Regioselectivity in the Reductive Cleavage of Pyrogallol Derivatives: Reductive Electrophilic Substitution of Acetals of 2,3-Dimethoxyphenol

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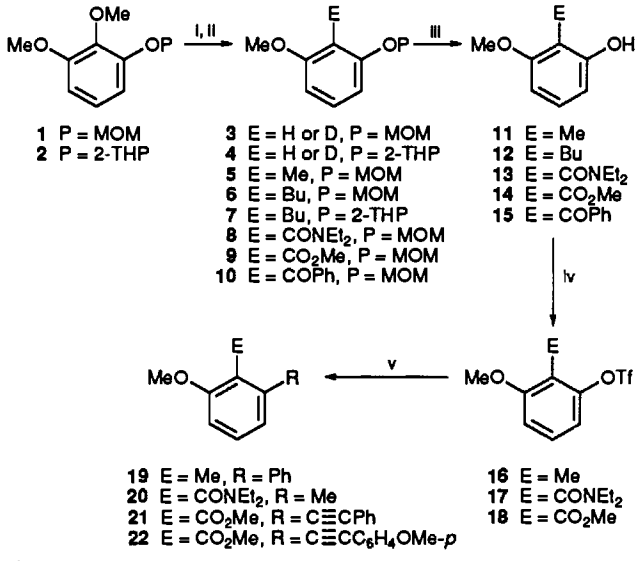
Acetals of 2,3-dimethoxyphenol were used as the starting materials for the transformation of 1,2,3-trioxygenated benzenes into various 1-oxygenated-2,3-dicarbon-substituted benzenes, *via* regioselective reductive electrophilic substitution of the 2-methoxy group, followed by conversion into the corresponding triflates and a Pd-catalysed cross-coupling reaction. The regioselectivity of the reductive cleavage is ascribed to twisting of the leaving methoxy group out of the plane of the aromatic ring by the two *ortho* substituents. According to this methodology, a new synthesis of lunularic acid is presented.

The reductive cleavage of carbon–oxygen bonds of aryl ethers is a topic of current interest, and several recent papers are devoted to the investigation of this reaction.[1] We have recently reported that the reductive cleavage of 1,2,3-trimethoxybenzene and its 5-substituted derivatives with alkali metals in tetrahydrofuran (THF) affords almost quantitative demethoxylation in the 2-position. The reaction proceeds *via* the intermediate formation of the corresponding 2,6-dimethoxyaryl carbanions, thus disclosing a new and efficient approach to the synthesis of 2- and 2,5-substituted resorcinol dimethyl ethers.[2]

In order to obtain more detailed information on the factors affecting the regioselectivity of this reaction, we have investigated the reductive cleavage of other derivatives of pyrogallol, and we now describe an extension of the above mentioned procedure allowing the transformation of derivatives of 1,2,3-trioxygenated benzene into 1-oxygenated-2,3-dicarbon-substituted aromatics. To this end, we have investigated the reductive electrophilic substitution of acetals of 2,3-dimethoxyphenol, compounds **1** and **2**, planning to complete the reaction sequence through successive selective hydrolysis of the acetal group, transformation of the 2,3-disubstituted phenols thus obtained into the corresponding triflates, and a Pd-catalysed cross-coupling reaction[3] of the last compound with nucleophilic reagents (Scheme 1). A previous report concerning the regioselective reductive electrophilic substitution of 1,2-dimethoxy-3-(methoxymethoxy)benzene **1** has already appeared.[4]



1 P = MOM
2 P = 2-THP

3 E = H or D, P = MOM
4 E = H or D, P = 2-THP
5 E = Me, P = MOM
6 E = Bu, P = MOM
7 E = Bu, P = 2-THP
8 E = $CONEt_2$, P = MOM
9 E = CO_2Me, P = MOM
10 E = COPh, P = MOM

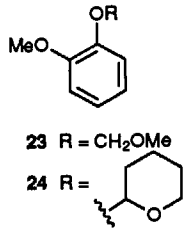
11 E = Me
12 E = Bu
13 E = $CONEt_2$
14 E = CO_2Me
15 E = COPh

16 E = Me
17 E = $CONEt_2$
18 E = CO_2Me

19 E = Me, R = Ph
20 E = $CONEt_2$, R = Me
21 E = CO_2Me, R = $C{\equiv}CPh$
22 E = CO_2Me, R = $C{\equiv}CC_6H_4OMe$-*p*

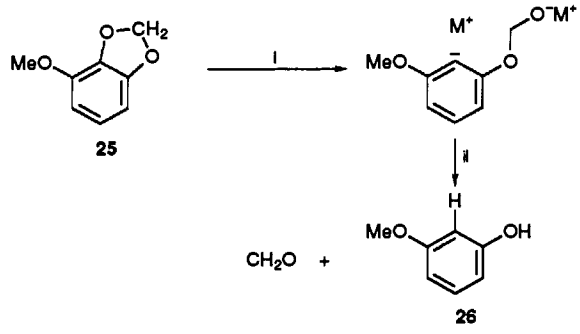
Scheme 1 *Reagents:* i, K, THF; ii, EX; iii, HCl, MeOH; iv, $(Tf)_2O$, pyridine; v, $[PdL_m]$, R_nM. MOM = methoxymethyl, 2-THP = tetrahydropyran-2-yl.

As a complementary approach, we have investigated the reductive cleavage of 1-methoxy-2,3-(methylenedioxy)benzene **25**; indeed, reductive dealkoxylation at the 2-position of



23 R = CH_2OMe
24 R =

compound **25** should lead, after aqueous work-up, to the formation of 3-methoxyphenol **26** (Scheme 2),[5] whilst trapping with electrophiles of the (supposed) 2,6-dialkoxy-substituted carbanionic intermediate should afford 2-substituted-3-methoxyphenols.



