Synthesis of 8-Heteroaryl-2′-deoxyguanosine Derivatives

Gerard Hobley, Vladimir Gubala,[1] María Del C. Rivera-Sánchez, José M. Rivera*

Department of Chemistry, College of Natural Sciences, University of Puerto Rico, Río Piedras Campus, San Juan 00931, Puerto Rico
Fax +1(787)7568242; E-mail: jmrivortz@mac.com

Received 14 December 2007

Abstract: We describe the synthesis of 8-heteroaromatic-2′-deoxyguanosine analogues using Suzuki–Miyaura or Stille conditions. Unprotected and protected 8-bromo-2′-deoxyguanosine was coupled with commercially available heteroarylboronic acids or the trialkyltin derivatives of 2-pyridylbromides either with or without microwave irradiation in good yields.

Key words: Stille reaction, nucleosides, nucleobases, palladium, coupling

The development of efficient strategies for the synthesis of nucleoside analogues is of great importance due to their potential uses in biological applications. For example, many nucleoside analogues have found uses as antibiotics and antivirals,[2] as probes for nucleic acid structure[3] and as chain terminators for DNA sequencing.[4] Our main interest is in guanine and its derivatives, which arises from the fact that they can self-associate to form macrocyclic, planar tetramers known as G-tetrads. These further associate through π-stacking interactions to form G-quadruplexes (GQ). These GQ can be formed from individual guanine subunits or from G-rich oligonucleotides that fold up into a variety of quadruplex structures.[5] The cation-templated self-assembly of guanosines into G-quadruplexes has been recognized since the 1960s.[6] More recent studies of G-quadruplex formation have been in diverse areas such as cancer research and nanotechnology.[5,7] We have demonstrated the aggregation of 8-aromatic-2′-deoxyguanosine analogues in organic solvents[8] and have shown their selective binding of cations in some cases.[9] We are particularly interested in the synthesis of 8-heteroaromatic-2′-deoxyguanosine [8-(HetAr)*d*G] derivatives. Heteroatoms and functional groups in the heteroaryl moieties can be used to increase the number of H bonds. We have shown that functional groups within an 8-phenyl ring can lead to supramolecular complexes with higher stability.[8]

Since Shaughnessy's method[10] of using the easily prepared 8-bromo-2′-deoxyguanosine (8-Br*d*G)[11] and commercially available boronic acids had proven successful in the synthesis of 8-aromatic-2′-deoxyguanosine analogues (8-Ar*d*G),[8] we decided to apply it to the synthesis of **8**-(HetAr)*d*G targets. However, although the method is useful in the coupling of a variety of heterocycles vide infra, we quickly realized that we needed to use a different method to couple the 2-pyridyl moiety. Because of the expense, reported instability[12] and relative scarcity of commercially available, functionalized 2-pyridyl boronic acids we decided to use Stille conditions as an alternative method.[13] This is not without precedent since the Stille methodology has been used for 2-pyridylstannane couplings to various aromatic skeletons[14] including a number of purine analogues.[15] Nonetheless, to the best of our knowledge it has never been used to make 8-(HetAr)*d*G derivatives. In our hands, when we tried to couple heteroaromatics to 3′,5′-isobutyric ester of 8-bromo-2′-deoxyguanosine (3′,5′-*i*-Bu-8-Br*d*G) using heteroaromatic tin compounds, tetrakistriphenylphosphinepalladium in refluxing toluene,[15f] the sole reaction product was that derived from replacement of the bromide in the substrate with a hydrogen atom. Under these conditions the reaction is extremely sluggish and on this substrate dehalogenation and hydrogenation ensues.

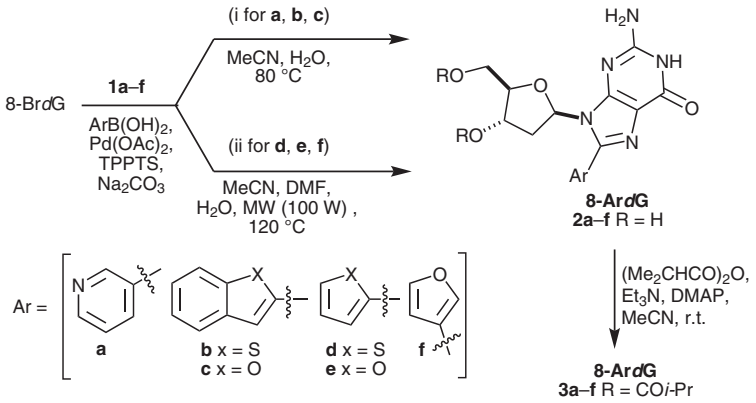
Recently, the coupling of heteroaromatics to various guanine analogues has been reported using Stille conditions: refluxing in xylene at 150 °C, tetrakistriphenyl phosphinepalladium and triphenylbismuth as a co-ligand.[15a] However, this work which parallels ours does not try the coupling reaction on 3′,5′-*i*-Bu-8-Br*d*G.

