mass spectrum, calcd for $C_{20}H_{21}FeN$ 331.1023, found 331.1023; m/z (relative intensity) 331 (M^+, 100), 266 (30), 250 (12), 209 (12), 165 (7). Anal. Calcd for $C_{20}H_{21}FeN$: C, 72.52; H, 6.39; N, 4.23. Found: C, 72.69; H, 6.20; N, 3.92.

Acetylation of *trans*-1-Ferrocenyl-2-(4-nitrophenyl)-ethylene (3a). Reaction of 0.0906 g (0.272 mmol) of **3a** under the acetylation conditions (method A) resulted in recovery of starting material only.

Acetylation of *trans*-1-Ferrocenyl-2-(4-bromophenyl)-ethylene (3b). Acetylation (method A) of **3b** (98.9 mg, 0.270 mmol) gave an orange solid residue. Column chromatography (alumina/CH_2Cl_2 followed by alumina/2:1 CH_2Cl_2-hexane) permitted the isolation of two major products: monoacetylated product **4b** (23%) and diacetylated product **6b** (10%).

For **4b**, an orange-red crystalline solid: mp 117.0-119.0 °C; ^1H NMR ($CDCl_3$) δ 7.59 and 7.06 (2 d, 4 H), 7.55 (s, 1 H), 4.30 and 3.85 (2 m, 4 H), 4.11 (s, 5 H), 2.27 (s, 3 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 197.3, 141.7, 136.9, 135.9, 132.0, 131.4, 121.8, 77.2, 71.4, 71.3, 69.7, 27.5; IR (CH_2Cl_2) 1656 (C=O) cm^{-1}; mass spectrum, calcd for $C_{20}H_{17}BrFe$ 409.9748, 407.9812, found 409.9789, 407.9813; m/z (relative intensity) 410, 408 (M^+, 99, 100), 345, 343 (30, 34), 165 (23).

For **6b**, an orange crystalline solid: ^1H NMR (CD_2Cl_2) δ 7.50 and 6.98 (2 d, 4 H), 7.26 (s, 1 H), 4.62, 4.35, 4.22, and 3.82 (4 m, 8 H), 2.25 and 2.20 (2 s, 6 H); IR (CH_2Cl_2) 1669 (C=O) cm^{-1}; mass spectrum, calcd for $C_{22}H_{19}BrFeO_2$ 451.9898, 449.9918, found 451.9882, 449.9910; m/z (relative intensity) 452, 450 (M^+, 93, 100), 345 (64), 165 (47).

The monoacetylation product **5b** was also observed in an intermediate column fraction: ^1H NMR ($CDCl_3$) δ 7.45 and 7.31 (2 d, 4 H), 6.74 and 6.69 (2 d, 2 H), 4.75 and 4.31 (2 m, 4 H), 4.47 (m, 4 H), 2.27 (s, 3 H).

Acetylation of *trans*-1-Ferrocenyl-2-(4-(dimethylamino)phenyl)ethylene (3c). Acetylation (method A) of **3c** (90.1 mg, 0.272 mmol) and separation of the product mixture by column chromatography (alumina/CH_2Cl_2) followed by preparative TLC (alumina/2:1 ether-hexane) permitted isolation of monoacetylated products **4c** (15%) and **5c** (25%), as well as diacetylated product **6c** (10%).

For **4c**, an orange-red crystalline solid: mp 152.0-154.0 °C; ^1H NMR ($CDCl_3$) δ 7.51 (s, 1 H), 7.03 and 6.81 (2 d, 4 H), 4.24 and 3.93 (2 m, 4 H), 4.10 (s, 5 H), 3.02 (s, 6 H), 2.21 (s, 3 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 199.1, 149.9, 140.0, 137.3, 130.3, 125.7, 112.6, 87.5, 71.3, 70.8, 69.6, 40.6, 29.7; mass spectrum, calcd for $C_{22}H_{23}FeNO$ 373.1129, found 373.1129.

For **5c**, an orange crystalline solid: mp 114.5-115.5 °C; ^1H NMR (CD_2Cl_2) δ 7.34 and 6.70 (2 d, 4 H), 6.68 and 6.51 (2 d, 2 H ($^3J_{HH(trans)}$ = 15.5 Hz)), 4.73 and 4.25 (2 m, 4 H), 4.45 (m, 4 H), 2.97 (s, 6 H), 2.29 (s, 3 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 202.1, 149.9, 128.3, 127.1, 125.8, 119.8, 112.6, 86.4, 79.9, 73.3, 70.5, 70.2, 67.7, 40.5, 27.8; mass spectrum, calcd for $C_{22}H_{23}FeNO$ 373.1129, found 373.1135; m/z (relative intensity) 373 (M^+, 100), 266 (72), 250 (19), 165 (20). Anal. Calcd for $C_{22}H_{23}FeNO$: C, 70.79; H, 6.21; N, 3.75. Found: C, 70.76; H, 6.01; N, 3.76.

For **6c**: ^1H NMR ($CDCl_3$) δ 7.32 (s, 1 H), 7.00 and 6.78 (2 d, 4 H), 4.69, 4.41, 4.24, and 3.96 (4 m, 8 H), 3.01 (s, 6 H), 2.32 (s, 3 H), 2.25 (s, 3 H).

