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A Versatile Approach to β-Amyloid Fibril-Binding Compounds Exploiting the Shirakawa/Hayashi Protocol for *trans*-Alkene Synthesis

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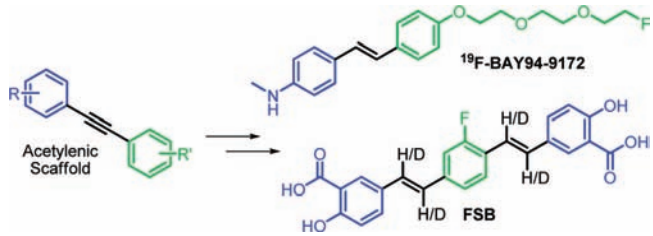
ABSTRACT



Application of the Sonogashira coupling reaction followed by a *trans*-selective alkyne reduction proved highly adaptable for the efficient synthesis of a class of β-amyloid fibril binding compounds possessing a styrylbenzene motif such as FSB, an FSB dimer, and ^{19}F-BAY94-9172.

In recent years, there has been high interest for the development of imaging agents for β-amyloid plaque detection as a diagnostic tool for Alzheimer's disease (AD).[1] The ability to visually detect Alzheimer's plaques is vital for preclinical and clinical drug development programs focused on the treatment of this dementia disease.[2,3] Positron emission tomography (PET) and magnetic resonance imaging (MRI) represent viable detection techniques for plaque identification via the exploitation of specifically isotope-labeled fibril-binding compounds. A promising class of such binders are the styrylbenzene derivatives as illustrated in Scheme 1, such as (*E*,*E*)-1-fluoro-2,5-bis(3-carboxy-4-hydroxystyryl)benzene (FSB)[3b−d] and (*E*)-4-(4-(2-(2-(2-fluoroethoxy)ethoxy)ethoxy)-styryl)-*N*-methylaniline (BAY94-9172), the latter of which has entered phase II clinical studies as an AD detection agent for PET studies.[4]

We have recently reported on a short synthesis of FSB exploiting the Mizoroki−Heck reaction as a key assembly step for the bis-styrylbenzene construction.[5] Although FSB was produced in an overall yield of 34%, we felt the synthesis

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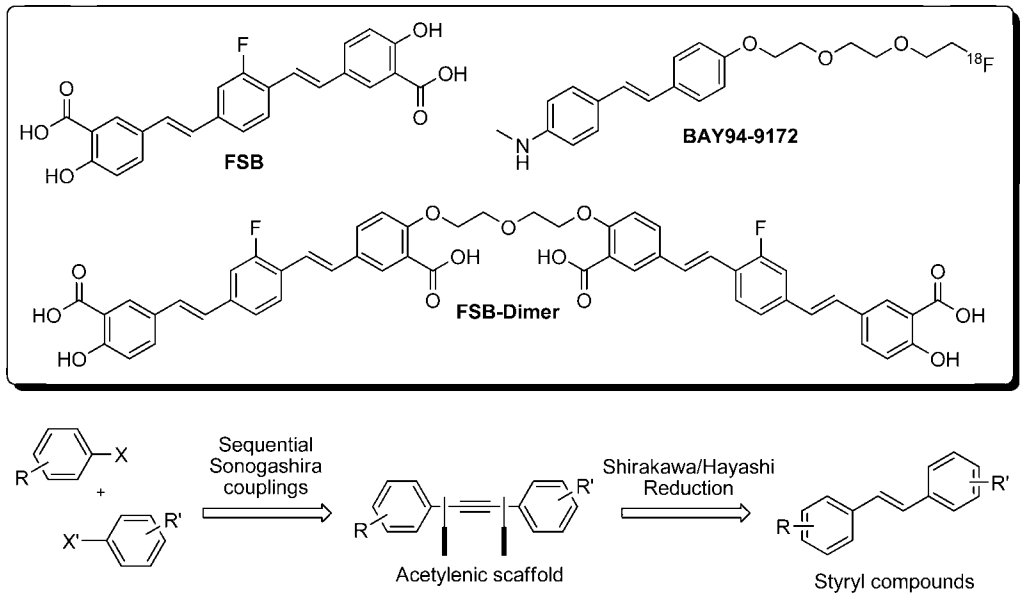
Scheme 1. β-Amyloid Fibril-Binding Compounds



