Novel Synthesis of Highly Functionalized Unsymmetrical Biphenyls

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Synopsis. Unsymmetrical biphenyls bearing methoxycarbonyl, formyl, and hydroxyl groups have been synthesized via aromatization of the aryltetrahydrobenzofuranone, followed by oxidative cleavage of the furan ring.

Recently, highly functionalized unsymmetrical biphenyls, e.g., steganone and WS-43708, have attracted considerable interest owing to their interesting biological activities.[1,2] The common methods for synthesizing unsymmetrical biphenyls are those based on crossed aryl–aryl coupling reactions,[3] including transition metal-catalyzed coupling reactions,[4,5] the nucleophilic addition of a Grignard reagent to an aryloxazoline derivative[6] and an intramolecular Ullmann coupling reaction utilizing salicyl alcohol as a template.[7] In contrast to extensive investigations of these aryl–aryl coupling reactions, less attention has been focused on the synthetic method of biphenyls via oxidative aromatizations.[8] In connection with synthetic studies in a search for a new antihyperlipidemic agent,[9] we now report on a new approach to synthesize unsymmetrical biphenyls (**8**,**9**) having methoxycarbonyl, formyl, and hydroxyl groups via aromatization of aryltetrahydrobenzofuranone (**4**), followed by an oxidative cleavage of the furan ring.

Results and Discussion

We recently reported on a facile synthesis of 1-aryltetralones based on a conjugate addition-aldol reaction utilizing cyanohydrins.[10] We applied this method to the synthesis of aryltetrahydrobenzofuranone (**4**). Thus, the conjugate addition of cyanohydrin (**1**) to methyl acrylate was examined under conditions similar to those employed in a conjugate addition using the phenyl derivatives of cyanohydrin.[10] The addition of an anion, generated from **1** and lithium diisopropylamide (LDA), to methyl acrylate proceeded smoothyl in THF at −78 °C. Without isolating the adduct, the reaction mixture was quenched with 3,4-dimethoxybenzaldehyde to afford the desired hydroxy-ester (**2**) in 96% yield as a mixture of diastereomers (Scheme 1). Cyclization of **2** was effected with trifluoroacetic acid to give the ester (**3**). Without purification of **3**, the crude product was deprotected with tetrabutylammonium fluoride to afford the aryltetrahydrobenzofuranone (**4**) in 69% yield from **2**. Several methods were examined for the dehydrogenation of **4**. By far, the best results were obtained when **4** was treated with pyridinium tribromide and triethylamine.[11,12] By this method the arylbenzofuran (**5**) was obtained in 91% yield.

Having secured a method for forming the arylbenzofuran, we turned our attention to a cleavage of the furan ring. It has been well documented that benzo[*b*]furans are oxidized to be converted into the corresponding hydroxy-aldehydes.[13] Thus, we initially conducted exploratory studies for a cleavage of the benzo[*b*]furan moiety of **5** by using methoxymethyl ether (**6**) in order to avoid any possible side reactions associated with the oxidation of unprotected **5** (Scheme 2). The methoxymethyl ether (**6**) was prepared from **5** under standard conditions. Attempts to oxidize **6** to the aldehyde (**8**) using oxidizing reagents, e.g., K_2CrO_4, $Na_2Cr_2O_7$, and CrO_3, were unsuccessful. The preparation of the aldehyde (**8**) could, however, be successfully accomplished via the diol (**7**). Thus, a treatment of **6** with osmium tetroxide in the presence of *N*-methylmorpholine *N*-oxide[14] afforded **7** in 88% yield. A treatment of **7** with sodium periodate afforded the protected biphenyl (**8**) in 91% yield.