Scheme 2 *Reagents:* i, 2 M; ii, water

Results

Two different acetalic groups, *i.e.*, methoxymethyl (MOM) and 2-tetrahydropyranyl (THP), were chosen to protect the phenolic function of 1,2-dimethoxyphenol during reduction with alkali metals in aprotic solvents. Accordingly, 1,2-dimethoxy-3-(methoxymethoxy)benzene **1** and 2,3-dimethoxyphenyl tetrahydropyran-2-yl ether **2**, were synthesized in good yields by known methods.[6,7] For comparison purposes, 1-methoxy-3-(methoxymethoxy)benzene **3**, 1-methoxy-2-(methoxymethoxy)benzene **23**, 3-methoxyphenyl tetrahydropyran-2-yl ether **4** and 2-methoxyphenyl tetrahydropyran-2-yl ether **24**, were prepared analogously from the corresponding phenols.

1-Methoxy-2,3-(methylenedioxy)benzene **25** was synthesized

Table 1 Reductive cleavage of compounds **1** and **2**[a]

Entry	Compound	Metal	Solvent	Time (*t*/h)	Product	Yield[b] (%)	D[c] (%)
1	**1**	K	THF	7	**3**	90[d]	ND[e]
2	**1**	K	THF	12	**3**	90	ND[e]
3	**1**	K	THF	17	**3**	91	>90
4	**1**	K	THF	48	**3**	87	>90
5	**1**	Na	THF	24	**3**	20[d]	ND[e]
6	**1**	Li	THF	24	**3**	53[f]	ND[e]
7	**1**	K	isooctane	24	**3**	51[d]	>90
8	**1**	K	Et_2O	24	**3**	84	78
9	**2**	K	THF	6	**4**	89	>90
10	**2**	Na	THF	24	**4**	8[d]	ND[e]

[a] Reactions were run at room temperature in the presence of 3 mol equiv. of metal. [b] Isolated yield, unless otherwise indicated. [c] Deuterium incorporation determined by ^1H NMR spectroscopic monitoring of the percentage of deuterium incorporation at the 2-position (see Experimental section). [d] Determined by ^1H NMR spectroscopy; no other product, aside from starting material, was detected to any considerable extent. [e] ND = Not determined. [f] Formation of considerable amounts of phenolic compounds was observed.

in 60% yield by the reaction of 3-methoxybenzene-1,2-diol with CH_2Br_2 under basic phase-transfer reaction conditions.[8]

Reductive Cleavage Reactions.—These reactions were carried out under Ar at room temperature in the presence of the freshly cut metal. Selected results are reported in Table 1. The results of D_2O-quenching experiments, carried out to check the formation of carbanionic intermediates, are also reported in Table 1.

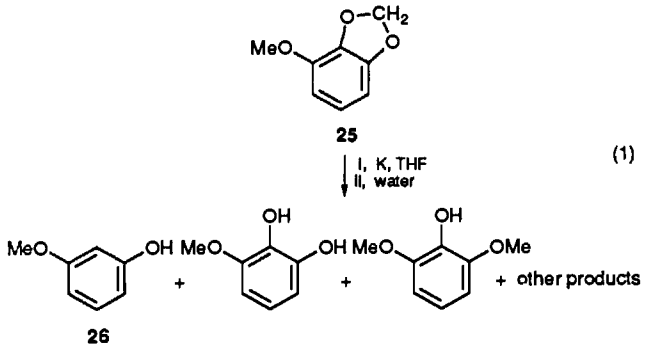
The regioselective demethoxylation in the 2-position of compound **1** can be conveniently performed by the action of potassium metal (3 mol equiv.) in anhydrous THF at room temperature for 12 h. Quenching of the reaction mixture with water or with anhydrous EtOH (*caution!*) afforded 1-methoxy-3-(methoxymethoxy)benzene **3** in good yield (Table 1, entry 2); D_2O-quenching showed almost quantitative formation of the corresponding arylpotassium derivative. This carbanion appears to be stable under the reaction conditions for a long time (Table 1, entries 3 and 4). Reductive cleavage with sodium metal was by far less effective, and led to recovery of the starting material to a high extent (Table 1, entry 5), whilst reductive cleavage with lithium metal afforded a high percentage of unidentified phenolic products (Table 1, entry 6).

Besides THF, 2,2,4-trimethylpentane (isooctane) and diethyl ether were tested as solvents for the reductive cleavage of compound **1** with potassium metal. Demethoxylation at the 2-position was observed in both cases: however, only moderate conversion took place in isooctane after 24 h reaction time (Table 1, entry 7), whilst a relatively low amount of the intermediate carbanion was evidenced in Et_2O (Table 1, entry 8).

No other products of dealkoxylation, such as 1-methoxy-2-(methoxymethoxy)benzene **23** or 1,2-dimethoxybenzene, were detected in the reaction mixtures, by either GLC or ^1H NMR (300 MHz) spectroscopy (estimated error < 5%).

Reductive cleavage of compound **2** with potassium metal in THF afforded a similar result: acetal **4**, the product of regioselective demethoxylation at the 2-position, was obtained in good yield after 6 h at room temperature. Again, the reaction proceeded through the almost quantitative intermediate formation of the 2,6-disubstituted aryl carbanion (Table 1, entry 9). When compound **2** was treated with sodium metal in THF, compound **4** was formed in only 8% yield in 24 h (Table 1, entry 10).

At variance with these results, reduction of the methylenedioxy derivative **25** with potassium metal in THF at room temperature for 24 h afforded a relatively complex reaction mixture [eqn. (1)]: starting material was recovered to a high extent (32%), together with a mixture of phenolic products containing the desired 3-methoxyphenol **26**, in low yield (< 20%, as estimated by ^1H NMR spectroscopy). By treatment with sodium metal, the reductive cleavage occurred practically not at all, and compound **25** was recovered unchanged after 24 h. These results showed the uselessness of this synthetic approach; accordingly, the reductive cleavage of acetal **25** was not further investigated.*



Reductive Electrophilic Substitution.—The reductive electrophilic substitution reactions (Scheme 1) were run in THF using potassium metal as the reducing agent. Reductions of compound **1** were run at room temperature for 12–18 h, while compound **2** was similarly reduced within 6 h. The results are reported in Table 2.

