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An Expedient Synthesis of the Fibril Binding Compound FSB via Sequential Pd-Catalyzed Coupling Reactions

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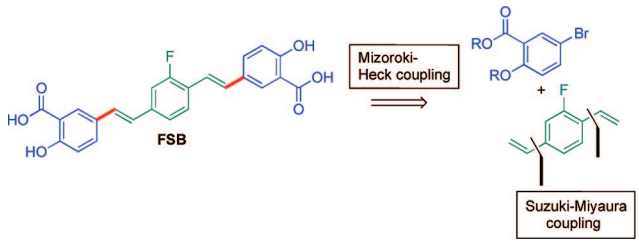
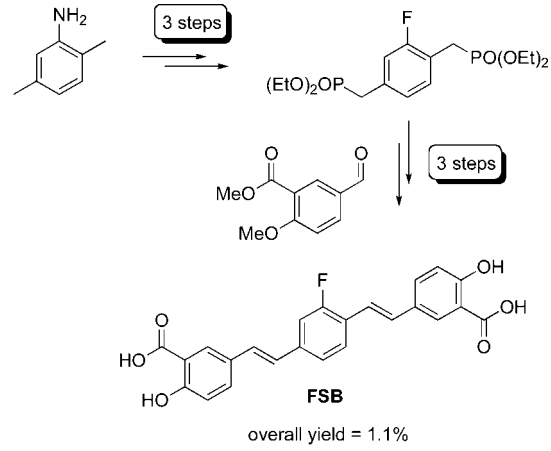
Received December 7, 2007



The styryl benzene derivative (*E*,*E*)-1-fluoro-2,5-bis(3-hydroxycarbonyl-4-hydroxy)styrylbenzene (FSB), well-known for its binding to β-amyloid peptide fibrils, was synthesized in an efficient manner exploiting two sequential palladium(0)-catalyzed coupling reactions in a 34% overall yield. This is a substantial improvement to the previously reported synthesis of FSB in 1.1%.

Alzheimer's disease (AD) is a form of senile dementia, which represents the third most prevalent disorder affecting senior citizens. AD is a fatal disorder resulting in the destruction of neuronal tissue in the brain and hence loss of memory, consciousness, and intellectual activity. The fibrillation and deposition of β-amyloid peptides (βAP1-40 and βAP1-42) into amyloid plaques has generally been accepted as the principle cause of AD.[1] Recently, (*E*,*E*)-1-fluoro-2,5-bis(3-hydroxycarbonyl-4-hydroxy)styrylbenzene (FSB) has emerged as a potential marker for detecting brain amyloids in mice by magnetic resonance imaging.[2–5] This work holds promise for developing effective probes for detection and monitoring changes in plaque sizes and distribution in living AD patients upon treatment with potential AD drugs, which target such β-amyloid plaques.[6]

SCHEME 1. Previously Reported Synthesis of FSB



The previous synthesis of FSB requires six steps in the longest linear sequence starting from dimethylaniline with a total yield of only 1.1% (Scheme 1).[3] A low-yielding Wittig–Horner reaction was exploited as the key assembling step. We have recently been interested in studying the binding and sequence selectivity of this fibril binding compound to a variety of peptide-based fibrils. We therefore required a more effective synthesis of FSB, as well as one that displays greater flexibility to the introduction of variations into the FSB structure. Considering the high unsaturated nature of this compound, as well as the substitution pattern of the two identical alkenes, we approached the synthesis of FSB exploring the use of two palladium(0)-catalyzed coupling reactions. In this Note, we report on a greatly improved synthesis of FSB exploiting this methodology to afford the fibril binding compound in only three linear steps.

The retrosynthetic analysis of FSB suggested two possible routes for accessing this styryl benzene by a Mizoroki−Heck coupling as indicated in Scheme 2. Route a proposes a double Pd(0)-catalyzed coupling between the vinyl benzoic acid derivative **1** and 1,4-dibromo-2-fluorobenzene (**2**).[7] Installation of the vinyl group in the former compound was envisaged to take place via a Suzuki−Miyaura cross-coupling with the aryl halide **3** or Mizoroki−Heck coupling from a corresponding triflate with vinyl acetate.[8] An alternative approach to FSB would proceed through the Mizoroki−Heck coupling of the bromide **3** with divinyl benzene **4** (route b). Similarly, the Mizoroki−Heck acceptor **4** could potentially be accessed from 1,4-dibromo-2-fluorobenzene (**2**) through the use of a Suzuki−Miyaura vinylation step.

