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An enantioselective synthesis of (−)-4-hydroxy-6-methoxy-3a,8a-dihydrofuro [2,3-*b*]benzofuran: an advanced intermediate in the synthesis of (−)-aflatoxin B_1 and G_1

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1. Introduction

The Aflatoxins (Fig. 1), secondary metabolites of the *fungus Aspergillus*, are among the most potent carcinogens known to man. The fused dihydrobisfuran ring system of these mycotoxins contains an electron rich double bond that undergoes metabolic activation to an epoxide, which can then generate covalent lesions upon intercalation into double stranded DNA.[1] Recent reports on the preparation and use of the 8,9-epoxide of Aflatoxin B_1 by Harris and co-workers[1] has provided new impetus to directly investigate the chemistry and metabolism of this highly carcinogenic species. In this context, the synthesis of precursors of the Aflatoxins would permit greater accessibility to this highly reactive class of compounds.

In 1967, Büchi and co-workers devised the first total synthesis of racemic Aflatoxin B_1 (**1**).[2] In 1971, Büchi and Weinreb reported a synthesis of Aflatoxin G_1 (**2**) as well as an improved synthesis of Aflatoxin B_1, which employed a von Pechmann condensation of 3-bromo-2-carbethoxy cyclopentenone with racemic 4-hydroxy-6-methoxy-3a,8a-dihydrofuro[2,3-*b*]benzofuran (**9**) in the final step.[3] We chose this chiral dihydrofurobenzofuran intermediate **9** as our target compound.

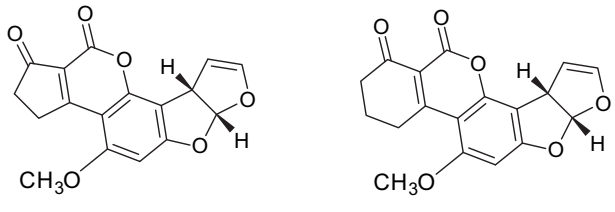

Fig. 1.

Since the pioneering work of Büchi's group, several partial and total syntheses of Aflatoxin class of compounds have appeared in the literature.[4] Although each synthesis addresses the problem of constructing the highly oxygenated ring system, none of these syntheses consider the question of enantiomeric purity. The first enantioselective synthesis of Büchi's furobenzofuran **9** will be reported in which the asymmetry is obtained through an optically active vinyl sulfoxide **5**.

We had previously showed that optically active *trans*-vinyl sulfoxides react with haloketenes to produce the *trans*-γ-thio-γ-butyrolactones with high enantioselectivity.[5] It was also demonstrated by our group that the absolute configuration of the starting vinyl sulfoxide controls the absolute configuration of the resulting *trans*-lactone.[6a] Since the first report, this laconization reaction has been used in the asymmetric synthesis of a variety of natural products.[6] We envisioned that this lactonization reaction could be applied to the (*S*)-vinyl sulfoxide **5** to yield the appropriately functionalized aryl-γ-thio-γ-butyrolactone, which would be important in construction of the naturally occurring enantiomer of the furo[2,3-*b*]benzofuran ring system found in the Aflatoxins and other natural products.

Thus, requisite vinyl sulfoxide **5** ($[\alpha]_D^{25}$ −106°, *c* 1.08, $CHCl_3$) was obtained through a Stille coupling[7] of the chiral *trans*-vinyl stannane[8] **4** ($[\alpha]_D^{25}$ −137°, *c* 1.71, $CHCl_3$) and the aromatic iodide **3**[9] (Scheme 1). While several recent examples of coupling of aryl iodides with vinyl stannanes have been reported,[10] this is a unique

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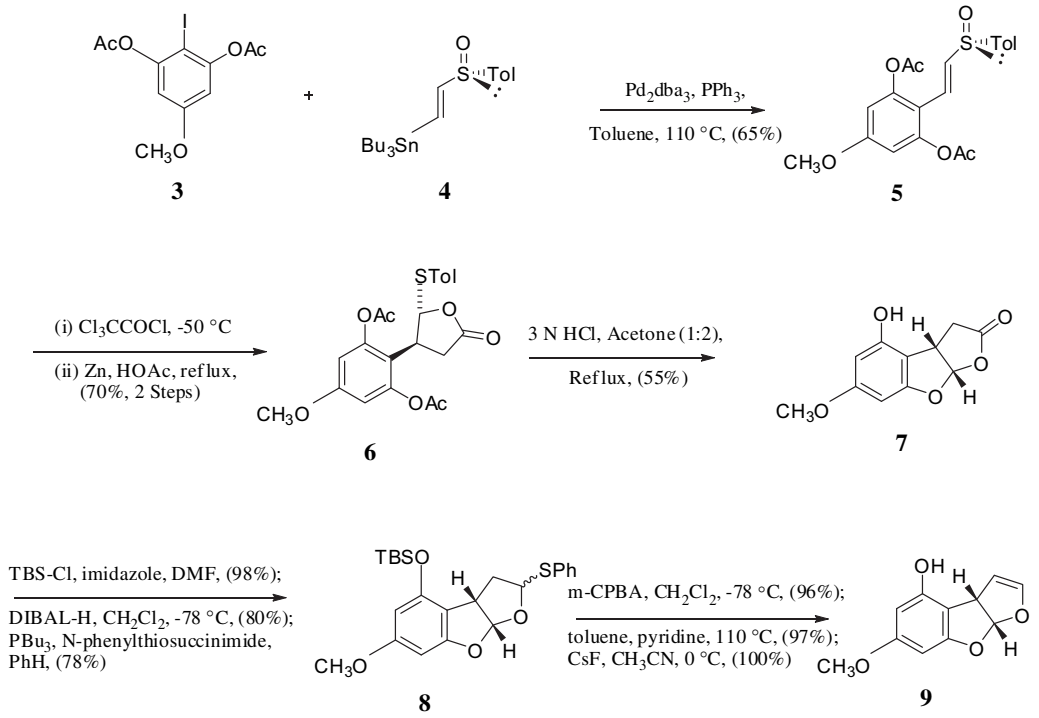