Herein we report two convenient methods for the direct functionalization of the C-8 position of 2′-deoxyguanosine with heteroaromatic substituents either on 8-Br*d*G using commercially available boronic acids (Suzuki–Miyaura conditions) or via 2-pyridylstannanes and (Stille conditions) upon 3′,5′-*i*-Bu-8-Br*d*G. The Stille reaction on this substrate is accompanied by a competitive side reaction, which by taking measures to increase the rate of Stille Coupling, can be significantly reduced. The methodology presented not only allows us to make a series of target molecules which we believe will have novel supramolecular properties but it should also be useful to others who wish to functionalize the C-8 position of guanine and its analogues.

Boronic acids (**1a–c**) were found to couple efficiently to 8-Br*d*G using the Shaughnessy method (Scheme 1, Table 1, entries 1–3) to yield the 8-(HetAr)*d*G derivatives **2a–c**.[16]

It was found, however, that the coupling reaction was very inefficient with the boronic acids **1d–f**. Since it has been reported that Suzuki couplings can be extremely efficient under microwave irradiation,[17] we modified the methodology by treating 8-Br*d*G with boronic acids **1d–f** in aqueous MeCN–DMF mixtures under microwave irradiation, obtaining the 8-(HetAr)*d*G products (**2d–f**, entries 4–6).[18]

SYNLETT 2008, No. 10, pp 1510–1514
Advanced online publication: 19.05.2008
DOI: 10.1055/s-2007-1077795; Art ID: S10207ST

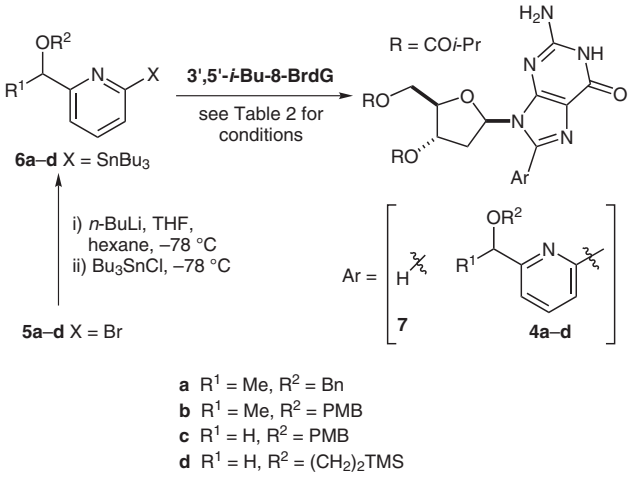


Scheme 1 Synthesis of 8-(HetAr)*d*G derivatives

Table 1 Results for the Synthesis of 8-(HetAr)*d*G Derivatives from Commercially Available Boronic Acids and 8-Br*d*G

Entry	Boronic acid	Product, yield (%)[c]	Ester, yield (%)[c]
1	**1a**[a]	**2a**, 79	**3a**, 89
2	**1b**[a]	**2b**, 88	**3b**, 91
3	**1c**[a]	**2c**, 81	**3c**, 65
4	**1d**[b]	**2d**, 77	**3d**, 89
5	**1e**[b]	**2e**, 82	**3e**, 90
6	**1f**[b]	**2f**, 94	**3f**, 80

[a] Conditions i, see Scheme 1.
[b] Conditions ii, see Scheme 1
[c] Isolated yield.



Scheme 2 Synthesis of 3′,5′-*i*-Bu-8-(2Py)*d*G analogues

As shown in Scheme 1, these 8-(HetAr)*d*G compounds were converted into their isobutyric esters[19] **3a–f** for future studies of their self-assembly in organic solvent.

We next turned our attention to the synthesis of target molecule **4a** (Scheme 2). The starting secondary alcohol was protected as the benzyl ether **5a**. This was converted into the tributyltin compound **6a** in good yield. We applied a modification of the method reported by Brill and Riva-Toniolo,[15b] where they describe the solid-phase reaction of 8-bromo-2,6-diaminopurines with various organostannanes. The initial coupling under homogeneous conditions used DMF as the solvent, copper(II) oxide as additive and much less of the ligand, bisdiphenylphosphinopropane (DPPP). We found that the reaction gave a mixture of the debrominated **7** and coupled product **4a** in a 1:1 ratio (entry 2, Table 2). Furthermore, **4a** turned out to be a 1:1 mixture of diastereomers as determined by ^{1}H and ^{13}C NMR, indicating no diastereoselectivity.

However, upon changing the additive to Cu(I)oxide[15b] and the equivalents of additive to two, we observed a significant improvement in the overall rate of the reaction and on the ratio of the two products (**7**/**4a**, entry 3).

Changing the ligand to triphenylarsine, which has weak donicity, led to improved yields of **4a** (entry 4) with further improvement by changing the solvent to *N*-methylpyrrolidinone (NMP, entry 5). The overall optimal combination of ligand and solvent was DPPP with NMP (entry 6). Under these conditions reducing the amount of additive [Cu(I)O], reduction in the initial amount of tin compound added or increasing the concentration of ligand (DPPP) had adverse effects on the rate of formation of the required product (data not shown). These results are in accord with those of other groups, who have sought to increase the rate of the Stille coupling reaction.[15b–e,13b]

These results encouraged us to attempt the synthesis of more challenging 8-(2Py)*d*G targets. The protected bromopyridines **5b–d** were converted into the tributyltin derivatives **6b–d**. Each of these was coupled to 3′,5′-*i*-Bu-8-Br*d*G as outlined in Table 2 (entries 7–9).[20] As can be seen the coupling reaction proceeds with moderate to good yields in all cases.