(1) For some recent reviews, see: (a) Selkoe, D. J. *Nat. Biotechnol.* **2000**, *18*, 823. (b) Hardy, J. *J. Alzheimer's Dis.* **2006**, *9*, 151. (c) Goedert, M.; Spillantini, M. G. *Science* **2006**, *314*, 777.

(2) Skovronsky, D. M.; Zhang, B.; Kung, M.-P.; Kung, H. F.; Trojanowski, J. Q.; Lee, V. M.-Y. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 7609.

(3) Sato, K.; Higuchi, M.; Iwata, N.; Saito, T. C.; Sasamoto, K. *Eur. J. Med. Chem.* **2004**, *39*, 573.

(4) Higuchi, M.; Iwata, N.; Matsuba, Y.; Sato, K.; Sasamoto, K.; Saido, T. C. *Nat. Neurosci.* **2005**, *8*, 527.

(5) Masuda, M.; Suzuki, N.; Taniguchi, S.; Oikawa, T.; Nonaka, T.; Iwatsubo, T.; Hisanaga, S.-i.; Goedert, M.; Hasewaga, M. *Biochemistry* **2006**, *45*, 6085.

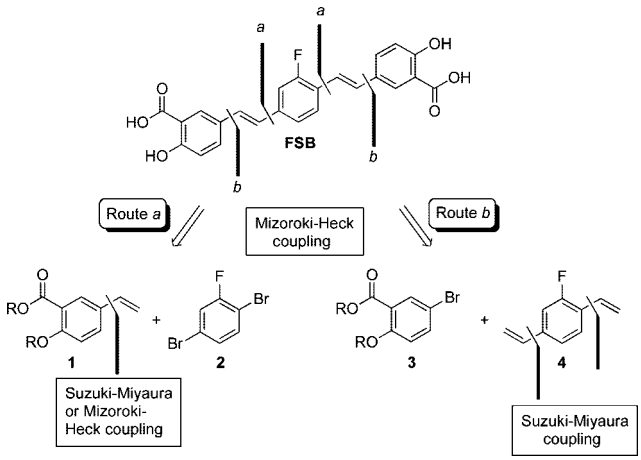
(6) Qu, W.; Kung, M.-P.; Hou, C.; Oya, S.; Kung, H. F. J. Med. Chem. **2007**, *50*, 3380 and references cited therein.

(7) For some recent reviews on the Heck reaction, see: (a) Heck, R. F. *Synlett* **2006**, 2855. (b) Phan, N. T. S.; Van Der Sluys, M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609. (c) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2005**, *61*, 11771.

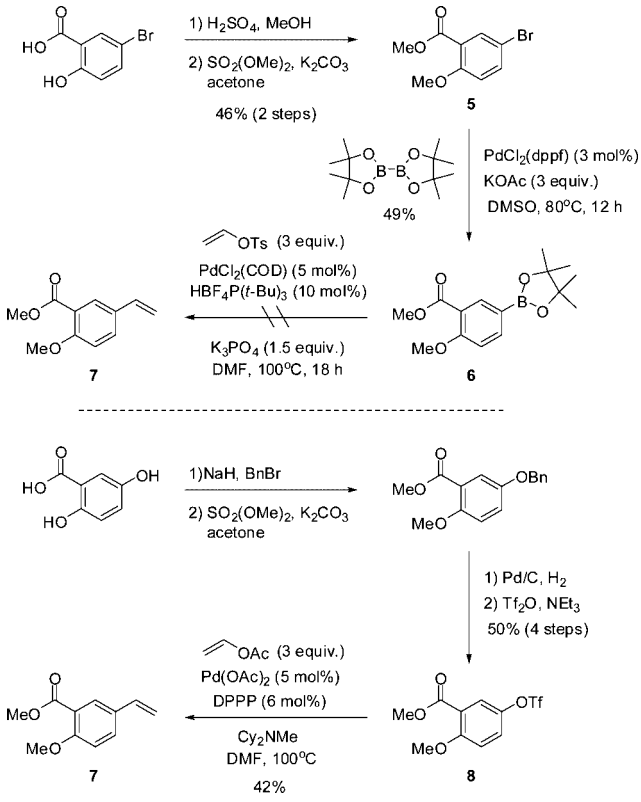
(8) For some recent reviews on the Suzuki−Miyaura reaction, see: (a) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633. (b) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419. (c) Nam, T. S. P.; Matthew, V.; Christopher, W. J. *Adv. Synth. Catal.* **2006**, *348*, 609.

