Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 7509–7513

TETRAHEDRON

The first total synthesis of Cicerfuran utilizing a one-pot synthesis of hydroxylated benzofurans

Zoltán Novák, Géza Timári*,† and András Kotschy*

Department of General and Inorganic Chemistry, Eötvös Loránd University, Pázmány Péter s. 1/A, H-1117 Budapest, Hungary

Received 27 May 2003; revised 30 June 2003; accepted 25 July 2003

Dedicated to Professor Csaba Szántay on the occasion of his 75th birthday.

Abstract—A simple one-pot procedure was elaborated for the preparation of hydroxylated benzofurans from halogenated phenols and was successfully applied to the first total synthesis of Cicerfuran, a natural defence agent of wild chickpea.

1. Introduction

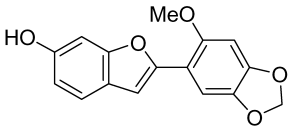
In nature's collection of biologically active heterocycles, benzo[*b*]furan derivatives[1–4] constitute a major group. They are usually important constituents of plant extracts used in traditional medicine,[2] and some of them, for example hydroxylated benzofurans such as Euparin[5] or Coumestrol,[6] also play an important role in the natural defence mechanism of their plant. Another important member of the hydroxybenzofuran family, Cicerfuran[7] (**1**, Fig. 1) is of particular interest since it is believed to protect wild chickpea from *Fusarium* wilt, a pathogen imposing a major constraint on the production of the world's third most important pulse crop, chickpea. Due to this effect a synthetic route leading to **1** and extendable to its analogues would be of general interest. An obvious route to **1** would utilize the cross-coupling of the benzofuran and sesamol moieties as demonstrated for analogous systems by Timári.[8] Unfortunately if we were to extend this procedure to the synthesis of analogues of **1**, then the selective preparation of differently substituted benzofurans would be needed, a task that has not been solved generally yet. An alternate approach, that relies on the sequential setup of the molecular skeleton with a concluding furan ring formation is presented in Scheme 1.

We envisaged the formation of **1** through the ring closure of the *o*-alkynyl-phenol **2**,[9–15] which in turn is available through the sequential Sonogashira coupling of aryl-halides **3** and **4** with a masked acetylene, such as 2-methyl-3-butyn-3-ol[16] or trimethylsilylacetylene.[17] The key step of this approach is the formation of the non-symmetrical diarylethyne (**2**) which upon liberating the hydroxyl group, hopefully spontaneously ring closes to the benzofuran.

In spite of the large number of publications describing the conversion of 2-halophenols to benzo[*b*]furans[9–15] the preparation of hydroxylated benzofurans has received only limited attention so far.[12,14,15] By analogy such a process would start from a halogenated dihydroxybenzene. These compounds usually fail to undergo Sonogashira coupling and all the successful procedures on similar systems utilize the selective protection of the different hydroxyl groups. If we could establish a single protecting group that allows for an efficient coupling and is easy to remove to initiate the ring closure to the benzofuran, then we would eliminate the need for the selective protection of the hydroxyl groups, and open up a more straightforward approach towards hydroxylated benzofurans including Cicerfuran and its analogues. To reach our goal we had to answer the following questions: (i) what protecting group shall we use to achieve the Sonogashira coupling on dihydroxylated bromobenzenes? (ii) How can we extend this approach to more complex molecules such as Cicerfuran?

2. Results and discussion

The first question we addressed was the Sonogashira coupling of hydroxylated bromobenzenes. To that end a



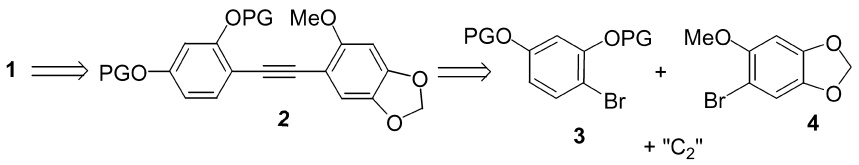
1

Figure 1. The structure of Cicerfuran.

