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NOVEL UNSATURATED PURINE NUCLEOSIDES[1]

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Abstract: The synthesis of a number of novel purine ribonucleosides bearing one degree of unsaturation at the 2-position is described. The two key reactions used in the synthesis of these compounds is a palladium-catalyzed cross-coupling reaction and an ozonolysis. These synthetic transformations have rarely been used in nucleoside chemistry. Isomerization of an allylpurine system to a vinylpurine system under the conditions of the cross-coupling reaction and also under fluoride ion catalysis is discussed. The novel 2-formylpurine nucleosides described appear to be easily hydrated.

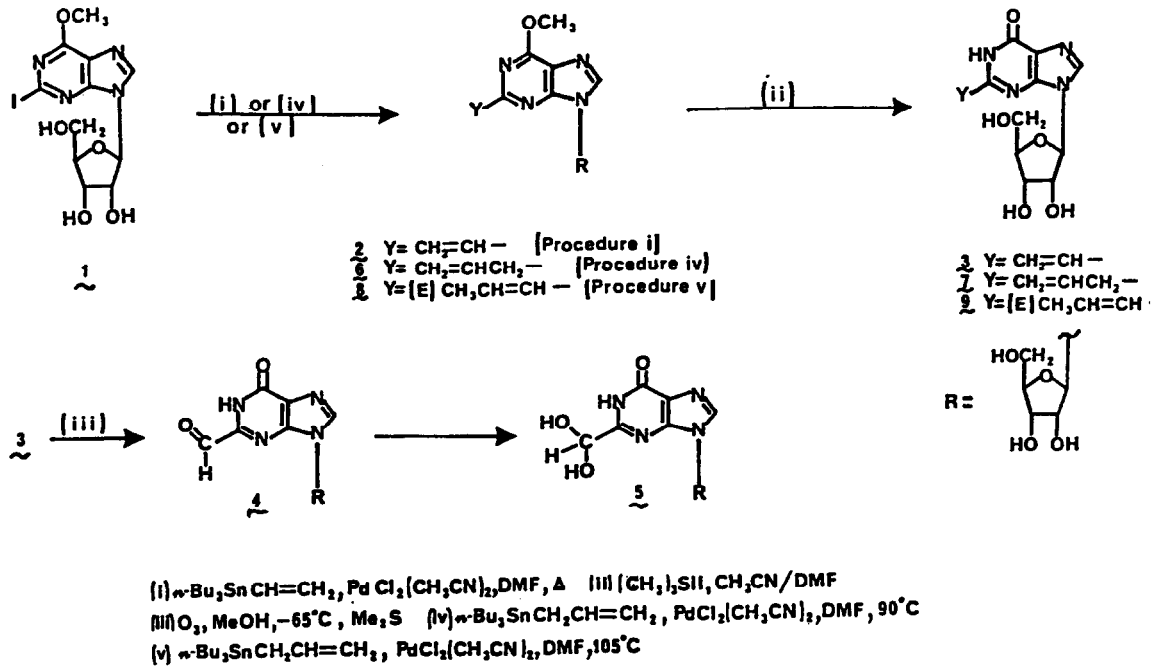
The design and synthesis of strategically modified nucleosides are of interest because of the potential biological value of these compounds as anticancer and antiviral agents.[2-8] One class of nucleosides currently being studied in our laboratory are purine ribonucleosides that contain modification at the 2-position of the base moiety.[9,10] In this paper, we describe the synthesis of novel purine and hypoxanthine nucleosides with one degree of unsaturation in the substitution at the 2-position. These compounds are not only of potential interest as antiviral and anticancer agents, but also as inhibitors of some key enzymes in purine metabolism.[11-14] Some of the steps utilized in the synthesis of these novel nucleosides have rarely been used in nucleoside chemistry.