10.1021/jo7026189 CCC: $40.75 © 2008 American Chemical Society
Published on Web 03/26/2008

SCHEME 2. Retrosynthetic Analysis of FSB

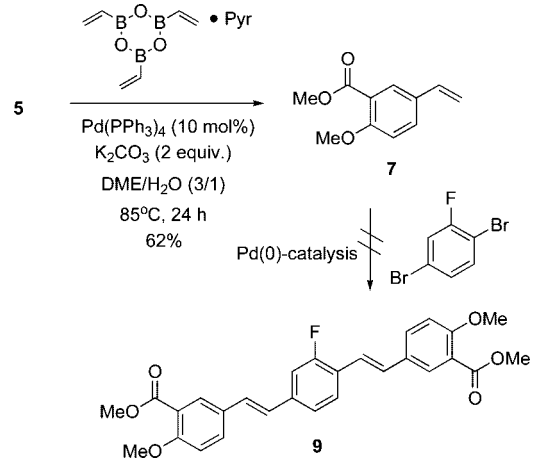


SCHEME 3. Preparation of Styrene 7



Initial efforts to access FSB via a more efficient synthesis were focused on route a (Scheme 2). This required the introduction of a vinyl group onto a salicylic acid derivative, which was pursued by means of three approaches. In the first case, 5-bromosalicylic acid was transformed to its methyl ester under Fischer conditions followed by methylation of the hydroxyl group furnishing the protected aryl bromide **5** (Scheme 3). Palladium-catalyzed boronation with bis(pinacolato)diboron afforded the boron ester **6** in 49% yield.[9] However, several attempts to cross-couple **6** with the vinyl tosylate to the disubstituted styrene **7** with an electron-rich Pd(0)-complex were unsuccessful.[10] Alternatively, **7** was prepared by using a

SCHEME 4. Coupling Attempts with Styrene 7



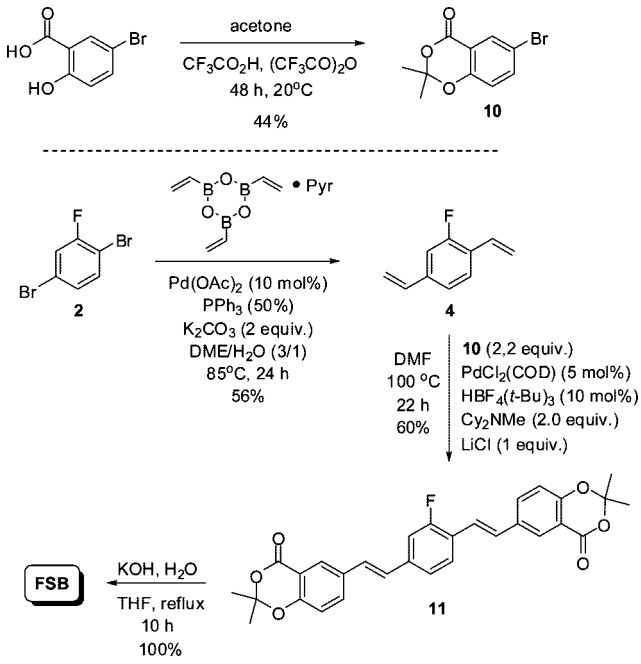
Mizoroki−Heck coupling approach from an aryl triflate.[11] Transformation of 5-hydroxysalicylic acid to the triflate **8** could be achieved in four steps in a 50% overall yield. Subsequent Mizoroki−Heck coupling with vinyl acetate in the presence of palladium acetate and the ligand dppp provided the required styrene **7**, though in a modest yield.[11]

Not quite satisfied with the efficiency of the synthesis of **7**, we finally resorted to a more practical route to this alkene, involving the direct Pd(0)-promoted Suzuki−Miyaura coupling of bromide **5** with the 2,4,6-trivinylcyclotriboroxane·pyridine complex in refluxing DME/H_2O (Scheme 4).[12] In this way, **7** could be secured in a 62% yield. The successful preparation of this styrene derivative was nevertheless overshadowed by its reluctance to couple with 1,4-dibromo-2-fluorobenzene (**2**) under a variety of conditions including those reported by Fu and Littke[13] using $Pd(OAc)_2$ and P(*t*-Bu)$_3$ and Jeffery with $Pd(OAc)_2$/K_2CO_3/Bu_4NBr.[14] In these cases, the reactions failed to proceed with no indication of the formation of the tetramethylated derivative **9** of FSB.