Inspection of Table 2 shows that alkylation with primary alkyl halides was achieved under mild reaction conditions: an excess (3 mol equiv.) of methyl iodide was added at 0 °C to the reaction mixture obtained by the action of potassium metal on compound **1**; after stirring of the mixture for 1 h, standard work-up afforded 1-methoxy-3-methoxymethoxy-2-methylbenzene **5** in satisfactory yield, as well as a small amount of the product of reductive demethoxylation (Table 2, entry 1). A similar result was obtained by employing butyl iodide as an electrophile, starting from either substrate **1** or **2**: the 2-butyl-substituted aromatics **6** and **7** were obtained in 57 and 60% yield, respectively (Table 2, entries 2 and 3).†

In contrast, quenching of the reaction mixture obtained by reductive cleavage of compound **1** with isopropyl iodide did not

* No products of bimolecular recombination of the liberated formaldehyde with aromatic anions (or radical anions) were detected.

† Quenching of the mixture obtained by the reductive cleavage of compound **1** with butyl bromide afforded compound **6** in 55% yield.

Table 2 Reductive electrophilic substitution of compounds **1** and **2**

Entry	Compound	Electrophile	Temp. (T/°C)	Time (t/h)	Product, E	Yield (%)[a,b]
1	**1**	MeI	0	1	**5**, Me	75
2	**1**	BuI	0	24	**6**, Bu	57
3	**2**	BuI	0	2	**7**, Bu	60
4	**1**	Pr^iI	0	24	**3**, H	88
5	**1**	$ClCONEt_2$	−40	2.5	**8**, $CONEt_2$	50[c]
6	**1**	$ClCO_2Me$	−40	2.5	**9**, CO_2Me	66
7	**1**	ClCOPh	−40	1	**10**, COPh	51[c]

[a] Isolated yield, unless otherwise indicated. [b] No other product, aside from **3** or **4**, was detected to any considerable extent. [c] Yield determined on the corresponding phenol, after acidic hydrolysis of the acetal moiety.

Table 3 Cross-coupling reactions

Compound	Catalyst (mol %)	R_nM (mol equiv.)	Solvent[a]	Temp. (T/°C)	Time (t/h)	Product [Yield (%)][b]
16	$Pd(PPh_3)_4$ (5)	$PhB(OH)_2$[c] (2)	DME	85	5	**19** (80)
17	$PdCl_2(PPh_3)_2$ (20)	$SnMe_4$[d] (3)	DMF	120	8	**20** (49)
18	$PdCl_2(PPh_3)_2$ (5)	PhC≡CH[e] (1.5)	DMF	90	16	**21** (90)
18	$PdCl_2(PPh_3)_2$ (5)	ArC≡CH[e,f] (1.5)	DMF	90	14	**22** (85)

[a] DME = 1,3-dimethoxyethane, DMF = dimethylformamide. [b] Isolated yields. [c] In the presence of both 6.5 mol equiv. of 2 mol dm^{-3} Na_2CO_3 and 3 mol equiv. of LiCl. [d] In two portions, according to ref. 3*a*, and in the presence of both 8 mol. equiv. of LiCl and 0.6 mol equiv. of PPh_3. [e] In the presence of 4.5 mol equiv. of Et_3N. [f] Ar = 4-(MeO)C_6H_4.

afford the desired alkyl-substituted derivative, but only the product of reductive demethoxylation, compound **3** (Table 2, entry 4). Similar results were previously observed during attempted reductive electrophilic substitution of 1,2,3-trimethoxybenzene and its 5-substituted derivatives with secondary alkyl halides.[2]

The carbanionic intermediate generated by the reductive cleavage of compound **1** with potassium metal was successfully trapped also with several carboxyl derivatives; *N*,*N*-diethyl-2-methoxy-6-(methoxymethoxy)benzamide **8**, methyl 2-methoxy-6-(methoxymethoxy)benzoate **9** and 2-methoxy-6-(methoxymethoxy)benzophenone **10** were obtained in satisfactory yields upon quenching with an excess (3 mol equiv.) of *N*,*N*-diethylcarbamoyl chloride, methyl chloromethanoate and benzoyl chloride, respectively (Table 2, entries 5–7).

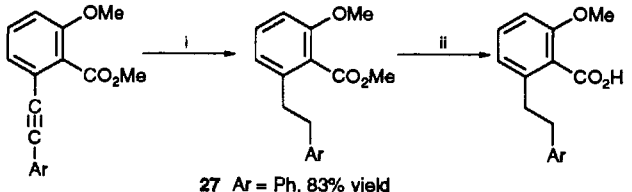
Synthesis of Triflates.—Mild acidic hydrolysis of compounds **5**–**10** (0.6 mol dm^{-3} HCl in methanol; room temp.; 1 h) allowed the removal of the acetal protecting group; the corresponding phenols **11**–**15** were obtained in almost quantitative yields. Phenols **13**–**15** were also prepared in high yield by acidic hydrolysis of compounds **8**–**10**, respectively, with 3 mol dm^{-3} HCl in aqueous propan-2-ol overnight at room temperature. Under the last reaction conditions, acetals **5** and **6** afforded complex reaction mixtures.

According to a known procedure,[3c] reaction of phenols **11**, **13** and **14** with trifluoromethanesulfonic anhydride in pyridine afforded the triflates **16**–**18** in 70–80% yield.