For compounds belonging to the hypoxanthine series, the immediate precursor was 2-iodo-6-methoxypurine nucleoside (1).[10] Replacement of the 2-iodo group with a vinyl group at this position was carried out by a palladium-catalyzed cross-coupling reaction reported previously by us.[10] Deprotection of the resulting 6-methoxy-2-vinyl compound 2 with trimethylsilyl iodide (TMSI) gave the α,β-unsaturated inosine 3. Ozonolysis of 3 in methanol at -65 °C followed by rapid reductive work-up with dimethyl sulfide, furnished the novel inosine carboxaldehyde 4 (Scheme 1). Rearrangement reactions of the intermediate secondary ozonide

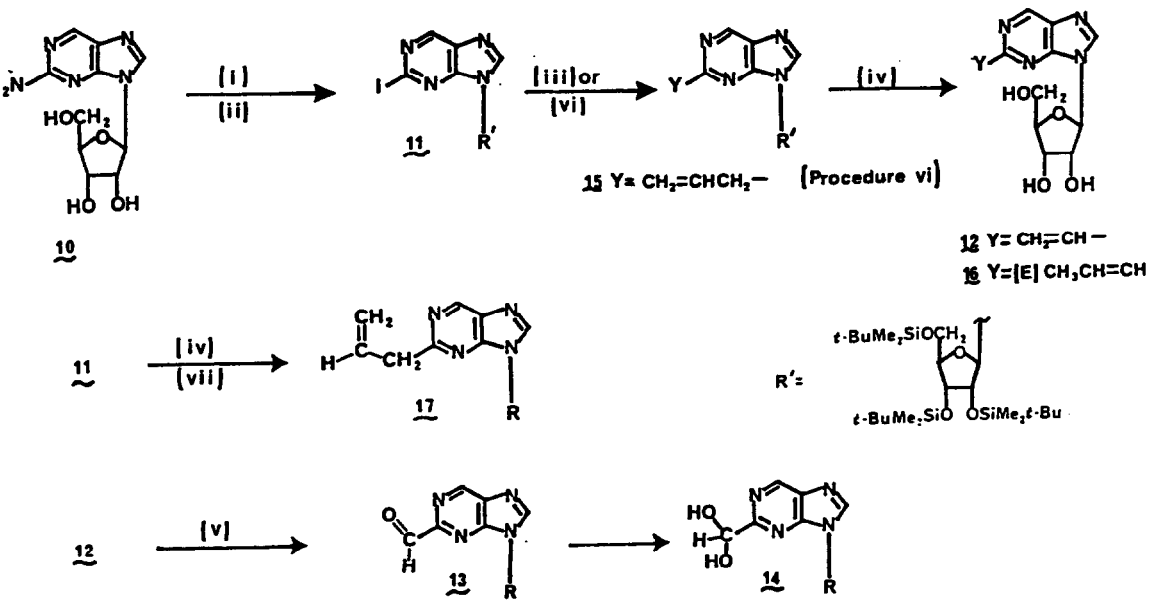
may be minimized by addition of dimethyl sulfide prior to warm up to room temperature. Compound 4 was purified by reversed-phase HPLC on Amberlite XAD-4 resin with ethanol-water as the eluting solvent to give 4 as a white solid in 55% yield. Interestingly, the high-field ^{13}C NMR spectrum of 4 showed that it existed in both the carbonyl form (C=O carbon at 185.5 ppm) and the hydrated carbonyl structure 5 (geminal diol carbon at 88.1 ppm). The resonance of the formyl carbon suggests that it may have partial characteristics of the carbonyl of an iminamidyl type linkage. It should be mentioned that ozonolysis reactions have rarely been in nucleoside synthesis.[15]

