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Regioselective reductive demethoxylation of 3,4,5-trimethoxystilbenes

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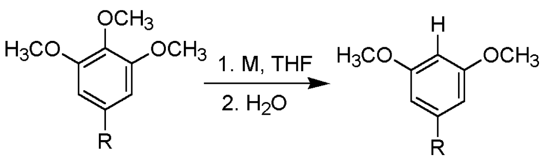
Abstract—Selective removal of the 4-methoxy group of 3,4,5-trimethoxystilbenes was performed under electron transfer conditions from Na metal in THF. Careful control of reaction conditions and quenching procedure allowed the synthesis of either (*E*)-3,5-dimethoxystilbenes or 3,5-dimethoxybibenzyls.

3,5-Dihydroxy-substituted stilbenes, as well as the corresponding bibenzyl derivatives, are an important class of natural products, which were isolated from many plants[1–3] and possess a variety of interesting biological and pharmacological properties.[1–8] Furthermore, it was recently shown that some 3,5-dimethoxy-substituted-stilbenes are potent and selective inhibitors of human cytochrome P450 1B1.[7] Accordingly, there is a continuous search for new approaches to their synthesis,[3,6–11] most of which rely on relatively expensive starting materials, as 3,5-dihydroxybenzaldehyde or derivatives of 3,5-dihydroxybenzyl alcohol.

Interestingly, 5-substitued derivatives of 1,2,3-trimethoxybenzene are particularly cheap and, therefore, attractive starting materials for similar syntheses, provided the possibility to operate a regioselective demethoxylation at the 2-position.

Despite their generally known inertness and high reductive potential, the C–O bond of aryl alkyl ethers can be cleaved by electron transfer from alkali metals in aprotic solvents. In the course of our extensive studies on the mechanism[12–14] and synthetic usefulness[12,15–17] of this reaction, we reported that several derivatives of 1,2,3-trimethoxybenzene undergo a highly regioselective demethoxylation at the 2-position, in almost quantitative yield.

According to this procedure, we reported alternative syntheses of several naturally occurring 5-substituted and 2,5-disubstituted resorcinols.[18–20] The main features of this approach are the following: (i) cheap and easy availability of starting materials; (ii) high regioselectivity; (iii) mild reaction conditions (Scheme 1).



Scheme 1. Regioselective reductive demethoxylation of 1,2,3-trimethoxybenzenes. M=Na or K; R=H, *n*-alkyl, $CH(OCH_3)_2$.

As an extension of this procedure, we wish now to report that reduction of (*E*)-3,4,5-trimethoxystilbenes, **1**, with Na metal in dry THF, allows the regioselective removal of the methoxy group in the 4-position; depending upon reaction conditions, competitive reduction of the carbon–carbon double bond occurs,[21] leading to the synthesis of either (*E*)-3,5-dimethoxystilbenes, **2**, or 3,5-dimethoxybibenzyls, **3**.[22]

1. Results and discussion

3,4,5-Trimethoxybenzaldehyde, a particularly cheap starting material, was reacted with $LiAlH_4$ to afford the corresponding benzyl alcohol. The crude carbinol was successively reacted with PBr_3 and triethylphosphite, affording 3,4,5-trimethoxybenzylphosphonate, in 63% overall yield. According to a general procedure,[23] the phosphonate was deprotonated with NaH in THF, and reacted with the appropriate arylaldehyde in the presence of 15-crown-5; the corresponding (*E*)-3,4,5-trimethoxystilbenes, **1a–e**, were recovered in good isolated yields (Scheme 2).

Keywords: reduction; electron transfer; regioselectivity; stilbenes.

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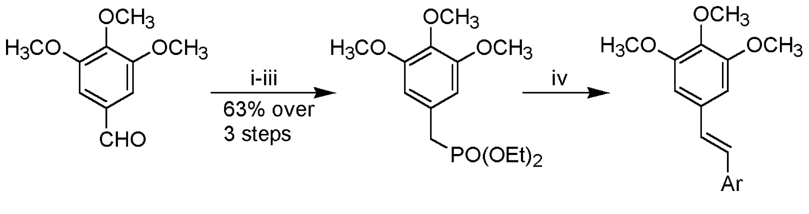
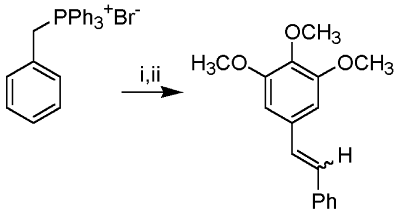


1a-e

Scheme 2. Synthesis of (*E*)-3,4,5-trimethoxystilbenes: i, $NaBH_4$; ii, PBr_3; iii, $P(OC_2H_5)_3$; iv, NaH, 15-crown-5, ArCHO; **1a**, Ar=C_6H_5, 93%; **1b**, Ar=2-$(CH_3O)C_6H_4$, 76%; **1c**, Ar=3-$(CH_3O)C_6H_4$, 82%, **1d**, Ar=4-$(CH_3O)C_6H_4$, 76%; **1e**, Ar=3,4,5-$(CH_3O)_3C_6H_2$, 61%.