Scheme 1.

approach to chiral vinyl sulfoxides via the chiral synthon **4**. Treatment of the resultant *trans*-vinyl sulfoxide **5** with dichloroketene, generated in situ, provided a 7:1 mixture of *trans*/*cis* dichlorolactones. Immediate dehalogenation of the crude dichlorolactones with zinc in acetic acid yielded the desired (3*S*,4*S*)-*trans*-lactone **6** ($[\alpha]_D^{25}=-72^\circ$, *c* 2.0, $CHCl_3$) as the sole product. This lactone was obtained in high yield (70% over two steps) and with greater enantioselectivity than 95% ee[11] Since we observed none of the enantiomeric (3*R*,4*R*)-*trans* lactone, epimerization appears to be mediated through the action of zinc salts produced in the reaction. Under these conditions, the more crowded (3*S*,4*R*)-*cis* lactone is equilibrated to the thermodynamically stable (3*S*,4*S*)-*trans* product.

Ring closure of the γ-thiobutyrolactone to the furobenzofuranone **7** ($[\alpha]_D^{25}$ −128°, *c* 0.605, acetone) was accomplished during the deprotection of the phenolic acetates in 55% yield and 80% ee[12] using 3 N HCl in refluxing acetone. Many attempts were made to increase the yield and the optical purity of the resultant furobenzofuranone **7**. One strategy involved synthesizing the aryl iodide **3** with a more labile protecting group. A number of protecting groups were employed and for various reasons were not suitable. Some of these groups include: 2,2,2-trifluoroethanesulfonate; bromomethanesulfonate; trimethylsilylethanesulfonate; benzyl; tosyl; trifluoroacetate; ethyl carbonate. A second strategy consisted of retaining the acetate protecting group and performing the cleavage as a separate step before attempting ring closure. Very quickly, the sensitivity of the γ-thiobutyrolactone **6** to basic conditions was displayed. Aqueous sodium bicarbonate in alcoholic solvents[3] quickly caused destruction of the lactone, most likely through ring opening, as evidenced by the formation of *p*-thiocresol. The use of other carbonates (Ag_2CO_3, Cs_2CO_3[13]) in ethereal solutions (DME, THF, ether) similarly only caused destruction of the lactone. A very efficient reagent for cleaving acetates, guanidine in methanol,[14] was also used. On model compounds, this reagent worked quickly and cleanly. However, on the γ-thiobutyrolactone **6**, ring opening of the lactone with subsequent elimination of the *p*-thiocresol was a major competing reaction, thus limiting the utility of this reagent for our purposes. Other nucleophilic reagents such as amines and thiolate ions were equally unsuccessful.

The benzofuranone **7** was then protected as the *tert*-butyldimethylsilyl ether and reduced with DIBAL-H to provide a 1:1 mixture of lactols. Treatment of lactols with *N*-phenylthiosuccinimide and tributylphosphine[15] yielded a 1:1 mixture of thioacetals **8**. Oxidation of the sulfide to sulfoxide, followed by sulfoxide elimination[16] yielded the silyl protected dihydrobenzofuran. Final deprotection with cesium fluoride gave the target compound **9** ($[\alpha]_D^{25}$ −194°, *c* 0.67, $CHCl_3$) in high yield and 80% ee.[12]

Due to their acute toxicity and carcinogenicity, the Aflatoxins continue to attract attention from workers in many fields, including organic synthesis. To our knowledge, this report constitutes the first asymmetric synthesis of Büchi's dihydrofurobenzofuran intermediate **9**. The key steps in the synthesis involve (1) an efficient Stille coupling of synthon **4** to form the *trans* vinyl sulfoxide **5** (2) chirality transfer from an optically active vinyl sulfoxide yield the optically active *trans* lactone after treatment of which with dichloroketene, and (3) closure of the lactone to yield the furobenzofuranone **7** upon deprotection of the phenolic acetates. This methodology is currently being extended to synthesize other related natural products.

