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Synthesis of a 4,6-Disubstituted Dibenzofuran β-Sheet Initiator by Reductive Radical Arylation of Benzene

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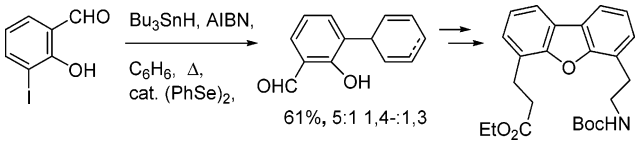
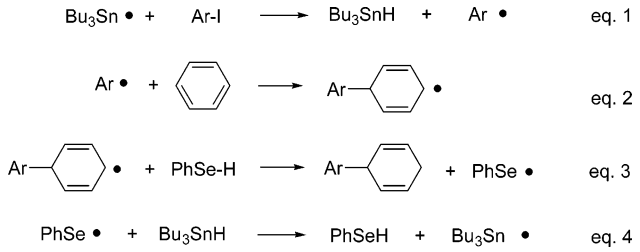
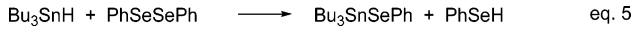


Tributyltin hydride mediated addition of 3-iodosalicylaldehyde to benzene in the presence of catalytic benzeneselenol affords (1,4-cyclohexadien-3-yl)salicylaldehyde. Homologation of the aldehyde group is followed by cycloetherification with dimethyl dioxirane to give a 4,6-disubstituted tetrahydrodibenzofuran. Adjustment of oxidation states and introduction of a second chain by Wittig olefination affords the β-sheet initiator, ethyl 4-(2-*tert*-butoxycarbonylaminoethyl)-6-dibenzofuranpropanoate.

We have recently described a process whereby cyclohexadienyl radicals, produced on rapid addition of aryl radicals to benzene in a stannane-mediated radical chain reaction, may be trapped by benzeneselenol to give a series of 3-aryl-1,4-cyclohexadienes.[1]

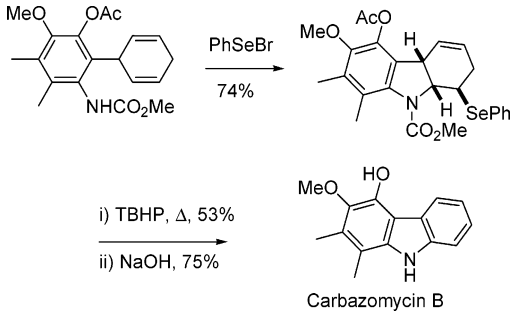


The complete propagation sequence, described by eqs 1−4, is facilitated by the generation of benzeneselenol in situ from diphenyl diselenide and tributyltin hydride (eq 5),[2] thereby eliminating the need to handle the noxious selenol itself.



When the aryl iodide bears a nucleophile in the *o*-position, subsequent activation of the cyclohexadienyl moiety leads to cyclization and provides a rapid entry into functionalized tetrahydrocarbazoles, dibenzofurans, etc.,[3] as illustrated by our synthesis of carbazomycin B (Scheme 1).[4]

SCHEME 1. Synthesis of Carbazomycin B



The phenylselenyl group introduced as electrophile in the carbazomycin synthesis provided a convenient handle for rearomatization, in view of the known oxidation of indolines to indoles by benzeneseleninic acid.[5] However, the simple elimination of the electrophile in this manner may be viewed as a lost opportunity for the introduction of further functionality in the broader context of complex molecule total synthesis. As a first step in the direction of exploiting this functionality more completely we describe here a synthesis of the β-sheet initiator (**13**),[6] from two simple precursors, 2-hydroxy-3-iodosalicyl aldehyde and benzene.

Although 3-iodosalicyl aldehyde has been prepared previously by mercuration of salicyl aldehyde followed by iodination,[7] and by formylation of 2-iodophenol,[8] we developed an alternative protocol from benzofuran which reproducibly gave good yields of clean product. Thus, metalation of benzofuran and quenching with trimethylsilyl chloride gave 2-trimethylsilylbenzofuran (**1**)[9] in high yield. A second metalation[10,11] with an iodine quench afforded crude 7-iodo-2-trimethylsilylbenzofuran (**2**) which, on ozonolysis, gave the desired iodoaldehyde **3** (Scheme 2).