(*E*)/(*Z*)-**1a**, 1:1 mixture

Scheme 3. Synthesis of (*E*)- and (*Z*)-3,4,5-trimethoxystilbene, (E)/(Z)-**1a**, as a 1:1 mixture of diastereoisomers: i, *n*-BuLi, THF, 0°C, 1 h; ii, −78°C, ArCHO, 4 h, then 12 h at rt; 69% yield.

Alternatively, we obtained a 1:1 geometric mixture of (*E*)- and (*Z*)-3,4,5-trimethoxystilbene, **1a**, by reacting benzyltriphenylphosphonium bromide with 3,4,5-trimethoxybenzaldehyde, under conventional Wittig olefination conditions (Scheme 3).

Reductions of stilbenes **1a–e** with Na metal were run in dry THF under Ar; selected results are reported in the Tables 1 and 2 (Scheme 4); it is worth noting that we did not investigate the formation of phenolic by-products, which can be obtained by competitive reductive cleavage of aliphatic carbon–oxygen bonds. Indeed, dealkylation is usually a minor reaction pathway in the reductive cleavage of 1,2,3-trimethoxy-substituted benzenes.[12]

Reduction of (*E*)-3,4,5-trimethoxystilbene, **1a**, taken as a model compound, was investigated in some detail (Table 1). Reaction of **1a** with 3 equiv. of Na metal at 0°C over 3 h, followed by aqueous work-up, led to the expected

Table 1. Reductive cleavage of 3,4,5-trimethoxystilbene **1a**

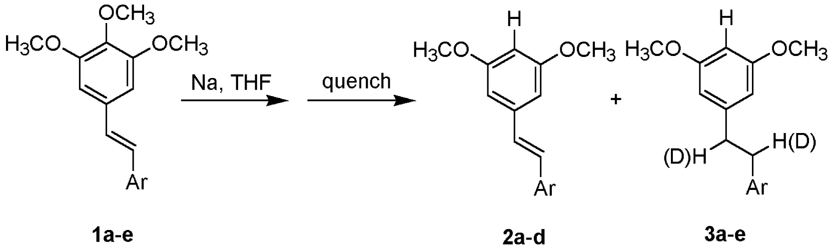
Entry	Starting material	Na (equiv.)	*T* (°C)	*t* (h)	Quencher	Products ratio[a]	Isolated product, yield (%)
1	**1a**	3	0	3	H_2O	**2a/3a**, 87:13	–
2	**1a**	6	0	3	H_2O	**2a/3a**, 72:28	–
3	**1a**	6	20	7	H_2O	**2a/3a**, <5:>95	**3a**, 78
4	**1a**	6	20	7	D_2O	**2a/3a**, <5:>95	**3a**-d_2, >95[b]
5	**1a**	6	20	7	$Br(CH_2)_2Br$	**2a/3a**, >95:<5	**2a**, 75
6	(*E*)/(*Z*)-**1a**[c]	6	20	7	H_2O	**2a/3a**, <5:>95	–
7	(*E*)/(*Z*)-**1a**[c]	6	20	7	$Br(CH_2)_2Br$	**2a/3a**, >95:<5	**2a**, 73
8	(*E*)/(*Z*)-**1a**[c]	1	20	4	H_2O	(*E*)/(*Z*)-**1a**[d]/**3a**, 45:55	–

[a] As determined by ^1H NMR spectroscopy.
[b] Deuteration percentage, as determined by ^1H NMR spectroscopy. No incorporation of deuterium on the aromatic ring was detected.
[c] 1:1 Mixture of geometric isomers.
[d] 4:1 Mixture of geometric isomers.