Keywords: cross-coupling; benzofurane; natural product.
* Corresponding authors. Tel.: +36-1-209-0555; fax: +36-1-209-0602; e-mail: kotschy@para.chem.elte.hu

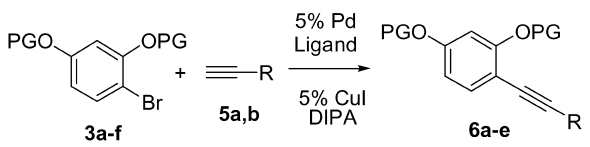
† Present address: Chinoin Co. Ltd., Tó u. 1-5., H-1045 Budapest, Hungary.

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4020(03)01170-0



Scheme 1. Retrosynthetic analysis of the preparation of Cicerfuran (PG=protecting group).

series of 2,4-dihydroxybromobenzene derivatives (**3a**–**f**) were prepared and reacted with phenylacetylene (**5a**) or trimethylsilylacetylene (**5b**) under different conditions (Scheme 2). The results are summarized in Table 1.



Scheme 2.

Table 1. The Sonogashira coupling of resorcine derivatives (**3a**–**f**) with acetylenes **5a**,**b**

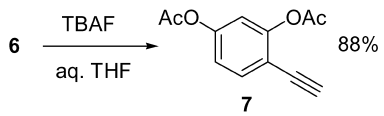
PG	R	Solvent	Time (h)	Conversion[a] (%)
H (**3a**)	Ph (**5a**)	DMF	24	0[b]
H (**3a**)	TMS (**5b**)	DIPA	24	0
TMS (**3b**)	TMS	DIPA	24	0[c]
TBS (**3c**)	Ph	DIPA	70	93
MOM (**3d**)	Ph	DIPA	70	95
Ac (**3e**)	Ph	DIPA	1	95[d]
Ac (**3e**)	TMS	DIPA	1	90[d] (**6**)
TFAc (**3f**)	Ph	DIPA	1	100[d]

[a] Reactions were run at 80°C with 2 equiv. of the alkyne in the presence of 5 mol% $Pd(OAc)_2$ and 5 mol% $P^tBu_3{\cdot}HBF_4$ unless otherwise stated. Conversions were determined by GC and the products were identified by GC-MS.
[b] Run with 5 mol% Pd_2dba_3, 20 mol% PPh_3.
[c] Both desilylation and dehalogenation of **3b** were observed.
[d] Reactions were run at 40°C.

The first coupling experiments on bromoresorcine (**3a**) were unsuccessful and we observed only the homocoupling of the alkyne. We attribute this inactivity (cf. the ready coupling of 2-bromophenol under the same conditions[18]) to the presence of the second hydroxyl group in the ring, which increases its electron density, especially under the alkaline conditions of the coupling. To compensate for the decreased reactivity in the following reactions we changed our catalyst to the highly active Pd–P^tBu_3 system introduced by Fu.[19,20] Unfortunately this catalyst was also ineffective with **3a**. An obvious way to eliminate the unwanted side effects of the hydroxyl groups is their silylation, alkylation or acylation. Changing **3a** to its trimethylsilyl analogue **3b** did not lead to the desired product, but resorcine and 4-bromoresorcine (**3a**) were both detected in the reaction mixture, the former demonstrating that the oxidative addition of the carbon–bromine bond to the palladium does take place under the applied conditions and the latter showing the lability of the TMS group. Change of the TMS group to the more robust *tert*-butyldimethylsilyl (TBS) group (**3c**) eliminated the desilylation pathway and the desired coupling took place providing very good conversion, although requiring prolonged heating at 80°C. The introduction of two methoxymethyl groups onto the bromoresorcine (**3d**) had a similar effect on its reactivity as the TBS group: a conversion of 95% was achieved in 70 h.

The protecting groups discussed so far only replaced the acidic hydrogen in **3a** but did not have a substantial influence on the electron density of the aromatic core. By acetylating the hydroxyl groups of **3a** we observed a marked increase in its reactivity, probably through the depletion of the electron density of the aromatic core. The diacetyl derivative (**3e**) reacted readily with both **5a** and **5b** already at 40°C and nearly full conversion was achieved in 1 h. The bis-trifluoroacetylated resorcine (**3f**) showed the highest reactivity (full conversion at 40°C in less than 1 h) but at the price of an increased lability which became obvious on workup that led to a complex mixture.

