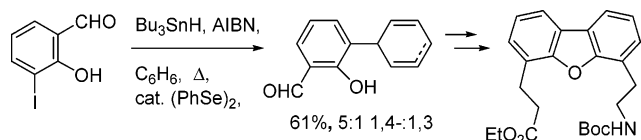## Synthesis of a 4,6-Disubstituted Dibenzofuran β-Sheet Initiator by Reductive Radical Arylation of Benzene

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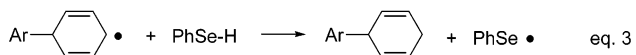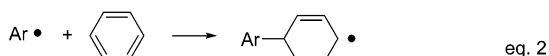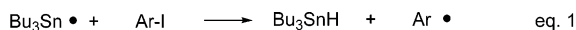
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Tributyltin hydride mediated addition of 3-iodosalicylaldehyde to benzene in the presence of catalytic benzeneselenol affords (1,4-cyclohexadien-3-yl)salicylaldehyde. Homologation of the aldehyde group is followed by cycloetherification with dimethyl 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]

$$Bu_3Sn\bullet + Ar\text{-}I \longrightarrow Bu_3SnH + Ar\bullet \qquad \text{eq. 1}$$

$$Ar\bullet + \text{⬡} \longrightarrow Ar\text{—⬡}\bullet \qquad \text{eq. 2}$$

$$Ar\text{—⬡}\bullet + PhSe\text{-}H \longrightarrow Ar\text{—⬡} + PhSe\bullet \qquad \text{eq. 3}$$

$$PhSe\bullet + Bu_3SnH \longrightarrow PhSeH + Bu_3Sn\bullet \qquad \text{eq. 4}$$
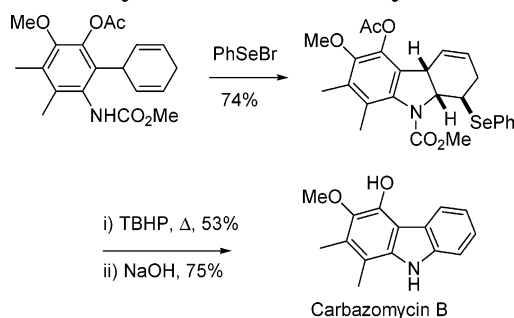
The complete propagation sequence, described by eqs 1–4, is facilitated by the generation of benzeneselenol in situ from diphenyl diselenide and tributyltin hydride (eq 5),[2] thereby eliminating the need to handle the noxious selenol itself.

$$Bu_3SnH + PhSeSePh \longrightarrow Bu_3SnSePh + PhSeH \qquad \text{eq. 5}$$
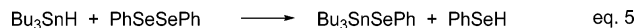
When the aryl iodide bears a nucleophile in the *o*-position, subsequent activation of the cyclohexadienyl moiety leads to cyclization and provides a rapid entry into functionalized tetrahydrocarbazoles, dibenzofurans, etc.,[3] as illustrated by our synthesis of carbazomycin B (Scheme 1).[4]

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(2) Crich, D.; Jiao, X.-Y.; Yao, Q.; Harwood, J. S. *J. Org. Chem.* **1996**, *61*, 2368–2373.
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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-

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(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.
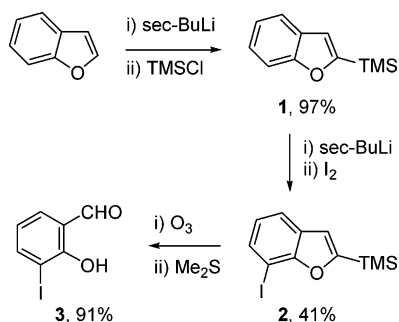(8) Feldman, K. S.; Eastman, K. J.; Lessene, G. *Org. Lett.* **2002**, *4*, 3525–3528.
(9) Gill, M. *Tetrahedron* **1984**, *40*, 621–626.
(10) Metalation of 2-substituted benzofurans is known to take place at the 7-position: Coture, A.; Grandclaudon, P.; Cires, L.; Ofenberg, H. *Synth. Commun.* **1997**, *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.
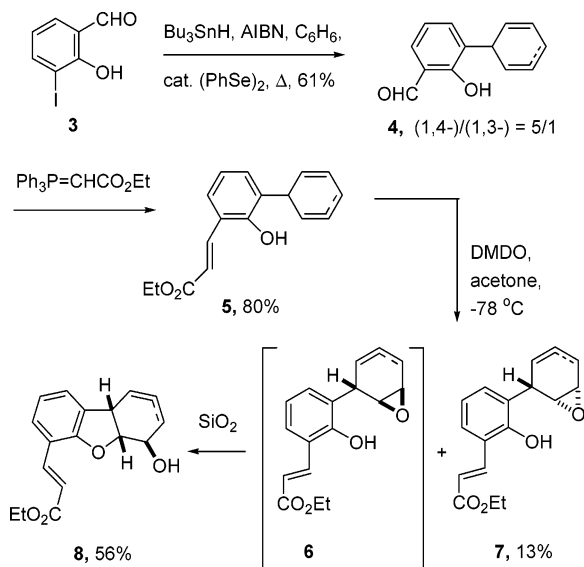(11) In principle, direct dimetalation of benzofuran at the 2- and 7-positions is possible, but we have found the two step protocol to be more suitable for our purposes: Chadwick, D. J.; Willbe, C. *J. Chem. Soc., Perkin Trans. 1* **1977**, 887–893.

SCHEME 2. Preparation of 3-Iodosalicylaldehyde

SCHEME 3. Reductive Radical Dearomatization and Cycloetherification

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

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 charcoal 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$_2$O[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

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
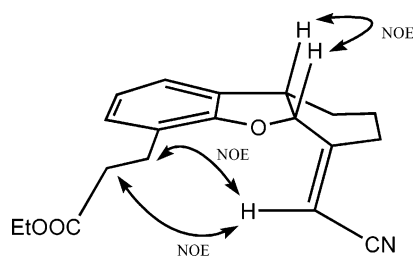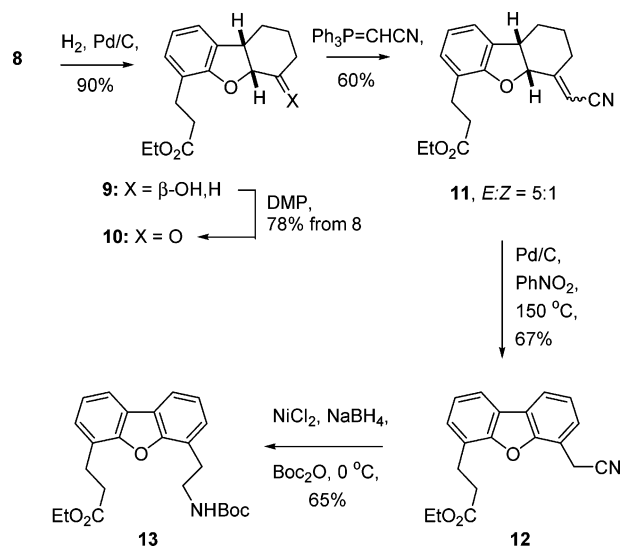
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(14) Caddick, S.; Judd, D. B.; Lewis, A. K. K.; Reich, M. T.; Williams, M. R. V. *Tetrahedron* **2003**, *59*, 5417−5423.

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

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