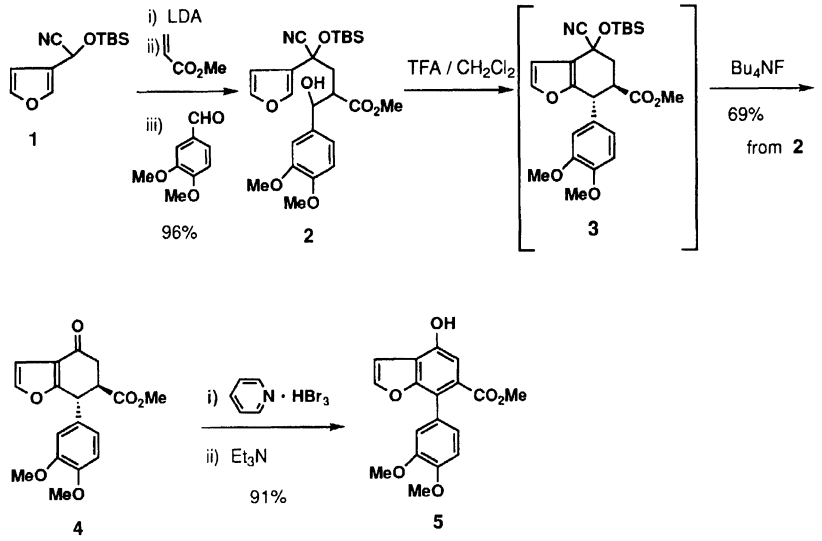
Finally, we attempted to synthesize biphenyl (**9**) via oxidation of the arylbenzofuran (**5**). After some experimentation, we found that the desired biphenyl (**9**) could be obtained in 51% yield by the reaction of **5** with osmium tetroxide in the presence of sodium periodate.[13a]

In conclusion, we have developed an efficient method for synthesizing highly functionalized unsymmetrical biphenyls. This method should be applicable not only to the synthesis of side-chain derivatives, but also to the elaboration of other polycyclic systems.

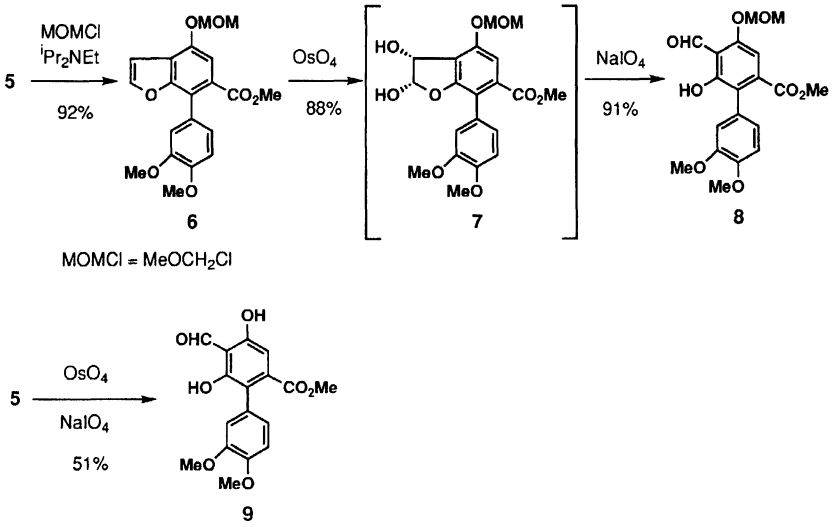
Experimental

α-(*t*-Butyldimethylsiloxy)-α-(furan-3-yl)acetonitrile (1). To a solution of 3-furaldehyde (180 g, 1.88 mol) in acetonitrile (3 L) was added successively KCN (182 g, 2.98 mol), TBSCl (360 g, 2.26 mol) and ZnI_2 (0.5 g) at room temperature under vigorous stirring. After one day, the insoluble materials were removed by filtration and rinsed thoroughly with Et_2O (500 cm^3). The filtrate was concentrated in vacuo and the residue was dissolved in Et_2O (1 L). The solution was washed with water (200 cm^3), dried ($MgSO_4$) and concentrated. The residue was distilled under reduced pressure to afford 411 g (92%) of **1**: Bp 95—102 °C/2—3 mmHg (1 mmHg=133.322 Pa); IR (film) 2250, 1515 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.20 (s, 6H, 2×$SiCH_3$), 0.90 (s, 9H, *t*-Bu), 5.44 (s, 1H, CHCN), 6.43 (d, J=3 Hz, 1H, ArH), 7.47 (d, J=3 Hz, 2H, ArH); MS m/z 237 (M^+).

Methyl γ-(*t*-Butyldimethylsiloxy)-γ-cyano-γ-(fu-



Scheme 1.