The palladium-catalyzed cross-coupling procedure was also used to synthesize the novel unsaturated nucleosides, 2-allylinosine [2-(2-propenyl)inosine] 7 and 2-(1-propenyl)inosine 9 (Scheme 1). Thus, treatment of the 2-iodo compound 1 with bis(acetonitrile)palladium II chloride with allyl tri-n-butylstannane in DMF at 100 °C for 6 h afforded a mixture of the 2-allyl-6-methoxypurine 6 and the rearranged product, the 2-(1-propenyl)-6-methoxypurine 8 in a ratio of 2.5 to 1 and a combined yield of 92%. Temperature and reaction time appear to be very important factors in these palladium-catalyzed reactions. Between 90 and 95 °C, selectivity of formation of the allyl product 6 is optimum (i.e. formation of the rearranged product 8 can be almost fully suppressed by lowering the reaction temperature). Alternatively, raising the reaction temperature to about 105 °C and increasing the reaction time result in high selectivity in the formation of 8. Finally, below 90 °C, the reaction is extremely sluggish. Our experimental data do not provide an unambiguous mechanistic interpretation of the pathway for the isomerization of the allyl group.[16] Deprotection of the allyl and vinyl nucleosides, 6 and 8, with TMSI in acetonitrile gave the target compounds 7 and 9, respectively, in about 64% yield. The latter products were purified by reversed-phase HPLC and characterized by their spectral data: UV, FTIR, FAB HRMS, and high-field NMR. In the case of compound 9, the high-field ^{1}H NMR spectrum (in DMSO-d_6) gave unequivocal evidence for the E-stereochemistry of the exocyclic double bond (J = 17.1 Hz).

For the novel compounds of the nebularine series, 2-aminonebularine (isoadenosine) 10[9] served as the starting material (Scheme 2). Compound 10 was converted to 11 by silylation followed by deamination-halogenation. Palladium-catalyzed cross-coupling of 2-iodopurine ribonucleoside 11 with vinyl tri-n-butylstannane followed by deprotection with fluoride ions



Scheme 1



Scheme 2

furnished 2-vinylnebularine 12 (63% yield for 2 steps). Cleavage of the vinyl group with ozone at 4 °C in ethanol-water gave the novel 2-formyl compound 13 in 61% yield after reductive work-up and purification by HPLC. Compound 13 was characterized spectroscopically as described for 4. It appears to be readily hydrated and both the aldehyde 13 and geminal diol 14 were clearly discerned in the high-field ^{1}H and ^{13}C NMR spectra.

Two approaches were examined for the synthesis of the new nucleoside, 2-allylnebularine (17). In the first approach, the silyl protected 2-iodo compound 11 was treated with allyl tri-n-butylstannane, and bis(acetonitrile) palladium II chloride in the presence of tri-o-tolylphosphine in refluxing toluene for 36 h to give the protected allyl compound 15 in 44% yield. However, when compound 15 was deprotected with tetraethylammonium fluoride and the reaction mixture worked up with ammonium chloride, the isomerized 2-(1-propenyl)purine nucleoside 16 was isolated in 81% yield. The persistence of this double bond isomerization even under neutral work-up conditions suggested that it was probably occurring through the involvement of fluoride ions used for the removal of the silyl protecting groups. This unexpected facile double bond isomerization in the deprotection step prompted examination of an alternative method of arriving at compound 17. This approach involved initial deprotection of 11 followed by cross-coupling with allyl tri-n-butylstannane and tetrakis(triphenylphosphine)palladium (0) in DMF at 100 °C for 18 h. Allylnebularine 17 was obtained in 50% yield after reversed-phase HPLC and was fully characterized by its physical data. As in the case of the aforementioned inosine series, raising the temperature of the cross-coupling reaction resulted in increased amounts of the isomerized product.

In summary, novel unsaturated nucleosides of the inosine and nebularine families have been prepared by two useful synthetic approaches that have seen little previous utilization in purine nucleoside chemistry. The aldehydes synthesized represent new congeners of hypoxanthine and purine nucleosides and no compounds related to these interesting systems have previously been reported. In terms of reactivity as it relates to carbon-carbon bond formation, the purine system is much less reactive than the hypoxanthine system. A temperature-dependent isomerization of an allyl nucleoside to a vinyl nucleoside was also observed under the conditions of cross-coupling. Biological studies assessing the RNA antiviral activities of these compounds are currently under investigation.