Dropwise addition of a benzene solution of tributytin hydride and AIBN (10 mol %) to a solution of **3** and 20 mol % diphenyl diselenide in benzene at reflux under Ar gave, after evaporation of the volatiles and chromatography over silica gel, 61% of the desired adduct **4** as 5:1 mixture of 1,4- and 1,3-dienes, as is typical for this kind of addition reaction.[1,3,4] A Wittig reaction afforded the α,β-

(1) Crich, D.; Hwang, J.-T. *J. Org. Chem*. **1998**, *63*, 2765−2770.
(2) Crich, D.; Jiao, X.-Y.; Yao, Q.; Harwood, J. S. *J. Org. Chem*. **1996**, *61*, 2368−2373.
(3) Crich, D.; Sannigrahi, M. *Tetrahedron* **2002**, *58*, 3319−3322.
(4) Crich, D.; Rumthao, S. *Tetrahedron* **2004**, *60*, 1513−1516.
(5) (a) Barton, D. H. R.; Luscinchi, W.; Milliet, P. *Tetrahedron* **1985**, *41*, 4727−4738. (b) Ninomia, I.; Hashimoto, C.; Kiguchi, T.; Naito, T.; Barton, D. H. R.; Luscinchi, X.; Milliet, P. *J. Chem. Soc., Perkin Trans. 1* **1990**, 529−532.
(6) Tsang, K. Y.; Diaz, H.; Graciani, N.; Kelly, J. W. *J. Am. Chem. Soc*. **1994**, *116*, 3988−4005.
(7) Whitmore, F. C.; Middleton, E. B. *J. Am. Chem. Soc*. **1923**, *45*, 1330−1334.
(8) Feldman, K. S.; Eastman, K. J.; Lessene, G. *Org. Lett*. **2002**, *4*, 3525−3528.
(9) Gill, M. *Tetrahedron* **1984**, *40*, 621−626.
(10) Metalation of 2-substituted benzofurans is known to take place at the 7-position: Coture, A.; Grandclaudon, P.; Cires, L.; Ofenberg, H. *Synth. Commun.* **1997**, *27*, 3669−3676. Likewise metalation of dibenzofuran was known to take place adjacent to the oxygen. Indeed, such a metalation is a key step in Kelly's original synthesis[6] of the present target molecule.
(11) In principle, direct dimetalation of benzofuran at the 2- and 7-positions is possible, but we have found the two step protocol to be more suitable for our purposes: Chadwick, D. J.; Willbe, C. *J. Chem. Soc., Perkin Trans. 1* **1977**, 887−893.

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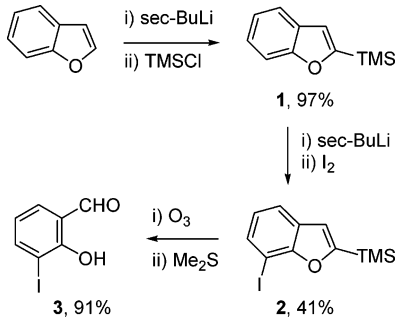
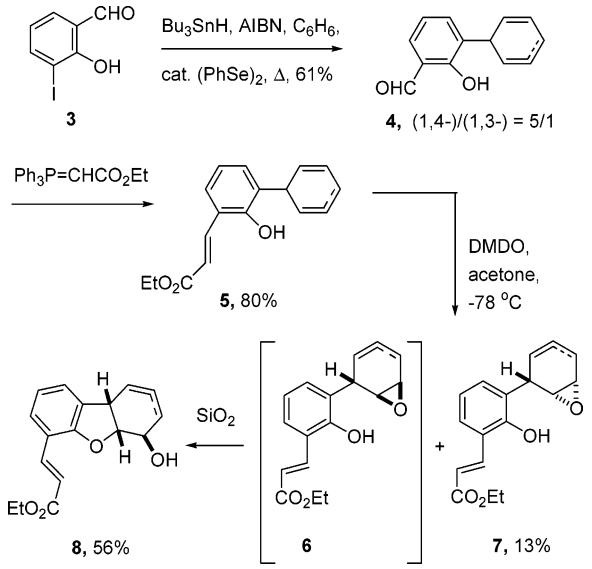
SCHEME 2. Preparation of 3-Iodosalicylaldehyde



SCHEME 3. Reductive Radical Dearomatization and Cycloetherification



unsaturated ester **5** uneventfully. This was exposed to dimethyl dioxirane in acetone at −78 °C[12] followed by concentration under vacuum and chromatography over silica gel when the desired tricyclic system **8** was obtained in 56% yield along with 13% of the epoxide **7** with the incorrect stereochemistry for cyclization. In this last step the dimethyl dioxirane reaction affords a mixture of the two diastereomeric alcohols **6** and **7**, favoring the former with a ratio of approximately 4:1, with cyclization of **6** taking place on passage over silica gel (Scheme 3). With *m*-CPBA as oxidant in place of DMDO, a lower selectivity of ∼2:1 favoring **8** over **7** was observed. The relative stereochemistry of **8** was anticipated on grounds of preferential epoxidation of **4** on the less substituted face followed by ring opening of the epoxide with inversion of configuration; it was confirmed by nOe measurements which revealed the proximity of the two bridgehead hydrogens. Interestingly, the same two hydrogens exhibited a ^3J coupling constant of 8.5 Hz which suggests a near coplanarity and, possibly, a boat conformation for this cyclohexene ring.