Scheme 2.

ran-3-yl)-α-(α-hydroxy-3,4-dimethoxybenzyl)butyrate (2). To a stirred solution of LDA in THF [prepared from 9.4 g (92.8 mmol) of diisopropylamine and 58 cm^3 (92.8 mmol) of butyllithium (1.6 mol cm^{-3} in hexane) in 100 cm^3 of THF] were successively added **1** (20.0 g, 84.4 mmol) in THF (20 cm^3), methyl acrylate (7.26 g, 84.4 mmol) in THF (100 cm^3) and 3,4-dimethoxybenzaldehyde (14.0 g, 84.4 mmol) in THF (20 cm^3) at −78 °C. After 10 min, AcOH (13 cm^3) was added. The mixture was poured into a mixture of H_2O (100 cm^3) and AcOEt (200 cm^3). The organic layer was separated, washed with water, dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by silica-gel chromatography using hexane/AcOEt (3 : 1) as an eluent afforded a mixture of four diastereoisomers (**2**) (41.1 g, 96%). The mixture was used in the next step.

(6*R,7*R**)-4-(*t*-Butyldimethylsiloxy)-4-cyano-7-(3,4-dimethoxyphenyl)-6-methoxycarbonyl-4,5,6,7-tetrahydrobenzo[*b*]furan (3).** To a stirred solution of the diastereomers (**2**) (40.0 g, 81.8 mmol) in 100 cm^3 of CH_2Cl_2 at 0 °C was added TFA (10 cm^3). After stirring at room temperature for 8 h, the reaction mixture was poured into water (100 cm^3). The organic layer was washed with water, dried ($MgSO_4$) and concentrated in vacuo to afford a mixture of two diastereomers (**3**) (40.1 g). The mixture was used in the next step without purification.

(6*R,7*R**)-7-(3,4-Dimethoxyphenyl)-6-methoxycarbonyl-4-oxo-4,5,6,7-tetrahydrobenzo[*b*]furan (4).** To a stirred solution of **3** (40.1 g) in CH_2Cl_2 (100 cm^3) was added dropwise Bu_4NF (1 mol dm^{-3} in THF, 90 cm^3, 90 mmol) at room temperature. After 1 h, the reaction mixture was poured into 10% citric acid (200 cm^3). The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Crystallization of the residue from MeOH gave **4** (18.6 g, 69% from **2**): Mp 177—179 °C; IR (KBr) 1740, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.79 (d, J=8.1 Hz, 2H, $COCH_2$), 3.33 (dd, J=7.3, 8.1 Hz, 1H, $CHCO_2$), 3.62 (s, 3H, CO_2Me), 3.79 (s, 3H, OMe), 3.82 (s, 3H, OMe), 4.66 (d, J=7.3 Hz, 1H, CHAr), 6.5—7.2 (m, 4H, ArH), 7.46 (d, J=3 Hz, 1H, ArH); MS m/z 330 (M^+). Anal. Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49%. Found: C, 65.31; H, 5.30%.

7-(3,4-Dimethoxyphenyl)-4-hydroxy-6-methoxycarbonylbenzo[*b*]furan (5). To a stirred solution of pyridinium tribromide (3.05 g, 9.56 mmol) in AcOH (20 cm^3) at room temperature was added **4** (2.64 g, 7.96 mmol) portionwise. The mixture was stirred at 50 °C for 20 min. The resulting mixture was poured into a mixture of chloroform and water (1:1, 200 cm^3). The organic layer was washed with brine and dried ($MgSO_4$). To the solution was added triethylamine (50 cm^3) at 0 °C. After 5 min, the mixture was acidified with 12 M HCl (pH=1) (1 M=1 mol dm^{-3}). The organic layer was washed with brine, dried ($MgSO_4$) and concentrated. Crystallization from MeOH afforded **5** (2.61 g, 91%): Mp 180—182 °C; IR (KBr) 3600, 1715, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.62 (s, 3H, CO_2Me), 3.79 (s, 3H, OMe), 3.82 (s, 3H, OMe), 6.5—7.2 (m, 5H, ArH), 7.36 (d, J=3 Hz, 1H, ArH), 9.0 (br, 1H, OH); MS m/z 328 (M^+). Anal. Calcd for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91%. Found: C, 65.64; H, 4.98%.

7-(3,4-Dimethoxyphenyl)-6-methoxycarbonyl-4-methoxymethoxybenzo[*b*]furan (6). To a stirred solution of **5** (2.0 g, 6.09 mmol) in CH_2Cl_2 (100 cm^3) were added dropwise ethyldiisopropylamine (1.05 g, 8.38 mmol) and chloromethyl methyl ether (590 mg, 7.32 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The solution was washed with water (20 cm^3), 10% citric acid and brine. The organic layer was dried ($MgSO_4$) and concentrated to give a yellow residue. The residue was crystallized from $CHCl_3$–diisopropyl ether to afford **6** (2.87 g, 92%): Mp 178—181 °C; IR (KBr) 1724 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.72 (s, 3H, CO_2Me), 3.79 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.91 (s, 3H, OMe), 5.30 (s, 2H, CH_2), 6.7—7.3 (m, 5H, ArH), 7.36 (d, J=3 Hz, 1H, ArH); MS m/z 372 (M^+). Anal. Calcd for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41%. Found: C, 64.55; H, 5.25%.