2. Experimental

2.1. 2,6-Diacetoxy-4-methoxyiodobenzene (3)

3,5-Diacetoxyanisole (1.80 g, 8.03 mmol) and silver trifluoroacetate (1.86 g, 8.43 mmol) were stirred together in CH_2Cl_2 (80 mL) at 25 °C for 1 h under a N_2 atmosphere. Iodine (2.44 g, 9.63 mmol) was added in one portion and stirring was continued for an additional 30 min. The solids were then filtered off and washed with CH_2Cl_2 (2×20 mL). The organic layer was then washed with aqueous saturated $Na_2S_2O_3$ solution (3×50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to yield a thick yellow oil containing the product as a 1:1 mixture of regioisomers (2.80 g, 100%) Careful crystallization with diethyl ether yielded the desired regioisomer (**3**) (0.61 g, 22%) as a white solid: mp 105–106 °C (ether); ^1H NMR ($CDCl_3$) δ 2.36 (6H, s), 3.79 (3H, s), 6.62 (2H, s); ^{13}C NMR ($CDCl_3$) δ 21.21, 55.81, 77.26, 107.16, 152.80, 161.04, 168.16; IR

(KBr) 2940 (w, m), 1765 (s), 1602 (m), 1572 (m), 1466 (m), 1423 (m), 1370 (m), 1320 (m), 1320 (m), 1280 (w), 1195 (s), 1151 (s), 1065 (m), 1040 (m), 961 (w), 884 (w) cm^{-1}; MS (El, 70 eV) 350 (M^+), 308, 266 (100%), 237, 181, 138, 110, 95, 69, 43. HRMS calcd for $C_{11}H_{11}O_5I$ 349.9651, found 349.9657. Anal. Calcd for $C_{11}H_{11}0_51$: C, 37.74; H,3.17. Found: C, 37.68; H, 3.16.

3. (*S*)-(*E*)-*p*-Tolyl-2-(tri-n-butylstannyl)vinyl sulfoxide (4)

To a solution of *trans*-1,2-bis(tri-*n*-butylstannyl)ethylene[19] (6.1 7 g, 10.2 mmol) in THF (33 mL) at −78 °C was added *n*-butyllithium (5.00 mL, 12.2 mmol, *c* 2.44 M in hexane) under a N_2 atmosphere. This mixture was stirred for 1 h at −78 °C, after which time it was added very rapidly to a solution of (*R*)-(+)-menthol *p*-tolylsulfinate (3.00 g, 10.2 mmol) in THF (100 mL) at −78 °C. The reaction mixture was stirred 15 min/at −78 °C and then quenched with a solution of aqueous saturated NH_4Cl (25 mL). After warming to room temperature, water (10 mL) and ether (100 mL) were added and the organic layer was separated. The remaining aqueous layer was washed with diethyl ether (2×75 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to yield a crude yellow oil. Column chromatography (4:1, hexane/ethyl acetate) provided an inseparable mixture of the product and menthol. Sublimation of menthol at 0.1 mmHg and 40 °C yielded the pure product (**3**) as yellow oil (3.02 g, 65%); $[\alpha]_D^{25}$ −137° (*c* 1 0.71, $CHCl_3$; lit.[8]=−140°). ^1H NMR ($CDCl_3$) δ 0.83 (9H, t), 0.95–1.05 (6H, m), 1.15–1.25 (6H, m), 1.25–1.55 (6H, m), 2.37 (3H, s), 6.54 (1H, d, *J*=18.1), 7.26 (2H, d, *J*=8.0), 7.32 (1H, d, *J*=18.1), 7.45 (2H, d, *J*=8.0); ^{13}C NMR ($CDCl_3$) δ 6 10.09, 13.60, 21.39, 27.16, 28.92, 125.03, 130.05, 136.03, 140.96, 141.44, 147.80; IR (neat) 2956 (br s), 1551 (w), 1492 (w), 1465 (m), 1376 (w), 1085 (s), 1051 (m) cm^{-1}; MS (El, 70 eV); HRMS calcd for $C_{21}H_{27}OSSn$. Anal. Calcd for $C_{21}H_{27}OSSn$: C, 55.40; H, 7.92; S, 7.05. Found: C, 55.46; H, 7.86; S, 7.13.

3.1. (*S*)-(*E*)-2-(2,6-Diacetoxy-4-methoxyphenyl)vinyl p-tolyl sulfoxide (5)