Table 2. Reductive cleavage of 3,4,5-trimethoxystibenes **1b–e**

Entry	Starting material	Na (equiv.)	*T* (°C)	*t* (h)	Quencher	Products ratio[a]	Isolated product, yield (%)
1	**1b**	6	0	2.5	H_2O	**2b/3b**, >95:<5	**2b**, 75
2	**1b**	6	0	7	H_2O	**2b/3b**, 52:48	–
3	**1b**	12	0	14	H_2O	**2b/3b**, <5:>95	**3b**, 56
4	**1b**	12	0	14	D_2O	**2b/3b**, <5:>95	**3b**-d_2, 77[b]
5	**1c**	6	20	9	H_2O	**2c/3c**, <5:>95	**3c**, 89
6	**1c**	6	20	9	D_2O	**2c/3c**, <5:>95	**3c**-d_2, 86[b]
7	**1c**	3	20	7	$Br(CH_2)_2Br$	**2c/3c**, >95:<5	**2c**, 71
8	**1d**	6	0	2	H_2O	**2d/3d**, >95:<5	**2d**, 68
9	**1d**	6	0	14	H_2O	**2d/3d**, 69:31	–
10	**1d**	6[c]	20	6	H_2O	**2d/3d**, <5:>95	**3a**, 65
11	**1e**	20[d]	20	18	H_2O	n.d.[e]	**3e**, 69
12	**1e**	20[d]	20	18	D_2O	n.d.[e]	**3e**-d_2, 25

[a] As determined by ^1H NMR spectroscopy.
[b] Deuteration percentage, as determined by ^1H NMR spectroscopy. No incorportion of deuterium on the aromatic ring was detected.
[c] In the presence of 1 equiv. of naphthalene.
[d] In the presence of 2 equiv. of naphthalene.
[e] Not determined.



Scheme 4. Reductive demethoxylation of 3,4,5-trimethoxystilbenes, **1**; quench: H_2O, D_2O, or $Br(CH_2)_2Br$; **2a–3a**, Ar=C_6H_5; **2b–3b**, Ar=2-$(CH_3O)C_6H_4$; **2c–3c**, Ar=3-$(CH_3O)C_6H_4$; **2d–3d**, Ar=4-$(CH_3O)C_6H_4$; **3e**, Ar=3,5-$(CH_3O)_2C_6H_3$.

regioselective demethoxylation at the 4-position affording, besides bibenzyl **3a** (hydropinosilvin dimethyl ether), (*E*)-stilbene **2a** (pinosilvin dimethyl ether), as major reaction product (Table 1, entry 1); no trace of the corresponding (*Z*)-stereoisomer was detected by ^1H NMR analysis of the crude reaction mixture.[24]

Increasing the relative amount of the metal, as well as reaction time and temperature, increases the relative amount of recovered bibenzyl **3a**, which was the only reaction product recovered after running the reduction with 6 equiv. of Na metal at rt over 7 h (Table 1, entry 3). Under these conditions, intermediate formation of a dianion was evidenced by quenching the reaction mixture with D_2O: ^1H NMR spectroscopy of the crude product showed quantitative incorporation of deuterium at both benzylic carbons (Table 1, entry 4). Oxidative quenching of the reaction mixture with 1.4 equiv. of $Br(CH_2)_2Br$ led to the exclusive recovery of stilbene **2a**, with no trace of the corresponding bibenzyl **3a** (Table 1, entry 5). It is worth noting that oxidation of the dianion is highly stereoselective leading, exclusively, to the formation of the (*E*)-stereoisomer.

To investigate the influence of the geometry at the ethylenic double bond on this reaction, we reacted Na with a 1:1 mixture of (*E*) and (*Z*)-3,4,5-trimethoxystilbene, **1a**. With 6 equiv. of Na at rt over 7 h, we obtained bibenzyl **3a**, as the only detected product (Table 1, entry 6). Intermediate formation of a dianion was evidenced by quenching the reduction mixture with $Br(CH_2)_2Br$; under these conditions, we recovered (*E*)-stilbene **2a**, as a single geometric isomer, in 73% isolated yield (Table 1, entry 7). Furthermore, a reaction performed with 1 equiv. of the metal over 4 h, allowed the recovery of a mixture containing 3,4,5-trimethoxystilbene (*E*)/(*Z*)-**1a**, in a 4:1 geometric ratio, together with (*E*)-3,5-dimethoxystilbene **2a** (55%) (Table 1, entry 8). It is worth noting that, under these conditions, reduction of the carbon–carbon double bond did not occur, and that we did not observe formation of (*Z*)-3,5-dimethoxystilbene.

According to the procedure described above, we investigated the reduction with Na metal in THF of stilbenes **1b–e**, bearing methoxyl substituents on both aromatic rings (Table 2).

