Pergamon

Tetrahedron Vol. 51, No. 31, pp. 8555-8564, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4020/95 $9.50+0.00

0040-4020(95)00456-4

A Facile Route to 3a,8a-Dihydrofuro[2,3-*b*]benzofurans.

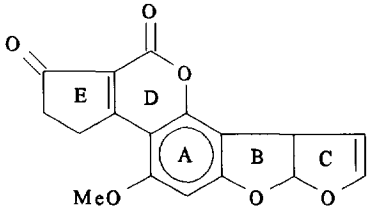
Cedric W. Holzapfel* and D. Bradley G. Williams

Department of Chemistry and Biochemistry, Rand Afrikaans University, P.O. Box 524, Auckland Park, 2006, South Africa.

Abstract: Consecutive employment of palladium-catalysis and samarium(II)iodide-induced radical chemistry allows access to analogues of the ABC enol ether tricycle of aflatoxin B_1 (**1**). The Pd-assisted coupling of tributylstannyl ethers of various 2-iodophenols with 2,5-diacetoxy-2,5-dihydrofuran (**4**) provided products that could be cyclised into 3a,8a-dihydrofuro[2,3-*b*]benzofurans using SmI_2. Elimination of an acetatosamarium species provides the requisite unsaturation *in situ*.

INTRODUCTION

Since the 1961 discovery[1] of aflatoxins as the agents causing pathological changes to a host of taxonomically divergent species, extensive biological studies of these compounds have been carried out. In addition, their curious and unique 3a,8a-dihydrofuro[2,3-*b*]benzofuran structure, exemplified by aflatoxin B_1 (**1**), has lured the interest of many researchers. This has resulted in the publication of many partial and total syntheses over a period of almost two decades.[2] Some notable recent work[3] has seen the formal total synthesis of enantiomerically pure aflatoxins.



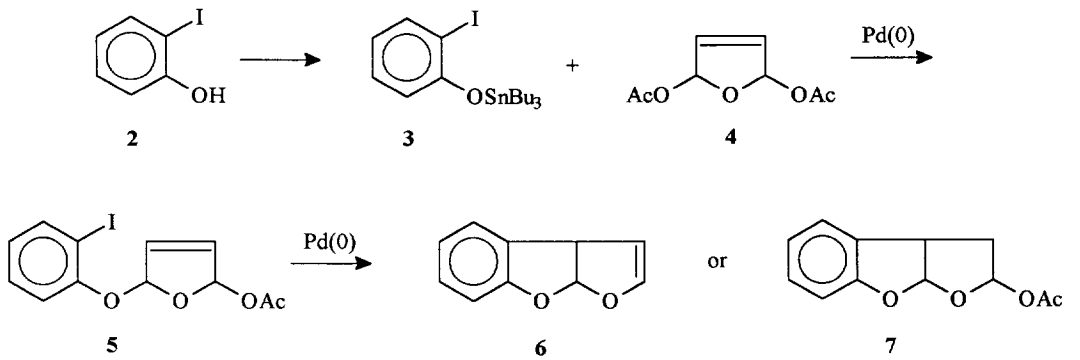
1

Notwithstanding this progress, there yet exists a need for the development of a synthetic pathway to the ABC tricycle that is both short and lends itself to chiral induction. We herein describe a new, direct route to analogues of the ABC tricycle of aflatoxin B_1 (**1**).

RESULTS AND DISCUSSION

Our work involving Pd-mediated reactions[4] suggested the possible synthesis of 3a,8a-dihydrofuro[2,3-*b*]benzofuran (**6**) from 2-iodophenol (**2**) and 2,5-diacetoxy-2,5-dihydrofuran[5] (**4**) (scheme 1). The envisaged

approach involved coupling of the tributylstannyl ether **3** and diacetate **4**, followed by the Pd(0)-catalysed cyclisation to afford **6** directly, or **7**, which could subsequently be converted into **6**.

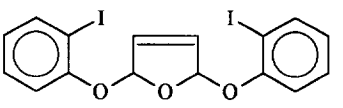


Scheme 1

Compound **3** was obtained by reaction of **2** with 0.5 molar equivalent of $(Bu_3Sn)_2O$ in toluene. Azeotropic removal of water, and evaporation to dryness afforded **3**. The diacetate **4** (stereochemistry undetermined) was obtained as the crystalline component of the mixture of two isomers generated by the reaction of furan with $Pb(OAc)_4$ in acetic acid at 60 °C.[5]