EXPERIMENTAL SECTION

Melting points provided are uncorrected, and were taken on a Thomas-Hoover melting point apparatus fitted with a microscope. Nuclear magnetic resonance spectra using tetramethylsilane as the internal standard were recorded on JOEL Model FX-90Q and Bruker Model WM-360 pulse Fourier transform spectrometers. A VG Analytical Model VG-II-250 MS system was used for the FAB-HRMS data. The ultraviolet spectra were recorded on a Varian Cary Model 219 spectrophotometer. Infrared spectra were recorded on a Mattson Cygnus Model 25 Fourier transform instrument. All solvents were distilled over appropriate drying agents before use. Flash chromatography was carried out on 230-400 mesh silica gel with methanol-dichloromethane as the eluting solvent. HPLC was performed on Amberlite XAD-4 resin (40-60 μm) with ethanol-water as the mobile phase.

2-Vinyl-9-(β-D-ribofuranosyl)hypoxanthine (3) was synthesized from 2-iodo-6-methoxy-9-(β-D-ribofuranosyl)purine (1) as previously described.[10]

2-Formyl-9-(β-D-ribofuranosyl)hypoxanthine (4). A solution consisting of 1.000 g (3.40 mmol) of 2-vinyl-9-(β-D-ribofuranosyl)hypoxanthine (3) and 500 mL of dry (Omnisolve) methanol was cooled to -65 °C in an isopropanol/dry ice bath. This mixture was ozonized for 15 min and then purged with nitrogen while slowly letting it warm to room temperature. Dimethyl sulfide (3 mL) was added and the solution was allowed to stir at room temperature for 12 h. The solvent was then removed under reduced pressure, and the residue was purified by HPLC. Compound 4 was obtained as a crystalline white solid in 55% yield (0.554 g, 1.87 mmol). Mp 161 °C; ^{13}C NMR (DMSO-d_6) δ (61.1, 61.2), (70.2, 70.3), (73.9, 74.1), (85.6, 85.7), (86.8, 87.2), 88.1, (123.2, 126.6), (138.9, 141.1), (147.0, 147.6), (147.9, 155.8), (156.4, 157.4), 185.5. ^{1}H NMR (Me_2SO-d_6) δ 3.60 (m, 2H), 3.93 (m, 1H), 4.13 (m, 1H), 4.50 (m, 1H), 5.10 (m, 2H), 5.50 (m, 2H), 5.89 (d, J = 5.86 Hz, 1H), 6.82 (d, J = 6.84 Hz, 1.5 H), 8.32 (s, 1H), 9.55 (s, 1H), 11.7 (s, 1H); UV (H_2O) λ_{max} 249, 270 nm (ϵ 4965); FTIR (KBr) 1692, 3300 cm^{-1}; FAB (HRMS) Calcd for $C_{11}H_{12}N_4O_5$ 297.0835 (M^++H); Found: 297.0831 (M^++H).

2-Allyl-9-(β-D-ribofuranosyl)hypoxanthine (7). A solution consisting of 1.090 g (2.67 mmol) of compound 1, 0.035 g (0.134 mmol) of $PdCl_2$ $(MeCN)_2$, and 5.00 mL of dry DMF was

purged with N_2 (1/2 h). Allyltributyltin (0.911 mL, 2.94 mmol) was added dropwise via gastight syringe. The reaction mixture was then stirred under N_2 at 90 °C for 6 h. It was cooled to ambient temperature, and the solvent removed under vacuum. The residue was flash chromatographed. Compound **6** was obtained as a low melting tan solid in 76% yield (0.654 g, 2.03 mmol): ^{1}H NMR (Me_2SO-d_6) δ 3.18 (d, 2H), 3.63 (m, 2H), 3.97 (m, 1H), 4.09 (s, 3H), 4.11 (m, 1H), 4.51 (m, 1H), 5.17 (m, 5H), 5.93 (d, 1H), 6.05 (m, 1H), 8.56 (s, 1H); UV (EtOH) λ_{max} 252 nm.