Reduction of (*E*)-2′,3,4,5-tetramethoxystilbene, **1b**, at rt led to the formation of several, unidentified, by-products. Fortunately, reaction of tetramethoxystilbene **1b** with 6 equiv. of Na, at 0°C, led to selective removal of the methoxy group in the 4-position, thus allowing isolation of 2′,3,5-trimethoxystilbene, **2b**, in 75% yield (Table 2, entry 1). Increasing the reaction time and the relative amount of the metal, resulted in competitive reduction of the ethylenic double bond; reduction with 12 equiv. of Na over 14 h, followed by quenching with H_2O, allowed isolation of 2′,3,5-trimethoxybibenzyl **3b** (batatasin IV dimethyl ether), in 56% yield (Table 2, entry 3). Under these conditions, quenching with D_2O led to 77% incorporation of deuterium at the methylenic positions (Table 2, entry 4).

Similar results were obtained in the reduction of (*E*)-3,3′,4,5-tetramethoxystilbene, **1c**: satisfactory isolated yields of the corresponding (*E*)-3,3′,5-trimethoxystilbene, **2c** (thunalbene dimethylether), and 3,3′,5-trimethoxybibenzyl, **3c** (batatasin III dimethyl ether), were obtained, depending upon reaction conditions and quenching procedure (Table 2, entries 5–7).

Somewhat different results were obtained in the reductive cleavage of (*E*)-3,4,4′,5-tetramethoxystilbene, **1d**, which proved particularly resistant to reduction of the ethylenic double bond. Indeed, reduction with 6 equiv. of Na metal at 0°C over 2 h, allowed the selective removal of the methoxy group at the 4-position, leading to the recovery of 3,4′,5-trimethoxystilbene, **2d** (resveraról trimethyl ether), in 68% isolated yield (Table 2, entry 8); the main product of this reaction did not change on increasing the reaction time to 14 h (Table 2, entry 9). We obtained quantitative reduction of the ethylenic double bond running the reaction at rt, in the presence of 6 equiv. of the metal and 1 equiv. of naphthalene. Under these reaction conditions, however, a double demethoxylation took place, leading to 3,5-dimethoxybibenzyl, **3a**, in 65% isolated yield (Table 2, entry 10).

Finally, we investigated the reductive cleavage of hexamethoxystilbene **1e**. Reductive cleavage of this compound poses several problems owing to its low solubility in THF and inertness to electron transfer reduction, probably due to the presence of six electron donor substituents of the aromatic rings. After several attempts, we were able to obtain demethoxylation of the methoxy groups at the 4- and 4′-positions, together with reduction of the carbon–carbon double bond, using 20 equiv. of Na metal in the presence of 2 equiv. of naphthalene. Accordingly, 3,3′,5,5′-tetramethoxybibenzyl, **3e**, was recovered in 69% isolated yield (Table 2, entry 11). Under similar reaction conditions, D_2O quenching evidenced only a minor amount of deuterium incorporation at the benzylic positions (Table 2, entry 12).

As a conclusion, we have shown that the methoxy group in the 4-position of 3,4,5-trimethoxystilbenes can be regioselectively removed under reductive electron transfer conditions. Furthermore, we observed that both reductive demethoxylation, and isomerization of (*Z*)- to (*E*)-stereoisomer, are faster than reduction of the ethylenic double bond.

However, reduction of the ethylenic double bond of 4′-methoxy-substituted-3,4,5-trimethoxystilbenes **1d** and **1e** occurs with concomitant cleavage of the methoxy groups at the 4′-position.

Accordingly, we were able to perform the synthesis of several resorcinolic (*E*)-stilbenes, **2**, or bibenzyls, **3**, from a common, easily accessible, cheap starting material, by careful control of reaction conditions (equiv. of the metal, reaction time and temperature, quenching procedure).

2. Experimental

2.1. General

Boiling and melting points are uncorrected; the air bath temperature on bulb-to-bulb distillation are given as boiling points. Starting materials were of the highest commercial quality and were purified by distillation or recrystallization immediately prior to use. D_2O was 99.8% isotopic purity. THF was distilled from Na/K alloy under N_2 immediately prior to use. ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ with $SiMe_4$ as internal standard. Deuterium incorporation was calculated by monitoring the ^1H NMR spectra of crude reaction mixtures, and comparing the integration of the signal corresponding to protons in the arylmethyl position with that of known signals. Resonances of the CHD protons are usually shifted 0.02–0.04 ppm (δ) upfield relative to the resonances of the corresponding CH_2 protons. Flash chromatography was performed on Merck silica gel 60 (40–63 μm), and TLC analyses on Macherey–Nagel silica gel pre-coated plastic sheets (0.20 mm). Elemental analyses were performed by the microanalytical laboratory of the Dipartimento di Chimica, Università di Sassari.