We have applied a set of conditions that make the rate of the Stille coupling reaction competitive to a problematic side reaction, obtaining reasonable yields of the target molecules. Using this method or the previously reported Suzuki–Miyaura conditions and a modification of these, we are now able to synthesize a library of 8-(HetAr)*d*G derivatives. We expect that these methodologies should also be useful to others who wish to attach functional groups to the C-8 position of purines.

Table 2 Coupling of 2-Pyridyl Stannanes to 3′,5′-*i*-Bu-8-Br*d*G under Various Conditions

Entry[e]	Tin compd[a]	Additive (equiv)	Reaction time (h)	Ligand (equiv)[b]	Solvent	Conversion (%)[c]	Ratio **7**/**4a**	Yield (%)
1	**6a**	none	3.5	DPPP (0.66)	DMF	33	1.2: 1[c]	Nd
2	**6a**	CuO (1)	14	DPPP (0.66)	DMF	nd	1: 1[d]	**4a** 39[d]
3	**6a**	Cu_2O (2)	1	DPPP (1)	DMF	>98	1: 6.3[c]	**4a** 70[c]
4	**6a**	Cu_2O (2)	1	$AsPh_3$ (2)	DMF	>98	1: 6.0[c]	**4a** 57[c]
5	**6a**	Cu_2O (2)	1	$AsPh_3$ (2)	NMP	>98	1: 6.2[c]	**4a** 59[c]
6	**6a**	Cu_2O (2)	1	DPPP (1)	NMP	>98	1: 7.7[c]	**4a** 74[d]
7	**6b**	Cu_2O (2)	1	DPPP (1)	NMP	nd	na	**4b** 80[d]
8	**6c**	Cu_2O (2)	1	DPPP (1)	NMP	nd	na	**4c** 60[d]
9	**6d**	Cu_2O (2)	1	DPPP (1)	NMP	nd	na	**4d** 61[d]

[a] In all cases, 2.0 equiv were used.
[b] With respect to the palladium.
[c] Calculated by HPLC analysis of the crude reaction mixtures; (nd) not done; (na) not applicable.
[d] Isolated yield.
[e] Other conditions: 3′,5′-*i*-Bu-8-Br*d*G (50 mg in 490 μL of solvent), 15 mol% $Pd(OAc)_2$, 115 °C.

Acknowledgment

We thank the NIH-SCoRE program for financial support, the National Science Foundation EPSCoR program for a graduate fellowship to V.G. and the NASA PR Space Grant Consortium as well as PRIDCO for a graduate fellowship to M.C.R.S.