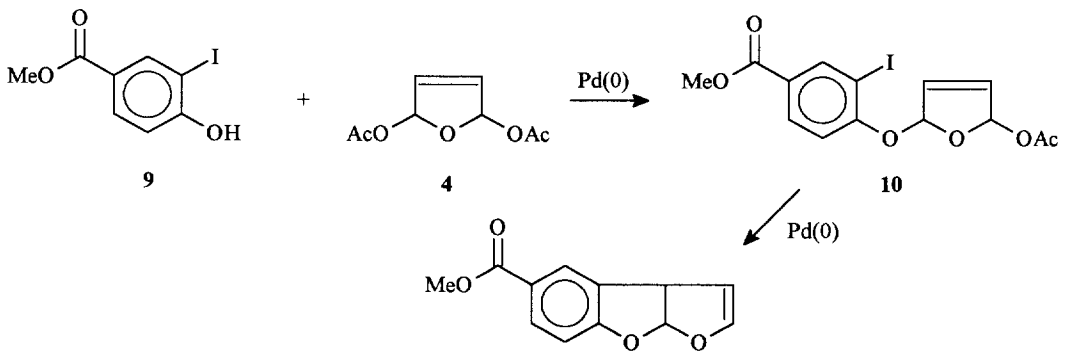
The Pd(0)-catalysed coupling of **3** and **4** in THF was investigated under several conditions. Using $Pd(PPh_3)_4$ as catalyst, the reaction proceeded at room temperature, but failed to reach completion, even with prolonged reaction times or elevated temperatures. This problem was overcome by using a catalyst prepared *in situ* by the treatment of $Pd(OAc)_2$ with six molar equivalents of $P(O^iPr)_3$.[6] However, this extremely active catalyst resulted in significant amounts of **8**, unless **4** was present in excess (2 molar equivalents). Under optimal conditions **5** was formed in a yield of 79%.

The attempted Heck-type cyclisation[7] of **5** under mild conditions furnished only unchanged starting material. Under the more drastic conditions required to effect Heck reactions of similar substrates[8] (unactivated olefins), compound **5** decomposed into several unidentified products. The oxidative addition of the aryl iodide to Pd(0) is in many cases the rate determining step, and is notably enhanced by the presence of electron-withdrawing substituents on the aryl ring.[9] It was therefore anticipated that the desired cyclisation would succeed if 2-iodophenol was replaced with methyl 4-hydroxy-3-iodobenzoate (**9**). Attempted coupling of **9** and **4** in the presence of the Pd(0) catalyst unexpectedly led directly to the desired dihydrofurobenzofuran **11**, in a yield of 36%, together with several byproducts (scheme 2). Compound **11** is presumably formed *via* the intermediate **10**, which would be subject to Pd-assisted cyclisation. The resulting unsaturated tricycle is then formed by the elimination



8

of an acetatopalladium species.[10] This strongly suggests a *trans* stereochemistry for compound **10**, in view of the known stereochemical course of both the Heck reaction and acetatopalladium elimination.[10,11] In turn, this suggests a *trans* stereochemistry for **4**, since Pd-catalysed allylic substitution generally proceeds with retention of configuration.[4c,12]



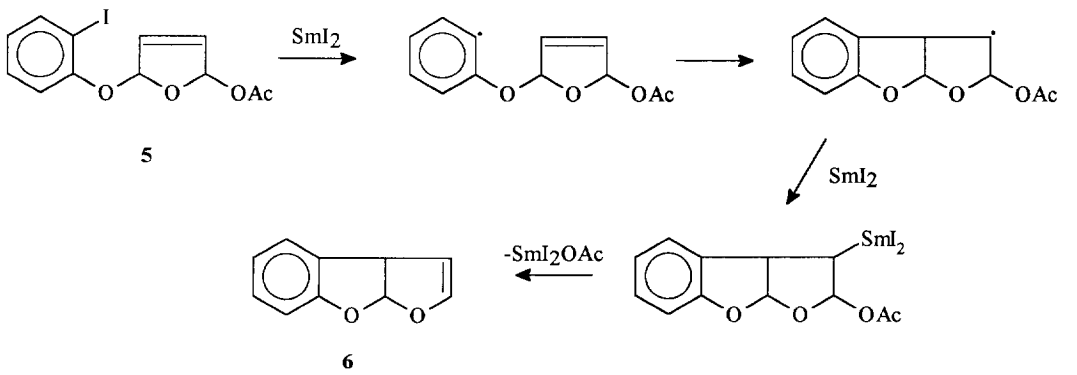
9 **4** **10** **11**

Scheme 2

As discussed above, the substrate **10** meets the main criteria for a facile intramolecular Heck-type cyclisation. Even in this favourable case, the tricycle **11** could not be prepared in an acceptable yield. We therefore sought an alternative to the Heck cyclisation, involving the generation of a highly reactive phenyl radical from **5**. Radical-mediated cyclisations of this type have proven to be an efficient route to the synthesis of heterocyclic compounds. Simple model compounds such as allyloxy-2-iodobenzenes have been cyclised to dihydrobenzofuran derivatives in the presence of tin hydrides.[13] In our initial attempts compound **5** was reacted with Bu_3SnH and AIBN in benzene under reflux. Once again this resulted in the formation of a complex mixture of compounds. We concluded that the cyclisation of **5** required the generation of the intermediate aryl radical under extremely mild conditions.