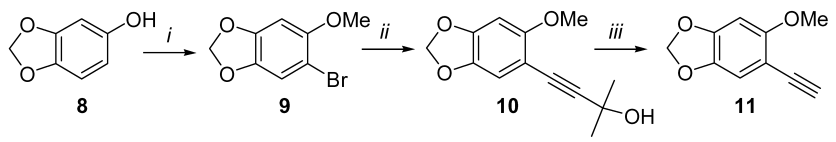
The coupling studies on bromoresorcine derivatives suggest that the optimal partner for such reactions might be the diacetyl derivative **3e**. Indeed we found that the coupling of **3e** and trimethylsilylacetylene (**5b**), when repeated on a larger scale led to **6** in an isolated yield of 78%. The removal of the TMS group was achieved using a standard procedure (Scheme 3).[12] Treatment of **6** with TBAF in aqueous THF gave an 88% isolated yield of **7**. Another advantage of the acetyl protection is the fact, that the introduction of the protecting group and the Sonogashira coupling can be carried out in one-pot. The acetylation of **3a** with 2 equiv. acetyl chloride in the presence of TEA in THF followed by the addition of 2 equiv. phenylacetylene, 5% $Pd(OAc)_2$, 7.5% $P^tBu_3{\cdot}HBF_4$, 5% CuI and 10 equiv. DIPA gave a 93% conversion to the diacetylated coupled product.



Scheme 3.

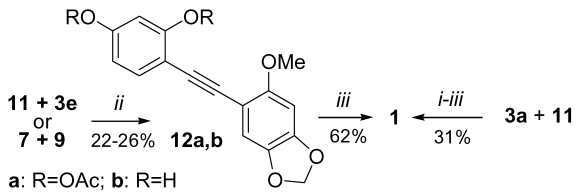
In order to extend this coupling procedure to the synthesis of Cicerfuran we also had to synthesize the coupling partner **11**. Commercially available sesamol (**8**, Scheme 4) was brominated[21] and methylated[22] to give **9**, which underwent Sonogashira coupling in the presence of $(PPh_3)_2PdCl_2$ with 2-methyl-3-butyn-2-ol readily to give **10** in 67% yield. Other catalyst systems that worked equally well in this coupling were Fu's Pd–P^tBu_3[19] and Pd/C, PPh_3 in aqueous DMA.[23] The liberation of the ethynyl group in **10** by KOH in boiling toluene[24] gave **11** in 84% yield. An alternate route to **11** would utilize the coupling of **9** with TMS-acetylene and deprotection using TBAF, but we preferred the former route for economic reasons.

To conclude the synthesis of Cicerfuran we had to carry out



Scheme 4. *Reagents and conditions*: (i) (a) Br_2, AcOH, 0°C, 5 min, 63%; (b) Me_2SO_4, KOH, dioxane, 65°C, 91%. (ii) 2-Methyl-3-butyn-2-ol, 6 mol% $(PPh_3)_2PdCl_2$, 6% CuI, DIPA, 70°C, 48 h, 67%. (iii) KOH, toluene, 110°C, 30 min, 84%.

a final Sonogashira coupling to prepare **12a** (Scheme 5) and liberate the protected hydroxyl groups to initiate the spontaneous ring closure to **1**. To obtain **12** we had two alternate strategies in hand. We could either couple **3e** with **11** or react **7** with **9**. On the basis of previous experience we were unable to establish preference for any of those routes so we tried both. The coupling reactions were run with 1.7 equiv. of alkyne at 50°C in diisopropylamine in the presence of 5 mol% $Pd(OAc)_2$, 5 mol% $P^tBu_3{\cdot}HBF_4$ and 5 mol% CuI. The coupling reactions were complete under these conditions in 210 or 90 min, respectively, but the isolated yields of **12a** were only a disappointing 26 and 22%.