Cross-coupling Reactions.—To test the flexibility of the proposed methodology, triflates **16**–**18** were allowed to react with different coupling reagents in the presence of a Pd catalyst (Scheme 1). According to this procedure compounds **19**–**22**, were obtained. Reaction conditions and yields are reported in Table 3.

Good yields were obtained in the cross-coupling reactions involving phenylboronic acid or acetylenes as the coupling reagents, while a somewhat lower yield was obtained in the synthesis of the amide **20**, an intermediate in the synthesis of several isocoumarins.[9] It is interesting to observe that the conditions needed in this last case are unusual. Indeed, the Pd-catalysed cross-coupling reaction of an electron-poor and hindered triflate such as **17** with an organostannane usually requires a small amount of catalyst and no addition of the phosphinic ligand.[3c] On the other hand, we obtained a satisfactory yield of the desired amide only under reaction conditions which are typical of electron-rich triflates.[3a]

Synthetic Applications.—As an application of the above reported methodology to the synthesis of natural products and analogues, acetylenes **21** and **22** were hydrogenated at room temperature and ambient pressure to afford methyl 2-methoxy-6-(2-phenylethyl)benzoate **27** and methyl 2-methoxy-6-[2-(4'-methoxyphenyl)ethyl]benzoate **28**, respectively (Scheme 3). Basic hydrolysis of the ester **28** afforded 2-methoxy-6-[2-(4'-methoxyphenyl)ethyl]benzoic acid **29**, the dimethyl ether of lunularic acid, a growth inhibitor found in *Lunularia cruciata*.[10] Conversion of compound **28** into lunularic acid has already been described.[10b]



27 Ar = Ph, 83% yield
28 Ar = C_6H_4OMe-*p*, 87% yield

21 Ar = Ph
22 Ar = C_6H_4OMe-*p*

29 Ar = C_6H_4OMe-*p*, 85% yield

Scheme 3 *Reagents and conditions:* i, H_2, Pd/C, 1 atm, room temp.; ii, KOH, aq. EtOH, reflux

Discussion

The synthetic procedure described herein shows the feasibility of transforming derivatives of 1,2,3-trioxygenated benzene into 1-oxygenated-2,3-dicarbon-substituted aromatics, and represents a considerable extension of our previous results with 1,2,3-trimethoxybenzene and its 5-substituted homologues.[2]

The main features of this highly regioselective reductive electrophilic substitution are the following: (i) easy access to

the starting materials; (ii) high regioselectivity due to *ipso*-substitution of the 2-methoxy group; (iii) the reaction conditions allow the introduction of several functionalities which are, in principle, not stable to reduction with alkali metals. Our reaction represents a useful alternative to the known metallation of 1-methoxy-3-(methoxymethoxy)benzene[6] **3** and of 3-methoxyphenyl tetrahydropyran-2-yl ether[11] **4** with alkyllithium derivatives, followed by reaction with electrophiles. Indeed, the high regioselectivity observed in the synthetic procedure described herein competes well with the results obtained in these metallation reactions.*

As already observed, the key step in the proposed reaction sequence is the regioselective reductive cleavage of suitable acetals of 2,3-dimethoxybenzene; this finding deserves a mechanistic comment. Indeed, it is worth noting that this procedure allows the regioselective removal of the 2-methoxy group in the presence of either a methoxymethoxy or a tetrahydropyran-2-yl group. This is at variance with previous reports showing that the reductive cleavage of aryl–oxygen bonds is more easily obtained with methoxymethyl[5,13] or tetrahydropyran-2-yl[13] aryl ethers than with the methyl ethers, and supports the hypothesis of Maercker[1d] concerning the relationship between the conformation of the ether linkage and the regioselectivity of the C–O bond scission under electron-transfer conditions. As in the case of 1,2,3-trimethoxybenzene, the high regioselectivity observed in the reductive cleavage of compounds **1** and **2** can be reasonably attributed, besides the relative stability of the resulting aromatic carbanions,[2,14] to twisting of the leaving methoxy group out of the plane of the aromatic ring, this being caused by the two *ortho* substituents.

Such an hypothesis is further supported by the results obtained in the reductive cleavage of the methylenedioxy derivative **25**; indeed, when the alkoxy substituent in the 2-position is forced into a conformation almost coplanar with the aromatic ring, reductive cleavage of the 1,2,3-trioxybenzene derivative is no longer regioselective.

Experimental

M.p.s were measured on a Büchi 510 melting point apparatus and are uncorrected. B.p.s refer to the temperature of the air-bath (Kugelrohr distillation). Solvents were distilled from Na/K alloy under N_2 immediately prior to use. All products and reagents were of the highest commercial quality from freshly opened containers and were used without further purification. Deuterium oxide was 99.8% isotopic purity. Silica gel 60 (particle sizes 40–63 μ) supplied by ICN was employed for flash chromatography. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured on a Varian VX 300 for samples in $CDCl_3$ solution with tetramethylsilane as internal standard. *J*-Values are in Hz. Deuterium incorporation was calculated as reported in ref. 2 (estimated error < 5%). IR spectra were recorded on a Perkin-Elmer 983 spectrometer for samples in CCl_4 solution. Elemental analyses were performed by the Microanalytical Laboratory of the Dipartimento di Chimica, Università di Sassari.

Preparation of Acetals **1–4**, **23–25**.—Compounds **1**, **3** and **23** were prepared according to ref. 6; compounds **2**, **4** and **24** were prepared as reported in ref. 7. Compound **25** was synthesized as described in ref. 8. All products were purified by distillation *in vacuo* and stored under Ar in a refrigerator. The products were characterised as follows.