Acetylation by method B and separation of the resulting product mixture by chromatography yields monoacetylated products **4c** (5%) and **5c** (15%) along with starting material (75%). The monoacetylation product **7c** was also detected in one of the preparative TLC bands (<5%) by ^1H NMR spectroscopy, but was not isolated: ^1H NMR ($CDCl_3$) δ 7.61 (s, 1 H), 7.57 and 6.99 (2 d, 4 H), 5.03 and 4.79 (2 m, 4 H), 4.15 (s, 5 H), 2.98 (s, 6 H), 2.41 (s, 3 H).

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Supplementary Material Available: Selected ^1H and ^{13}C NMR spectra for **3-6** (13 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS. Ordering information is given on any current masthead page.

Regioselective Reductive Electrophilic Substitution of Derivatives of 3,4,5-Trimethoxybenzaldehyde

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The behavior of several protected derivatives of 3,4,5-trimethoxybenzaldehyde has been investigated under conditions of electron transfer from alkali metals in aprotic solvents. The 4-methoxy group can be regioselectively removed in good to high yield under such conditions, and an appropriate choice of the protecting group, metal, and solvent allows its substitution with a variety of electrophiles. 3,4,5-Trimethoxybenzaldehyde dimethyl acetal, **1**, is the starting material of choice for a new general synthetic approach to several polysubstituted resorcinol dimethyl ethers. Investigation of the mechanism of demethoxylation, with the aid of labeling experiments, showed that reductive demethoxylation is strongly influenced by the nature of the aldehyde protective group employed.

As polysubstituted resorcinols are an important class of natural products with significant biological and pharmacological properties,[1] there is a continuous search for new approaches to their synthesis.[2-11] We have recently reported a synthetic procedure involving the one-pot regioselective reductive electrophilic substitution of the 2-

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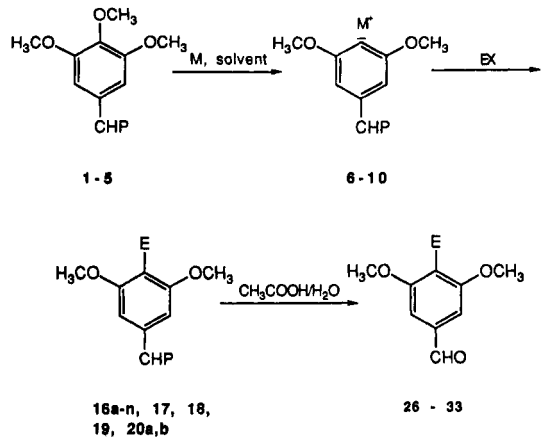
Scheme I[a]



[a] Key: P = aldehyde protecting group = $(OCH_3)_2$, $(OC_2H_5)_2$, $(OC_4H_9)_2$, OCH_2CH_2O, $(CH_3)NCH_2CH_2N(CH_3)$; M = Na, K; EX = electrophilic reagent.

methoxy group of 1,2,3-trimethoxybenzene and its 5-alkyl-substituted homologues under electron-transfer conditions from alkali metals,[12] leading to the synthesis of several substituted resorcinol dimethyl ethers. The synthetic usefulness of such a procedure relies upon the quantitative formation, in the reductive demethoxylation step, of 2,6-dimethoxy-substituted arylmetal compounds, according to a two-electron reduction process, and is restricted to 1,2,3-trimethoxybenzene and to 3,4,5-trimethoxytoluene. We have therefore examined the possibility of extending our research on this type of reductive electrophilic substitution to suitable derivatives of the inexpensive reagent 3,4,5-trimethoxybenzaldehyde, with the carbonyl group appropriately protected toward reduction by the alkali metal, and wish to report here a more general approach to the synthesis of 2,5-disubstituted resorcinols, according to Scheme I.

A preliminary report concerning the regioselective reductive alkylation of 3,4,5-trimethoxybenzaldehyde dimethyl acetal, 1, as well as a new synthetic approach to the natural antibiotics 1,3-dihydroxy-2-butyl-5-pentylbenzene (stemphol) and 1,3-dihydroxy-2-hexyl-5-propylbenzene (DB2073) has already appeared.[13]

Results

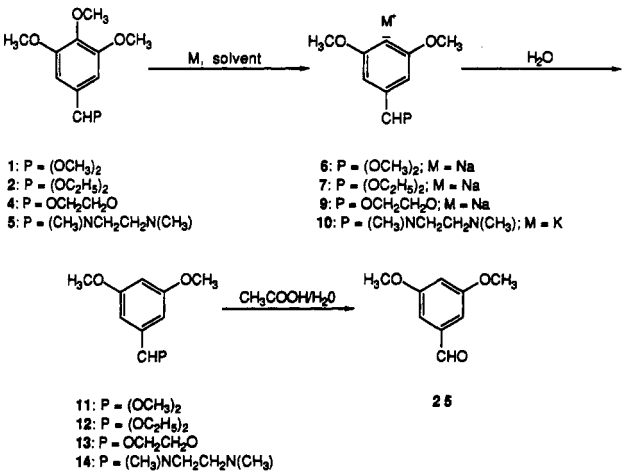
Reduction of Acetals with Na Metal. The regioselective demethoxylation in the 4-position of compounds 1 (P = $(OCH_3)_2$), 2 (P = $(OC_2H_5)_2$), and 4 (P = OCH_2CH_2O) can be conveniently performed by the action of Na metal (3 equiv) in anhydrous THF at room temperature for 24 h. At this stage, quenching of the reaction mixtures with water or with anhydrous EtOH (*caution*!) afforded compounds 11, 12, and 13, respectively (Table I, entries 1–3), according to Scheme II, together with different, low amounts of phenolic products, formed by competitive demethylation reactions,[12] which were easily removed from the reaction mixture during workup. Acidic hydrolysis of compounds 11–13 afforded the benzaldehyde 25, a known compound. In any case, no products of demethoxylation in the 3-position were formed.