Scheme 5. *Reagents and conditions*: (i) AcCl, TEA, THF, rt. (ii) 5 mol% $Pd(OAc)_2$, 7.5% P^tBu_3, 5% CuI, DIPA, 50°C. (iii) 2.5 equiv. KOH, aq. MeOH, rt.

Some of the loss we attribute to the sensitivity of the product, therefore we tried to convert **12a** to **1** without isolation. Following the coupling of **3e** and **11** under the described conditions the inorganic salts and the solvent were removed and the crude coupling product was taken up in aqueous methanol and refluxed for 2 h in the presence of at least 2.5 equiv. KOH (smaller amounts of KOH led only to partial conversion). The NMR of the crude product showed the presence of 2 products, **1** and **12b** in a ratio of 2:1, from which Cicerfurane (**1**) was isolated by chromatography in a 36% overall yield. Application of the one-pot procedure starting from **3a** led to a similar result. The acetylation of **3a** by acetyl chloride was followed by a Sonogashira coupling with 1 equiv. of **11** and concluded by the liberation of the hydroxyl groups by KOH to give **1** in 31% yield.

In conclusion we elaborated a convenient synthetic procedure for the preparation of 6-hydroxy-benzofuranes that was also extended to the first total synthesis of Cicerfuran.

3. Experimental

3.1. General

Melting points were determined on a hotplate and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Brucker DRX-250 spectrometer in $CDCl_3$ and CH_3SOCH_3. For ^1H NMR spectra the residual peak of $CHCl_3$ (7.26 ppm) and CH_3SOCH_3 (2.50 ppm) were used as the internal reference, while for ^{13}C NMR spectra the central peak of $CDCl_3$ (77.0 ppm) and the central peak CD_3SOCD_3 (39.43 ppm) were used as the reference. The IR spectra were obtained on a Bruker IFS-55 FTIR spectrometer. Combination gas chromatography and low resolution mass spectrometry was obtained on a Hewlett-Packard 5790A Gas Chromatograph (30 m×0.25 mm column with 0.25 μm RH-5 MS+ coating, He carrier gas) and VG 12-250 Mass Spectrometer (Ion source: EI+, 70 eV, 250°C; interface: 250°C). Silica gel was used for flash column chromatography.

3.2. One-pot protection-coupling-ring closure procedure

A dry Schlenk flask is charged with **3a** (189 mg, 1 mmol), triethylamine (202 mg, 278 μL, 2 mmol) and abs. THF (1.2 mL). Acetyl chloride (147 mg, 133 μL, 2 mmol) is added dropwise to the solution at 25°C followed by diisopropylamine (1.2 mL), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), $P^tBu_3{\cdot}HBF_4$ (21.7 mg, 0.075 mmol), CuI (10 mg, 0.05 mmol) and acetylene (2 mmol). The reaction is purged with argon and it was stirred at 60°C. After full conversion (appr. 2 h) MeOH (4 mL) and water (0.8 mL) containing KOH (560 mg, 10 mmol) is added to the reaction mixture and stirring is continued at 75°C for 2 h. The mixture is cooled to 25°C and neutralized with 10% HCl. The resulting suspension is extracted with DCM, and the organic phase is dried over $MgSO_4$. After removal of the solvent the crude product is purified by column chromatography.

3.2.1. 1,3-Diacetoxy-4-trimethylsilylethynylbenzene (6e). A dry Schlenk flask was charged with **3e** (650 mg, 2.38 mmol), $Pd(OAc)_2$ (30 mg, 0.125 mmol, 5%), CuI (15 mg, 0.077 mmol, 2.5%), $P(^tBu)_3{\cdot}HBF_4$ (36 mg, 0.125 mmol), and diisopropylamine (5 mL). After the addition of trimethylsilylacetylene (491 mg, 690 μL, 5 mmol, 2 equiv.) the reaction mixture was sealed and stirred under argon at 40°C for 1 h. Following its cooling to room temperature the reaction mixture was diluted with ether, filtered through a Celite pad and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford **6e** (538 mg, 1.85 mmol) as a yellow oil. Yield: 78%. ^1H NMR ($CDCl_3$; 250 MHz): δ 7.22 (d, 1H, J=8.4 Hz), 6.69–6.75 (m, 2H), 2.06 (s, 3H), 2.01 (s, 3H), 0.0 (s, 9H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 168.4, 168.0, 152.3, 150.9, 133.3, 119.0, 116.0, 114.7, 99.6, 98.8, 20.9, 20.6, −0.3; MS (EI, 70 eV) *m/z* (% relative intensity, ion): 290(5, $[M^+]$), 247(42), 206(83), 191(100), 174(22). IR (KBr) ν_{max}: 2959, 1774, 1609, 1493, 1369, 1251, 1190, 1144, 1101, 1013 cm^{-1}; Anal. calcd for $C_{15}H_{18}O_4Si$: C, 62.04; H, 6.25. Found: C, 61.97; H, 6.44.