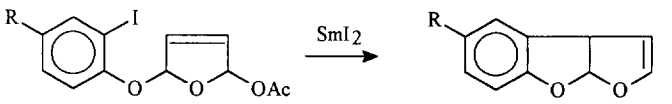
In recent years, samarium(II)iodide has been shown[14] to be a remarkably mild and effective reducing agent,

capable of forming highly reactive phenyl radicals from their iodo precursors at room temperature. These radicals have been successfully utilised to effect cyclisations[15] of the nature required by us. Treatment of **5** with freshly prepared[16] SmI_2 afforded the desired tricyclic enol ether **6** in a yield of 59%. This product presumably arises *via* a reduction-elimination sequence, as outlined in scheme 3. Analogous elimination reactions have been described



Scheme3

elsewhere.[17] In addition to **6**, variable amounts of **2** were detected, possibly arising by Lewis-acid (Sm^{3+}) catalysed decomposition of **5**. However, reductive cleavage of the allyl-oxygen bond in **5** is an alternative possibility.[18] The proportion of **2** increased when SmI_2 that was not freshly prepared was used. The methodology described here was used to prepare a variety of analogues of **5** and **6**, namely **12-15** and **16-19**, respectively, in moderate to good yields (schemes 4a, 4b).



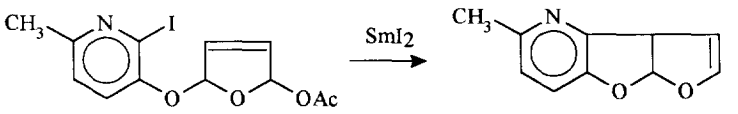
12: R = CH_3
13: R = $CH(CH_3)_2$
14: R = Cl

16: R = CH_3
17: R = $CH(CH_3)_2$
18: R = Cl

Scheme 4a

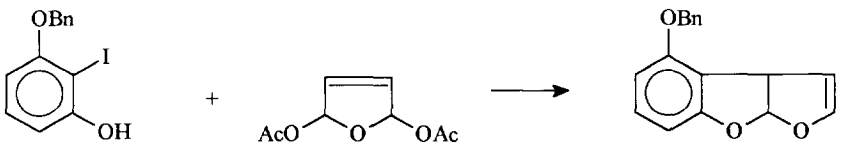
Additionally, the resorcinol derivative **20** was subjected to the same set of conditions as described above, to produce **21** (scheme 5). Interestingly enough, the unprotected 2-iodoresorcinol could not be successfully coupled to **4**.

We have outlined here a mild, direct route to several functionalised 3a,8a-dihydrofuro[2,3-*b*]benzofurans, the first step of which is amenable to chiral induction in the presence of appropriate chiral ligands.[19] We are currently investigating the application of this methodology to a formal total synthesis of aflatoxin B_1.



15 **19**

Scheme 4b



20 **4** **21**

Scheme 5

EXPERIMENTAL SECTION

General

All solvents were purified and dried prior to use.[20] Other reagents were used as received. IR spectra were recorded on a Perkin-Elmer 881 spectrometer, and were performed in $CHCl_3$. Only characteristic peaks are indicated, in reciprocal wavenumber (cm^{-1}). All ^1H and ^{13}C NMR spectra were recorded on a Varian VXR 200 spectrometer, and were, unless otherwise stated, recorded in $CDCl_3$. ^1H NMR data are recorded in the order: chemical shift (δ, reported in ppm, and referenced to the residual solvent peaks of $CDCl_3$ [$\delta_H = 7.24$ and $\delta_H = 77.0$ ppm]), number of protons, multiplicity (br, broad; s, singlet; d, doublet; t, triplet; hp, heptet; m, multiplet), coupling constant/s (J, in Hertz). Mass spectra, as well as accurate mass determinations, were recorded on a Finnigan-Matt 8200 spectrometer at an electron impact of 70 eV. Major peaks are listed with intensities as percentages of the base peak. Accurate mass determinations were performed by manual peak matching. All reactions were performed under an atmosphere of nitrogen, unless otherwise stated.

***2,5-Diacetoxy-2,5-dihydrofuran* (4).**[5] To a solution of $Pb(OAc)_4$ (5.0 g, 11.3 mmol) in acetic acid (10 ml) at 60 °C was added furan (0.85 ml, 11.4 mmol). The reaction was allowed to proceed for one hour, and then

allowed to cool to room temperature. The acetic acid was removed *in vacuo* until a thick paste remained. To this was added ether (30 ml), and the vessel was vigorously shaken until the lead salts formed a loose precipitate. Filtration through celite, followed by evaporation of the solvent, afforded the crude product. Bulb to bulb vacuum distillation (90 °C, 0.1 mm Hg) provided compound **4** (1.98 g, 10.6 mmol, 94%) as a 2:1 (by NMR) mixture of isomers. IR ν 1757 cm^{-1}; ^1H NMR (data for the major isomer are in bold script) δ **2.06 (3H, s)**, 2.08 (3H, s), **6.19 (1H, s)**, 6.21 (1H, s), 6.73 (1H, s), **6.96 (1H, s)**; ^{13}C NMR δ **20.9**, 21.1, 100.0, **101.5**, 130.9, **131.3**, 169.7, **169.9**; m/z 127 (3), 84 (5), 68 (3), 43 (100).