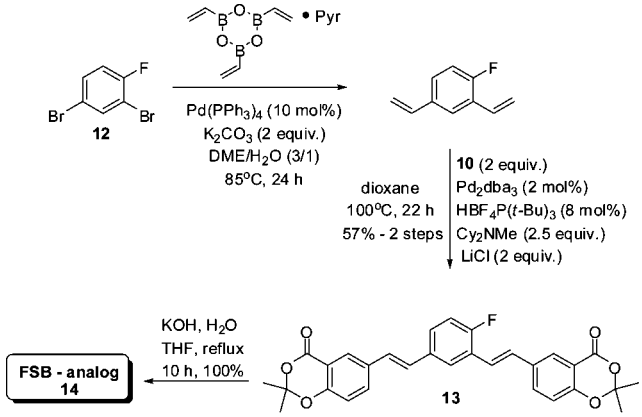
To overcome these problems, we proceeded to examine route b, as illustrated in Scheme 5. In this case, 5-bromosalicylic acid was first converted to the acetal ester **10**,[15] thereby simplifying the deprotection of the hydroxyl and carboxylic acid groups at the end of the synthesis. Vinylation of 1,4-dibromo-2-fluorobenzene with trivinylcyclotriboroxane, using slightly modified conditions of a previously reported method,[12] provided the required 2,5-divinyl-1-fluorobenzene **4** in a 56% yield. Mizoroki−Heck coupling of **4** with 2.2 equiv of the bromide **10** did not take place under previously reported conditions with use of a bulky phosphine ligand (Pd_2dba_3, P(*t*-Bu)$_3$, Cy_2NMe in dioxane at 40 °C).[13] However, after some experimentation it was found that by adding lithium chloride to the reaction mixture in DMF and raising the reaction temperature to 100 °C, an acceptable 60% yield of the protected FSB **11** was obtained. Changing the phosphine ligand to X-Phos and P(*o*-Tol)$_3$, for example, or application of the conditions developed by Jeffery[11] did not improve the yield of this Mizoroki−Heck step. Furthermore, coupling with the iodide derivative of **10** did provide full

(9) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508.
(10) (a) Hansen, A. L.; Ebran, J.-P.; Gøgsig, T.; Skrydstrup, T. *J. Org. Chem.* **2007**, *72*, 6464. (b) Hansen, A. L.; Ebran, J.-P.; Ahlquist, M.; Norrby, P.-O.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3349.
(11) Cabri, W.; Candiani, I.; Bedeschi, A. *J. Org. Chem.* **1992**, *57*, 3558.
(12) Kerins, F.; O'Shea, D. F. *J. Org. Chem.* **2002**, *67*, 4968.
(13) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989.
(14) Diez-Barra, E.; García-Martínez, J. C.; Merino, S.; del Ray, R.; Rodríguez-Lopez, J.; Sánchez-Verdú, P.; Tejeda, T. *J. Org. Chem.* **2001**, *66*, 5664.
(15) Bajwa, N.; Jennings, M. P. *J. Org. Chem.* **2006**, *71*, 3646.

SCHEME 5. Synthesis of FSB



SCHEME 6. Synthesis of FSB Analogue



conversion, but afforded a complex mixture of products as observed by NMR analysis of the crude reaction mixture. Finally, a deprotection step with KOH/H_2O in refluxing THF provided a quantitative yield of FSB in an overall yield of 34%.

Next we decided to test this three-step protocol in the synthesis of the FSB analogue (*E*,*E*)-1-fluoro-2,4-bis(3-hydroxycarbonyl-4-hydroxy)styrylbenzene, the results of which are shown in Scheme 6. Applying the previously reported method for the vinylation of 1,3-dibromo-4-fluorobenzene (**12**), using the 2,4,6-trivinylcyclotriboroxane·pyridine complex, afforded the desired 1-fluoro-2,4-divinylbenzene. Mizoroki−Heck coupling with 2 equiv of **10** to 1-fluoro-2,4-divinylbenzene in dioxane as the solvent provided the analogue-precursor **13** in a 57% isolated yield over two steps. Once again deprotection with KOH in refluxing THF/H_2O allowed for the quantitative isolation of the desired FSB-analogue **14** providing an excellent overall yield of 57%.