3.2.2. 1,3-Diacetoxy-4-ethynylbenzene (7). 6e (538 mg,

1.85 mmol) was dissolved in a mixture of THF (11 mL) and water (1.3 mL) at 0°C and TBAF (2.17 mmol, 2.17 mL, 1 M in THF) was added to the solution. The reaction mixture was left to warm up to 25°C. After the starting material disappeared (1 h by GC) water (13 mL) was added to the mixture and half of the volume of the solvent was removed under reduced pressure. The remaining solution was extracted with diethylether, the combined organic phases were dried over $MgSO_4$ and the solvent was removed in vacuum. The crude product was purified by silica gel column chromatography to afford **7** (353 mg, 1.62 mmol) as yellow oil. Yield: 88%. ^{1}H NMR ($CDCl_3$; 250 MHz): δ 7.50 (d, 1H, J=8.2 Hz), 6.88–7.00 (m, 2H), 3.24 (s, 1H), 2.31 (s, 3H), 2.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 168.4, 168.3, 152.5, 151.2, 133.8, 119.1, 116.1, 113.7, 82.0, 77.8, 20.9, 20.7; MS (EI, 70 eV) m/z (% relative intensity, ion): 218(5, [M$^+$]), 217(12), 176(39), 134(100), 105(15), 78(31). IR (KBr) ν_{max}: 3279, 2926, 1769, 1610, 1493, 1369, 1191, 1144, 1099, 1013 cm^{-1}; Anal. calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 65.85; H, 4.78.

3.2.3. 1-Bromo-2-methoxy-4,5-methylenedioxybenzene (9).[22] Sesamol (7.29 g, 52.8 mmol) was dissolved in glacial acetic acid (16 mL), cooled to 0°C and a solution of bromine (6.64 g, 2.13 mL, 41.5 mmol) in glacial acid (9 mL) was added to it dropwise. The reaction mixture was poured onto ice and the separated greenish solid was filtered, and dried over P_2O_5 in vacuum resulting in bromosesamol (7.2 g, 33.0 mmol). Yield: 66%; mp: 87–88°C (lit.: 88°C). ^{1}H NMR (d_6-DMSO; 250 MHz): δ 9.8 (br, 1H), 7.04 (s, 1H), 6.58 (s, 1H), 5.95 (s, 2H); ^{13}C NMR (d_6-DMSO, 62.5 MHz): δ 148.7, 147.2, 140.5, 111.6, 101.4, 98.30, 98.25; MS (EI, 70 eV) m/z (% relative intensity, ion): 218(80), 216(85, [M$^+$]), 187(14), 160(54), 158(57), 132(37), 130(39), 109(76), 108(100), 95(91).

To a solution of bromosesamol (7.20 g, 33 mmol) in dioxane (34 mL) was added KOH (6.72 g, 120 mmol) and dimethyl sulfate (3.20 mL, 34 mmol). The reaction mixture was stirred at 65°C for 10 h and was left standing at room temperature overnight. Then it was poured onto ice and the white crystals were filtered, washed with water and dried over P_2O_5 in vacuum to give **9** (6.94 g, 30 mmol). Yield: 91%; mp: 75–77°C; ^{1}H NMR ($CDCl_3$; 250 MHz): δ 6.99 (s, 1H), 6.56 (s, 1H), 5.94 (s, 2H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 151.1, 147.7, 141.8, 112.6, 101.7, 101.3, 95.8, 57.1; MS (EI, 70 eV) m/z (% relative intensity, ion): 232(81), 230(90, [M$^+$]), 217(89), 215(96), 187(39), 65(39), 53(100).