Table I. Reductive Cleavage of Compounds 1, 2, 4, and 5[a]

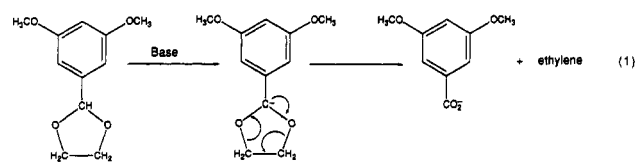
entry	compd	metal	solvent	product	yield,[b] %
1	1	Na	THF	11	90
2	2	Na	THF	12	93
3	4	Na	THF	13	54
4	1	Na	Et_2O	11	60[c]
5	1	Na	isooctane	11	4[c]
6	2	Na	Et_2O	12	76[c]
7	2	Na	isooctane	12	41[c]
8	1	K	THF	11	32[d]
9	1	K	THF	11	77[e]
10	1	K	isooctane	11	13[c]
11	5	K	THF	14	80
12	5	Na	THF	14	27[c]

[a] All reactions run at room temperature for 24 h, except entry 9. [b] Isolated yield, unless otherwise indicated. [c] Determined by ^1H NMR; no other product, unless starting material, was evidenced to a considerable extent. [d] 43% of 21 also formed. [e] At −20 °C for 6 h, 2% of 21 also formed.

Scheme II



While good yields were obtained in the reductive demethoxylation of compounds 1 and 2, reduction of 4 afforded compound 13 in only 54% yield; careful examination of the acidic fraction obtained in the reductive cleavage of 4 led to the recovery of 3,5-dimethoxybenzoic acid in 22% yield; no 3,4,5-trimethoxybenzoic acid was detected. This finding strongly supports a competitive deprotonation of acetal 13[14] in the highly basic reaction medium, followed by the known fragmentation to the corresponding carboxylate anion and ethylene[15] according to eq 1.



Besides THF, other solvents, such as Et_2O and 2,2,4-trimethylpentane (isooctane), were tested as solvents for the reductive demethoxylation of compounds 1 and 2 with Na metal; in the case of 1, a moderate conversion to 11 took place after 24 h at room temperature in Et_2O whereas, under similar conditions, 1 was almost unreactive in isooctane (Table I, entries 4 and 5). Interestingly, 2 was more

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Table II. Reductive Electrophilic Substitution of Compounds 1, 2, 4, and 5

entry	compd	metal	electrophile (equiv)	T, °C	t, h	product, E =	yield,[a] %
1	1	Na	MeI (1.5)	0	24	**16a**, Me	71[b]
2	1	Na	EtBr (1.5)	0	24	**16b**, Et	75[b]
3	1	Na	*n*-BuBr (1.5)	0	24	**16c**, *n*-Bu	86[b]
4	1	Na	*n*-hexylBr (1.5)	0	24	**16d**, *n*-hexyl	84[b]
5	1	Na	*i*-PrI (1.5)	0	24		0[b,c]
6	4	Na	*n*-BuBr (1.5)	0	24	**19**, *n*-Bu	25[d]
7	5	K	*n*-BuBr (1.5)	0	24		0[c]
8	1	Na	Me_3SiCl (1.5)	−40	6	**16f**, $SiMe_3$	83
9	1	Na	EtCHO	−78	6		0[c]
10	1	Na	*t*-BuCHO (1.5)	0	24	**16h**, CHOH-*t*-Bu	74
11	1	Na	PhCOCl (3)	−40	2	**16i**, COPh	72
12	1	Na	ClCOOMe (3)	−40	3	**16l**, COOMe	75
13	2	Na	ClCOOMe (3)	−40	3	**17**, COOMe	65
14	5	K	ClCOOMe (3)	−40	3		0[c]
15	1	Na	NMF (1.5)[e]	0	4	**16m**, CHOHAr[f]	67
16	1	Na	NMF (3)[e,g]	0	3	**16n**, CHO	45

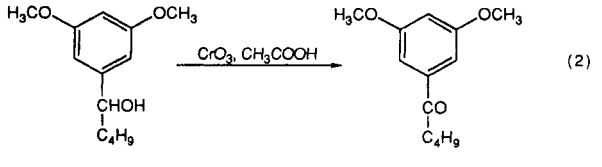
[a] Determined on isolated products. [b] From ref 13. [c] Only the product of reductive demethoxylation was obtained. [d] 27% of **13** was also formed. [e] NMF = *N*-methylformanilide. [f] Ar = 2,6-dimethoxy-4-benzaldehyde dimethyl acetal. [g] Inverse addition.

reactive than **1** in both solvents; indeed, **12** was obtained in 76 and 41% yield in Et_2O and isooctane, respectively (Table I, entries 6 and 7).

Reduction of Acetals with K Metal. Reduction of compound **1** with K metal gave more complex results. Indeed, when the reaction was performed at room temperature in the presence of 3 equiv of finely divided K metal in anhydrous THF, complete conversion of the starting material could not be achieved even after 24 h, and **11** was obtained in 32% yield (Table I, entry 8), together with 43% yield of 1-(3,5-dimethoxyphenyl)ethanol, **21** (Scheme III). Lowering the reaction temperature to −20 °C yielded **11** in 77% yield (Table I, entry 9), together with a small amount (2%) of **21**. On the contrary, **21** was obtained in 68% yield when the reaction was performed at 45 °C in the presence of 4.5 equiv of K.