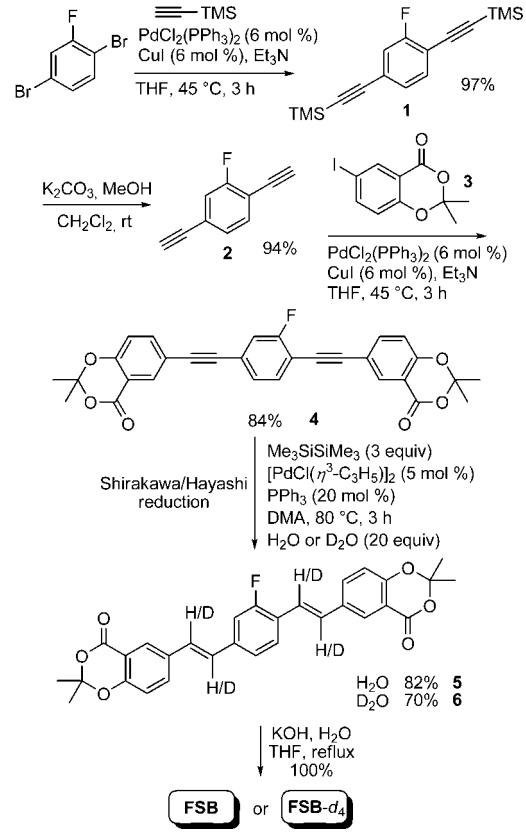
could be improved as well as modified to be flexible enough to allow for the introduction of alternative isotope labeling. In this paper, we demonstrate a highly effective synthesis of FSB, an FSB dimer, and BAY94-9172 through a common assembly strategy (Scheme 1) exploiting a sequence of Sonogashira coupling steps and an ensuing stereoselective alkyne reduction to the corresponding *trans*-alkene with water as the hydrogen source.

To evaluate the efficiency of the Sonogashira/reduction protocol for the installation of the *trans*-alkene functionalities in the fibril-binding compounds, this approach was first tested on the synthesis of FSB as shown in Scheme 2.

Coupling of 1,4-dibromo-2-fluorobenzene with TMS-acetylene exploiting traditional Sonogashira coupling conditions provided the bis-acetylene **1** in near-quantitative yield.[6] Liberation of the acetylenes to **2** was accomplished with potassium carbonate in methanol (94%),[7] which was followed by a second Sonogashira double coupling with the acetal derivative of 4-iodosalicylic acid **3** providing compound **4** in 84% yield.

For the stereoselective reduction of the disubstituted alkynes to the *trans*-olefins, we examined a recently reported method by Shirakawa and Hayashi.[8] In this protocol, the reduction is catalyzed by a Pd(II) source in the presence of hexamethyldisilane and remarkably with H_2O as the hydrogen source. This reduction step performed admirably with **4** providing the protected FSB **5** in 82% yield with no sign of any of the potential cis isomers. Although the original Shirakawa/Hayashi protocol called for 1.5 equiv of $Me_3SiSiMe_3$ and 2.5 equiv of H_2O, the simultaneous reduction of the two acetylenes required 5 equiv of the disilane

Scheme 2. Synthesis of FSB



(6) For some references on the Sonogashira reaction, see: (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874. (c) Sasaki, T.; Morin, J.-F.; Lu, M.; Tour, J. M. *Tetrahedron Lett.* **2007**, *48*, 5817. (d) Yi, C.; Hua, R. *J. Org. Chem.* **2006**, *71*, 2535. (e) Köllhofer, A.; Pullmann, T.; Plenio, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1056, and references therein.