3.2.4. 1-(3′-Hydroxy-3′-methyl-butyn-1′-yl)-2-methoxy-4,5-methylenedioxybenzene (10). A dry Schlenk flask was charged with **9** (1.16 g, 5 mmol), $PdCl_2(PPh_3)_2$ (176 mg, 0.25 mmol, 5%), CuI (50 mg, 0.25 mmol, 5%) and diisopropylamine (15 mL), followed by the addition of 2-methyl-3-butyn-2-ol (2.9 mL, 2.52 g, 30 mmol, 6 equiv.). The reaction mixture was stirred under argon in 80°C oil bath for 24 h. After this time (75% conversion) $PdCl_2(PPh_3)_2$ (44 mg, 0.063 mmol, 1.25%), CuI (10 mg, 0.05 mmol, 1%) and alkyne (0.60 mL, 1.25 equiv.) were added and the reaction was continued for another 24 h, when it was complete. The precipitate (diisopropyl-ammonium bromide) was removed by filtration and the solvent was evaporated under reduced pressure to give a brown solid. The crude product was purified by silica gel column chromatography to afford **10** (784 mg, 3.35 mmol) as a white solid. Yield: 67%; mp: 145–148°C; ^{1}H NMR ($CDCl_3$; 250 MHz): δ 6.80 (s, 1H), 6.48 (s, 1H), 5.92 (s, 2H), 3.81 (s, 3H), 2.27 (br, 1H), 1.61 (s, 6H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 156.6, 148.8, 140.9, 112.1, 103.6, 101.5, 96.7, 94.8, 78.4, 65.7, 56.8, 31.5; MS (EI, 70 eV) m/z (% relative intensity, ion): 235(71, [M+1$^+$]), 234(90, [M$^+$]), 220(48), 219(55), 218(54), 216(59), 203(92), 201(52), 177(62), 176(95), 175(71), 161(100), 147(64), 115(52). IR (KBr) ν_{max}: 3293, 2991, 2222, 1617, 1502, 1485, 1466, 1247, 1199, 1163, 1089, 1034, 931 cm^{-1}; Anal. calcd for $C_{13}H_{14}O_4$: C, 66.66%; H, 6.02%. Found: C, 66.80%; H, 5.91%.

3.2.5. 1-Ethynyl-2-methoxy-4,5-methylenedioxybenzene (11). KOH (1.88 g, 33.5 mmol) was added to the solution of **10** (784 mg, 3.35 mmol) in toluene (60 mL) and the reaction mixture was placed into an oil bath preheated at 110°C and stirred vigorously. The reaction was followed by TLC. The deprotection started after 15–20 min and was complete in 5–10 min. In certain runs it was necessary to add more KOH (in 200 mg portions) to the hot mixture to complete the hydrolysis. The resulting suspension was cooled to room temperature, the KOH was filtered off and the toluene was evaporated. The brown crude product was recrystallized from cyclohexane to afford **11** (495 mg, 2.81 mmol) as a yellow solid. Yield: 84%; mp: 69–72°C; ^{1}H NMR ($CDCl_3$; 250 MHz): δ 6.87 (s, 1H), 6.50 (s, 1H), 5.94 (s, 2H), 3.84 (s, 3H), 3.23 (s, 1H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 157.5, 149.3, 140.8, 112.5, 102.6, 101.6, 94.4, 80.2, 79.8, 56.7; MS (EI, 70 eV) m/z (% relative intensity, ion): 176(100, [M$^+$]), 161(74), 133(15), 103(28), 75(56), 53(61). IR (KBr) ν_{max}: 3303, 2981, 2918, 2107, 1622, 1503, 1482, 1420, 1360, 1269, 1192, 1149, 1077, 1034, 1002, 926, 749 cm^{-1}; Anal. calcd for $C_{10}H_8O_3$: C, 68.18; H, 4.58. Found: C, 67.97; H, 4.74.