In summary, we have reported on a greatly improved synthesis of FSB in three linear steps with an overall yield of 34% from 1,4-dibromo-2-fluorobenzene (26% from 5-bromosalicylic acid) exploiting two palladium-catalyzed coupling reactions in comparison to the 1.1% overall yield previously reported in six steps. Additionally an FSB analogue was prepared applying the developed method in an overall yield of 57% proving the adaptability of the reported protocol. Further work is now underway to make use of this synthetic route for the preparation of alternative analogues of FSB and to study their fibril binding properties. In addition, studies are currently in progress to examine the amino acid sequence selectivity of FSB with a variety of fibril structures. These results will be reported in due course.

Experimental Section

2-Fluoro-1,4-divinylbenzene (4). 1,4-Dibromo-2-fluorobenzene (102 mg, 0.394 mmol), $Pd(OAc)_2$ (8.92 mg, 0.039 mmol), PPh_3 (27 mg, 0.197 mmol), K_2CO_3 (110 mg, 0.788 mmol), and 2,4,6-trivinylcyclotriboroxane·pyridine complex (95 mg, 0.39 mmol) were added to a sample vial in a glovebox. DME (3.5 mL) and H_2O (1 mL) were then added and the sample vial was fitted with a Teflon sealed screwcap and removed from the glovebox. The reaction mixture was heated to 85 °C for 24 h and then cooled to 20 °C; H_2O (5 mL) was added and the crude reaction was extracted with ether (3 × 20 mL). The combined organic phases were washed with H_2O (2 × 15 mL) and brine (2 × 10 mL). The organic phase was dried over $MgSO_4$. After concentration in vacuo at 20 °C, the crude product was purified by flash chromatography on silica gel with pentane as eluent. This afforded 33 mg of the title compound (56% yield) as a clear colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.44 (t, 1H, J = 8 Hz), 7.14 (dd, 1H, J = 2, 8 Hz), 7.09 (dd, 1H, J = 2, 11.6 Hz), 6.85 (dd, 1H, J = 11.2, 17.6 Hz), 6.66 (dd, 1H, J = 10.8, 17.6 Hz), 5.82 (dd, 1H, J = 1.2, 17.6 Hz), 5.75 (d, 1H, J = 17.6 Hz), 5.36 (dd, 1H, J = 1.2, 11.2 Hz), 5.29 (d, 1H, J = 10.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.9, 159.4, 139.2, 139.1, 135.8, 129.3, 127.3, 124.9, 122.3, 116.5, 115.3, 113.3, 113.0. ^{19}F NMR (377 MHz, $CDCl_3$) δ (ppm) –119.5. GCMS $C_{10}H_9F$ [M^+] calcd 148, found 148.

6-Bromo-2,2-dimethylbenzo[1,3]dioxin-4-one (10). 5-Bromosalicylic acid (0.5 g, 2.3 mmol) in trifluoroacetic acid (3.45 mL, 20 mmol) was cooled to 0 °C. Trifluoroacetic anhydride (3.2 mL, 10 mmol) and acetone (0.5 mL, 6.9 mmol) were added and the mixturewas reacted for 48 h at 20 °C. The crude reaction mixture was concentrated in vacuo, quenched with saturated $NaHCO_3$, and extracted with EtOAc (3 × 25 mL). The combined organic phases were washed with water (2 × 25 mL) and brine (2 × 25 mL). The organic phase was dried over $MgSO_4$. After concentration in vacuo the crude product was purified by flash chromatography on silica gel with EtOAc/pentane 1:19 as eluent. This afforded 258 mg of the title compound (44% yield) as a white solid. Mp 65.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.08 (d, 1H, J = 2.4 Hz), 7.64 (dd, 1H, J = 2.4, 8.8 Hz), 6.87 (d, 1H, J = 8.8 Hz), 1.73 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.0, 155.1, 139.3, 132.2, 119.3, 115.2, 115.0, 107.0, 26.0, 25.9. HRMS $C_{10}H_9BrO_3$ [M + Na^+] calcd 278.9633, found 278.9633.