References and Notes

(1) Current address: Dublin City University, Biomedical Diagnostics Institute, Glasnevin, Dublin 9, Ireland.
(2) (a) De Clercq, E.; Field, H. J. *Br. J. Pharmacol.* **2005**, *147*, 1. (b) Simons, C. *Nucleoside Mimetics: Their Chemistry and Biological Properties*, 1st ed., Vol. 3; Gordon and Breach: Amsterdam, **2001**.
(3) (a) Benner, S. A. *Acc. Chem. Res.* **2004**, *37*, 784. (b) Henry, A. A.; Romesberg, F. E. *Curr. Opin. Chem. Biol.* **2003**, *7*, 727. (c) Kool, E. T. *Acc. Chem. Res.* **2002**, *35*, 936. (d) Kool, E. T.; Morales, J. C.; Guckian, K. M. *Angew. Chem. Int. Ed.* **2000**, *39*, 990.
(4) França, L. T. C.; Carrilho, E.; Kist, T. B. L. *Q. Rev. Biophys.* **2002**, *35*, 169.
(5) Burge, S.; Parkinson, G. N.; Hazel, P.; Todd, A. K.; Neidle, S. *Nucleic Acids Res.* **2006**, *34*, 5402.
(6) Gellert, M.; Lipsett, M. N.; Davies, D. R. *Proc. Natl. Acad. Sci. U.S.A.* **1962**, *48*, 2013.
(7) (a) Riou, J. F.; Morjani, H.; Trentesaux, C. *Ann. Pharm. Fr.* **2006**, *64*, 97. (b) Davis, J. T. *Angew. Chem. Int. Ed.* **2004**, *43*, 668. (c) Pitchiaya, S.; Krishnan, Y. *Chem. Soc. Rev.* **2006**, *35*, 1111. (d) Feldkamp, U.; Niemeyer, C. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 1856. (e) Beissenhirtz, M. K.; Willner, I. *Org. Biomol. Chem.* **2006**, *4*, 3392.
(8) Gubala, V.; Betancourt, J. E.; Rivera, J. M. *Org. Lett.* **2004**, *6*, 4735.
(9) Gubala, V.; De Jesus, D.; Rivera, J. M. *Tetrahedron Lett.* **2006**, *47*, 1413.
(10) Western, E. C.; Daft, J. R.; Johnson, E. M.; Gannett, P. M.; Shaughnessy, K. H. *J. Org. Chem.* **2003**, *68*, 6767.
(11) (a) Gillet, L. C. J.; Scharer, O. D. *Org. Lett.* **2002**, *4*, 4205. (b) Gannett, P. M.; Sura, T. P. *Synth. Commun.* **1993**, *23*, 1611.
(12) (a) Hodgson, P. B.; Salingue, F. H. *Tetrahedron Lett.* **2004**, *45*, 685. (b) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302.
(13) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73. (c) For a recent computational analysis of the Stille Reaction, including ligand and solvent effects, see: Alvarez, R.; Faza, O. N.; Cardenas, D. J.; De Lera, A. R. *Adv. Synth.Catal.* **2007**, *349*, 887. (d) Alvarez, R.; Faza, O. N.; Lopez, C. S.; De Lera, A. R. *Org. Lett.* **2006**, *8*, 35.
(14) (a) Champouret, Y. D. M.; Chaggar, R. K.; Dadhiwala, I.; Fawcett, J.; Solan, G. A. *Tetrahedron* **2006**, *62*, 79. (b) Galaup, C.; Couchet, J. M.; Bedel, S.; Tisnes, P.; Picard, C. *J. Org. Chem.* **2005**, *70*, 2274. (c) Lee, S. H.; Jang, B. B.; Kafafi, Z. H. *J. Am. Chem. Soc.* **2005**, *127*, 9071. (d) Gronowitz, S.; Bjork, P.; Malm, J.; Hornfeldt, A.-B. *J. Organomet. Chem.* **1993**, *460*, 127. (e) Zoppellaro, G.; Enkelmann, V.; Geies, A.; Baumgarten, M. *Org. Lett.* **2004**, *6*, 4929. (f) Bour, C.; Suffert, J. *Org. Lett.* **2005**, *7*, 653. (g) Kim, D. H.; Ohshita, J.; Lee, K. H.; Kunugi, Y.; Kunai, A. *Organometallics* **2006**, *25*, 1511.
(15) (a) Arsenyan, P.; Ikaunieks, M.; Belyakov, S. *Tetrahedron Lett.* **2007**, *48*, 961. (b) Brill, W. K. D.; Riva-Toniolo, C. *Tetrahedron Lett.* **2001**, *42*, 6515. (c) Mamos, P.; Van Aerschot, A. A.; Weyns, N. J.; Herdewijn, P. A. *Tetrahedron Lett.* **1992**, *33*, 2413. (d) Kaucher, M. S.; Davis, J. T. *Tetrahedron Lett.* **2006**, *47*, 6381. (e) Chi, T.; Keane, C.; Eaton, B. E. *Nucleosides Nucleotides* **1995**, *14*, 1631. (f) Sessler, J. L.; Wang, B.; Harriman, A. *J. Am. Chem. Soc.* **1995**, *117*, 704. (g) Ozola, V.; Persson, T.; Gronowitz, S.; Horfeldt, A.-B. *J. Heterocycl. Chem.* **1995**, *32*, 863. (h) Moriarty, R. M.; Epa, W. R.; Awasthi, A. K. *Tetrahedron Lett.* **1991**, *31*, 5877.
(16) Suzuki couplings were performed according to the procedures outlined in ref. 8 and 10.
Analytical Data
Compound **2a**: yield 79% (391 mg, 1.14 mmol); mp 225 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.89 (br s, 1 H), 8.85

(d, J = 2 Hz, 1 H), 8.71 (dd, J = 5, 1 Hz, 1 H), 8.09 (dt, J = 8, 2 Hz, 1 H), 7.59 (dd, J = 8, 5 Hz, 1 H), 6.50 (s, 2 H), 6.06 (t, J = 7 Hz, 1 H), 5.19 (d, J = 5 Hz, 1 H), 4.96 (t, J = 6 Hz, 1 H), 4.33 (br m, 1 H), 3.80 (m, 1 H), 3.64 (m, 1 H), 3.53 (m, 1 H), 3.17 (m, 1 H), 2.08 (ddd, J = 13, 6, 2 Hz, 1 H). ^{13}C NMR (80 MHz, DMSO-d_6): δ = 174.1, 173.6, 153.7, 151.1, 149.6, 118.8, 115.9, 83.3, 79.8, 72.1, 61.1, 31.9, 31.2, 27.1, 16.5. IR (neat): 3206, 1677, 1631, 1560, 1244 cm^{-1}. Anal. Calcd for $C_{15}H_{16}N_6O_4$: C, 52.32; H, 4.68; N, 24.41. Found: C, 51.65; H, 4.73; N, 24.16.