2.2. Preparation of starting materials

2.2.1. 3,4,5-Trimethoxybenzylbromide. 3,4,5-Trimethoxybenzaldehyde (15.0 g, 76 mmol) was dissolved in 150 mL of CH_3OH in a 250 mL two-necked flask equipped with reflux condenser and magnetic stirrer, under dry N_2. The solution was chilled to 0°C and $NaBH_4$ (3.5 g, 92 mmol, 1.2 equiv.) was added in small portions over 1 h. The resulting mixture was stirred overnight at rt. The solvent was evaporated, and the residue partitioned between Et_2O (30 mL) and H_2O (30 mL), stirred for a few min, and the organic phase separated. The aqueous phase was extracted with Et_2O (2×30 mL), the organic phases were collected, washed with brine (30 mL), dried (Na_2SO_4) and evaporated.

The crude product (13.3 g, 67 mmol, 88%) appeared homogeneous by TLC analysis R_f=0.25 (petroleum ether/AcOEt=7:3), did not show any IR carbonyl stretching absorption (IR (neat) 3250 cm^{-1}), and was not further characterized.

3,4,5-Trimethoxybenzyl alcohol (10.0 g, 50 mmol), obtained as described above, was dissolved in 150 mL of dry CH_2Cl_2 in a 250 mL two-necked flask equipped with reflux condenser and magnetic stirrer, under dry N_2. The mixture was chilled to -5°C, and a solution of PBr_3 (3.5 mL, 10.1 g, 37 mmol), dissolved in CH_2Cl_2 (10 mL), was added dropwise. The resulting mixture was stirred for 45 min at -5°C. The reaction mixture was poured onto 200 g of ice, neutralized with $NaHCO_3$, and the organic phase separated. The aqueous phase was extracted with CH_2Cl_2 (3×20 mL), and the organic phases were collected, washed with brine (30 mL), dried (Na_2SO_4) and evaporated. The crude product (12.7 g, 49 mmol, 98%) was not further purified.

Light yellow oil; δ_H 3.83 (3H, s, CH_3O), 3.86 (6H, s, $2\times CH_3O$), 4.45 (2H, s, CH_2), 6.60 (2H, s, 2×ArH) (^1H NMR in agreement with a literature report[25]); δ_C 34.2, 56.0, 60.8, 105.9, 133.1, 145.0, 153.2.

2.2.2. Diethyl 3,4,5-trimethoxybenzylphosphonate. 3,4,5-Trimethoxybenzylbromide (11.7 g, 45 mmol), obtained as described above, and triethylphosphite (7.8 mL, 7.46 g, 45 mmol) were mixed in a 100 mL flask equipped with magnetic stirrer and a fractionating Vigreux column equipped with a condenser, under dry N_2. The flask was heated at 140°C for 2 h, then at 180°C for 10 min to distil away all formed ethyl bromide. The reaction mixture was chilled to rt, diluted with Et_2O (30 mL) and H_2O (30 mL), and the organic phase was separated. The aqueous phase was extracted with Et_2O (2×30 mL), the organic phases were collected, washed with 5% NaOH (30 mL), dried (Na_2SO_4) and evaporated. The residue was purified by fractional distillation, affording 10.4 g (33 mmol, 73%) of a colourless oil, which was characterized as following.

Bp 170°C/1 mm Hg; δ_H 1.27 (6H, t, J=7.2 Hz, $2\times CH_3$), 3.09 (2H, d, J=21.3 Hz, CH_2P), 3.83 (3H, s, CH_3O), 3.85 (6H, s, $2\times CH_3O$), 3.98–4.09 (4H, m, $2\times CH_2O$), 6.53 (2H, d, J=2.7 Hz, 2×ArH) (^1H NMR in agreement with a literature report[26]); δ_C 16.3 (d, J=6 Hz), 33.8 (d, J=138 Hz), 56.0, 60.7, 62.0 (d, J=7 Hz), 106.7 (d, J=7 Hz), 126.9 (d, J=9 Hz), 136.8 (d, J=4 Hz), 153.0 (d, J=3 Hz); IR (neat) 1580 cm^{-1}.