A solution consisting of 1.000 g of **6** (3.11 mmol), 2.450 g (14.8 mmol) of KI and 3.50 mL (67.1 mmol) of acetonitrile in dry DMF (5.0 mL) was purged with nitrogen for 30 min. Trimethylsilyl chloride (1.83 mL, 14.4 mmol) was added dropwise to the solution, and the mixture was stirred for 3 h at room temperature. The reaction was quenched by the addition of 3.0 mL of 3M NaOH in 7.0 mL of H_2O to bring the pH of the reaction to 7. The solvents were removed in vacuo and the residue was purified by HPLC to give 2-allylinosine (**7**) as a white solid (0.613 g, 1.99 mmol, 64%): mp 137-139 °C; ^{13}C NMR (Me_2SO-d_6) δ 30.6, 61.4, 70.5, 73.7, 85.7, 87.0, 118.1, 122.4, 132.6, 138.5, 148.5, 156.5, 157.0; ^{1}H NMR (Me_2SO-d_6) δ 3.42, (d, 2H), 3.60 (m, 2H), 3.97 (m, 1H), 4.12 (m, 1H), 4.52 (m, 1H), 5.20 (m, 5H), 5.84 (d, 1H), 6.07 (m, 1H), 8.25 (s, 1H), 12.04 (bs, 1H); UV (H_2O) λ_{max} 249 nm (ϵ 11102); FAB (HRMS) Calcd for $C_{13}H_{16}N_4O_5$: 309.1199 (M^++H). Found: 309.1162 (M^++H).

E-2-(1-Propenyl)-9-(β-D-ribofuranosyl)hypoxanthine (9). A solution consisting of 1.000 g (2.45 mmol) of compound **1**, and 0.270 g (0.105 mmol) of $PdCl_2(MeCN)_2$ in dry DMF (5 mL) was purged with N_2 (1/2 h) and allyltributyltin (0.836 mL, 2.70 mmol) was added and the reaction was carried out as described for synthesis of **6** except for reaction temperature and time (105 °C, 24 h). Compound **8** was obtained as a low-melting solid in 63% yield (0.474 g, 1.54 mmol); ^{1}H NMR (Me_2SO-d_6) δ 1.93 (dd, 3H, J = 1.46, 8.3 Hz), 3.62 (m, 2H), 3.95 (m, 1H), 4.08 (m, 4H), 4.61 (m, 1H), 5.07 (m, 2H), 5.46 (m, 1H), 5.93 (d, 1H), 6.45 (dd, 1H, J = 1.46, 16.6 Hz), 7.11 (m, 1H), 8.50 (s, 1H); UV (H_2O) λ_{max} 261 nm.

A solution consisting of 1.000 g (3.11 mmol) of compound **8** was deprotected as described for **7** to give E-2-(1-propenyl)-9-(β-D-ribofuranosyl)hypoxanthine **9** as a white solid (0.613 g, 1.99 mmol, 64%): mp 221-223 °C; ^{13}C NMR (Me_2SO-d_6) δ 18.1, 61.3, 70.4, 73.8, 85.5, 87.1, 122.6, 123.5, 138.4, 138.8, 148.7, 152.0, 156.8; ^{1}H NMR (Me_2SO-d_6) δ 1.92 (dd, 3H, J = 6.84,

small), 3.58 (m, 2H), 3.94 (m, 1H), 4.13 (m, 1H), 4.53 (m, 1H), 5.18 (m, 1H), 5.38 (m, 1H), 5.44 (d, 1H), 5.87 (d, 1H), 6.30 (dd, 1H, J = 17.1, 1.5 Hz), 7.10 (m, 1H), 8.26 (s, 1H), 12.17 (s, 1H); UV (H_2O) λ_{max} 260 (ϵ 6123), 290 (ϵ 6290) nm; FAB (HRMS) Calcd for $C_{13}H_{16}N_4O_5$: 309.1199 (M^++H). Found: 309.1210 (M^++H).