Compound **2b**: white solid, yield 88% (164 mg, 304 μmol); mp 203 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.87 (s, 1 H), 8.05 (m, 1 H), 7.97 (m, 1 H), 7.94 (s, 1 H), 7.46 (m, 2 H), 6.59 (s, 2 H), 6.45 (t, J = 7 Hz, 1 H), 5.24 (d, J = 5 Hz, 1 H), 5.04 (t, J = 6 Hz, 1 H), 4.46 (m, 1 H), 3.88 (q, J = 9, 5 Hz, 1 H), 3.72 (m, 1 H), 3.62 (m, 1 H), 3.27 (m, 1 H), 2.15 (m, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 157.1, 153.7, 152.8, 141.9, 132.6, 129.3, 128.8, 128.6, 117.8, 88.5, 85.2, 71.8, 62.7, 37.1. IR (neat): 2928, 1679, 1631, 1101, 940 cm^{-1}.

Compound **2c**: grey solid, yield 81% (179.4 mg, 468.0 μmol). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.89 (br s, 1 H), 7.79 (br d, J = 7 Hz, 1 H), 7.70 (br d, J = 8 Hz, 1 H), 7.46 (br s, 1 H), 7.43 (br t, J = 8 Hz, 1 H), 7.36 (br t, J = 7 Hz, 1 H), 6.57 (br s, 2 H), 6.50 (t, 1 H), 5.25 (br s, 1 H), 4.97 (br s, 1 H), 4.45 (br s, 1 H), 3.85 (br s, 1 H), 3.68 (m, 1 H), 3.54 (m, 1 H), 3.23 (quin, J = 7 Hz, 1 H), 2.17 (br ddd, J = 7 Hz, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 157.1, 154.8, 154.0, 152.6, 146.5, 137.9, 128.2, 126.2, 124.2, 122.4, 118.3, 11.9, 108.5, 88.4, 84.9, 71.6, 62.5, 37.7. IR (KBr): 3144, 2949, 1678, 1566, 750 cm^{-1}.

(17) Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**, *43*, 6250.

(18) **General Procedure for a Microwave-Assisted Suzuki Coupling Using the Synthesis of Compound 2d as an Example**

Palladium(II) acetate (2.10 mg, 9.30 μmol), TPPTS (13.0 mg, 23.1 μmol), Na_2CO_3 (69.5 mg, 656 μmol) and 8-BrdG (125 mg, 345 μmol) were placed in a microwave reaction vessel. To this was added H_2O–MeCN–DMF (2:1:1). The corresponding boronic acid (0.5 equiv of **1d**) was added and the mixture irradiated with microwaves at 100 W, 120 °C with constant cooling for 5 min. The addition of the boronic acid and microwave irradiation was repeated until TLC revealed that the starting material was consumed. The reaction mixture was then poured into H_2O (25 mL) and pH was adjusted to 6–7 (0.1 M HCl). The precipitate formed was stirred at 0 °C for another 30 min, filtered, and dried in vacuo to give compound **2d** as a solid.

Analytical Data

Compound **2d**: yield 77% (88.2 mg, 265 μmol). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.81 (s, 1 H), 7.75 (d, J = 6 Hz, 1 H), 7.50 (d, J = 4 Hz, 1 H), 7.22 (dd, J = 5, 4 Hz, 1 H), 6.47 (s, 2 H), 6.27 (t, J = 8 Hz, 1 H), 5.20 (d, J = 5 Hz, 1 H), 4.96 (t, J = 5 Hz, 1 H), 4.39 (d, J = 3 Hz, 1 H), 3.83 (t, J = 3 Hz, 1 H), 3.64 (m, 1 H), 3.54 (m, 1 H), 3.33 (m, 1 H), 2.09 (m, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 156.9, 153.8, 153.0, 141.4, 140.1, 139.8, 132.9, 126.0, 125.3, 125.0, 122.7, 117.8, 88.3, 84.6, 71.2, 62.1, 31.1. IR (neat): 1687, 1612, 1437, 999 cm^{-1}.

Compound **2e**: yield 82% (98.8 mg, 283 μmol). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.11 (s, 1 H), 7.92 (s, 1 H), 6.96 (d, J = 4 Hz, 1 H), 6.70 (dd, J = 3, 2 Hz, 1 H), 6.56 (s, 2 H), 6.38 (t, J = 7 Hz, 1 H), 5.21 (d, J = 4 Hz, 1 H), 5.10 (br s, 1 H), 4.40 (br s, 1 H), 3.81 (t, J = 3 Hz, 1 H), 3.64 (m, 1 H), 3.51 (m, 1 H), 3.18 (m, 1 H), 2.10 (m, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 152.4, 145.0, 144.9, 138.2, 120.4, 118.2, 116.8, 112.6, 111.5, 88.6, 85.3, 71.9, 62.9, 37.8. IR (neat): 1688, 1619, 1527, 1446, 1379, 951 cm^{-1}.