According to our previous findings,[16] **21** is the product of demethoxylation of **1** in the 4-position followed by Wittig rearrangement of the acetal function induced by reductive electron transfer. The overall reaction involves cleavage of the three C–O bonds and formation of one C–C bond.

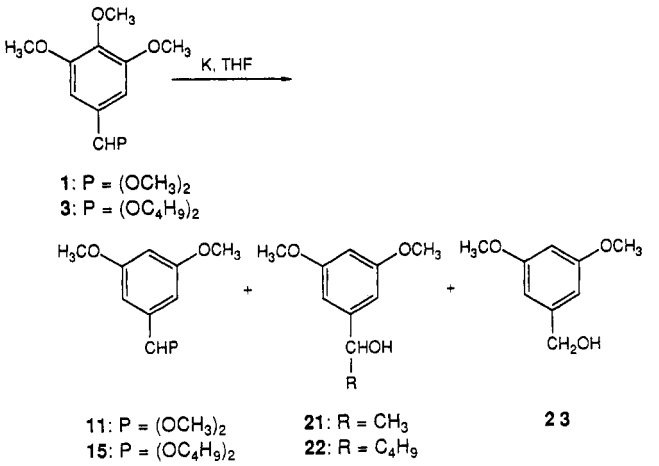
Although more complex results are possible in the case of other acetals of 3,4,5-trimethoxybenzaldehyde due to competition between reductive elimination (leading to 3,4,5-trimethoxybenzylic alcohol, **23**) and Wittig rearrangement,[16] we have nonetheless investigated the synthesis of 1-(3,5-dimethoxyphenyl)-1-pentanol **22** by reduction of 3,4,5-trimethoxybenzaldehyde dibutyl acetal, **3** (P = $(OC_4H_9)_2$). Subsequent oxidation of **22** would lead to (3,5-dimethoxyphenyl)-1-pentanone, **24**, a known intermediate in the synthesis of olivetol dimethyl ether.[17] Accordingly, reduction of **3** with 4.5 equiv of K in THF at 45 °C for 24 h led to a complex reaction mixture containing **22** as the main product. Oxidation of the crude product with CrO_3 in glacial acetic acid according to eq 2, followed by $NaHCO_3$ workup to separate acidic products, afforded **24** in 19% overall yield.



(2)

22 **24**

Scheme III



As aromatic acetals were found to be inert toward reductive Wittig rearrangement with alkali metals in hydrocarbon solvents,[16] we attempted to achieve reductive demethoxylation of **1** with K in isooctane. However, this reaction was very sluggish, affording **11** in only 13% yield after 24 h at room temperature (Table I, entry 10).

Reduction of the Aminal. The search for an aldehyde protecting group stable toward reduction with K metal led us to test the reactivity under our reaction conditions of 1,3-dimethyl-2-(3,4,5-trimethoxyphenyl)imidazolidine, **5**. Demethoxylation of **5** in the 4-position was carried out by reaction with 3 equiv of K metal in THF at room temperature for 24 h. After aqueous workup 1,3-dimethyl-2-(3,5-dimethoxyphenyl)imidazolidine, **14**, was isolated in 80% yield, thereby demonstrating the stability of the aminal moiety to the reaction conditions (Table I, entry 11). **14** was converted by acidic hydrolysis into **25**. When **5** was reduced with 3 equiv of Na metal in THF **14** was formed in 27% yield in 24 h (Table I, entry 12).

Reductive Electrophilic Substitution. Due to the good yields obtained in the reductive demethoxylation reaction, compound **1** was used as a model to investigate the reductive electrophilic substitution reaction. The reactivity of **1** was checked using Na in THF as the reducing agent and several electrophiles. Some reactions were also carried out on compounds **2**, **4**, and **5**. The results are reported in Table II. Alkylation of **6** with primary alkyl halides was achieved under mild reaction conditions: an excess (1.5 equiv) of the alkyl halide was added at 0 °C to the reaction mixture obtained by the action of Na metal on **1** under the conditions reported above; after 24 h of

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stirring at room temperature, standard workup afforded good yields of the alkylated products **16a–d** (Table II, entries 1–4) together with minor amounts of the product of reductive demethoxylation.[13] By contrast, reductive alkylation with a secondary alkyl halide, i.e., 2-iodopropane, did not afford a substitution product (Table II, entry 5); only the product of demethoxylation was obtained. A similar result was previously observed during attempted reductive electrophilic substitution of 1,2,3-trimethoxybenzene with secondary alkyl halides.[12,13]

Interestingly, under similar conditions, reductive electrophilic substitution of **4** with Na metal and 1-bromobutane afforded an almost equal amount of **19** (the product of alkylation) and of **13** (the product of reductive demethoxylation) (Table II, entry 6). An even worse result was obtained in the K metal-promoted reductive electrophilic substitution of **5** with 1-bromobutane. Indeed, no product of alkylation was formed under such reaction conditions (Table II, entry 7); only **14** (the product of reductive demethoxylation) was obtained.

Silylation of **6** was easily achieved by reduction of **1** with Na metal, followed by addition of 1.5 equiv of Me_3SiCl at −40 °C, to give the trimethylsilyl derivative **16f** in good yield (Table II, entry 8).