Selective crystallisation of the major isomer was effected by taking up the mixture of isomers in an equal volume of ether and cooling the solution to its freezing point, followed by warming to room temperature, and re-cooling. This procedure was repeated four times, at which stage the crystals no longer dissolved at room temperature. The mother liquors were removed from the solid material, which was then washed with cold ether. Removal of the residual solvent *in vacuo* afforded 637 mg of the crystalline, major isomer, the NMR data of which correspond to the bolded data above (mp. Riechert hot-stage app., uncorr.:50-51 °C; lit:[5] 51-52 °C). Vacuum removal of the solvent from the mother liquors afforded 1.343 g of a 1:1 isomeric mixture of **4**.

General route to *2-iodophenols*.[21] A solution of the phenol (1.0 mmol) in THF (0.9 ml) was diluted with water (0.9 ml). I_2 (279 mg, 1.1 mmol) and $NaHCO_3$ (92 mg, 1.1 mmol) were crushed together and added to the solution in one portion. After a reaction time of three hours, residual I_2 was destroyed by the addition of a 5% aqueous solution of $Na_2S_2O_3$ until the brown colour disappeared. The aqueous solution was extracted with ether (4 × 5 ml). The ethereal solution was dried (Na_2SO_4) and the solvent removed *in vacuo*. Silica gel chromatography afforded the pure 2-iodophenol. The following compounds were produced in this manner (2-iodophenol and 2-iodopicolin-3-ol are available commercially):

2-Iodo-4-methylphenol. (119 mg, 51%);^1H NMR δ 2.23 (3H, s), 5.12 (1H, br s), 6.85 (1H, d, J = 8.3), 7.02 (1H, dd, J = 8.2 and 0.7), 7.46, (1H, d, J = 0.7); ^{13}C NMR δ 19.9, 85.4, 114.7, 130.8, 131.9, 138.3, 152.7; m/z 234 (91), 107 (88).

2-Iodo-4-isopropylphenol. (113 mg, 43%);^1H NMR δ 1.19 (6H, d, J = 6.9), 2.80 (1H, hp, J = 7.1), 5.15 (1H, br s), 6.90 (1H, d, J = 8.3), 7.08 (1H, dd, J = 8.3 and 2.2), 7.48 (1H, d, J = 2.0); ^{13}C NMR δ 24.1, 33.0, 85.6, 114.8, 128.3, 135.9, 143.2, 152.8; m/z 262 (92), 247 (97), 135 (17), 120 (100), 91 (53).

2-Iodo-4-chlorophenol. (99 mg, 39%); ^1H NMR δ 5.31 (1H, br s), 6.90 (1H, d, J = 8.6), 7.19 (1H, dd, J = 8.7 and 2.5), 7.61 (1H, d, J = 2.5); ^{13}C NMR δ 89.4, 115.7, 126.1, 130.1, 137.2, 153.9; m/z 256 (29), 254 (100), 219 (2), 129(19), 127 (31).

Methyl 3-iodo-4-hydroxybenzoate. (106 mg, 38%); IR ν 1728 cm^{-1}; ^1H NMR δ 3.97, (3H, s), 5.92 (1H, br s), 6.98 (1H, d, J = 8.5), 7.91 (1H, dd, J = 8.6 and 2.0), 8.35 (1H, d, J = 2.0); ^{13}C NMR δ 52.2, 85.1, 114.7, 124.5, 132.0, 140.3, 158.8, 165.4; m/z 278 (81), 247 (100), 219 (13), 151 (3).

2-Iodoresorcinol. (109 mg, 46%); ^1H NMR ($CDCl_3/CD_3OD$) δ 6.34 (2H, d, J = 8.1), 6.91 (1H, t, J = 8.1);

^{13}C NMR δ 75.9, 106.3, 129.6, 156.7; m/z 236 (100), 218 (16), 109 (4).