1,2-*Dimethoxy*-3-(*methoxymethoxy*)*benzene* **1**. Liquid, b.p. 95 °C/1 mmHg; δ_H 3.51 (3 H, s, *Me*OCH$_2$), 3.87 (6 H, s, 2 × MeO), 5.22 (2 H, s, CH_2), 6.63 (1 H, dd, *J* 8.5 and 1.5, ArH), 6.79 (1 H, dd, *J* 8.5 and 1.5, ArH) and 6.98 (1 H, t, *J* 8.5, ArH).

2,3-*Dimethoxyphenyl tetrahydropyran*-2-*yl ether* **2**. Liquid, b.p. 135 °C/1 mmHg; δ_H 1.55–2.06 (6 H, m, 3 × CH_2), 3.56–3.66 (1 H, m, *H*CHO), 3.85 (3 H, s, MeO), 3.88 (3 H, s, MeO), 3.92–4.02 (1 H, m, *H*CHO), 5.43 (1 H, t, *J* 3.0, CHO_2), 6.61 (1 H, d, *J* 8.0, ArH), 6.80 (1 H, d, *J* 8.0, ArH) and 6.96 (1 H, d, *J* 8.0, ArH).

1-*Methoxy*-3-(*methoxymethoxy*)*benzene* **3**. Liquid, b.p. 80 °C/1 mmHg (lit.,[6] 123–123.5 °C/17 mmHg); δ_H 3.48 (3 H, s, *Me*OCH$_2$), 3.79 (3 H, s, MeO), 5.17 (2 H, s, CH_2), 6.55 (1 H, ddd, *J* 8.0, 2.5 and 1.0, ArH), 6.61 (1 H, t, *J* 2.5, ArH), 6.64 (1 H, ddd, *J* 8.0, 2.5 and 1.0, ArH) and 7.19 (1 H, t, *J* 8.0, ArH).

3-*Methoxyphenyl tetrahydropyran*-2-*yl ether* **4**. Liquid, b.p. 115 °C/1 mmHg (lit.,[11] 108–110 °C/0.02 mmHg); δ_H 1.56–2.08 (6 H, m, 3 × CH_2), 3.55–3.65 (1 H, m, *H*CHO), 3.79 (3 H, s, MeO), 3.85–3.95 (1 H, m, *H*CHO), 5.41 (1 H, t, *J* 3.5, HCO_2), 6.55 (1 H, dd, *J* 8.0 and 1.0, ArH), 6.60–6.70 (2 H, m, 2 × ArH) and 7.18 (1 H, d, *J* 8.0, ArH).

1-*Methoxy*-2-(*methoxymethoxy*)*benzene* **23**. Liquid, b.p. 75 °C/1 mmHg (lit.,[15] 110–110.5 °C/8 mmHg); δ_H 3.51 (3 H, s, *Me*OCH$_2$), 3.87 (3 H, s, MeO), 5.22 (2 H, s, CH_2), 6.84–6.94 (2 H, m, 2 × ArH), 6.94–7.02 (1 H, m, ArH) and 7.12–7.18 (1 H, m, ArH).

2-*Methoxyphenyl tetrahydropyran*-2-*yl ether* **24**. Liquid, b.p. 120 °C/1 mmHg; δ_H 1.56–2.14 (6 H, m, 3 × CH_2), 3.55–3.65 (1 H, m, *H*CHO), 3.85 (3 H, s, MeO), 3.95–4.06 (1 H, m, *H*CHO), 5.39 (1 H, t, *J* 3.5, HCO_2), 6.84–7.02 (3 H, m, 3 × ArH) and 7.13 (1 H, dd, *J* 8.0 and 1.5, ArH).

1-*Methoxy*-2,3-(*methylenedioxy*)*benzene* **25**. Liquid which solidified upon storage, b.p. 60 °C/1 mmHg (lit.,[16] 52 °C/0.2 mmHg); δ_H 3.90 (3 H, s, MeO), 5.95 (2 H, s, CH_2), 6.53 (2 H, d, *J* 8.5, 2 × ArH) and 6.78 (1 H, t, *J* 8.5, ArH).

The above compounds were further characterised by acidic hydrolysis (0.6 mol dm^{-3} HCl in MeOH; room temp; 1 h) to the corresponding known phenols.

General Procedure for the Reductive Cleavage of Acetals **1**, **2** *and* **25**.—Reductive cleavage reactions were performed as reported in refs. 2 and 17, starting with 2.5–5 mmol of the appropriate substrate and 3 mol equiv. of the freshly cut metal. The mixture was stirred at room temperature for the time indicated (Table 1), then was chilled to 0 °C, quenched by slow dropwise addition of water (*caution!*) and extracted with diethyl ether. The organic phase was washed successively with saturated aq. $NaHCO_3$ and water, dried (K_2CO_3) and evaporated to afford the crude liquid products, which were recognised by comparison with known samples.

In the case of compound **25**, the aqueous phase was acidified with conc. HCl, stirred at room temperature for 1 h, and extracted with Et_2O (4 × 10 cm^3). The organic phase was dried (K_2CO_3), and evaporated to afford a crude mixture which was characterised by GLC and ^{1}H NMR spectroscopy.

D_2O quenching was performed as described in ref. 2.

General Procedure for the Reductive Electrophilic Substitution of Acetals **1** *and* **2**.—Reduction of the appropriate acetal was performed as described above. The reaction mixture was chilled to the reported temperature, the appropriate amount of the electrophile dissolved in anhydrous THF (5 cm^3) was added dropwise, and the resulting mixture was stirred for several hours (Table 2). The reaction was quenched by slow dropwise addition of water (*caution!*) and worked up as reported above to afford the crude liquid products, which were characterised as follows.

* Metallation of 3-methoxyphenol **26**, with Bu^{t}Li–Bu^{t}OLi (2:1) (LICLIOR) is a non-regioselective reaction; see ref. 12, metallation of compound **26** with BuLi is also non-regioselective; see ref. 11.