Several carbonyl derivatives were also tested as electrophiles. Reaction of **6** with propanal did not afford carbinol **16g** even at −78 °C (Table II, entry 9). However, the addition reaction of **6** to the carbonyl group of a nonenolizable aldehyde, namely 2,2-dimethylpropanal, readily occurred within 24 h at 0 °C (Table II, entry 10). Good results were also obtained employing acyl chlorides as electrophiles: reaction of **6** with 1.5 equiv of PhCOCl or $ClCOOCH_3$ at −40 °C afforded good yields of ketone **16i** and of methyl ester **16l**, respectively (Table II, entries 11 and 12). Under similar conditions, the methyl ester **17** was obtained in 65% yield starting from compound **2** (Table II, entry 13). No product of substitution was formed in the reaction of $ClCOOCH_3$ with the product of the K metal-promoted demethoxylation of **5** (Table II, entry 14); only **14** was recovered. As a note of caution it is stressed that where acyl chlorides are employed as electrophiles immediate workup of the reaction mixtures is required in order to prevent acidic cleavage of the aldehyde protecting group.

Reaction of **6** with *N*-methylformanilide (NMF) led to the formation of two different products, **16m** and **16n**, depending on the reaction conditions; direct addition of 1.5 equiv of NMF to the reduction mixture chilled to 0 °C afforded the symmetric carbinol **16m** (Table II, entry 15), whereas inverse addition of the reduction mixture to a solution of 3 equiv of NMF in THF, at 0 °C, afforded aldehyde **16n** (Table II, entry 16). It is noteworthy that under inverse addition conditions the excess metal can be conveniently filtered off.

Deuterium Incorporation Studies. A comparison of the results obtained in the reductive electrophilic substitutions suggests that either the formation and/or the reactivity of the arylsodium compounds is affected by the different protective group employed. This hypothesis was confirmed by D_2O quenching experiments (Table III). By monitoring the percentage of deuterium incorporation in the 4-position of compounds **11–14** by ^1H NMR spectroscopy at 300 MHz it was possible to ascertain the almost quantitative formation of the corresponding 2,6-dimethoxy-substituted arylmetal compounds in the reductive cleavage of **1** and **2** with Na metal in THF (Table III, entries 1 and 2). Formation of a similar intermediate was found to occur to a much lower extent in the reductive cleavage of the ethylene acetal **4** under similar conditions (Table III, entry 3), as well as in the reduction of compounds **1** and **2** in solvents of low polarity (Table III, entries 5–7). Finally, it was not possible to detect the formation of any deuteriated product of demethoxylation in the reductive cleavage of the aminal **5** with K metal (Table III, entry 4). This seems to rule out the formation of the arylpotassium compound **10**.

Table III. Product Distribution in Deuterium Labeling Experiments

entry	starting material	metal	solvent	quencher	ArD/ArH[a,b]
1	1	Na	THF	D_2O	92/8
2	2	Na	THF	D_2O	78/22
3	4	Na	THF	D_2O	56/44
4	5	K	THF	D_2O	c
5	1	Na	Et_2O	D_2O	58/42
6	2	Na	Et_2O	D_2O	31/69
7	2	Na	isooctane	D_2O	21/79
8	4	Na	THF-d_8	H_2O	c
9	5	K	THF-d_8	H_2O	c

[a] Determined by ^1H NMR at 300 MHz in $CDCl_3$ by monitoring the percentage of deuterium incorporation in the 4-position (see Experimental Section). [b] Ar = 3,5-dimethoxybenzaldehyde acetal or aminal. [c] No deuterium incorporation was detected.

A possible explanation of this behavior is the formation of intermediate aryl radicals, which may abstract hydrogen atoms from components of the reaction medium, according to what has been reported in the literature for the reductive cleavage of several diaryl[18,19] and aryl alkyl ethers.[12,20] Involvement of the solvent as a donor of hydrogen atoms toward aryl radicals has been suggested, inter alia, in the K metal-promoted aromatic $S_{RN}1$ reactions in liquid ammonia[21,22] and in the reductive cleavage of aromatic ethers and esters with K metal/18-crown-6/THF.[19] Contrary to this expectation, under our reaction conditions no incorporation of deuterium was detected in the products of reductive cleavage of **4** with Na and of **5** with K in THF-d_8, followed by quenching with H_2O (Table III, entries 8 and 9).

Discussion

The synthetic procedure described overcomes some of the limits encountered in the reductive electrophilic substitution of 5-alkyl-substituted 1,2,3-trimethoxybenzenes.[12] The regioselective substitution of **1** leads to a new and efficient way of synthesis of various 2,5-disubstituted resorcinol dimethyl ethers, starting from a readily available material. Versatile functionalities were introduced in the 4-position that can be further manipulated in the presence of the 1-aldehyde group, protected as an acetal. Futhermore, the 1-carbonyl function, when protected as acetal,[23] aminal,[24] or α-amino alkoxide,[25] can be used to direct substitution on the aromatic nucleus via ortho lithiation and subsequent reaction with electrophilic reagents.[26]

From a practical standpoint, our reaction can be compared with a directed ortho metalation reaction of suitable

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derivatives of 3,5-dimethoxybenzaldehyde or 3,5-dimethoxybenzoic acid, followed by reaction with electrophiles.[26] Although no systematic study has been reported, the metalation of 3,5-dimethoxybenzaldehyde dimethyl acetal with BuLi, followed by reaction with an aliphatic aldehyde, affords good yield of the product of substitution in the 4-position.[27] On the other hand, a detailed investigation of the metalation of the diethyl amide of 3,5-dimethoxybenzoic acid[28] and of 2-(3,5-dimethoxyphenyl)-4,4-dimethyl-2-oxazoline[5] has been reported. The regioselectivity of such reactions varies dramatically when the alkyllithium derivative or the solvent is varied, but high regioselectivity is possible in the metalation at C_2, not at C_4.[5,28]

It should also be pointed out that the reductive electrophilic substitution described here was performed using Na metal as the reducing agent and not K, as in the case of the 5-alkyl-substituted derivatives;[12] furthermore, we have reported reaction conditions for the introduction of several functionalities which are, in principle, not stable to reduction with alkali metals. The excess metal can be filtered off as shown for the synthesis of **16n**.