(*E*)-3,4,5-Trimethoxystilbenes **1a–e** were synthesized according to a general procedure described in Ref. 23; isolated yields are reported in Scheme 2. Compounds **1a**,[27] **1c**,[28] **1d**[28] and **1e**[29] are already known, and were characterized by comparison with literature data. Compound **1b**[28] is already known, but not described. Accordingly, it was characterized as follows.

2.2.3. (*E*)-2′,3,4,5-Tetramethoxystilbene, 1b. Purified by flash chromatography (petroleum ether/AcOEt=1:1), colourless oil, which solidifies upon standing; R_f=0.36 (petroleum ether/AcOEt=1:1); mp 79–80°C (AcOEt/petroleum ether); (Found: C, 71.85; H 6.92; $C_{18}H_{20}O_4$ requires C, 71.97; H, 6.73); δ_H 3.87 (3H, s, CH_3O), 3.90 (3H, s, CH_3O), 3.92 (6H, s, $2\times CH_3O$), 6.76 (2H, s, 2×ArH), 6.88–7.01 (2H, m, 2×ArH), 7.05 (1H, d, J=16.2 Hz, CH), 7.22–7.31 (1H, m, ArH), 7.37 (1H, d, J=16.2 Hz, CH), 7.58 (1H, dd, J=7.5, 1.8 Hz, ArH); δ_C 55.5, 56.1, 60.9, 103.5, 110.9, 120.7, 122.9, 126.2, 126.4, 128.6, 129.1, 133.7, 138.1, 153.3, 156.8; IR (neat) 1573 cm^{-1}.

2.2.4. Synthesis of (*E*)- and (*Z*)-3,4,5-trimethoxystilbene, (*E*)/(*Z*)-1a. *n*-Butyllithium (4.8 mL of a 1.6 M solution in hexane, 7.7 mmol) was added dropwise to a magnetically stirred solution of benzyltriphenylphosphonium bromide (3.35 g, 7.7 mmol) in dry THF (10 mL), chilled at 0°C under an Ar atmosphere. After the mixture was stirred for 1 h, the reaction temperature was lowered to −78°C, and a solution of 3,4,5-trimethoxybenzaldehyde (1.50 g, 7.6 mmol) dissolved in dry THF (5 mL) was added dropwise. Stirring was continued at −78°C for 4 h, the reaction mixture was allowed to warm to rt, and stirred for 12 h. The reaction mixture was diluted with petroleum ether (10 mL) and H_2O (10 mL), and the organic phase was separated. The aqueous phase was extracted with Et_2O (2×20 mL), the organic phases were collected, washed with 1N HCl (10 mL), saturated $NaHCO_3$ (10 mL), H_2O (10 mL), dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography (petroleum ether/AcOEt=9:1, R_f: (*E*)-isomer=0.20, (*Z*)-isomer=0.28), to afford a white solid (1.46 g, 5.7 mmol, 69%), consisting of a 1:1 diastereoisomeric mixture of (*E*)- and (*Z*)-3,4,5-trimethoxystilbene. The composition of this mixture was determined comparing its ^{1}H NMR spectrum with literature spectra of authentic samples.[27,28]

2.2.5. (*Z*)-3,4,5-Trimethoxystilbene. Purified by flash chromatography (petroleum ether/AcOEt=9:1), colourless oil; R_f=0.28 (petroleum ether/AcOEt=91); δ_H 3.64 (6H, s, 2×CH_3O), 3.83 (3H, s, CH_3O), 6.46 (2H, s, 2×ArH), 6.50 (1H, d, J=12.4 Hz, CH), 6.60 (1H, d, J=12.4 Hz, CH), 7.23–7.35 (5H, m) (^{1}H NMR in agreement with a literature report[28]).

2.3. Reduction of trimethoxystilbenes 1. General procedure

Two to three pieces of freshly cut Na metal (3–20 equiv., see Tables 1 and 2) were placed under Ar in a 50 mL two-necked flask equipped with reflux condenser and magnetic stirrer, and suspended in dry THF (5 mL) at the reported temperature (Tables 1 and 2). The appropriate stilbene (3 mmol), dissolved in dry THF (5 mL) was added dropwise, each metal piece was cut into 2–3 smaller pieces with a spatula, and the reaction mixture was vigorously stirred for the reported time (Tables 1 and 2).

The reaction mixture was chilled to 0°C and quenched by slow dropwise addition of H_2O (10 mL: *Caution*! Na metal reacts violently with H_2O, with evolution of H_2; quenching must be operated under inert atmosphere), the cold bath removed and, after several minutes stirring at rt, the resulting mixture extracted with Et_2O (3×10 mL). The organic phases were collected, washed with brine (10 mL), dried (Na_2SO_4) and the solvent distilled off.