Compound **2f**: grey solid, yield 94% (45 mg, 135 μmol). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.76 (br s, 1 H), 8.17 (s, 1 H), 7.86 (t, J = 1 Hz, 1 H), 6.87 (br d, J = 1 Hz, 1 H), 6.43 (br s, 2 H), 6.17 (t, 1 H), 5.22 (d, 1 H), 5.00 (t, 1 H), 4.40 (br dt, J = 3 Hz, 1 H), 3.81 (m, 1 H), 3.64 (m, 1 H), 3.55 (m, 1 H), 3.22 (q, J = 7 Hz, 1 H), 2.09 (ddd, J = 7, 3 Hz, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 157.3, 153.6, 152.6, 144.6, 143.3, 140.9, 117.6, 117.0, 111.6, 88.4, 84.7, 71.4, 62.5, 37.2. IR (KBr): 3341, 3143, 2919, 1678, 1568, 877 cm^{-1}.

(19) Esterifications were performed according to the procedures outlined in ref. 8.

Analytical Data

Compound **3a**: yield 89% (63.0 mg, 129 μmol); mp 126 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.0 (br s, 1 H), 8.88 (d, J = 2 Hz, 1 H), 8.74 (dd, J = 5, 1 Hz, 1 H), 8.10 (d, J = 8 Hz, 1 H), 7.68 (dd, J = 5, 8 Hz, 1 H), 6.61 (s, 2 H), 6.13 (t, J = 7 Hz, 1 H), 5.50 (q, J = 3 Hz, 1 H), 4.45 (dd, J = 11, 5 Hz, 1 H), 4.30 (dd, J = 11, 7 Hz, 1 H), 4.20 (m, 1 H), 3.57 (q, J = 7 Hz, 1 H), 2.57 (m, 2 H), 2.44 (q, J = 5 Hz, 1 H), 1.12 (d, J = 2 Hz, 1 H) 1.10 (s, 6 H), 1.08 (s, 3 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 176.0, 175.7, 156.7, 153.3, 152.1, 150.2, 139.3, 144.2, 136.5, 126.3, 123.6, 117.4, 84.72, 81.8, 74.7, 63.5, 34.0, 33.1, 33.0, 18.71, 18.68, 18.60, 18.59. IR (neat): 1727, 1689, 1627, 1150 cm^{-1}. Anal. Calcd for $C_{23}H_{28}N_6O_6$: C, 57.02; H, 5.82; N, 17.35. Found: C, 54.86; H, 5.99; N, 15.51.

Compound **3b**: yield 91% (128 mg, 237 μmol); mp 201 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.83 (s, 1 H), 8.01 (m, 1 H), 7.93 (m, 2 H), 7.42 (m, 2 H), 6.54 (s, 2 H), 6.41 (t, J = 7 Hz, 1 H), 5.00 (t, J = 6 Hz, 1 H), 4.42 (m, 1 H), 3.68 (m, 1 H), 3.57 (m, 1 H), 3.23 (m, 1 H), 2.53 (m, 2 H), 2.09 (m, 1 H), 1.10 (m, 6 H), 1.05 (m, 6 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 206.9, 175.8, 175.6, 156.9, 153.7, 153.0, 141.4, 140.1, 139.8, 132.9, 126.0, 125.3, 125.0, 122.7, 117.8, 88.3, 84.6, 71.2, 62.1, 37.2, 31.1, 18.5, 18.4. IR (neat): 1734, 1683, 1635, 1597, 1190, 1156 cm^{-1}. Anal. Calcd for $C_{26}H_{29}N_5O_6S$: C, 57.87; H, 5.42; N, 12.96. Found: C, 58.03; H, 5.67; N, 12.59.

Compound **3c**: yellow solid, yield 65% (133.8 mg, 256 μmol). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.04 (br s, 1 H), 7.78 (d, J = 7 Hz, 1 H), 7.69 (d, J = 8 Hz, 1 H), 7.44 (br s, 1 H), 7.43 (br t, J = 8 Hz, 1 H), 7.36 (t, J = 7 Hz, 1 H), 6.66 (br s, 2 H), 6.65 (m, 1 H), 5.56 (br d, 1 H), 4.45 (br d, 1 H), 4.28 (br d, 1 H), 4.24 (m, 1 H), 3.58 (br quin, 1 H), 2.61 (br quin, J = 7 Hz, 1 H), 2.50 (m, 1 H), 2.47 (m, 1 H), 1.14 (d, J = 7 Hz, 1 H), 1.05 (d, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 176.8, 176.5, 157.8, 155.0, 154.5, 152.8, 146.6, 138.1, 128.3, 126.42, 124.41, 122.6, 118.5, 112.0, 108.5, 85.3, 82.5, 75.3, 64.3, 35.2, 33.9, 33.8, 19.3, 19.3. IR (KBr): 3308, 3138, 2973, 2935, 2877, 1737, 1687, 1570, 1258, 751 cm^{-1}.