3.2.6. 6-(2′-(2″,4″-Diacetoxyphenyl)ethynyl)-1-methoxy-3,4-methylenedioxybenzene (12a). A 10 mL dry Schlenk flask was purged with argon and charged with **3e** (219 mg, 0.80 mmol), **11** (237 mg, 1.35 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol, 5%), CuI (1.52 mg, 0.008 mmol, 1%), $P(^tBu)_3$-HBF_4 (12 mg, 0.04 mmol, 5%), and diisopropylamine (1 mL). The reaction mixture was stirred under argon at 50°C for 1.5 h, than it was cooled to 25°C, diluted with ether, filtered through a Celite pad and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford **12** (73 mg, 0.2 mmol) as white solid. Yield: 26%; mp: 153–154°C; ^{1}H NMR ($CDCl_3$; 250 MHz): δ 7.53 (d, 1H, J=8.5 Hz), 6.95–7.02 (m, 2H), 6.87 (s, 1H), 6.52 (s, 1H), 5.95 (s, 2H), 3.84 (s, 3H), 2.36 (s, 3H), 2.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 168.7, 168.5, 156.8, 151.6, 150.5, 149.2, 141.0, 133.0, 119.1, 116.0, 115.5, 111.9, 103.7, 101.6, 94.7, 91.1, 86.3, 56.6, 21.1, 20.8; MS (EI, 70 eV) m/z (% relative intensity, ion): 368(82, [M$^+$]), 326(100), 295(31), 285(35), 270(57), 241(92), 69(75). IR (KBr) ν_{max}: 2971, 1761, 1614, 1502, 1486, 1424, 1369, 1196, 1033 cm^{-1}; Anal. calcd for $C_{20}H_{16}O_7$: C, 65.22; H, 4.38. Found: C, 65.37; H, 4.49.

3.2.7. Cicerfuran (1).[7] A dry Schlenk flask was charged with **3e** (200 mg, 0.73 mmol), **11** (193.4 mg, 1.09 mmol),

$Pd(OAc)_2$ (8.3 mg, 0.0366 mmol, 5%), CuI (7.1 mg, 0.0366 mmol, 5%), $P^tBu_3 \cdot HBF_4$ (10.6 mg, 0.0366 mmol), and diisopropylamine (1 mL). The reaction mixture was stirred under argon at 50°C for 1.5 h, then it was cooled to 25°C, diluted with ether (30 mL), filtered through a Celite pad and concentrated under reduced pressure. The yellow residue was dissolved in a mixture of MeOH (10 mL) and water (2 mL) containing KOH (160 mg, 2.5 mmol) and it was refluxed for 2 h. The brown solution was cooled to 25°C and neutralized with 10% HCl. The resulting suspension was extracted with DCM, and the organic phase was dried over $MgSO_4$. After removal of the solvent the crude product was purified by silica gel column chromatography to afford **1** (75 mg, 0.264 mmol) as white crystals, which showed identical properties with literature data. Yield: 36%; mp: 145–147°C; ^{1}H NMR (d_6-DMSO; 250 MHz): δ 9.6 (br, 1H), 7.37 (d, 1H, J=8.5 Hz), 7.35 (s, 1H), 7.11 (s, 1H), 6.96 (s, 1H), 6.92 (s, 1H), 6.71 (d, 1H, J=8.5 Hz), 6.03 (s, 2H), 3.90 (s, 3H); ^{13}C NMR (d_6-DMSO, 62.5 MHz): δ 155.4, 154.0, 151.8, 150.1, 147.7, 141.0, 121.3, 120.9, 111.1, 104.6, 104.4, 101.5, 97.2, 95.4, 56.3; MS (EI, 70 eV) *m/z* (% relative intensity, ion): 284(91, [M^+]), 269(100), 241(47), 211(11), 183(15), 155(22), 142(26). IR (KBr) ν_{max}: 3480, 1627, 1504, 1487, 1454, 1370, 1262, 1197, 1175, 1149, 1038, 933, 820 cm^{-1}; Anal. calcd for $C_{16}H_{12}O_5$: C, 67.60; H, 4.25. Found: C, 67.88; H, 4.40.