D_2O quenching was performed by slow dropwise addition of 1 mL of the electrophile to the reduction mixture chilled at 0°C, followed by aqueous work-up as described above.

Quenching with $Br(CH_2)_2Br$ (1.4 equiv.) was performed by slow dropwise addition of the electrophile to the reduction mixture chilled at 0°C, followed by aqueous work up as described above.

Crude products were purified and characterized as follows.

2.3.1. (*E*)-3,5-Dimethoxystilbene (2a). Purified by flash chromatography (petroleum ether/AcOEt=7:3), colourless oil, which solidifies upon standing; R_f=0.50 (petroleum ether/AcOEt=7:3); bp 180°C/1 mm Hg (lit.,[30] 123°C/0.02 mm Hg); δ_H 3.79 (6H, s, 2×CH_3O), 6.38 (1H, t, J=2.1 Hz, ArH), 6.66 (2H, d, J=2.1 Hz, 2×ArH), 7.01 (1H, d, J=16.5 Hz, CH), 7.07 (1H, d, J=16.5 Hz, CH), 7.21–7.28 (1H, m, ArH), 7.30–7.38 (2H, m, 2×ArH), 7.45–7.51 (2H, m, 2×ArH); δ_C 55.2, 99.9, 104.5, 126.5, 127.6, 128.6, 129.1, 137.0, 139.3, 160.9; IR (neat) 1580 cm^{-1}.

2.3.2. 3,5-Dimethoxybibenzyl (3a). Purified by flash chromatography (petroleum ether/AcOEt=9:1); colourless oil; R_f=0.41 (petroleum ether/AcOEt=9:1); bp 130°C/1 mm Hg (lit.,[31] 86–88°C/0.1 mm Hg); δ_H 2.81–2.95 (4H, m, 2×CH_2), 3.76 (6H, s, 2×CH_3O), 6.31 (1H, t, J=2.1 Hz, ArH), 6.34 (2H, d, J=2.1 Hz, 2×ArH), 7.15–7.22 (3H, m, 3×ArH), 7.25–7.31 (2H, m, 2×ArH); δ_C 37.7, 38.2, 55.2, 97.9, 106.5, 125.9, 128.3, 128.4, 141.7, 144.2, 160.7.

2.3.3. (*E*)-2′,3,5-Trimethoxystilbene (2b). Purified by flash chromatography (petroleum ether/AcOEt=9:1), colourless oil; R_f=0.37 (petroleum ether/AcOEt=9:1); bp 185°C/1 mm Hg; δ_H 3.81 (6H, s, 2×CH_3O), 3.87 (3H, s, CH_3O), 6.38 (1H, t, J=2.4 Hz, ArH), 6.69 (2H, d, J=2.4 Hz, 2×ArH), 6.89 (1H, d, J=7.8 Hz, ArH), 6.96 (1H, t, J=7.8 Hz, ArH), 7.04 (1H, d, J=16.6 Hz, CH), 7.22 (1H, td, J=7.8, 1.8 Hz, ArH), 7.46 (1H, d, J=16.6 Hz, CH), 7.57 (1H, dd, J=7.8, 1.8 Hz, ArH); δ_C 55.2, 55.3, 99.6, 104.5, 110.8, 123.9, 126.0, 126.4, 128.7, 128.9, 139.9, 156.8, 160.8 (^{1}H and ^{13}C NMR in agreement with a literature report[32]); IR (neat) 1590 cm^{-1}.

2.3.4. 2′,3,5-Trimethoxybibenzyl (3b). Purified by flash chromatography (petroleum ether/AcOEt=9:1); colourless oil; R_f=0.41 (petroleum ether/AcOEt=9:1); bp 175°C/1 mm Hg; (Found: C, 74.77; H 7.63; $C_{17}H_{20}O_3$ requires C, 74.96; H, 7.42); δ_H 2.71–2.95 (4H, m, 2×CH_2), 3.74 (6H, s, 2×CH_3O), 3.81 (3H, s, CH_3O), 6.30 (1H, t, J=2.4 Hz, ArH), 6.37 (2H, d, J=2.4 Hz, 2×ArH), 6.83–6.91 (2H, m, 2×ArH), 7.09–7.12 (1H, m, ArH), 7.14–7.22 (1H, m, ArH); δ_C 32.2, 36.4, 55.1, 55.2, 97.7, 106.4, 110.1, 120.3, 127.1, 129.8, 130.0, 144.8, 157.4, 160.6.