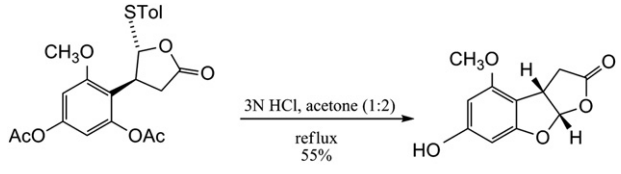
A mixture of aryl iodide (3) (1.39 g, 3.96 mmol), Pd_2dba_3[7] (182 mg, 0.20 mmol), and PPh_3 (104 mg, 0.40 mmol) were dissolved in dry toluene (20 mL). This mixture was warmed to 110 °C and a solution of the stannyl sulfoxide (**4**) (2.16 g, 4.80 mmol) in toluene (8 mL) was added via a syringe pump over a period of 2 h. After completion of the addition, the mixture was refluxed an additional hour, filtered through a short bed of silica gel and concentrated in vacuo. Elution of the resulting oil (ethyl acetate/hexane, 2:1) yielded the desired compound (**5**) (1.00 g, 65%) as a tan solid: mp 122–124 °C; recrystallization provided an analytically pure sample: mp 125–126 °C (diethyl ether); $[\alpha]_D^{25}$ −106° (*c* 1.08, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.10 (6H, s), 2.41 (3H, s), 3.79 (3H, s), 6.78 (1H, d, *J*=15.6), 7.15 (1H, d, *J*=15.8), 7.33 (2H, d, *J*=7.88), 7.52 (2H, d, *J*=8.18); ^{13}C NMR ($CDCl_3$) δ 20.61, 21.28, 55.68, 106.97,113.43,124.45, 124.80, 130.14, 137.33, 140.92, 141.72, 150.33, 160.57, 168.19; IR (film) 2940 (w), 1768 (br s), 1618 (s), 1568 (w), 1458 (w), 1436 (w), 1373 (w), 1319 (m), 1193 (s), 1164 (m), 1139 (m), 1041(s) cm^{-1}; MS (CI, NH_3) 406 (M+NH_4), 389 (M+H,100%), 371, 268, 193, 164, 136, 106, 77; HRMS calcd for $C_{20}H_{20}O_6SH$ 389.1059, found 389.1067. Anal. Calcd for $C_{20}H_{20}O_6S$: C, 61.84; H, 5.18. Found: C, 61.65; H, 5.21.

3.2. (3*S*),(4*S*)-3-(2,6-Diacetoxy-4-methoxyphenyl)-4-(p-tolyl) thio-*y*-butyrolactone (6)

Under a N_2 atmosphere, freshly activated anhydrous zinc dust (2.46 g, 37.6 mmol) and anhydrous cuprous chloride (3.72 g, 37.6 mmol) were refluxed together in THF (50 mL) for 1 h. The resulting suspension of zinc/copper couple was cooled to −45 °C and a solution of the vinyl sulfoxide (5) (0.73 g, 1.88 mmol) in THF (10 mL) was added. With strong stirring, freshly distilled trichloroacetyl chloride (1.05 mL, 9.40 mmol) was added drop wise over 5 min at −45 °C. After 10 min, the solids were filtered off and washed with ethyl acetate (2×20 mL). The organic layer was washed with aqueous saturated $NaHCO_3$ solution (1×20 mL), dried over $MgSO_4$, filtered, and concentrated to yield a 7:1 mixture of *trans* and *cis* dichlorolactones as a brown oil, which was immediately dehalogenated.

The crude dichlorolactones were heated for 6 h at 80 °C in the presence of glacial acetic acid (20 mL) and zinc dust (4.91 g, 75.2 mmol). Upon complete dehalogenation, the solids were filtered off and washed with ethyl acetate (2×25 mL). The organic layer was washed with aqueous saturated $NaHCO_3$ solution (5×25 mL), dried over $MgSO_4$, filtered, and concentrated to yield the crude *trans* lactone as a yellow oil. Elution with hexane/ethyl acetate (4:1) provided the dehalogenated *trans* lactone (**6**) as a white foam (560 mg, 70% over two steps); $[\alpha]_D^{25}$ −72° (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.32 (6H s), 2.33 (3H, s), 2.53 (1H, d, *J*=1.75), 2.55 (1H, d, *J*=5.58), 3.75 (3H, s), 3.76 (1H, m), 5.51 (1H, d, *J*=3.87), 6.57 (2H, s), 7.14 (2H, d, *J*=7.89),7.41 (2H, d, *J*=8.07); ^{13}C NMR ($CDCl_3$) δ 20.74, 20.99, 34.24, 37.10, 55.52, 90.83, 106.95, 117.54, 126.86, 129.95, 134.28, 139.30, 149.72, 159.36, 168.64, 175.54; IR (film) 2944 (w), 2368 (m), 1770 (br s), 1622 (s), 1494 (s), 1435 (m), 1370 (m), 1321 (m), 1177 (s), 1036 (s) cm^{-1}; MS (Cl, NH_3) 448 (M+NH_4), 431 (M+H), 413, 371, 282 (100%), 263, 136; HRMS calcd for $C_{22}H_{22}O_7SH$ 431.1164, found 431.1153. Anal. Calcd for $C_{22}H_{22}O_7S$: C, 61.38; H, 5.15. Found: C, 61.41; H, 5.25.

3.3. (3a*S*,8a*S*)-4-Hydroxy-6-methoxy-3a,8a-dihydrofuro[2,3-*b*]benzofuran-2(3*H*)-one (7)