(2*S, 3*R**)-2,3-Dihydroxy-7-(3,4-dimethoxyphenyl)-6-methoxycarbonyl-4-methoxymethoxy-2,3-dihydrobenzo[*b*]furan (7).** To a stirred solution of **6** (2.0 g, 5.38 mmol) in dioxane–water (10:1, 22 cm^3) were added osmium tetroxide (0.5% in 2-propanol, 5 cm^3) and *N*-methylmorpholine *N*-oxide (3.18 g, 21.4 mmol) at room temperature. The mixture was stirred at 50 °C for 2 d. The reaction mixture was allowed to cool to room temperature and was then quenched by the addition of aqueous sodium hydrogensulfite (10%, 50 cm^3). The solvent was removed under reduced pressure, and the residue was dissolved in $CHCl_3$ (100 cm^3). The solution was washed with 10% citric acid and brine, dried ($MgSO_4$) and concentrated. Crystallization of the residue form MeOH afforded **7** (1.92 g, 88%): Mp 148—149 °C; IR (KBr) 3300, 1724 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.74 (s, 3H, CO_2Me), 3.77 (s, 3H, OMe), 3.88 (s, 3H, OMe), 3.91 (s, 3H, OMe), 5.30 (s, 2H, CH_2), 5.4—6.4 (m, 4H, HOCHOAr and HOCHAr), 6.5—6.9 (m, 4H, ArH); MS m/z 406 (M^+). Anal. Calcd for $C_{20}H_{22}O_9$: C, 59.11; H, 5.46%. Found: C, 59.12; H, 5.29%.

3-Formyl-2-hydroxy-3′,4′-dimethoxy-6-methoxycarbonyl-4-methoxymethoxybiphenyl (8). To a solution of **7** (1 g, 2.46 mmol) in acetone (20 cm^3) was added dropwise sodium metaperiodate solution (1.04 g, 4.92 mmol in 2 cm^3 of water) at room temperature. After 30 min, precipitates were collected by filtration, washed with water, dried ($MgSO_4$) and concentrated under reduced pressure. Recrystallization of the solid from $CHCl_3$–diisopropyl ether gave **8** (843 mg, 91%): Mp 189—190 °C; IR (KBr) 3600, 1724, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.76 (s, 3H, CO_2Me), 3.77 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.91 (s, 3H, OMe), 5.32 (s, 2H, OCH_2O), 6.5—6.9 (m, 4H, ArH), 9.1 (br, 1H, OH), 10.2 (br, 1H, CHO); MS m/z 376 (M^+). Anal. Calcd for $C_{19}H_{20}O_8$: C, 60.64; H, 5.36%. Found: C, 60.75; H, 5.28%.

3-Formyl-2,4-dihydroxy-3′,4′-dimethoxy-6-methoxycarbonyl Biphenyl (9). To a solution of **5** (2.0 g, 6.09 mmol) in THF (20 cm^3) were added osmium tetroxide (0.5% in 2-propanol, 5 cm^3) and sodium metaperiodate (2.87 g, 13.4 mmol) at room temperature. The mixture was stirred at 50 °C for 2 d. The reaction mixture was allowed to cool to room temperature and was then quenched by the addition of aqueous sodium hydrogensulfite (10%, 50 cm^3). The solvent was removed under reduced pressure, and the residue was dissolved in $CHCl_3$. The organic solution was washed with 10% citric acid and brine, dried ($MgSO_4$) and concentrated in vacuo. Crystallization of the residue from MeOH afforded **9** (1.03 g, 51%): Mp 191—193 °C; IR (KBr) 3600, 1730, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ=3.81 (s, 3H, OMe), 3.85 (3H, OMe), 3.89 (s, 3H, OMe), 6.5—7.0 (m, 4H, ArH), 9.21 (br, 1H, OH), 9.86 (br, 1H, CHO), 10.18 (br, 1H, OH); MS m/z 332 (M^+). Anal. Calcd for $C_{17}H_{16}O_7$: C, 61.44; H, 4.85%. Found: C, 61.18; H, 5.02%.

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