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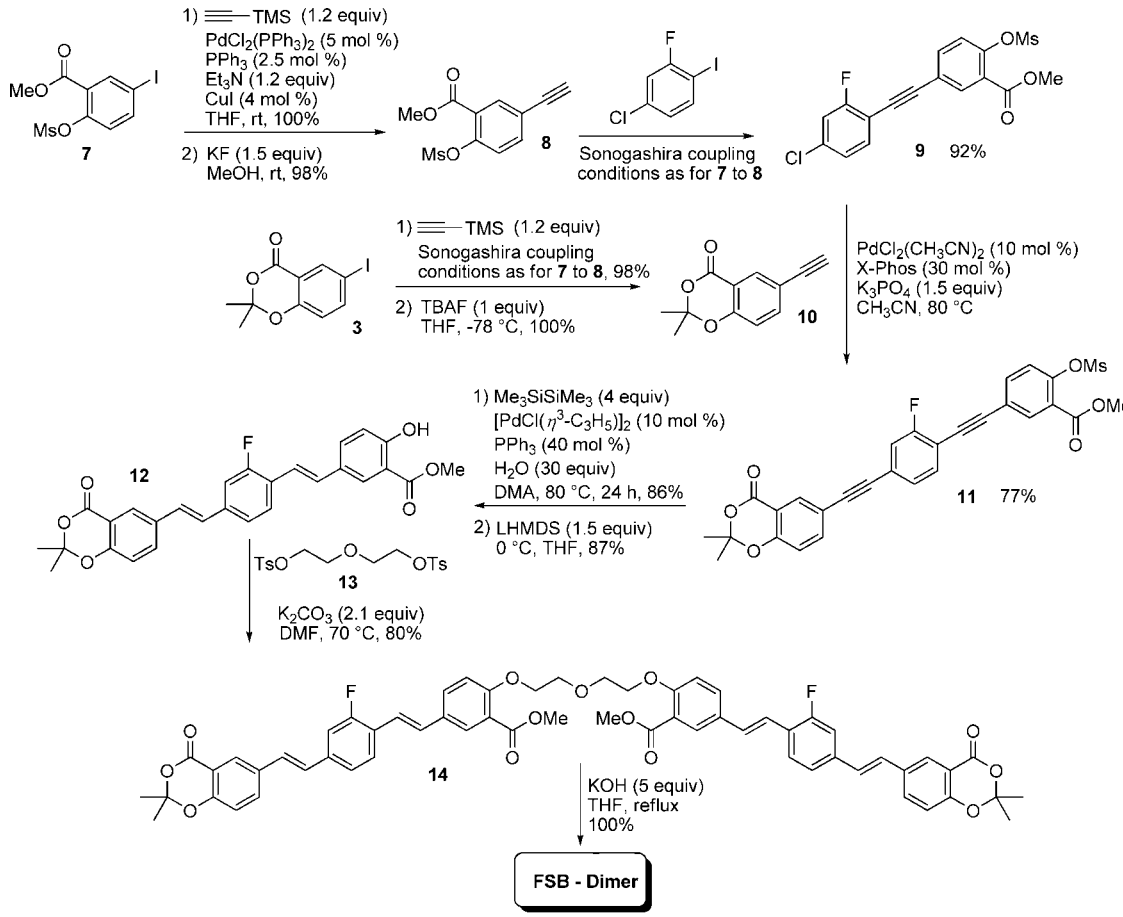
Scheme 3. Synthesis of FSB Dimer



and 20 equiv of water for effective reduction. More importantly, the method is sufficiently flexible to allow for the preparation of the corresponding tetradeuterated derivative of **6** by simply replacing water with D_2O. Undoubtedly, this approach would also represent a viable method for the facile introduction of tritium in such compounds.

Finally, a quantitative deprotection of **5** under basic conditions provided FSB in an overall yield of 63% for the five steps. This synthetic route to FSB is a substantial improvement of other reported syntheses of FSB.[3b,5]

In work directed toward the investigation of FSB's binding selectivity with β-amyloid fibrils, we became interested in developing an approach to access FSB dimers constructed around a poly(ethylene glycol) spacer of varying lengths such as the one depicted in Scheme 1. These compounds could be exploited in binding studies with the fibril structure as a means of determining distances between FSB binding sites. Although a synthetic route based on the above FSB synthesis could be applied, it nevertheless requires that the two aryl hydroxyl groups are distinguished for selective functionalization. This in turn necessitates two sequential Sonogashira couplings in order to introduce the two functionally different salicylic acid derivatives to the central aromatic core. An example of a synthesis of an FSB dimer with a diethylene glycol linker is illustrated in Scheme 3.