As befits a series of reactions beginning from a mixture of skipped and conjugated dienes(**4**), each of **5**−**8** was contaminated with a small amount of a regioisomer which was difficult to separate and ultimately of no consequence as the next step involved hydrogenation to

(12) Eaton, P. E.; Wicks, G. E. *J. Org. Chem*. **1988**, *53*, 5353−5355.

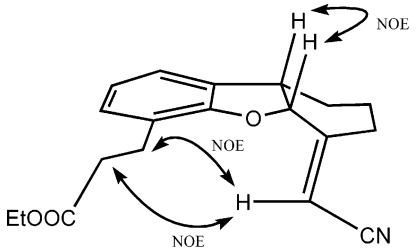
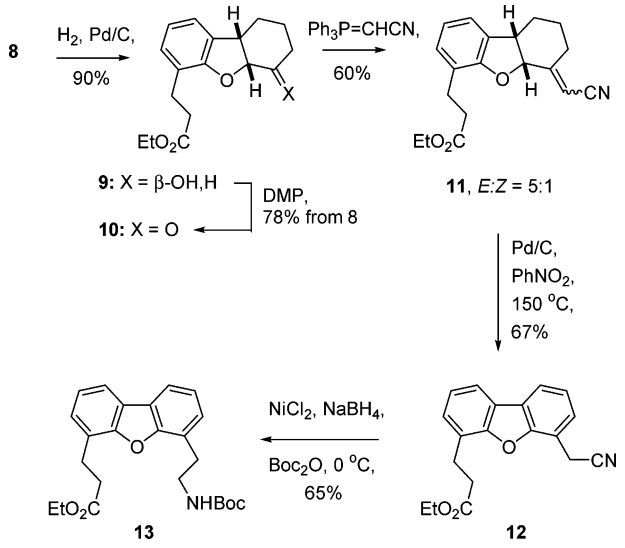


FIGURE 1. Key nuclear Overhauser interactions establishing the stereochemistry of **11***E*.

SCHEME 4. Completion of the Synthesis



9 which was achieved cleanly over palladium on charcoal (Scheme 4). Dess−Martin oxidation of **9** afforded the ketone **10** which, on heating with cyanomethylene triphenylphosphorane afforded the alkene **11** as a 5:1 *E*/*Z* mixture. The *E*-configuration of the major isomer in **11** was revealed by nOe interactions of the olefinic hydrogen with the methylene groups of the second side chain; together with the 8.5 Hz coupling of the two bridgehead hydrogens this points to a boat conformation for the exomethylidene substituted ring (Figure 1). Migration of the exo-cyclic double bond into the ring and final aromatization was achieved by heating over palladium characoal in the presence of nitrobenzene as hydrogen acceptor, as described by Cossy.[13] Finally, reduction of the cyano group with nickel boride in the presence of Boc_2O[14] afforded the target **13** (Scheme 4). This synthesis of **13** requires eight steps from the iodide **3** making it two steps longer than the existing synthesis from dibenzofuran.[6] However, the widespread availability of iodophenols and the several stages at which diversity might be introduced render this a more flexible synthesis with the potential for the ready formation of analogues.

In conclusion, the reductive radical dearomatization of benzene followed by a cyclo-etherification reaction provides a powerful means of entry into tetrahydrodibenzofuran derivatives. With suitable manipulation of the functionality resulting from the cyclization step the

(13) Cossy, J.; Belotti, D. *Org. Lett.* **2002**, *4*, 2557−2559.
(14) Caddick, S.; Judd, D. B.; Lewis, A. K. K.; Reich, M. T.; Williams, M. R. V. *Tetrahedron* **2003**, *59*, 5417−5423.

chemistry affords a straightforward synthesis of 4,6-disubstituted dibenzofurans, illustrated here by the synthesis of Kelly's β-sheet initiator **13**, which nicely complements existing approaches to dibenzofurans[15] and Wacker-type ring closures of 6-(2-hydroxyphenyl)cyclohexene to tetrahydrodibenzofuran.[16]

Supporting Information Available: Full experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0478914

(15) Sargent, M. V.; Stransky, P. O. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: Orlando, 1984; Vol. 35, pp 1−81.

(16) (a) Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3036−3037. (b) Hosokawa, T.; Miyagi, S.; Murahashi, S.-I.; Sonoda, A. *J. Org. Chem.* **1978**, *43*, 2752−2757.