Compound **3d**: yield 89% (113 mg, 231 μmol); mp 134 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.85 (s, 1 H), 7.76 (d, J = 5 Hz, 1 H), 7.48 (d, J = 5 Hz, 1 H), 7.10 (dd, J = 5, 4 Hz, 1 H), 6.53 (s, 2 H), 6.32 (t, J = 7 Hz, 1 H), 5.50 (m, 1 H), 4.32 (m, 1 H), 4.30 (m, 1 H), 4.20 (m, 1 H), 3.64 (m, 1 H), 2.57 (m, 2 H), 2.43 (m, 1 H), 1.11 (m, 6 H), 1.05 (m, 6 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 176.6, 176.4, 157.1, 153.8, 152.7, 141.9, 132.5, 129.4, 128.7, 128.5, 117.7, 85.3, 82.5, 75.4, 64.1, 34.5, 33.7, 19.3. IR (neat): 1733, 1672, 1593, 1152 cm^{-1}. Anal. Calcd for $C_{22}H_{27}N_5O_6S$: C, 53.98, H, 5.56; N, 14.31. Found: C, 53.84; H, 6.01; N, 14.27.

Compound **3e**: yield 90% (111 mg, 234 μmol); mp 167 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.88 (s, 1 H), 7.90 (d, J = 5 Hz, 1 H), 6.96 (d, J = 5 Hz, 1 H), 6.69 (dd, J = 5, 4 Hz, 1 H), 6.54 (s, 2 H), 6.44 (t, J = 7 Hz, 1 H), 5.46 (m, 1 H), 4.40 (m, 1 H), 4.22 (m, 1 H), 4.16 (m, 1 H), 3.50 (m, 1 H), 2.57

(m, 2 H), 2.41 (m, 1 H), 1.12 (m, 6 H), 1.03 (m, 6 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 176.6, 176.3, 157.1, 153.9, 152.3, 145.1, 144.7, 138.4, 117.9, 112.9, 112.5, 85.1, 82.3, 75.3, 64.3, 35.0, 33.7, 19.3. IR (neat[1]): 1732, 1681, 1153, 1077, 764 cm^{-1}. Anal. Calcd for $C_{22}H_{27}N_5O_7$: C, 55.81; H, 5.75; N, 14.79. Found: C, 55.44; H, 6.02; N, 14.67.

Compound **3f**: yellow solid, yield 80% (228 mg, 481 μmol). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.83 (br s, 1 H), 8.14 (s, 1 H), 7.87 (t, *J* = 1 Hz, 1 H), 6.88 (d, *J* = 1 Hz, 1 H), 6.50 (br s, 2 H), 6.22 (t, 1 H), 5.49 (quin, *J* = 7, 4 Hz, 1 H), 4.40 (m, 1 H), 4.24 (m, 1 H), 4.19 (br ddd, *J* = 7 Hz, 1 H), 3.61 (quin, *J* = 7 Hz, 1 H), 2.59 (quin, *J* = 7 Hz, 1 H), 2.52 (br quin, *J* = 7 Hz, 1 H), 2.43 (ddd, *J* = 7, 4 Hz, 1 H), 1.12 (dd, *J* = 7 Hz, 1 H), 1.05 (dd, *J* = 7 Hz, 1 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 176.4, 176.2, 157.0, 153.5, 152.3, 144.6, 142.7, 140.8, 117.5, 116.7, 111.3, 84.8, 82.1, 75.1, 64.0, 34.4, 33.6, 33.6, 19.2, 19.2, 19.1, 19.1. IR (KBr): 1738, 1687, 1596, 1254, 875 cm^{-1}.

(20) **General Procedure for a Stille Coupling Using the Synthesis of Compound 4a as an Example**

3′,5′-*i*-Bu-8-Br*d*G (50.0 mg, 103 μmol), DPPP (6.35 mg, 15.4 μmol), $Pd(OAc)_2$ (3.45 mg, 15.4 μmol), Cu_2O (29.5 mg, 206 μmol), and NMP (490 μL) were mixed. After this, compound **6a** (115 mg, 206 μmol) was added to the mixture. The mixture was heated to 115 °C for 1 h after which HPLC analysis of the crude reaction mixture showed that the starting material was consumed. Therefore, the mixture was filtered through Celite and the solvents removed under reduced pressure. The product was isolated by column chromatography (50% EtOAc in Et_2O) yielding **4a** as a white solid.

Analytical Data

Compound **4a**: white solid, yield 74% (47.0 mg, 75.9 μmol); mp 169 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.89 (s, 1 H), 8.02 (m, 2 H), 7.58 (m, 2 H), 7.36 (m, 4 H), 7.30 (m, 1 H), 6.54 (s, 2 H), 5.46 (m, 1 H), 4.67 (q, *J* = 7 Hz, 1 H), 4.53 (s, 1 H), 4.51 (s, 1 H), 4.47 (m, 1 H), 4.31 (m, 1 H), 4.06 (m, 1 H), 3.59 (m, 1 H), 2.50 (m, 2 H), 2.34 (m, 1 H), 1.53 and 1.51 (d, *J* = 7 Hz, 3 H), 1.15–1.06 (m, 12 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 176.0, 175.5, 161.27, 156.6, 153.2, 152.7, 149.0, 143.7, 143.6, 138.4, 138.1, 128.19, 128.17, 127.39, 127.36, 122.3, 120.1, 117.3, 85.4, 81.4, 77.3, 74.9, 70.1, 63.6, 33.9, 33.1, 21.4, 21.3, 18.7, 18.6, 18.5. IR (neat): 1732, 1690, 1631, 1587, 1156 cm^{-1}. Anal. Calcd for $C_{32}H_{38}N_6O_7$: C, 62.12; H, 6.19; N, 13.58. Found: C, 60.88; H, 6.15; N, 12.98.