6a >95% ee **7a** 80% ee

The lactone (**6**) (665 mg, 1.54 mmol) was heated at 80 °C with acetone (6 mL) and 3 N aqueous HCl solution (3 mL) for 1.5–3.0 h. Upon consumption of all starting material, the mixture was cooled to room temperature and partitioned between ethyl acetate (20 mL) and aqueous saturated NaCl solution (20 mL). After removing the organic layer, the aqueous layer was washed with ethyl acetate (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Chromatography of the crude oil yielded a crystalline solid (188 mg, 55%) mp 177–179 °C; $[\alpha]_D^{25}$ −128° (*c* 0.605, acetone); ^1H NMR (acetone-d_6) δ 2.80 (1H, dd, *J*=1.70, 18.0), 3.08 (1H, dd, *J*=9.25, 18.0), 3.69 (3H, s), 4.24 (1H, ddd, *J*=1.77, 6.05, 9.19), 6.07 (1H, d, *J*=1.84), 6.08 (1H, d, *J*=1.89), 6.57 (1H, d, *J*=6.01), 8.87 (1H, br s); ^{13}C NMR (acetone-d_6) δ 33.64, 41.21, 55.72, 89.43, 96.65, 106.05, 109.48, 155.57, 160.47, 163.41, 174.84; IR (KBr) 3288 (br s), 2978 (w), 1733 (br s), 1648 (s), 1644 (s), 1514 (s), 1477 (s), 1412 (m), 1369 (w), 1210 (m), 1134 (s), 1035 (m), 996 (s) cm^{-1}; MS (El, 70 eV) 222 (M^+), 193 (100%), 149, 137; HRMS calcd for $C_{11}H_{11}O_5$ 222.0528, found 222.0520. Anal. Calcd for $C_{11}H_{11}O_5$: C, 59.46; H, 4.54. Found: C, 59.55; H, 4.43.

3.4. (3a*S*,8a*S*)-4-(*tert*-Butyldimethylsilyloxy)-3a,8a-dihydro-6-methoxyfuro[2,3-*b*]benzofuran-2(3*H*)-one

The furanone (**7**) (153 mg, 0.688 mmol) was dissolved in dry DMF (6 mL) under an N_2 atmosphere. Imidazole (190 mg, 2.75 mmol) followed by TBS chloride (207 mg 1.38 mmol) were

added and the mixture was allowed to stir for 3 h at room temperature. The organic layer was then partitioned between ethyl acetate (10 mL) and aqueous saturated ammonium chloride solution (10 mL). The organic layer was removed and the aqueous layer was washed with ethyl acetate (3×10 mL). The combined organic layers were dried over MgSO4, filtered, and concentrated. Chromatography (hexane/ethyl acetate, 4:1) provided the protected furanone as a thick colorless oil (220 mg, 98%); $[\alpha]_D^{25}$ −107° (*c* 1.03, CHCI3); ^{1}H NMR (CDCI3) 60.13 (3H, s), 0.18 (3H, s), 0.88 (9H, s), 2.83 (1H, d, *J*=4.01), 2.84 (1H, d, *J*=7.40), 3.64 (3H, s), 4.02 (1H, ddd, *J*=4.12, 6.20, 7.13), 5.91 (1H, d, *J*=2.05), 6.06 (1H, d, *J*=2.04), 6.39(1H, d, *J*=6.12); ^{13}C NMR ($CDCl_3$) 6−4.42, −4.16, 17.94, 25.52, 33.23, 40.64, 55.55, 90.18, 98.82, 108.27, 108.66, 153.13, 159.39, 162.44, 174.18; IR (film) 2933 (s), 1791 (s), 1699 (s), 1683 (m), 1634 (s), 1558 (m), 1540 (m), 1506 (m), 1456 (m), 1143 (w) cm^{-1}; MS (El, 70 eV) 336 (M^+), 321, 307, 291, 279, 251, 166, 97,73 (100%); HRMS calcd for $C_{17}H_{24}O_5Si$ 336.1393, found 336.1392. Anal. Calcd for $C_{17}H_{24}O_5Si$: C, 60.71; H, 7.19. Found: C, 60.72; H, 7.29.

3.5. (3a*S*,8a*S*)-4-(*tert*-Butyldimethylsilyloxy)-2,3,3a,8a,tetrahydro-2-hydroxy-6-methoxyfuro[2,3-*b*] benzofuran

The silyl protected furanone (223 mg, 0.663 mmol) was dissolved in CH_2Cl_2 (15 mL) and cooled to −78 °C. DIBAL (0.723 mL, 0.723 mmol, *c* 1 M in CH_2Cl_2) was added drop wise over 5 min. After stirring 30 min at −78 °C, the reaction was quenched with aqueous saturated ammonium chloride solution (10 mL), the organic layer was removed, and the aqueous layer was washed with CH_2Cl_2 (4×20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Chromatography (hexane/ethyl acetate, 2:1) yielded the lactol as a colorless oil containing a 1:1 mixture of diastereomers (179 mg, 80%).

3.6. (3a*S*,8a*S*)-4-(*tert*-Butyldimethylsilyloxy)-6-methoxy-2-(phenylthio)-2,3,3a,8a-tetrahydrofuro[2,3-*b*]benzofuran (8)