THF appears to be the solvent of choice for the synthetic protocol we have described, as solvents of lower polarity reduce the reactivity of the substrates investigated toward the reductive demethoxylation reaction, as well as the amount of the arylmetal compound formed. Similar solvent effects have been observed in the reductive cleavage of alkyl aryl ethers[20,29] and of aromatic acetals.[16]

The contrasting results obtained with different aldehyde protecting groups suggest that, as already observed in the reductive demethoxylation of 5-alkyl-substituted 1,2,3-trimethoxybenzenes,[12] the nature of the substituent para to the leaving methoxy group strongly influences the mechanism(s) of the C–O bond cleavage. The reaction pathway usually considered for the cleavage of aryl–O bonds of aryl ethers under reductive electron transfer conditions is depicted in eqs 2–7.[18,19]

$$\mathrm{ArOR} + e^- \rightarrow \mathrm{ArOR}^{\bullet -} \quad (3)$$

$$\mathrm{ArOR}^{\bullet -} \rightarrow \mathrm{Ar}^{\bullet} + \mathrm{RO}^- \quad (4)$$

$$\mathrm{Ar}^{\bullet} + e^- \rightarrow \mathrm{Ar}^- \quad (5)$$

$$\mathrm{Ar}^{\bullet} + \mathrm{SH} \rightarrow \mathrm{ArH} + \mathrm{S}^{\bullet} \quad (6)$$

$$\mathrm{ArOR}^{\bullet -} + e^- \rightarrow \mathrm{ArOR}^{2-} \quad (7)$$

$$\mathrm{ArOR}^{2-} \rightarrow \mathrm{Ar}^- + \mathrm{RO}^- \quad (8)$$

The decay of the aryl radicals according to eq 6 competes with their reduction to aryl anions (eq 5) and therefore with the formation of the species able to suffer electrophilic attack. Indeed, the results of D_2O-quenching experiments strongly suggest that decay of aryl radicals by hydrogen atom abstraction (eq 6) is a major reaction pathway both in the reductive demethoxylation of compound **5** in THF and in the reductive cleavage of acetals **1** and **2** in solvents of lower polarity. Such a reaction cannot be excluded also for compound **4** in THF, though in this case deprotonation of the acetal moiety according to eq 1 was evidenced. The results obtained in THF-d_8 argue against the solvent as the source of the hydrogen atoms. The source of hydrogen atoms could be the substrate itself, as shown in the reductive cleavage of anisole with K metal in hydrocarbon solvents[20] and in the electrochemical reduction of aryl diethyl phosphates.[30] Further work is in progress to elucidate this point.

A final remark concerns the observed behavior of the aldehyde protecting groups toward reduction with alkali metals under aprotic conditions. The acyclic acetals proved to be resistant to the reduction with Na metal, but underwent cleavage and Wittig rearrangement in the presence of K. Synthetic exploitation of the latter reactivity was proposed (compound **24**). The dioxolane protecting group, while resistant to reductive electron transfer from Na, is not stable to the highly basic reaction medium and undergoes deprotonation and fragmentation (eq 1). Finally, the dimethylimidazolidine protecting group, though not useful in the reductive electrophilic substitution reaction, proved to be resistant both to Na and K metal.

Experimental Section

General Procedures. All products and reagents were of the highest commercial quality from freshly opened containers and were further purified by distillation or recrystallization. 3,4,5-Trimethoxybenzaldehyde was purchased from Janssen. Solvents were distilled from Na under N_2 immediately prior to use. Deuterium oxide (minimum isotopic purity 99.8% deuterium) was purchased from Aldrich. Boiling and melting points are uncorrected. ^{1}H NMR spectra were recorded on a Varian T-60 (60-MHz) or on a Varian VXR 300 (300-MHz) spectrometer in $CDCl_3$ solution with Me_4Si as internal standard; coupling constants are reported in hertz. Deuterium incorporation was calculated by monitoring the ^{1}H NMR spectra recorded at 300 MHz of the products of reductive demethoxylation and comparing the integration of the signal corresponding to the proton in the 4-position with the integral of the protons in the 2- and 5-position. The IR spectra were recorded on a Perkin-Elmer 983 spectrophotometer. Elemental analyses were performed by the Microanalytical Laboratory of the Dipartimento di Chimica, Università di Sassari.

Preparation of Starting Materials. Compound **1** was prepared as described in ref 13. All other acetals were prepared according to a standard procedure.[31] Compound **5** was prepared according to a known procedure.[24]

3,4,5-Trimethoxybenzaldehyde dimethyl acetal (1): bp 180 °C (10 Torr); ^{1}H NMR (300 MHz) δ 2.98 (s, 6 H, $CH(OCH_3)_2$), 3.80 (s, 3 H, OCH_3), 3.87 (s, 6 H, 2 OCH_3), 5.29 (s, 1 H, CH), 6.73 (s, 2 H, phenyl).