Compound **4b**: white solid, yield 80% (253 mg, 398 μmol); mp 209 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.89 (s, 1 H), 8.01 (m, 2 H), 7.55 (m, 2 H), 7.28 (d, *J* = 8 Hz, 2 H), 6.91 (d, *J* = 8 Hz, 2 H), 6.54 (s, 2 H), 5.45 (m, 1 H), 4.64 (m, 1 H), 4.48 (m, 1 H), 4.45 (d, *J* = 14 Hz, 1 H), 4.43 (d, *J* = 14 Hz, 1 H), 4.07 (m, 1 H), 3.58 (m, 1 H), 2.35 (m, 1 H), 1.49 (t, *J* = 6 Hz, 3 H), 1.09 (d, *J* = 7 Hz, 6 H), 1.07 (d, *J* = 7 Hz, 6 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 176.0, 175.6, 161.4, 158.7, 156.6, 153.2, 149.0, 143.6, 138.2, 130.3, 129.09, 129.07, 122.3, 120.1, 117.4, 113.59, 113.57, 85.4, 81.4, 76.94, 76.90, 74.9, 69.7, 63.7, 55.0, 48.4, 33.9, 33.1, 30.1, 29.0, 21.4, 21.3, 18.6, 18.53, 18.49, 17.2. IR (neat): 1724, 1681, 1635, 1566, 1153, 817 cm^{-1}. Anal. Calcd for: $C_{33}H_{40}N_6O_8$: C, 61.10; H, 6.22; N, 12.96. Found: C, 60.61; H, 6.20; N, 12.88.

Compound **4c**: white solid, yield 60% (192 mg, 302 μmol); mp 182 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.91 (s, 1 H), 8.00 (m, 2 H), 7.54 (m, 2 H), 7.33 (d, *J* = 8 Hz, 2 H), 6.93 (d, *J* = 8 Hz, 2 H), 6.57 (s, 2 H), 5.50 (m, 1 H), 4.65 (s, 2 H), 4.58 (s, 2 H), 4.88 (dd, *J* = 12, 6 Hz, 1 H), 4.29 (dd, *J* = 12, 7 Hz, 1 H), 4.09 (m, 1 H), 3.76 (s, 3 H), 3.50 (m, 1 H), 2.52 (m, 2 H), 2.35 (m, 1 H), 1.10 (d, *J* = 7 Hz, 6 H) 1.07 (d, *J* = 7 Hz, 6 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 176.0, 175.5, 158.8, 157.3, 156.7, 153.3, 152.7, 149.1, 143.5, 138.1, 130.0, 129.2, 122.4, 121.1, 117.3, 113.7, 85.1, 81.4, 74.8, 71.9, 71.6, 63.8, 55.0, 34.4, 33.12, 33.09, 18.7, 18.6. IR (neat): 1734, 1691, 1629, 1588, 1571, 1249 cm^{-1}. Anal. Calcd for $C_{32}H_{38}N_6O_8$: C, 60.56; H, 6.03; N, 13.24. Found: C, 60.65; H, 6.00; N, 13.12.

Compound **4d**: white solid, yield 61% (187 mg, 305 μmol); mp 193 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.88 (s, 1 H), 7.99 (m, 2 H), 7.56 (t, *J* = 7 Hz, 1 H), 7.47 (d, *J* = 7 Hz, 1 H), 6.55 (br s, 2 H), 5.50 (m, 1 H), 4.59 (s, 1 H), 4.47 (dd, *J* = 12, 6 Hz, 1 H), 4.26 (dd, *J* = 12, 7 Hz, 1 H), 4.09 (m, 1 H), 3.66 (t, *J* = 8 Hz, 2 H), 3.49 (m, 1 H), 2.60 (m, 1 H), 2.52 (m, 1 H), 2.37 (m, 1 H), 1.14 (dd, *J* = 7, 3 Hz, 6 H), 1.06 (d, *J* = 7 Hz, 6 H), 0.99 (t, *J* = 8 Hz, 2 H), 0.03 (s, 9 H). ^{13}C NMR (125 MHz; DMSO-d_6): δ = 175.9, 175.5, 157.6, 156.6, 153.3, 152.7, 148.9, 143.5, 138.0, 122.2, 120.6, 117.3, 85.1, 81.4, 74.8, 72.4, 67.6, 63.8, 34.5, 33.2, 33.1, 18.69, 18.65, 17.7, –1.30. IR (neat): 1731, 1671, 1564, 1460, 1189 cm^{-1}. Anal. Calcd for $C_{29}H_{42}N_6O_7Si$: C, 56.66; H, 6.89; N, 13.67. Found: C, 56.59; H, 6.89; N, 12.85.