Tri-*n*-butylphosphine (88.3 μl, 0.354 mmol) was added to a solution of *N*-phenylthiosuccinimide (73.5 mg, 0.354 mmol) in benzene (2 mL) at 25 °C under N_2. After stirring for 15 min, a solution of the lactols (100 mg, 0.295 mmol) in benzene (0.5 mL) was added rapidly. The resulting solution was allowed to stir at 25 °C for 15 min, at which time water (2 mL) was added. The organic layer was removed, dried over Na_2SO_4, filtered, and concentrated. The resulting crude oil yielded the desired compound (**8**) upon elution with hexane/ethyl acetate (6:1) as colorless oil containing a 2:1 mixture of diastereomers (99.2 mg, 78%). Major isomer: ^{1}H NMR ($CDCl_3$) δ 0.22 (3H, s), 0.26 (3H, s), 2.18 (1H, ddd, *J*=8.66, 10.7, 12.8), 2.61 (1H, dd, *J*=4.7, 12.5), 3.72 (3H, s), 3.96 (1H, dd, *J*=6.00,8.61), 5.30 (1H, dd, *J*=4.90, 10.6), 5.36 (1H, d, *J*=5.80), 5.94 (1H, d, *J*=2.04), 6.07 (1H, d, *J*=1.95), 7.26 (3H, m), 7.51 (2H, m); ^{13}C NMR ($CDCl_3$) δ −4.42, −4.11, 17.97, 25.57, 37.46, 44.44, 55.41, 85.85, 89.27, 98.85, 109.10, 111.55, 127.28, 128.90, 131.26, 134.06, 152.76, 161.00, 161.73; IR (film) 3059 (w), 2954 (s), 2360 (s), 1734 (s), 1616 (m), 1496 (m), 1369 (m), 1254 (m), 1195 (m), 1147(m), 1082 (m) cm^{-1}; MS (El, 70 eV) 430 (M^+), 401, 321 (100%), 293, 263, 73; HRMS calcd for $C_{23}H_{30}O_4SSi$ 430.1634, found 430.1632. Anal. Calcd for $C_{23}H_{30}O_4SSi$: C, 64.16; H, 7.02. Found: C, 64.23; H, 7.04.

Minor isomer: ^{1}H NMR ($CDCl_3$) δ 0.25 (3H, s), 0.30 (3H, s), 1.00 (9H, s), 2.52 (1H, dd, *J*=1.18, 13.2), 2.68 (1H, ddd *J*=7.80, 9.00, 13.6), 3.57 (3H, s), 4.00 (1H, dd, *J*=6.16, 8.70), 5.37(1H, d, *J*=6.00), 5.72 (1H, dd, 1.18, 7.80), 5.98 (1H, d, *J*=2.01), 6.13 (1H, d, *J*=1.98), 7.26 (3H, m), 7.50 (2H, m); ^{13}C NMR ($CDCl_3$) δ 5−4.28, −4.07, 18.01, 25.62, 38.27, 44.50, 55.36, 88.31, 89.62, 98.62, 110.24, 112.90, 126.96, 128.63, 131.51, 135.88, 152.54, 161.20, 161.88; IR (film) 3059 (w), 2954 (s), 2360 (s), 1734 (s), 1616 (m), 1496 (m), 1369 (m), 1254 (m), 1195 (m), 1147(m), 1082 (m) cm^{-1}; MS(El, 70 eV) 430 (M^+), 401, 321 (100%), 293, 263, 73; HRMS calcd for $C_{23}H_{30}O_4SSi$ 430.1634, found 430.1632. Anal. Calcd for $C_{23}H_{30}O_4SSi$: C, 64.16; H, 7.02. Found: C, 64.23; H, 7.04.

3.7. (3a*S*,8a*S*)-4-(*tert*-Butyldimethylsilyloxy)-6-methoxy-2-(phenylsulfinyl)2,3,3a,8a-tetrahydrofuro[2,3-*b*]benzofuran