3.2.8. 6-(2′-(2″,4″-Dihydroxyphenyl)ethynyl)-1-methoxy-3,4-methylenedioxybenzene (12b). ^{1}H NMR (d_6-DMSO; 250 MHz): δ 9.6 (br, 2H), 7.90 (d, 1H, J=8.5 Hz), 6.77 (br s, 2H), 6.37 (dd, 1H, J=8.5 Hz, 2.2 Hz), 6.25 (d, 1H, J=2.2 Hz), 5.95 (s, 2H), 3.65 (s, 3H); ^{13}C NMR (d_6-DMSO, 62.5 MHz): δ 164.8, 164.2, 152.1, 147.8, 146.7, 140.2, 115.2, 108.2, 102.4, 100.8, 95.0. The other signals overlap with **1**.

Acknowledgements

The authors thank Dr. K. Torkos for providing the necessary analytical background. The financial support of the Hungarian Ministry of Education (FKFP-0125/2001) is gratefully acknowledged.

References

1. Keay, B. A. *Comprehensive Heterocyclic Chemistry II*, Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 2, p 395.
2. Schneiders, G. E.; Stevenson, R. *J. Org. Chem.* **1979**, *44*, 4710.
3. Yang, Z.; et al. *Tetrahedron Lett.* **1991**, *32*, 2061.
4. Murae, T.; Tanahashi, Y.; Takahashi, T. *Tetrahedron* **1968**, *24*, 2177.
5. Kamthong, B.; Robertson, A. *J. Chem. Soc.* **1939**, 925.
6. Emerson, O. H.; Bickoff, E. M. *J. Am. Chem. Soc.* **1958**, *80*, 4381.
7. Stevenson, P. C.; Veitch, N. C. *Phytochemistry* **1998**, *48*, 947.
8. Soós, T.; Timári, G.; Hajós, G. *Tetrahedron Lett.* **1999**, *40*, 8607.
9. There are several publications describing the synthesis of benzo[*b*]furans starting from *o*-halophenols. Some recent representative examples include Refs. 10–15.
10. Friedrichsen, W. *Comprehensive Heterocyclic Chemistry II*, Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 2, p 351.
11. Arcadi, A.; Cacchi, S.; Di Giuseppe, S.; Fabrizi, G.; Marinelli, F. *Synlett* **2002**, 453.
12. Hiroya, K.; Suzuki, N.; Yasuhara, A.; Egawa, Y.; Kasano, A.; Sakamoto, T. *J. Chem. Soc. Perkin Trans. 1* **2000**, 4339.
13. Kundu, N. G.; Pal, M.; Mahanty, J. S.; De, M. *J. Chem. Soc. Perkin Trans. 1* **1997**, 2815.
14. Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280.
15. Sogawa, A.; Tsukayama, M.; Nozaki, H.; Nakayama, M. *Heterocycles* **1996**, *43*, 201.
16. Chow, H.-F.; Wan, C.-W.; Low, K.-H.; Yeung, Y.-Y. *J. Org. Chem.* **2001**, *66*, 1910.
17. Mio, M. J.; Kopel, L. C.; Braun, J. B.; Gadzikwa, T. L.; Hull, K. L.; Brisbois, R. G.; Markworth, C. J.; Grieco, P. A. *Org. Lett.* **2002**, *4*, 3199.
18. Villemin, D.; Goussu, D. *Heterocycles* **1989**, *29*, 1255.
19. Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729.
20. Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295.
21. Alewander, B. H.; Oda, T. A.; Brown, R. T.; Gertler, S. I. *J. Org. Chem.* **1958**, *23*, 1969.
22. Tseng, T.-H.; Tsheng, Y.-M.; Lee, Y.-J.; Hsu, H.-L. *J. Chin. Chem. Soc. (Taipei)* **2000**, *47*, 1165.
23. Novák, Z.; Szabó, A.; Répási, J.; Kotschy, A. *J. Org. Chem.* **2003**, *68*, 3327.
24. Neenan, T. X.; Whitesides, G. M. *J. Org. Chem.* **1988**, *53*, 2489.