2-Iodo-9-[2,3,5-tri-O-(tert-butyldimethylsilyl)-β-D-ribofuranosyl]purine (11). This precursor was prepared from isoadenosine 10 by silylation followed by radical halogenation.[9] The overall yield of 11 from guanosine (6 steps) was 34%.

2-Formyl-9-(β-D-ribofuranosyl)purine (13). A solution of 0.238 g (0.858 mmol) of 2-vinyl-9-(β-D-ribofuranosyl)purine (12), prepared as described for 3, in 270 mL of 15% ethanol/water was cooled to 4 °C and then ozonized for 10 min. The reaction mixture was worked up as described for ozonolysis of 3. This procedure furnished 0.147 g (0.525 mmol, 61%) of compound 13 as a white solid: mp 115-117 °C; ^{13}C NMR (Me_2SO-d_6) δ (61.1, 61.4), (70.3, 70.8), (73.6, 73.8), (85.8, 86.9), (87.0, 87.4), 90.8, (133.1, 133.3), (134.8, 135.1), (147.8, 148.0), (151.1, 151.4), (153.2, 162.7), 190.8; ^1H NMR (Me_2SO-d_6) δ 3.62 (m, 4H), 4.02 (m, 2H), 4.22 (m, 3H), 4.55 (m, 2H), 4.95 (m, 3H), 5.52 (m, 2H), 6.22 (m, 2H), 6.56 (d, 1H), 9.01 (s, 1H), 9.09 (s, 1H), 9.39 (s, 1H), 9.43 (s, 1H), 10.07 (s, 1H); UV (EtOH) λ_{max} 276 nm; FTIR (KBr) 1718 cm^{-1} FAB (HRMS) Calcd for $C_{11}H_{12}N_4O_5$: 281.0886 (M^++H); Found: 281.0887 (M^++H).

E-2-(1-Propenyl)-9-(β-D-ribofuranosyl)purine (16). Bis(acetonitrile) palladium II chloride (0.021 g, 0.080 mmol) and tri-O-tolylphosphine (0.049 g, 0.160 mmol) were added to a 100 mL RBF containing 0.963 g (1.33 mmol) of compound 11. The flask was placed on the vacuum line to remove residual oxygen. Freshly distilled toluene (50 mL) was added to the flask followed by 0.46 mL (1.46 mmol) of allyltributyltin. The mixture was purged with N_2 (1/2 h) and then heated under toluene reflux (under N_2) for 16 h. At this time, an additional 0.2 mL (0.645 mmol) of allyltributyltin was added and the reaction allowed to proceed for an additional 10 h. Upon cooling, ethyl ether (40 mL) was added and the reaction mixture extracted with 10% Na_2EDTA (2x20 mL) and water (20 mL). The organic layer was dried (Na_2SO_4), and the solvents were removed under reduced pressure. The residue was taken up in hexanes and eluted through a short silica gel scrubber column with 1:1 hexanes/ethyl ether.

Final purification by flash chromatography on silica gel (1:1 hexanes/ethyl ether) provided 0.322 g of starting material, and 0.213 g (0.337 mmol, 44%) of the protected allyl compound 15 as a tan oil: ^{1}H NMR ($CDCl_3$) δ -0.16-0.13 (m, 18H), 0.80-0.95 (m, 27H), 3.79 (d, 2H), 4.01 (m, 2H), 4.13 (m, 1H), 4.32 (m, 1H), 4.64 (t, 1H), 5.10 (m, 2H), 6.05 (d, 1H), 6.20 (m, 1H), 8.44 (s, 1H), 9.05 (s, 1H); UV (EtOH) λ_{max} 267 nm.