A mixture of the thioacetals (**9**) (80.0 mg, 0.186 mmol) and anhydrous sodium carbonate (98.4 mg, 0.929 mmol) were stirred together in CH_2Cl_2 (4 mL) at −78 °C under N_2. A solution of 60% *m*-CPBA (53.4 mg, 0.186 mmol) in CH_2Cl_2 (1 mL) was added drop wise over 5 min. After stirring an additional 15 min at −78 °C, aqueous saturated Na_2CO_3 solution (1 mL) was added. The organic layer was decanted from the solids and washed with 0.5 N aqueous NaOH solution (5×5 mL). The organic layer was then dried over anhydrous Na_2CO_3, filtered and concentrated to yield the crude sulfoxides as colorless oil (80.0 mg, 96%). Purification on silica (3:1, hexane/ethyl acetate) provided a 2:1:1 mixture of three diastereomers. Major diastereomer: ^{1}H NMR ($CDCl_3$) δ 0.10 (3H, s), 0.16 (3H, s), 0.89 (9H, s), 1.99 (1H, ddd, *J*=1.76, 5.99, 13.2), 2.80 (1H, dt, *J*=8.90, 13.2), 3.69 (3H, s), 4.03 (1H, ddd, *J*=1.66, 5.58, 9.04), 4.69 (1H, dd, *J*=6.00, 8.23), 5.88 (1H, d, *J*=2.00), 6.06 (1H, d, *J*=1.99) 6.38 (2H, d, *J*=5.57), 7.48 (3H, m), 7.54 (2H, m) ^{13}C NMR ($CDCl_3$) δ 8−4.33, −4.28, 17.94, 25.51, 27.05, 44.20, 55.50, 89.62, 89.53, 97.53, 99.12, 109.43, 112.84, 124.11, 129.21, 131.20, 140.07, 152.82, 140.07, 152.82, 160.33, 161.91; IR (film) 2930 (m), 1630 (s), 1624 (s), 1558 (s), 1497 (m), 1436 (m), 1256 (w), 1196 (m), 1140 (s), 1081(s). Anal. Calcd for $C_{23}H_{30}O_5SSi$: C, 61.86; H, 6.77. Found: C, 61.57; H, 6.87. Minor diastereomer A ^{1}H NMR ($CDCl_3$) δ 50.21 (3H, s), 0.24 (3H, s), 0.98 (6H, s), 2.48 (1H, ddd, *J*=3.04, 6.86, 13.6), 2.76 (1H, ddd, *J*=7.07, 9.18, 13.5), 3.69 (3H, s), 3.87 (1H, ddd, *J*=2.89, 5.56, 9.11), 4.60 (1H, d, *J*=7.18), 5.94 (1H, d, *J*=2.05), 6.03 (1H, d, *J*=1.97), 6.32 (1H, d, *J*=5.66), 7.51 (3H, m), 7.62 (2H, m); ^{13}C NMR ($CDCl_3$) δ 5−4.34, −4.10, 18.13, 25.64, 32.10, 44.47, 55.54, 89.73, 95.65, 99.29, 109.81, 112.97, 125.19,129.11, 131.45, 140.13, 152.80, 160.24, 162.01; IR (film) 2930 (m), 1630 (s), 1624 (s), 1558 (s), 1497 (m), 1436 (m), 1256 (w), 1196 (m), 1140 (s), 1081(s). Anal. Calcd for $C_{23}H_{30}O_5SSi$: C, 61.86; 1−1, 6.77. Found: C, 61.57; H, 6.87. Minor diastereomer B ^{1}H NMR ($CDCl_3$) δ 50.27 (3H,s), 0.34 (3H, s), 1.03 (6H, s), 2.63 (1H, ddd, *J*=7.27, 8.95, 14.5), 3.12 (1H, d, *J*=14.8), 3.76 (3H, s), 4.05 (1H, dd, *J*=6.00, 8.58), 4.89 (1H, t, *J*=6.85), 6.35 (1H, d, *J*=5.89), 7.51 (3H, m), 7.63 (2H, m); ^{13}C NMR ($CDCl_3$) δ 5−4.03, −4.00, 18.04, 25.71, 33.14, 43.88, 55.54, 89.86, 99.27, 99.66, 109.45, 113.19, 125.31, 128.76, 131.18, 139.98, 153.20, 159.13, 162.41; IR (film) 2930 (m), 1630 (s), 1624 (s), 1558 (s), 1497 (m), 1436 (m), 1256 (w), 1196 (m), 1140 (s), 1081 (s). Anal. Calcd for $C_{23}H_{30}O_5SSi$: C, 61.86; H, 6.77. Found: C, 61.57; H, 6.87.

3.8. (3a*S*,8a*S*)-4-(*tert*-Butyldimethylsilyloxy)-3a,8a-dihydro-6-methoxyfuro[2,3-*b*]benzofuran

A solution of the crude sulfoxides (80.0 mg, 0.179 mmol) in toluene (4 mL) and dry pyridine (28.9 μl, 0.358 mmol) were heated at 110 °C for 40 min. Aqueous saturated Na_2CO_3 solution (2 mL) was added. The organic layer was removed and the aqueous layer was washed with ethyl acetate (1×2 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. Chromatography (6:1, hexane/ethyl acetate) of the resulting oil provided the vinyl ether as a colorless oil (55.4 mg, 97%); $[\alpha]_D^{25}$ −155° (*c* 0.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 60.25 (3H, s), 0.26 (3H, s), 1.01 (9H, s), 3.72 (3H, s), 4.50 (1H, dt, *J*=7.18, 2.18), 5.29 (1H, dd, *J*=2.35, 2.80), 5.94 (1H, d, *J*=2.00), 6.14 (1H, d, *J*=2.00), 6.42 (1H, dd, *J*=2.16, 2.82), 6.64 (1H, d, *J*=7.16); ^{13}C NMR

($CDCl_3$) δ −4.32, −4.18, 18.06, 25.60, 48.42, 55.50, 89.77, 98.82, 103.06,110.50, 112.11, 144.67, 152.22, 159.86, 161.37; IR (film) 2955 (s), 2845 (s), 1683 (br s), 1622 (s), 1496 (m), 1471 (m), 1471 (m), 1435 (m), 1333 (w), 1254 (m), 1202 (s), 1142, 1087 (s), 966 (s); MS (El, 70 eV) 320 (M^+), 291 (100%), 263, 235, 189, 73; HRMS calcd for $C_{17}H_{24}O_4Si$ 320.1444, found 320.1438. Anal. Calcd for $C_{17}H_{24}O_4Si$: C, 63.81; H, 7.56. Found: C, 63.89; H, 7.59.