1-*Methoxy*-3-*methoxymethoxy*-2-*methylbenzene* **5**. Oil, purified by flash chromatography [CH_2Cl_2–hexane (1:1)]; δ_H 2.13 (3 H, s, MeAr), 3.48 (3 H, s, $MeOCH_2$), 3.82 (3 H, s, MeO), 5.19 (2 H, s, CH_2), 6.57 (1 H, d, *J* 8.5, ArH), 6.72 (1 H, d, *J* 8.5, ArH) and 7.09 (1 H, t, *J* 8.5, ArH).

2-*Butyl*-1-*methoxy*-3-(*methoxymethoxy*)*benzene* **6**. Oil, purified by flash chromatography [CH_2Cl_2–hexane (1:1)]; δ_H 0.92 (3 H, t, *J* 7.0, $MeCH_2$), 1.28–1.54 (4 H, m, $MeCH_2CH_2$), 2.66 (2 H, t, *J* 7.0, CH_2Ar), 3.48 (3 H, s, $MeOCH_2$), 3.81 (3 H, s, MeO), 5.17 (2 H, s, CH_2O), 6.56 (1 H, d, *J* 8.0, ArH), 6.71 (1 H, d, *J* 8.0, ArH) and 7.08 (1 H, t, *J* 8.0, ArH).

2-*Butyl*-3-*methoxyphenyl tetrahydropyran*-2-*yl ether* **7**. Oil, purified by flash chromatography [ethyl acetate–hexane (0.5:9.5)]; δ_H 0.93 (3 H, t, *J* 7.0, $MeCH_2$), 1.24–2.16 (10 H, m, 5 × CH_2), 2.60–2.68 (2 H, m, CH_2Ar), 3.47–3.62 (1 H, m, *H*CHO), 3.80 (3 H, s, MeO), 3.82–3.88 (1 H, m, *H*CHO), 5.42 (1 H, t, *J* 3.5, HCO_2), 6.54 (1 H, d, *J* 8.5, ArH), 6.76 (1 H, d, *J* 8.5, ArH) and 7.07 (1 H, t, *J* 8.5, ArH).

Methyl 2-*methoxy*-6-(*methoxymethoxy*)*benzoate* **9**. Oil, purified by flash chromatography [ethyl acetate–hexane (7:3)]; δ_H 3.46 (3 H, s, $MeOCH_2$), 3.82 (3 H, s, *Me*OAr), 3.92 (3 H, s, MeOCO), 5.17 (2 H, s, CH_2), 6.60 (1 H, d, *J* 8.5, ArH), 6.76 (1 H, d, *J* 8.5, ArH) and 7.27 (1 H, t, *J* 8.5, ArH).

Compounds **5**–**7** and **9** were further characterised by acidic hydrolysis to the corresponding phenols (see below). Crude *N*,*N*-diethyl-2-methoxy-6-(methoxymethoxy)benzamide **8** and 2-methoxy-6-(methoxymethoxy)benzophenone **10** were not characterised, but were directly hydrolysed to the corresponding phenols.

General Procedure for the Acidic Hydrolysis of Compounds **5**–**10**.—The appropriate acetal (2–3 mmol) was added under Ar to a stirred 0.6 mol dm^{-3} solution of HCl in MeOH [obtained by adding AcCl (1 cm^3) to MeOH (20 cm^3)] chilled to 0 °C. The mixture was stirred at room temperature for 1 h, diluted with water (20 cm^3), and the MeOH was evaporated off under reduced pressure. The resulting mixture was extracted with Et_2O (4 × 20 cm^3). The organic phase was dried ($CaCl_2$) and evaporated to afford the crude product which was characterised as follows.

3-*Methoxy*-2-*methylphenol* **11**. Oil which solidified upon storage, m.p. 33–34 °C (lit.,[18] 33–36 °C); purified by flash chromatography [ethyl acetate–hexane (3:7)]; δ_H 2.12 (3 H, s, *Me*Ar), 3.80 (3 H, s, MeO), 5.32 (1 H, br s, OH), 6.44 (2 H, t, *J* 8.5, 2 × ArH) and 7.00 (1 H, t, *J* 8.5, ArH); ν/cm^{-1} 3610 and 3462.

2-*Butyl*-3-*methoxyphenol* **12**. *Oil*, b.p. 175 °C/20 mmHg; purified by flash chromatography [ethyl acetate–hexane–acetic acid (10:10:1)]; δ_H 0.92 (3 H, t, *J* 8.0, $MeCH_2$), 1.25–1.48 (4 H, m, $MeCH_2CH_2$), 2.62 (2 H, t, *J* 8.0, CH_2Ar), 3.79 (3 H, s, MeO), 4.91 (1 H, br s, OH), 6.42 (1 H, d, *J* 8.0, ArH), 6.46 (1 H, d, *J* 8.0, ArH) and 7.01 (1 H, t, *J* 8.0, ArH); δ_C 14.0, 22.7, 22.9, 31.4, 55.6, 103.2, 108.2, 117.1, 126.6, 154.2 and 158.6; ν/cm^{-1} 3609 and 3407 (Found: C, 72.9; H, 8.7. $C_{11}H_{16}O_2$ requires C, 73.30; H, 8.95%).

N,N-*Diethyl*-2-*hydroxy*-6-*methoxybenzamide* **13**. Oil which solidified upon storage, m.p. 137–139 °C (lit.,[19] 139–140 °C); purified by flash chromatography [ethyl acetate–hexane–acetic acid (10:10:1)]; δ_H 1.00–1.30 (6 H, br m, 2 × $MeCH_2$), 3.15–3.70 (4 H, br m, 2 × CH_2), 3.78 (3 H, s, MeO), 6.39 (1 H, d, *J* 8.0, ArH), 6.54 (1 H, d, *J* 8.0, ArH), 7.12 (1 H, t, *J* 8.0, ArH) and 7.96 (1 H, br, s, OH).