To a solution consisting of 0.311 g (0.491 mmol) of compound 15 and 10 mL of dry acetonitrile was added 3.93 mL (1.96 mmol) of tetraethylammonium fluoride (0.5 M solution in acetonitrile). The resulting solution was allowed to stir at room temperature for 3 h under nitrogen. The reaction was worked up by the addition of 0.276 g (5.16 mmol) of ammonium chloride and 10 mL of water. This solution was allowed to stir for 12 h at room temperature. The acetonitrile was then removed and the aqueous portion extracted with chloroform (15 mL) and ethyl ether (15 mL). The chloroform portion was then back extracted with water (20 mL). The aqueous portions were combined and concentrated. The residue was taken up in methanol and purified on preparative silica gel plates using 17% methanol/chloroform for development. Recrystallization from water gave 0.116 g (3.98 mmol, 81%) of the isomerized compound 16 as a white solid: mp 86-88 °C ; ^{13}C NMR (Me_2SO-d_6) δ 18.3, 61.7, 70.8, 73.8, 86.0, 87.6, 131.0, 132.7, 135.7, 145.5, 148.4, 151.7, 158.4; ^{1}H NMR (Me_2SO-d_6) δ 1.94 (dd, 3H, J = 8.30, 1.46 Hz), 3.63 (m, 2H), 3.98 (q, 1H), 4.20 (q, 1H), 4.67 (q, 1H), 5.09 (t, 1H), 5.24 (d, 1H), 5.50 (d, 1H), 6.03 (d, 1H), 6.56 (dd, 1H, J = 17.1, 1.5 Hz), 7.10 (m, 1H), 8.73 (s, 1H), 9.08 (s, 1H); UV (H_2O) λ_{max} 231 nm (ϵ 17441); 268 nm (ϵ 11290); 287 nm (ϵ 9660); FAB (HRMS) Calcd for $C_{13}H_{16}N_4O_4$: 293.1250 (M^++H). Found: 293.1270 (M^++H).

2-Allyl-9-(β-D-ribofuranosyl)purine (17). To a solution consisting of 0.909 g (1.26 mmol) of compound 11 in acetonitrile (20 mL) was added 10.0 mL (5.04 mmol) of tetraethylammonium fluoride (0.5 M solution in acetonitrile). The solution was stirred under N_2 for 1 h, at which time 0.710 g of ammonium chloride (13.24 mmol) and 10 mL of water was added and stirring was continued for an additional 12 h. The reaction was worked up as described for the deprotection of 15 to give deprotected 11 as a white solid (0.364 g, 0.960 mmol, 76%): mp 163-165 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.61 (m, 2H), 3.95 (m, 1H), 4.18 (m, 1H), 4.56 (m, 1H), 5.04 (t, 1H), 5.27 (d, 1H), 5.55 (d, 1H), 5.96 (d, 1H), 8.78 (s, 1H), 8.98 (s, 1H); UV (EtOH) λ_{max} 278.5 nm.

Tetrakis (triphenylphosphine)palladium (0) (0.0162 g, 0.014 mmol) was added to a 100 mL RB flask containing 0.1060 g (0.280 mmol) of deprotected 11 in a glove box. The flask was then placed on a vacuum line to remove residual oxygen. Dry DMF (20 mL) was added to the reaction flask via double-tipped needle followed by 0.095 mL (0.308 mmol) of allyltributyltin. The reaction mixture was purged with N_2 (0.5 h) and then heated at 100 °C under N_2 for 18 h. The solution was filtered and the DMF was then removed under reduced pressure. The residue was purified by HPLC to give 17 as a highly hygroscopic white solid (0.062 g, 0.214 mmol, 76%): ^{1}H NMR (Me_2SO-d_6) δ 3.67 (m, 4H), 3.97 (m, 1H), 4.18 (m, 1H), 4.65 (m, 1H), 5.15 (m, 4H), 5.49 (d, 1H), 6.02 (d, 1H), 6.18 (m, 1H), 8.76 (s, 1H), 9.11 (s, 1H); ^{13}C NMR (Me_2SO-d_6) δ 43.1, 61.3, 70.4, 73.4, 85.8, 87.0, 116.6, 132.2, 135.1, 144.9, 148.1, 151.4, 162.3; UV (H_2O) λ_{max} 267 nm, 247 nm (sh); FAB (HRMS) Calcd for $C_{13}H_{16}N_4O_4$: 293.1250 (M^++H). Found: 293.1230 (M^++H).

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