3.9. (3a*S*,8a*S*)-4-Hydroxy-6-methoxy-3a(*S*),8a(*R*)-dihydrofuro [2,3-*b*]benzofuran (9)

The silyl protected vinyl ether (50.0 mg, 0.156 mmole) was dissolved in dry CH_3CN (4 mL) at 0 °C under N_2. Anhydrous cesium fluoride (28.4 mg, 0.187 mmol) was added and the mixture stirred for 3 h at 0 °C. Aqueous saturated sodium bicarbonate solution (2 mL) was added and the organic layer was removed. The aqueous layer was then washed with ethyl acetate (1×5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to yield the crude vinyl ether. Column chromatography (2:1, hexane/ethyl acetate) provided the pure compound (32.0 mg, 100%): mp 153–155 °C An analytical sample was obtained after crystallization: mp 156–157 °C (CH_2Cl_2/hexane); $[\alpha]_D^{25}$ −194° (*c* 0.67, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.72 (3H, s), 4.56 (1H, dd, *J*=7.16, 2.04), 5.34 (1H, t, *J*=2.56), 5.37 (1H, br s), 5.93 (1H, d, *J*=1.95),6.11 (1H,d,*J*=1.86), 6.44(1H,t,*J*=2.40), 6.68(1H,d,*J*=7.18); ^{13}C NMR ($CDCl_3$) δ 647.89, 55.60, 89.50, 95.30, 102.89, 106.49, 112.35, 144.75, 152.25, 160.19, 161.59; IR (KBr) 3391 (br s), 1645 (s), 1614 (s), 1508 (m), 1442 (m), 1370 (w), 1212 (m), 1192 (m), 1147 (m), 1062 (5), 966 (s); MS (El, 70 eV) 206 (M^+), 191, 177 (100%), 149, 69; HRMS calcd for $C_{11}H_{10}O_4$ 206.0579, found 206.0573. Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.88. Found: C, 63.14; H, 4.78.

3.10. (3a*S*,8a*S*)-6-Methoxy-4-[2(*R*)-methoxy-2-(trifluoromethyl)phenylacetoxy]-3a(*S*),8a(*S*)-dihydrofuro[2,3-*b*]benzofuran 10

The dihydrofuran (**9**) (12 mg, 0.058 mmol) was dissolved in dry pyridine (0.5 mL) and cooled to 0 °C. Excess *R* (+) MPTA chloride[17] (0.10 mL) was added drop wise. The reaction was allowed to warm to room temperature and stir for 3 h. Pyridine was then removed in vacuo, benzene (2 mL) was added and the organic layer was washed with aqueous saturated $NaHCO_3$ solution (1×2 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. ^1H NMR (benzene-d_6) of Mosher's ester **10** indicated an 8.1:1 ratio of diastereomers (80% ee), as determined by integration of the vinyl proton signals at 4.21 and 5.91, and the acetal proton at 6.43. Column chromatography (4:1, hexane/ethyl acetate) provided an analytical sample of the Mosher's ester (22 mg, 90%); $[\alpha]_D^{25}$ −82° (*c* 0.44, $CHCl_3$); ^1H NMR (benzene-d_6) δ 3.06 (3H, s), 3.43 (3H, d, *J*=1.11), 3.97 (1H, dt, *J*=2.19, 7.23), 4.71 (1H, t, *J*=2.58), 5.91 (1H, t, *J*=2.47), 6.22 (2H, d, 7.18), 6.32 (2H, d, *J*=2.03), 6.39 92H, d, *J*=2.05), 7.07 (3H, m), 7.75 (2H, m; IR (film) 2942 (w), 1771 (s), 1635 (s), 1496 (s), 1472 (m), 1456 (m), 1182 (br s), 1128 (s) cm^{-1}; MS (El, 70 eV) 423,422 (M^+), 394, 393, 220, 190, 189(100%), 105; HRMS calcd for $C_{21}H_{17}O_6F_3$ 422.0977, found 422.0987. Anal. Calcd for $C_{21}H_{17}O_6F_3$: C, 59.72; H, 4.06. Found: C, 59.73; H, 4.15.

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Supplementary data

Supplementary data associated with this article, includes copy of ^1H and ^{13}C NMR. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.10.003.

References and notes

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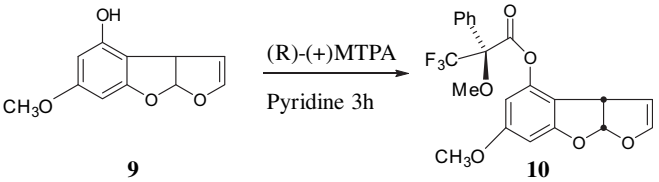
9. Compound **3** was synthesized in two steps from 5-methoxyresorcinol[18] together with the regioisomer, 2,4-diacetoxy-6-methoxyiodobenzene. First, acetylation (AcCl, pyr, THF) gave the bis protected phenol in 75% yield. Iodination (AgO_2CCF_3, I_2, CH_2Cl_2) provided a 1:1 mixture of regioisomer **3** in 44% yield.
10. For a leading reference see: Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.
11. Analysis of lactone **6** by HPLC on a Chiracel-OD column indicated that **6** was 98% ee: HPLC conditions—(95:5 hexanes/isopropanol 0.6 mL/min), t_R (−) lactone=24.8 min; t_R (+)lactone=28 min. $[\alpha]_D^{25}$ −72° (*c* 2.0, chloroform)
12. The enantiomeric purity of the final dihydrofuran **9** was determined via its Mosher's ester **10** (Ref. 17). Integration of signals for the two vinyl ether protons at 4.71 and 5.91 and the acetal proton at 6.43 indicate a ratio of 8.1:1 of the two distereomers of the ester, corresponding to an ee of 80%.



9 **10**

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