Methyl 2-*hydroxy*-6-*methoxybenzoate* **14**. Oil which solidified upon storage, m.p. 43–45 °C (lit.,[20] 40–42 °C); purified by flash chromatography [ethyl acetate–hexane (3:7)]; δ_H 3.86 (3 H, s, MeOAr), 3.96 (3 H, s, MeOCO), 6.42 (1 H, d, *J* 8.5, ArH), 6.60 (1 H, d, *J* 8.5, ArH), 7.34 (1 H, t, *J* 8.5, ArH) and 11.51 (1 H, br s, OH); ν/cm^{-1} 3279, 1696 and 1660.

2-*Hydroxy*-6-*methoxybenzophenone* **15**. *Oil* which solidified upon storage, m.p. 134–136 °C; purified by flash chromatography [ethyl acetate–hexane (2:8)]; δ_H 3.51 (3 H, s, Me), 6.42 (1 H, dd, *J* 8.5 and 1.0, ArH), 6.65 (1 H, dd, *J* 8.5 and 1.0, ArH), 7.38 (1 H, t, *J* 8.5, ArH), 7.41 (2 H, td, *J* 7.0 and 1.5, 2 × ArH), 7.51 (1 H, tt, *J* 7.5 and 1.5, ArH), 7.62 (2 H, dt, *J* 7.0 and 1.5, 2 × ArH) and 10.62 (1 H, br s, OH); ν/cm^{-1} 3384 and 1625 (Found: C, 74.0; H, 5.5. $C_{14}H_{12}O_3$ requires C, 73.67; H, 5.31%).

Synthesis of Trifluoromethanesulfonates **16**–**18**.—These compounds were synthesized according to a general procedure described in ref. 3*c*. Crude products were purified by flash chromatography and characterised as follows.

3-*Methoxy*-2-*methylphenyl trifluoromethanesulfonate* **16**. Pale yellow *oil*, purified by flash chromatography [ethyl acetate–hexane (7:3)]; δ_H 2.22 (3 H, s, *Me*Ar), 3.85 (3 H, s, MeO), 6.85 (2 H, t, *J* 8.0, 2 × ArH) and 7.21 (1 H, t, *J* 8.0, ArH); δ_C 9.5, 55.9, 109.6, 113.2 (q, *J* 1), 118.6 (q, *J* 318), 120.2, 127.0, 148.8 and 159.0 (Found: C, 40.4; H, 3.5. $C_9H_9F_3O_4S$ requires C, 40.00; H, 3.36%).

2-*Diethylcarbamoyl*-3-*methoxyphenyl trifluoromethanesulfonate* **17**. Pale yellow *oil*, which solidified upon storage, m.p. 56 °C; purified by flash chromatography [ethyl acetate–hexane (6:4)]; δ_H 1.09 (3 H, t, *J* 7.0, $MeCH_2$), 1.25 (3 H, t, *J* 7.0, $MeCH_2$), 3.12–3.21 (2 H, m, $MeCH_2$), 3.28–3.42 (1 H, m, *H*CHMe), 3.76–3.90 (1 H, m, *H*CHMe), 3.85 (3 H, s, MeO), 6.92 (1 H, d, *J* 9.0, ArH), 6.96 (1 H, d, *J* 9.0, ArH) and 7.38 (1 H, t, *J* 9.0, ArH); δ_C 12.4, 13.5, 38.7, 42.8, 56.1, 110.6, 113.3 (q, *J* 1), 118.4 (q, *J* 318), 120.7, 130.4, 145.8, 156.9 and 162.5; ν/cm^{-1} 1645 (Found: C, 43.8, N, 4.2, H, 4.7. $C_{13}H_{16}F_3NO_5S$ requires C, 43.93; N, 3.93; H, 4.53%).

Methyl 2-*methoxy*-6-(*trifluoromethanesulfonyl*)*benzoate* **18**. Pale yellow *oil*, purified by flash chromatography [ethyl acetate–hexane (3:7)]; δ_H 3.88 (3 H, s, *Me*OAr), 3.93 (3 H, s, MeOCO), 6.95 (2 H, t, *J* 9.0, 2 × ArH) and 7.44 (1 H, t, *J* 9.0, ArH); δ_C 52.8, 56.5, 111.3, 113.4 (q, *J* 1), 118.5 (q, *J* 318), 132.1, 146.8, 158.3, 158.4 and 163.6; ν/cm^{-1} 1743 (Found: C, 37.8; H, 2.9. $C_{10}H_9F_3O_6S$ requires C, 38.22; H, 2.89%).

Cross-coupling Reactions.—Cross-coupling reactions were carried out according to known procedures. Reaction conditions and yields are reported in Table 3. The products were characterised as follows.

3-*Methoxy*-2-*methylbiphenyl* **19**. Synthesized according to a procedure described in ref. 3*b*; pale yellow *oil*, b.p. 120 °C/1 mmHg; purified by flash chromatography [CH_2Cl_2–hexane (1:9)]; δ_H 2.13 (3 H, s, *Me*Ar), 3.85 (3 H, s, MeO), 6.86 (2 H, t, *J* 8.0, 2 × ArH), 7.19 (1 H, t, *J* 8.0, ArH) and 7.26–7.44 (5 H, m, Ph); δ_C 13.3, 55.5, 108.8, 122.2, 124.3, 125.9, 126.7, 128.0, 129.3, 141.8, 143.3 and 157.9 (Found: C, 84.9; H, 7.3. $C_{14}H_{14}O$ requires C, 84.81; H, 7.12%).