***2-Iodo-3-benzyloxyphenol* (20)**. To a solution of 2-iodoresorcinol (472 mg, 2.0 mmol) in DMF (14 ml) was added NaH (34 mg, 1.0 mmol, 70% suspension in mineral oil). The suspension was stirred until it became clear (30 min.). Benzyl bromide (0.12 ml, 1.01 mmol) was added and the solution was stirred overnight. The solvent was removed *in vacuo* and the residue purified by chromatography (3:1 hexane:EtOAc) to afford pure **17** (209 mg, 64%). ^{1}H NMR δ 5.13 (2H, s), 5.48 (1H, br s), 6.43 (1H, d, J = 8.3), 6.68 (1H, d, J = 8.1), 7.15 (1H, t, J = 8.2), 7.31-7.52 (5H, m); ^{13}C NMR δ 71.1, 79.0, 104.7, 108.2, 127.0, 127.9, 128.6, 130.1, 136.5, 156.3, 157.9; m/z 326 (9), 235 (2), 199(9), 91 (100).

General procedure towards *2-acetoxy-5-aryloxy-2,5-dihydrofurans*. A solution of the 2-iodophenol (0.8 mmol) and *bis*(tributyltin) oxide (0.20 ml, 0.39 mmol) in toluene (40 ml) was heated under reflux for 2 hours with concomitant azeotropic removal of water. Evaporation to dryness afforded the stannyl ether as a light yellow oil, which was taken up in THF (2.0 ml). The catalyst was prepared using a modification of the procedure of Trost,[6] by adding $P(O^{i}Pr)_3$ (0.12 ml, 0.49 mmol) to $Pd(OAc)_2$ (18 mg, 0.08 mmol) and stirring until the solution became homogeneous (20 min.). THF (2.0 ml) and diacetate **4** (298 mg, 1.6 mmol) were added to the catalyst, whereafter the solution containing the stannyl ether was added. The reaction was allowed to proceed for 14 hours, after which time the solvent was removed *in vacuo*. Column chromatography afforded the coupled product. The following compounds were synthesised as described:

***2-Acetoxy-5-(2-iodophenoxy)-2,5-dihydrofuran* (5)**. (219 mg, 79%); IR ν 1744 cm^{-1}; ^{1}H NMR δ 2.07 (3H, s), 6.12 (1H, t, J = 1.1), 6.27 (1H, dt, J = 5.8 and 1.1), 6.40 (1H, dt, J = 5.8 and 1.1), 6.77 (1H, t, J = 1.1), 6.79 (1H, ddd, J = 7.7, 6.7 and 2.1), 7.20-7.34 (2H, m), 7.76 (1H, d, J = 7.8 and 1.3); ^{13}C NMR δ 21.2, 88.2, 99.9, 107.0, 117.6, 124.7, 129.6, 130.9, 131.5, 139.4, 156.4, 170.1; m/z 287 (100), 259 (79), 143 (17), 115 (9).

***2-Acetoxy-5-(2-iodo-4-methylphenoxy)-2,5-dihydrofuran* (12)**. (173 mg, 60%); IR ν 1741 cm^{-1}; ^{1}H NMR δ 2.07 (3H, s), 2.25 (3H, s), 6.06 (1H, t, J = 1.2), 6.25 (1H, dt, J = 5.8 and 1.2), 6.39 (1H, dt, J = 5.8 and 1.1), 6.76 (1H, t, J = 1.1), 7.07-7.10 (2H, m), 7.58 (1H, d, J = 2.2); ^{13}C NMR δ 20.1, 21.1, 88.3, 99.9, 107.4, 117.9, 130.1, 130.8, 131.6, 139.6, 145.9, 154.4, 170.1; m/z 360 (1), 300 (8), 234 (36), 126 (7), 43 (100).

***2-Acetoxy-5-(2-iodo-4-isopropylphenoxy)-2,5-dihydrofuran* (13)**. (242 mg, 78%); IR ν 1748 cm^{-1}; ^{1}H NMR δ 1.19 (6H, d, J = 7.0), 2.07 (3H, s), 2.81 (1H, hp, J = 7.1), 6.08 (1H, t, J = 1.1), 6.25 (1H, dt, J = 5.8 and 1.2), 6.39 (1H, dt, J = 5.8 and 1.1), 6.76 (1H, t, J = 1.1), 7.13-7.17 (2H, m), 7.61 (1H, d, J = 2.1); ^{13}C NMR δ 21.2, 24.0, 33.1, 88.2, 99.9, 107.4, 117.8, 127.6, 130.8, 131.6, 137.2, 145.7, 154.5, 170.1; m/z 388 (4), 329 (19), 262 (100), 247 (95), 202 (17), 126 (32), 91 (29), 43 (100).

***2-Acetoxy-5-(4-chloro-2-iodophenoxy)-2,5-dihydrofuran* (14)**. (216 mg, 71%); IR ν 1749 cm^{-1}; ^{1}H NMR δ 2.08 (3H, s), 6.07 (1H, t, J = 1.1), 6.27 (1H, dt, J = 5.8 and 1.1), 6.39 (1H, dt, J = 5.8 and 1.1), 6.77 (1H, t, J = 1. 1), 7.15 (1H, d, J = 8.8), 7.26 (1H, dd, J = 8.8 and 2.4), 7.74 (1H, d, J = 2.4); ^{13}C NMR δ 21.1, 88.4, 99.9, 107.1, 118.2, 128.9, 129.4, 131.2 (×2), 138.5, 155.3, 170.0; m/z 381 (1), 379 (2), 322 (14), 320 (42), 256 (56),

255 (28), 254 (71), 253 (46), 196 (8), 194 (26), 127 (81), 126 (58), 43 (100).