2.3.5. (*E*)-3,3′,5-Trimethoxystilbene (2c). Purified by flash chromatography (petroleum ether/AcOEt=7:3), colourless oil; R_f=0.48 (petroleum ether/AcOEt=7:3); bp 190°C/1 mm Hg; δ_H 3.83 (6H, s, 2×CH_3O), 3.85 (3H, s, CH_3O), 6.40 (1H, t, J=2.1 Hz, ArH), 6.67 (2H, d, J=2.1 Hz, 2×ArH), 6.82 (1H, ddd, J=8.1, 2.7, 0.6 Hz, ArH), 7.01 (1H, d, J=17.4 Hz, CH), 7.07 (1H, d, J=17.4 Hz, CH), 7.04–7.12 (2H, m, ArH), 7.27 (1H, t, J=8.1, ArH); δ_C 55.2, 55.3, 100.0, 104.6, 111.7, 113.4, 119.3, 128.9, 129.1, 129.6, 138.5, 139.2, 159.8, 160.9 (^{1}H and ^{13}C NMR in agreement with a literature report[32]); IR (neat) 1590 cm^{-1}.

2.3.6. 3,3′,5-Trimethoxybibenzyl (3c). Purified by flash chromatography (petroleum ether/AcOEt=9:1); colourless oil; R_f=0.37 (petroleum ether/AcOEt=9:1); bp 160°C/1 mm Hg; δ_H 2.75–2.84 (4H, m, 2×CH_2), 3.67 (6H, s, 2×CH_3O), 3.69 (3H, s, CH_3O), 6.23 (1H, t, J=2.4 Hz, ArH), 6.26 (2H, d, J=2.4 Hz, 2×ArH), 6.62–6.74 (3H, m, 3×ArH), 7.09–7.16 (1H, m, ArH) (^1H NMR in agreement with a literature report[33]); δ_C 37.7, 38.0, 55.1, 55.2, 97.9, 106.4, 111.2, 114.1, 120.8, 129.3, 143.3, 144.1, 159.6, 160.7.

2.3.7. (*E*)-3,4′,5-Trimethoxystilbene (2d). Purified by flash chromatography (petroleum ether/AcOEt=9:1), colourless oil, which solidifies upon standing; R_f=0.54 (petroleum ether/AcOEt=9:1); mp 52–54°C (CH_3OH) (lit.,[27] 56.5–57.5°C, CH_3OH); δ_H 3.70 (3H, s, CH_3O), 3.71 (6H, s, 2×CH_3O), 6.28 (1H, t, J=2.1 Hz, ArH), 6.55 (2H, d, J=2.1 Hz, 2×ArH), 6.75–6.80 (2H, m, 2×ArH), 6.79 (1H, d, J=16.5 Hz, CH), 6.94 (1H, d, J=16.5 Hz, CH), 7.30–7.35 (2H, m, 2×ArH); δ_C 55.2, 55.2, 99.5, 104.2, 114.0, 126.4, 127.7, 128.6, 129.8, 139.6, 159.3, 160.9; IR (neat) 1590 cm^{-1}.

2.3.8. 3,4′,5-Trimethoxybibenzyl (3d). Partially purified by flash chromatography (petroleum ether/AcOEt=9:1); colourless oil; R_f=0.48 (petroleum ether/AcOEt=9:1); δ_H 2.76–2.84 (4H, m, 2×CH_2), 3.76 (6H, s, 2×CH_3O), 3.78 (3H, s, CH_3O), 6.24 (1H, t, J=2.1 Hz, ArH), 6.26 (2H, d, J=2.1 Hz, 2×ArH), 6.67–6.74 (2H, m, 2×ArH), 6.94–7.05 (2H, m, 2×ArH) (^1H NMR in agreement with a literature report[34]); this product was not further characterized.

2.3.9. 3,3′,5,5′-Tetramethoxybibenzyl (3e). Purified by flash chromatography (petroleum ether/AcOEt=8:2), white solid; R_f=0.32 (petroleum ether/AcOEt=8:2); mp 105–106°C (AcOEt) (lit.,[35] 106–108°C, CH_2Cl_2/petroleum ether); δ_H 2.85 (4H, s, 2×CH_2), 3.77 (12H, s, 4×CH_3O), 6.32 (2H, t, J=2.1 Hz, 2×ArH), 6.36 (4H, d, J=2.1 Hz, 4×ArH); δ_C 38.0, 55.3, 98.0, 106.5, 144.1, 160.8.

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