N,N-*Diethyl*-2-*methoxy*-6-*methylbenzamide* **20**. Synthesized according to a procedure described in ref. 3*a*; pale yellow oil, b.p. 145 °C/1 mmHg (lit.,[10] 99–100 °C/0.13 mmHg); purified by flash chromatography [ethyl acetate–hexane (7:3)]; δ_H 1.02 (3 H, t, *J* 7.0, $MeCH_2$), 1.25 (3 H, t, *J* 7.0, $MeCH_2$), 2.24 (3 H, s, *Me*Ar), 3.11 (2 H, q, *J* 7.0, $MeCH_2$), 3.32–3.48 (1 H, m, *H*CHMe), 3.72–3.86 (1 H, m, *H*CHMe), 3.79 (3 H, s, MeO), 6.73 (1 H, d, *J* 8.0, ArH), 6.80 (1 H, d, *J* 8.0, ArH) and 7.19 (1 H, t, *J* 8.0, ArH); ν/cm^{-1} 1628.

Methyl 2-*methoxy*-6-(*phenylethynyl*)*benzoate* **21**. Synthesized according to a procedure described in ref. 21; pale yellow *oil*, purified by flash chromatography [CH_2Cl_2–hexane (7:3)]; δ_H 3.86 (3 H, s, *Me*OAr), 3.97 (3 H, s, MeOCO), 6.92 (1 H, dd, *J* 8.5 and 0.5, ArH), 7.16 (1 H, dd, *J* 8.5 and 0.5, ArH), 7.31–7.38 (4 H, m, 4 × ArH) and 7.47–7.51 (2 H, m, 2 × ArH); ν/cm^{-1} 2200 and 1730 (Found: C, 76.4; H, 5.3. $C_{17}H_{14}O_3$ requires C, 76.67; H, 5.30%).

Methyl 2-methoxy-6-[(4-methoxyphenyl)ethynyl]benzoate **22**. Synthesized according to a procedure described in ref. 21; pale yellow *oil* which solidified upon storage, m.p. 113–115 °C (from hexane); purified by flash chromatography [CH_2Cl_2–hexane (6:4)]; δ_H 3.82 (3 H, s, *Me*OAr), 3.85 (3 H, s, *Me*OAr), 3.97 (3 H, s, MeOCO), 6.84–6.92 (3 H, m, 3 × ArH), 7.13 (1 H, dd, *J* 8.0 and 1.0, ArH), 7.32 (1 H, t, *J* 8.0, ArH) and 7.38–7.46 (2 H, m, 2 × ArH); δ_C 52.4, 55.3, 56.0, 85.0, 93.0, 110.9, 114.0, 114.8, 122.5, 124.0, 125.7, 130.5, 133.1, 156.1, 159.8 and 167.5; ν/cm^{-1} 2210 and 1739 (Found: C, 72.6; H, 5.15. $C_{18}H_{16}O_4$ requires C, 72.96; H, 5.44%).

Methyl 2-Methoxy-6-(2-phenylethyl)benzoate **27**.—Compound **21** (0.26 g, 0.97 mmol) was dissolved in acetic acid (5 cm^3) and hydrogenated at room temperature and ambient pressure in the presence of 10% Pd/C (45 mg) during 12 h. The mixture was filtered, diluted with water (40 cm^3), and extracted with CH_2Cl_2 (4 × 20 cm^3). The organic phase was washed successively with water (3 × 20 cm^3) and saturated aq. $NaHCO_3$ (2 × 20 cm^3), and dried ($CaCl_2$). Evaporation of the solvent, and flash chromatography [ethyl acetate–hexane (2:8)], afforded pure *compound* **27** (0.220 g, 83%) as a pale yellow oil which solidified upon storage; m.p. 76–78 °C; δ_H 2.84–2.88 (4 H, m, 2 × CH_2), 3.83 (3 H, s, *Me*OAr), 3.93 (3 H, s, MeOCO), 6.79 (2 H, dd, *J* 8.0 and 3.0, 2 × ArH) and 7.12–7.34 (6 H, m, 6 × ArH); δ_C 35.8, 37.6, 52.2, 55.9, 108.7, 121.6, 126.0, 128.4, 130.4, 140.2, 141.5, 156.4 and 168.8; ν/cm^{-1} 1733 (Found: C, 75.2; H, 6.7. $C_{17}H_{18}O_3$ requires C, 75.53; H, 6.71%).

2-Methoxy-6-[2-(4-methoxyphenyl)ethyl]benzoic Acid **29**.—Compound **22** (0.450 g, 1.5 mmol) was dissolved in acetic acid (5 cm^3)–EtOH (30 cm^3) and hydrogenated according to the above procedure. Crude product **28** (0.400 g, 87%), a pale yellow oil which solidified upon storage, was dissolved in water (5 cm^3)–EtOH (5 cm^3) containing 7 mol equiv. of KOH (0.51 g, 9.1 mmol). The mixture was stirred at reflux temperature for 4 days, then was chilled to room temperature, diluted with water (20 cm^3), and the EtOH was evaporated off under reduced pressure. The resulting mixture was extracted with CH_2Cl_2 (4 × 20 cm^3) and the extract was dried ($CaCl_2$). Evaporation of the solvent, and flash chromatography [ethyl acetate–hexane (4:6)], afforded pure title acid **29** (0.320 g, 85%) as a pale yellow oil, m.p. 105–106 °C (from toluene–hexane) (lit.,[10b] 102–103 °C); δ_H 2.82–3.06 (4 H, m, 2 × CH_2), 3.76 (3 H, s, MeO), 3.89 (3 H, s, MeO), 6.76–6.86 (4 H, m, 4 × ArH), 7.11 (2 H, d, *J* 8.5, 2 × ArH), 7.31 (1 H, t, *J* 8.5, ArH) and 10.41 (1 H, br s, CO_2H); δ_C 36.4, 36.8, 55.2, 56.1, 108.9, 113.7, 121.7, 122.4, 129.3, 131.0, 133.7, 141.5, 156.7, 157.8 and 172.6; ν/cm^{-1} 3510, 3069 and 1700.

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