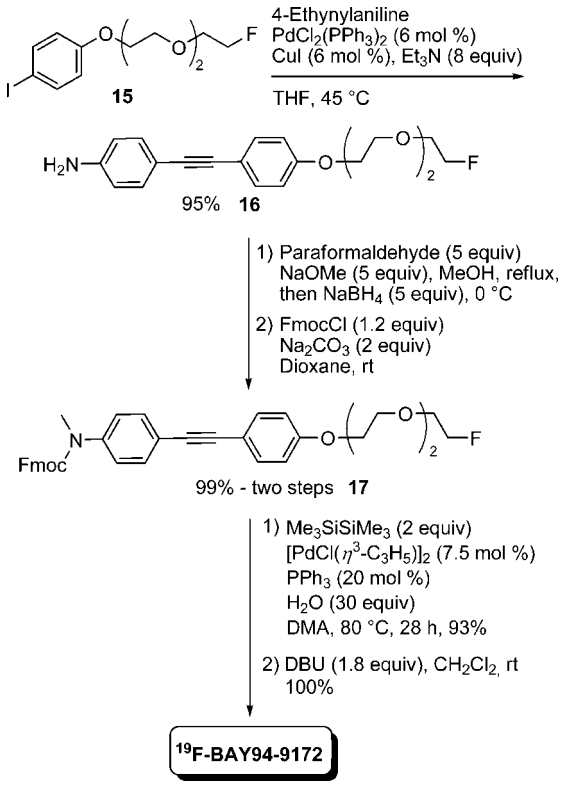
The synthesis of the FSB-dimer began with 4-iodosalicylic acid, which was easily converted to the mesylate **7** in two steps. Pd-catalyzed coupling with TMS-acetylene provided in nearly quantitative yield the terminal alkyne **8** after a desilylation step. Subsequent Sonogashira coupling with 4-chloro-2-fluoro-1-iodobenzene provided the diaryl acetylene **9** in a 92% yield. This compound could in turn be subjected to a third Sonogashira coupling with the acetylene **10** prepared from the salicylic acid derivative **3** in two steps. More demanding coupling conditions were required in this case due to the need of an aryl chloride, but the use of Buchwald's conditions performed well providing the diacetylene **11** in a 77% yield.[9] Application of the alkyne reduction step again proved effective (86% yield), leading to the protected FSB derivative. Longer reaction time (24 h) and 30 equiv of H_2O were nevertheless required for obtaining a high yield of the bis-styrylbenzene.

The final steps in the synthesis of the FSB dimer initially require a selective deprotection of one of the two phenolic hydroxy groups. Gratifyingly, this could be accomplished by means of short treatment with 1.5 equiv of LHMDS in THF for 10 min at 0 °C, selectively removing the mesyl group in a satisfactory 87% yield to give **12**.[10] To conclude, 2 equiv of the phenol **12** were reacted with the ditosylate **13** in the presence of potassium carbonate affording the protected FSB dimer **14**, which was quantitatively deprotected leading

to the isolation of the target compound as a yellow solid in a good 37% overall yield from the mesylate **7**.

To further evaluate the usefulness of the Sonogashira/reduction protocol as a viable approach to accessing this class of β-amyloid fibril-binding compounds, we turned our attention toward the synthesis of ^{19}F-BAY94-9172. As illustrated in Scheme 4, this synthesis began with **15**, which was obtained from 4-iodophenol in three steps.[4c] The Pd-catalyzed coupling step with commercially available 4-ethynyl aniline proceeded as expected, leading to the diarylalkyne **16**, which was reductively methylated and protected as its Fmoc derivative **17** before the reduction step. Again, this reduction performed efficiently leading to the stilbene derivative, which was Fmoc-deprotected using DBU in dichloromethane completing the short synthesis of ^{19}F-BAY94-9172.

Scheme 4. Synthesis of ^{19}F-BAY94-9172



In conclusion, we have successfully applied a Sonogashira coupling reaction combined with a stereoselective alkyne reduction as a viable approach to an important class of fibril-binding compounds. Furthermore, as exemplified in the synthesis of FSB, this synthetic route also allows for the simple and multiple introduction of deuterium labeling. Further work is now in progress through a combination of isothermal calorimetry and solution- and solid-phase NMR studies to understand the binding interactions of such compounds with β-amyloid fibrils, the results of which can lead to the development of even more potent and selective fibril binders.

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Supporting Information Available: Experimental details and copies of ^{1}H NMR and ^{13}C NMR spectra for new and selected coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) LHMDS proved superior compared to LDA where the latter also removed the acetal protection group.