(*E*,*E*)-1-Fluoro-2,5-bis(2,2-dimethylbenzo[1,3]dioxin-4-one)styrylbenzene (11). 10 (80.2 mg, 0.31 mmol), $HBF_4P(t\text{-}Bu)_3$ (4.0 mg, 0.014 mmol), lithium chloride (6.0 mg, 0.14 mmol), and Cy_2NMe (61 μL, 0.28 mmol) were added to a sample vial in a glovebox. **4** (21.0 mg, 0.14 mmol) in DMF (1 mL) and $PdCl_2(COD)$ (2.0 mg, 0.007 mmol) in DMF (2 mL) were then added and the sample vial was fitted with a Teflon sealed screwcap and removed from the glovebox. The reaction mixture was reacted for 22 h at 100 °C and then allowed to cool to 20 °C. Et_2O (70 mL) was added and the crude reaction mixture was washed with water (4 × 50 mL) and brine (1 × 50 mL). The organic phase was dried over Na_2SO_4. After concentration in vacuo the crude product was purified by flash chromatography on silica gel with CH_2Cl_2 as eluent. Recrystallization in CH_2Cl_2 afforded 43 mg of the title compound (60% yield) as colorless crystals. Mp 280 °C dec. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.12 (d, 1H, J = 2.0 Hz), 8.11 (d, 1H, J = 2.0 Hz), 7.74

(dd, 1H, $J = 2.0, 8.8$ Hz), 7.67 (dd, 1H, $J = 2.0, 8.8$ Hz), 7.56 (t, 1H, $J = 8.0$ Hz), 7.28–7.04 (m, 6H), 6.99 (d, 2H, $J = 8.8$ Hz), 1.76 (s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.1, 161.2, 159.6, 155.7, 138.44, 138.35, 134.6, 134.5, 132.5, 132.0, 128.91, 128.86, 127.9, 127.80, 127.77, 127.6, 127.5, 127.4, 124.4, 124.3, 122.9, 122.8, 121.4, 121.3, 117.81, 117.79, 113.92, 113.89, 113.5, 113.3, 106.79, 106.76, 26.0 (4C). ^{19}F NMR (377 MHz, $CDCl_3$) δ (ppm) –118.0. HRMS $C_{30}H_{25}FO_6$ [M + Na^+] calcd 523.1533, found 523.1537.

(*E*,*E*)-1-Fluoro-2,5-bis(3-hydroxycarbonyl-4-hydroxy)styrylbenzene (FSB)[3]. Potassium hydroxide (7.6 mg, 0.14 mmol) in H_2O (1.5 mL) was added to a solution of **11** (13.5 mg, 0.03 mmol) in THF (3 mL) and the reaction mixture was refluxed for 10 h at 85 °C and then allowed to cool to 20 °C. The crude suspension was acidified (pH ~1) with HCl (2 M) and the precipitated solid was collected and washed several times with water. Hot acetonitrile was used to transfer the solid to a flask and coevaporation with toluene and chloroform afforded 11.2 mg of FSB (quantitative yield) as a yellow powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.00 (d, 1H, $J = 2$ Hz), 7.98 (d, 1H, $J = 2$ Hz), 7.83 (dd, 1H, $J = 2, 8.8$ Hz), 7.79 (dd, 1H, $J = 2, 8.4$ Hz), 7.76 (t, 1H, $J = 8.4$ Hz), 7.47 (dd, 1H, $J = 1.6, 8.4$ Hz), 7.43 (dd, 1H, $J = 1.6, 14$ Hz), 7.34 (d, 1H, $J = 16.4$ Hz), 7.33 (d, 1H, $J = 16.4$ Hz), 7.14 (d, 1H, $J = 16.4$ Hz), 7.13 (d, 1H, $J = 16.4$ Hz), 6.984 (d, 1H, $J = 8.4$ Hz), 6. 977 (d, 1H, $J = 8.8$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 171.7, 171.6, 161.1, 161.0, 158.6, 138.6, 133.0, 132.9, 129.7, 128.8, 128.7, 128.2, 128.1, 127.3, 125.3, 123.5, 123.4, 122.8, 118.2, 117.73, 117.67, 113.6, 112.9, 112.7. ^{19}F NMR (377 MHz, DMSO-d_6) δ (ppm) –119.2.

Acknowledgment. We are grateful for generous financial support from the Danish National Research Foundation, the Carlsberg Foundation, the Lundbeck Foundation, and the University of Aarhus.

Supporting Information Available: Experimental details and copies of ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra for compounds **4**, **10**, **11**, **FSB**, **13**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO7026189