2-Acetoxy-5-(2-iodopicolin-3-oxy)-2,5-dihydrofuran **(15)**. (214 mg, 74%); IR ν 1755 cm^{-1}; ^1H NMR δ 2.07 (3H, s), 2.47 (3H, s), 6.05 (1H, t, J = 1.1), 6.27 (1H, dt, J = 5.8 and 1.1), 6.41 (1H, dt, J = 5.8 and 1.1), 6.76 (1H, t, J = 1.1), 6.99 (1H, d, J = 8.1), 7.31 (1H, d, J = 8.1); ^{13}C NMR δ 21.1, 23.3, 99.9, 107.3, 112.8, 123.0, 123.1, 125.1, 131.2, 154.8, 163.2, 170.7; m/z 362 (67), 302 (69), 301 (10), 236 (70), 235 (63), 175 (24), 127 (81), 108 (41), 43 (100).

2-Acetoxy-5-(3-benzyloxy-2-iodophenoxy)-2,5-dihydrofuran. (250 mg, 69%); IR ν 1750 cm^{-1}; ^1H NMR δ 2.08 (3H, s), 5.15 (2H, s), 6.15 (1H, t, J = 1.1), 6.28 (1H, dt, J = 5.8 and 1.2), 6.43 (1H, dt, J = 5.8 and 1.1), 6.60 (1H, dd, J = 8.3 and 1.2), 6.79 (1H, t, J = 1.1), 6.91 (1H, dd, J = 8.3 and 1.2), 7.21 (1H, t, J = 8.2), 7.30-7.53 (5H, m); ^{13}C NMR δ 21.2, 71.1, 80.8, 99.9, 107.1, 107.6, 110.6, 127.0, 127.8, 128.5, 129.8, 130.9, 131.5, 136.5, 158.0, 158.7, 170.1; m/z 452 (3), 392 (11), 326 (43), 199 (33), 127 (47), 126 (13), 91 (100), 43 (91).

5-Methoxycarbonyl-3a,8a-dihydrofuro[2,3-b]benzofuran **(11)**. CAUTION: potential carcinogen.[22] (26 mg, 36%); IR ν 1711 cm^{-1} ^1H NMR δ 3.86 (3H, s), 4.60 (1H, dt, J = 7.2 and 2.7), 5.22 (1H, t, J = 2.7), 6.45 (1H, t, J = 2.6), 6.74 (1H, d, J = 7.3), 6.90 (1H, d, J = 8.8), 7.88 (1H, d, J = 1.7), 7.88 (1H, dd, J = 8.9 and 1.9); ^{13}C NMR δ 49.9, 51.9, 103.3, 109.7, 112.3, 123.9, 126.1, 128.3, 131.4, 145.3, 161.7, 166.6; m/z 218 (95), 189 (77), 187 (100), 159 (28), 131 (47), 103 (40); Mass calcd for $C_{12}H_{10}O_4$ 218.0579, found 218.0581.

General procedure for the preparation of *3a,8a-dihydrofuro[2,3-b]benzofurans*. CAUTION: these compounds may reasonably be anticipated to be carcinogens.[22] A 0.1 M solution of SmI_2 in THF was prepared as follows: Powdered Sm metal (902 mg, 6.0 mmol) was gently flamed under a stream of argon. The metal was allowed to cool, whereafter freshly distilled THF (40 ml) was added. 1,2-Di-iodoethane (1.127 g, 4.0 mmol) was added and the solution was stirred for 3 hours, after which time the solution had turned a deep blue colour. Reactions using SmI_2 were performed immediately after preparation thereof.

To a solution of 2-acetoxy-5-aryloxy-2,5-dihydrofuran (0.33 mmol) in degassed HMPA (0.5 ml) was added the SmI_2 solution (10 ml, 1.0 mmol). After a reaction time of 2 hours, the solution was filtered through a 5 cm plug of silica, concentrated, and chromatographed on silica to afford the desired tricycle. The following compounds were generated using this methodology:

3a,8a-Dihydrofuro[2,3-b]benzofuran **(6)**. (31 mg, 59%); ^1H NMR δ 4.56 (1H, dt, J = 7.3 and 2.0), 5.20 (1H, t, J = 2.7), 6.44 (1H, dd, J = 2.7 and 2.3), 6.68 (1H, d, J = 7.3), 6.83-6.95 (2H, m), 7.08-7.23 (2H, m); ^{13}C NMR δ 50.4, 103.4, 110.1, 111.5, 121.5, 124.1, 127.7, 128.5, 145.2, 157.8; m/z 160 (86), 131 (100), 103 (23), 77 (21); Mass calcd for $C_{10}H_8O_2$ 160.0524, found 160.0527.