3,4,5-Trimethoxybenzaldehyde diethyl acetal (2): bp 170 °C (3 Torr); ^{1}H NMR (300 MHz) δ 1.25 (t, J = 7, 6 H, 2 CH_3), 3.50–3.65 (m, 4 H, 2 CH_2), 3.84 (s, 3 H, OCH_3), 3.88 (s, 6 H, 2 OCH_3), 5.40 (s, 1 H, CH), 6.71 (s, 2 H, phenyl).

3,4,5-Trimethoxybenzaldehyde dibutyl acetal (3): bp 155–157 °C (1 Torr); ^{1}H NMR (300 MHz) δ 0.92 (t, J = 7, 6 H, 2 CH_3), 1.35–1.49 (m, 4 H, 2 CH_2), 1.55–1.66 (m, 4 H, 2 CH_2), 3.42–3.60 (m, 4 H, 2 CH_2O), 3.82 (s, 3 H, OCH_3), 3.87 (s, 6 H, 2 OCH_3), 5.40 (s, 1 H, CH), 6.70 (s, 2 H, phenyl).

3,4,5-Trimethoxybenzaldehyde ethylene acetal (4): bp 145–146 °C (1 Torr); ^{1}H NMR (300 MHz) δ 3.84 (s, 3 H, OCH_3), 3.88 (s, 6 H, 2 OCH_3), 4.10–4.16 (m, 4 H, 2 CH_2), 5.74 (s, 1 H, CH), 6.72 (s, 2 H, phenyl).

1,3-Dimethyl-2-(3,4,5-trimethoxyphenyl)imidazolidine (5): bp 112–115 °C (1 Torr); ^{1}H NMR (300 MHz) δ 2.20 (s, 6 H, 2 NCH_3), 2.52–2.59 (m, 2 H, CH_2), 3.18 (s, 1 H, CH), 3.38–3.44 (m, 2 H, CH_2), 3.85 (s, 3 H, OCH_3), 3.89 (s, 6 H, 2 OCH_3), 6.69 (s, 2 H, phenyl).

Compounds **1–5** were further characterized by acidic hydrolysis (CH_3COOH:H_2O = 5:1, reflux, 5 h) to 3,4,5-trimethoxybenzaldehyde.[32]

General Procedure for the Reductive Demethoxylation. A solution of the appropriate 3,4,5-trimethoxybenzaldehyde derivative (4 mmol) in anhydrous THF (5 mL) was added dropwise

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to a suspension of the freshly cut metal (0.012 g-atom) in anhydrous THF (30 mL) under dry N_2 or Ar. The mixture was stirred at room temperature for 24 h and then chilled to 0 °C, quenched by slow dropwise addition of H_2O (10 mL) (*caution*!), and extracted with Et_2O (3 × 20 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (2 × 30 mL), dried (K_2CO_3), and evaporated to afford the crude liquid products. Deuterium oxide quenching was performed by slow dropwise addition of 2 mL of D_2O to the reaction mixture chilled to 0 °C followed by stirring of the mixture for 2 h at room temperature and workup as above.

Compounds 11–14 were further characterized by acidic hydrolysis (CH_3COOH:H_2O = 5:1, reflux, 5 h) to 3,5-dimethoxybenzaldehyde.[33]

General Procedure for the Reductive Electrophilic Substitution. A solution of the appropriate 3,4,5-trimethoxybenzaldehyde derivative (4 mmol) in anhydrous THF (5 mL) was added dropwise to a suspension of the freshly cut metal (0.012 g-atom) in anhydrous THF (30 mL) under dry N_2 or Ar. The mixture was stirred at room temperature for 24 h and then chilled to the reported temperature. The appropriate amount of electrophile dissolved in anhydrous THF (5 mL) was slowly added, and the resulting mixture was stirred for several hours (Table II). The reaction was quenched by slow dropwise addition of H_2O or 1 N NaOH in the case of compounds **16i**, **16l**, and **17** (10 mL) (*caution*!) and extracted with Et_2O (3 × 20 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (2 × 30 mL), dried (K_2CO_3), and evaporated to afford the crude product which was purified by distillation, flash chromatography, or recrystallization. Several products were recovered contaminated with small amounts of the corresponding aldehydes (<5%); complete characterization was therefore obtained by hydrolysis (CH_3COOH:H_2O = 5:1, 10 mL, reflux, 5 h) to the corresponding aldehydes. The products were characterized as follows.

3,5-Dimethoxy-4-(trimethylsilyl)benzaldehyde (30). Purified by flash chromatography (AcOEt:hexane = 1:9): colorless liquid which solidifies upon standing; ^1H NMR (300 MHz) δ 0.31 (s, 9 H, 3 $SiCH_3$), 3.84 (s, 6 H, 2 OCH_3), 6.99 (s, 2 H, phenyl), 9.94 (s, 1 H, CHO). Anal. Calcd for $C_{12}H_{18}O_3Si$: C, 60.46; H, 7.63. Found: C, 60.15; H, 7.81.

