/z* [M + Na] calcd for $C_{35}H_{37}N_5O_8$: 678.2540; found: 678.2554.

General Procedure for the Reduction of Azides Using Zn; Synthesis of Amino Acid Nucleoside 6: To a stirred solution of azide **5** (0.105 g, 0.16 mmol) in AcOH–THF (1:1, 5 mL) was added zinc (0.0009 g, 10 mmol%) and the reaction was stirred for 3 h at r.t. (25 °C). After the disappearance of the starting material (by TLC), Zn was removed by filtration and the filtrate was diluted with EtOAc (15 mL). The organic layer was thoroughly washed with $NaHCO_3$ solution. It was separated and dried over anhyd Na_2SO_4. The filtrate was concentrated and the crude product was purified by flash chromatography on silica gel (230–400 mesh) using 20% MeOH–$CHCl_3$ to obtain the corresponding C-2 amino acid nucleoside **6** as a colorless gummy solid (0.080 g, 80%).

Compound **6**: R_f (MeOH–$CHCl_3$, 4:1) 0.35; $[\alpha]_D$ +12 (c = 2, $CHCl_3$). IR neat): 3584, 3064, 3031, 2953, 2919, 1739, 1733, 1694, 1455, 1368, 1267, 1155, 1111, 736, 698, 666 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.92 (br s, 1 H), 7.21–7.33 (m, 15 H), 7.06 (s, 1 H), 5.77 (d, J = 10.4 Hz, 1 H), 4.99 (d, J = 11.6 Hz, 1 H), 4.86 (d, J = 11.2 Hz, 1 H), 4.73 (d, J = 11.6 Hz, 1 H), 4.65 (d, J = 11.2 Hz, 1 H), 4.50–4.60 (m, 3 H), 4.10–4.04 (m, 1 H), 3.61–3.80 (m, 6 H), 3.46 (s, 3 H), 2.41 (m, 1 H), 1.93 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.0, 163.8, 150.7, 138.5, 138.3, 136.0, 129.0, 128.9, 128.4, 128.3, 128.2, 111.6, 80.0, 79.5, 75.7, 75.3, 73.8, 68.8, 52.5, 51.0, 49.9, 30.8, 12.9. HRMS: *m/z* [M + Na] calcd for $C_{35}H_{39}N_3O_8$: 652.2635; found: 652.2662.

General Procedure for the Reduction of Azide 10 Using Pd/C: A suspension of 10% Pd/C (0.040 g) and azide **10** (0.040 g, 0.06 mmol) in MeOH (2 mL) under hydrogen atmosphere was stirred for 12 h at ambient temperature (25 °C). The catalyst was filtered and washed with MeOH (20 mL). The filtrate was concentrated and the crude product was purified by flash column chromatography (10% $CHCl_3$–MeOH) to get the corresponding amino triol **27** as a gummy solid (0.017 g, 82%).

Compound **27**: R_f (MeOH–$CHCl_3$, 1:9) 0.2; $[\alpha]_D$ +6.5 (c = 2, DMF). IR (neat): 3417, 1659, 1651, 1644, 1049, 1026, 1004, 826, 764 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ = 10.32 (s, 1 H), 7.50 (d, J = 8.1 Hz, 1 H), 5.60 (d, J = 8.0 Hz, 1 H), 5.56 (d, J = 10.0 Hz, 1 H), 4.45 (t, J = 6.0 Hz, 1 H), 3.73 (d, J = 12.0 Hz, 1 H), 3.53–3.66 (m, 5 H), 3.20–3.35 (m, 2 H), 1.89–2.13 (m, 5 H). ^{13}C NMR (100 MHz, DMSO): δ = 177.2, 163.8, 151.5, 141.9, 103.0, 81.1, 79.9, 72.0, 61.9, 52.6, 51.1, 50.1, 21.6. HRMS: *m/z* [M + Na] calcd for $C_{13}H_{19}N_3O_8$: 368.1070; found: 368.1065.

(22) For reviews, see: (a) Reissig, H. U. *Top. Curr. Chem.* **1988**, *144*, 73. (b) Reissig, H. U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (c) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321.

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