5-Methyl-3a,8a-dihydrofuro[2,3-b]benzofuran **(16)**. (35 mg, 61%) ^1H NMR δ 2.28 (3H, s), 4.53 (1H, dt, J = 7.2 and 2.3), 5.20 (1H, t, J = 2.7), 6.44 (1H, t, J = 2.5), 6.66 (1H, d, J = 7.2), 6.77 (1H, d, J = 8.3), 6.94 (1H, dd, J = 8.1 and 1.2), 6.99 (1H, d, J = 1.2); ^{13}C NMR δ 20.7, 50.4, 103.4, 109.6, 111.6, 124.6, 128.8, 130.8, 130.9, 145.1, 155.6; m/z 174 (76), 145 (100), 131 (11), 117 (10); Mass calcd for $C_{11}H_{10}O_2$ 174.0681, found 174.0678.

5-Isopropyl-3a,8a-dihydrofuro[2,3-b]benzofuran **(17)**. (32 mg, 48%); ^{1}H NMR δ 1.20 (6H, d, J = 7.0), 2.84 (1H, hp, J = 7.0), 4.53 (1H, dm, J = 7.2), 5.21 (1H, dd, J = 2.7 and 2.6), 6.43 (1H, dd, J = 2.9 and 2.2), 6.66 (1H, d, J = 7.2), 6.79 (1H, d, J = 8.1), 6.99 (1H, dd, J = 8.2 and 2.0), 7.02-7.06 (1H, m); ^{13}C NMR δ 24.3, 24.4, 33.6, 50.5, 103.4, 109.6, 111.7, 122.0, 126.4, 127.6, 142.4, 145.1, 155.8; m/z 202 (51), 187 (100), 173 (22), 158 (19); Mass calcd for $C_{13}H_{14}O_2$ 202.0994, found 202.0994.

5-Chloro-3a,8a-dihydrofuro[2,3-b]benzofuran **(18)**. (40 mg, 62%); ^{1}H NMR δ 4.55 (1H, dt, J = 6.9 and 2.1), 5.19 (1H, t, J = 2.7), 6.47 (1H, t, J = 2.5), 6.69 (1H, d, J = 7.2), 6.80 (1H, d, J = 8.4), 7.10 (1H, dd, J = 8.4 and 2.3), 7.15 (1H, d, J = 2.2); ^{13}C NMR δ 50.4, 102.9, 111.0, 112.0, 124.3, 125.8, 128.4, 129.6, 145.6, 156.5; m/z 196 (21), 194 (67), 167 (32), 165 (100), 131 (26); Mass calcd for $C_{10}H_7{}^{35}ClO_2$ 194.0134, found 194.0132.

5-Methyl-3a,8a-dihydrofuro[2,3-b]-4-azabenzofuran **(19)**. (44 mg, 76%); ^{1}H NMR δ 2.46 (3H, s), 4.55 (1H, dt, J = 7.1 and 2.5), 5.38 (1H, t, J = 2.7), 6.49 (1H, t, J = 2.5), 6.70 (1H, d, 7.3), 6.88 (1H, d, J = 8.1), 7.02 (1H, d, J = 8.3); ^{13}C NMR δ 23.3, 51.2, 102.5, 110.8, 116.8, 122.0, 145.7, 149.5, 149.6, 151.2; m/z 175 (95), 147 (97), 146 (100), 118 (71); Mass calcd for $C_{10}H_9NO_2$ 175.0633, found 175.0635.

4-Benzyloxy-3a,8a-dihydrofuro[2,3-b]benzofuran **(21)**. (46 mg, 46%); ^{1}H NMR δ 4.63 (1H, dt, J = 7.2 and 2.3), 5.10 (2H, s), 5.34 (1H, t, J = 2.6), 6.43 (1H, t, J = 2.5), 6.50 (1H, d, J = 8.3), 6.55 (1H, d, J = 8.1), 6.68 (1H, d, J = 7.2), 7.08 (1H, t, J = 8.3), 7.26-7.61 (5H, m); ^{13}C NMR δ 48.8, 70.0, 102.7, 103.4, 105.1, 111.9, 127.2, 128.0, 128.3, 128.6, 129.5, 137.0, 144.8, 155.3, 159.0; m/z 266 (14), 237 (7), 175 (7), 147 (5), 105 (47), 91 (100); Mass calcd for $C_{17}H_{14}O_3$ 266.0943, found 266.0943.

Acknowledgement. The authors thank the South African Foundation for Research and Development, AECI and SASOL for financial support.