1-(2,6-Dimethoxy-4-formylphenyl)-2,2-dimethyl-1-propanol (31): mp 125–126 °C (from CH_2Cl_2–pentane); IR (CCl_4) 3566 (OH) cm^{-1}; ^1H NMR (300 MHz) δ 0.94 (s, 9 H, 3 CH_3), 3.87 (br s, 3 H, OCH_3), 3.93 (br s, 3 H, OCH_3), 4.24 (d, *J* = 12, 1 H, OH), 4.98 (d, *J* = 12, 1 H, CH), 7.08–7.12 (m, 2 H, phenyl), 9.93 (s, 1 H, CHO). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.63; H, 8.01. Found: C, 67.06; H, 8.31.

3,5-Dimethoxy-4-formylbenzophenone (32): purified by flash chromatography (AcOEt:hexane = 3:7); mp 127–128 °C (from CH_2Cl_2–pentane); IR (CCl_4) 1701, 1683 (CO) cm^{-1}; ^1H NMR (300 MHz) δ 3.80 (s, 6 H, 2 OCH_3), 7.16 (s, 2 H, phenyl), 7.42–7.48 (m, 2 H, phenyl), 7.56–7.62 (m, 1 H, phenyl), 7.80–7.84 (m, 2 H, phenyl). Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.09; H, 5.23. Found: C, 70.66; H, 5.02.

Methyl 2,6-dimethoxy-4-formylbenzoate (33): mp 107–109 °C (from CH_3COOH/H_2O); IR (CCl_4) 1742 ($COOCH_3$), 1707 (CHO) cm^{-1}; ^1H NMR (300 MHz) δ 3.93 (s, 6 H, 2 OCH_3), 3.95 (s, 3 H, CH_3OCO), 7.14 (s, 2 H, phenyl), 9.88 (s, 1 H, CHO). Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40. Found: C, 59.05; H, 5.78.

2,2′,6,6′-Tetramethoxy-4,4′-bis[(dimethoxymethyl)-phenyl]methanol (16m): mp 131–132 °C (from CH_3OH/H_2O); IR (CCl_4) 3551 (OH) cm^{-1}; ^1H NMR (300 MHz) δ 1.61 (br s, 1 H, OH), 3.31 (s, 6 H, $CH(OCH_3)_2$), 3.76 (s, 3 H, CH_3OCO), 5.31 (s, 1 H, CH acetal), 5.61 (d, *J* = 3, 1 H, CH alcohol), 6.61 (s, 2 H, phenyl). Anal. Calcd for $C_{23}H_{32}O_9 \cdot {}^1/_2H_2O$: C, 59.85; H, 7.22. Found: C, 60.16; H, 6.90.

3,5-Dimethoxy-4-formylbenzaldehyde Dimethyl Acetal (16n). Purified by flash-chromatography (AcOEt:hexane = 2:8): colorless liquid which solidifies upon standing; IR (CCl_4) 1689 (CO) cm^{-1}; ^1H NMR (300 MHz) δ 3.35 (s, 6 H, $CH(OCH_3)_2$), 3.92 (s, 3 H, CH_3OCO), 5.35 (s, 1 H, CH acetal), 6.69 (s, 2 H, phenyl), 10.49 (s, 1 H, CHO). Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.98; H, 6.73. Found: C, 59.60; H, 6.85.

1-(3,5-Dimethoxyphenyl)ethanol (21). A solution of **1** (3 g, 12.4 mmol) in anhydrous THF (10 mL) was added dropwise to a suspension of freshly cut K metal (1.45 g, 0.037 g-atom) in anhydrous THF (90 mL) under dry Ar. The mixture was stirred at 45 °C for 24 h and then chilled to 0 °C, quenched by slow dropwise addition of H_2O (10 mL) (*caution*!), and extracted with Et_2O (3 × 20 mL). The organic phase was washed with H_2O (2 × 30 mL), dried ($CaCl_2$), and evaporated to afford the crude product which was purified by column chromatography (AcOEt:hexane = 3.7): bp 130–132 °C (5 Torr) (lit.[34] bp 92.5 °C (0.3 Torr).

1-(3,5-Dimethoxyphenyl)-1-pentanone (24). A solution of **3** (3.4 g 10.1 mmol) in anhydrous THF (10 mL) was added dropwise to a suspension of freshly cut K metal (1.8 g, 0.047 g-atom) in anhydrous THF (90 mL) under dry Ar. The mixture was stirred at 45 °C for 24 h and then chilled to 0 °C, quenched by slow dropwise addition of H_2O (10 mL) (*caution*!), and extracted with Et_2O (3 × 20 mL). The organic phase was washed with H_2O (2 × 30 mL), dried ($CaCl_2$), and evaporated to afford the crude product, which, without further purification, was added at room temperature to a suspension of CrO_3 (0.5 g, 8.2 mmol) in 10 mL of glacial acetic acid under dry N_2. After vigorous stirring for 2 h, the reaction mixture was poured into a saturated aqueous solution of $NaHSO_3$ (30 mL) and extracted with petroleum ether (3 × 30 mL). The organic phase was washed with saturated aqueous $NaHSO_3$ (2 × 30 mL), saturated aqueous $NaHCO_3$ (2 × 30 mL), and H_2O (2 × 30 mL) and dried ($CaCl_2$). Evaporation of the solvent and flash chromatography (AcOEt:hexane = 1:9) afforded pure **24** (0.45 g, 2 mmol, 19%): bp 140–142 °C (3 Torr) (lit.[17] bp 175–177 °C (11 Torr)).

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Supplementary Material Available: Characterization data (boiling point, melting point, IR, and ^1H NMR) for compounds **11–14**, **16a–d**, **16f**, **16h–l**, **17**, **19**, **21**, **24–29** (3 pages). Ordering information is given on any current masthead page.

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