REFERENCES

1. Review: Busby, W.F. and Wogan, G.N. in *Chemical Carcinogens*, 2nd ed., Searle, C., Ed., American Chemical Society, Washington, DC, **1984**, vol 182, 945.
2. a) Büchi, G.; Foulkes, D.M.; Kumono, M; Mitchell, G.F. and Schneider, R.S. *J. Am. Chem. Soc.*, **1967**, 89, 6745.
   b) Büchi, G. and Weinreb, S.M. *J. Am. Chem. Soc.*, **1969**, 91, 5408.
   c) Büchi, G. and Weinreb, S.M. *J. Am. Chem. Soc.*, **1971**, 93, 746.
   d) Büchi, G.; Francisco, M.A.; Liesch, J.M. and Schuda, P.F. *J. Am. Chem. Soc.*, **1981**, 103, 3497.
   e) Wolff, S. and Hoffman, H.M.R. *Synthesis*, **1988**, 10, 760.
   f) Sloan, C.P.; Cuevas, J.C.; Quesnelle, C. and Snieckus, V. *Tetrahedron Lett.*, **1988**, 29, 4685.
   g) Schmidt, B. and Hoffman, H.M.R. *Tetrahedron*, **1991**, 47, 9357.
   h) Bujons, J.; Roura, L. and Messguer, A. *Synlett.*, **1994**, 437.

3. a) Marino, J.P. *Pure and Appl. Chem.*, **1993**, 65, 667.
   b) Civitello, E.R. and Rapoport, H. *J. Org. Chem.*, **1994**, 59, 3775.
4. a) Holzapfel, C.W. and Williams, D.B.G. *Synth. Commun.*, **1994**, 24, 2139.
   b) Bredenkamp, M.W.; Holzapfel, C.W. and Toerien, F. *Synth. Commun.*, **1992**, 22, 2447.
   c) Engelbrecht, G.J. and Holzapfel, C.W. *Heterocycles*, **1991**, 32, 1267.
   d) Holzapfel, C.W.; Huyser, J.J.; van der Merwe, T.L. and van Heerden, F.R. *Heterocycles*, **1991**, 32, 1445.
5. Elming, N. and Clauson-Kaas, N. *Acta Chem. Scand.*, **1952**, 6, 535.
6. Trost, B.M. and Grese, T.A. *J. Org. Chem.*, **1992**, 57, 686.
7. Heck, R.F. *Palladium Reagents in Organic Synthesis*, Academic Press, New York, **1985**.
8. Samizi, K. and Ogasawara, K. *Synlett*, **1994**, 499.
9. Fauvarque, J.-F.; Pflüger, F. and Troupel, M. *J. Organomet. Chem.*, **1981**, 208, 419.
10. a) Arai, I. and Daves, G.D., Jr. *J. Am. Chem. Soc.*, **1978**, 100, 287.
    b) Arai, I. and Daves, G.D., Jr. *J. Org. Chem.*, **1978**, 43, 4110.
11. Davies, S.G. *Organotransition Metal Chemistry; Application to Organic Synthesis*, Pergamon, Oxford, **1984**, 226.
12. Trost, B.M. and Verhoeven, T.R. in *Comprehensive Organometallic Chemistry*, Wilkinson, G.; Stone, F.G.A. and Abel, E.W., Eds., Pergamon Press, New York, **1982**, vol 8, 799.
13. Shankaran, K.; Sloan, C.P. and Snieckus, V. *Tetrahedron Lett.*, **1985**, 26, 6001.
14. Review: Molander, G.A. *Chem. Rev.*, **1992**, 92, 29.
15. a) Hasegawa, E. and Curran, D.P. *J. Org. Chem.*, **1993**, 58, 5008.
    b) Molander, G.A. and Harring, L.S. *J. Org. Chem.*, **1990**, 55, 6171.
16. Molander, G.A. and Hahn, G. *J. Org. Chem.*, **1986**, 51, 1135.
17. Ujikawa, O.; Inanaga, J. and Yamaguchi, M. *Tetrahedron Lett.*, **1989**, 30, 2837.
18. Olivero, S. and Duñach, E. *Synlett.*, **1994**, 531.
19. Frost, C.G. and Williams, M.J., *Synlett*, **1994**, 551.
20. Perrin, D.D.; Armarego, W.L.F. and Perron, D.R. *Purification of Laboratory Chemicals*, 2nd ed., Pergamon Press, New York, **1980**.
21. Thomsen, I. and Torssell, K.B.G. *Acta Chem. Scand.*, **1991**, 45, 539.
22. a) Wogan, G.N.; Edwards, G.S. and Newberne, P.M. *Cancer Research*, **1971**, 31, 1936.
    b) Coles, B.F.; Smith, J.R.L. and Garner, R.C. *Biochemical and Biophysical Research*, **1977**, 26, 888.

(*Received in UK* 18 *May* 1995; *accepted* 9 *June* 1995)