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Metalation Reactions. XVI. Polylithiation of 1,3,5- and 1,2,4-Trimethoxybenzene

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Abstract - Polylithiation reactions of 1,3,5- and 1,2,4-trimethoxybenzenes have been investigated. Results showed that it is possible to substitute all arylic hydrogens through one-pot sequential bimetalation/monometalation, monometalation/bimetalation or three monometalations. This reaction is strongly affected by steric hindrance.

Aromatic organolithium compounds can be conveniently prepared by the metal-hydrogen exchange reaction; they are useful intermediates in the synthesis of a variety of compounds containing functional or non-functional substituents in molecular sites otherwise accessible only through multi-step reactions.[1-5] The importance of these reactions is exemplified by some significant and creative applications in the synthesis of several different classes of aromatic intermediates and natural products.[4,6-12]

It was previously shown[13-15] that aromatic compounds with suitable directing groups can undergo either one-step dilithiation or a one-pot, two steps dilithiation reaction. It is thus possible to introduce into the aromatic moiety two identical or two different substituents. Crowther and coworkers[13] reported the lithiation of anisole and of all the isomeric dimethoxy- and trimethoxybenzenes under a variety of reaction conditions. They showed that 1,3,5- (**1**) and 1,2,4-trimethoxybenzene (**2**) could be lithiated in a one-step reaction to give, after treatment with electrophiles, pentasubstituted benzenes. There was no report of substitution of the last arylic hydrogen.

In the present work the trimethoxybenzenes **1** and **2** were reexamined to check the possibility of introducing identical or different groups by trimetalation reaction. The potentiality and limits of this method (*e.g.*

steric effects[16]) were also investigated.

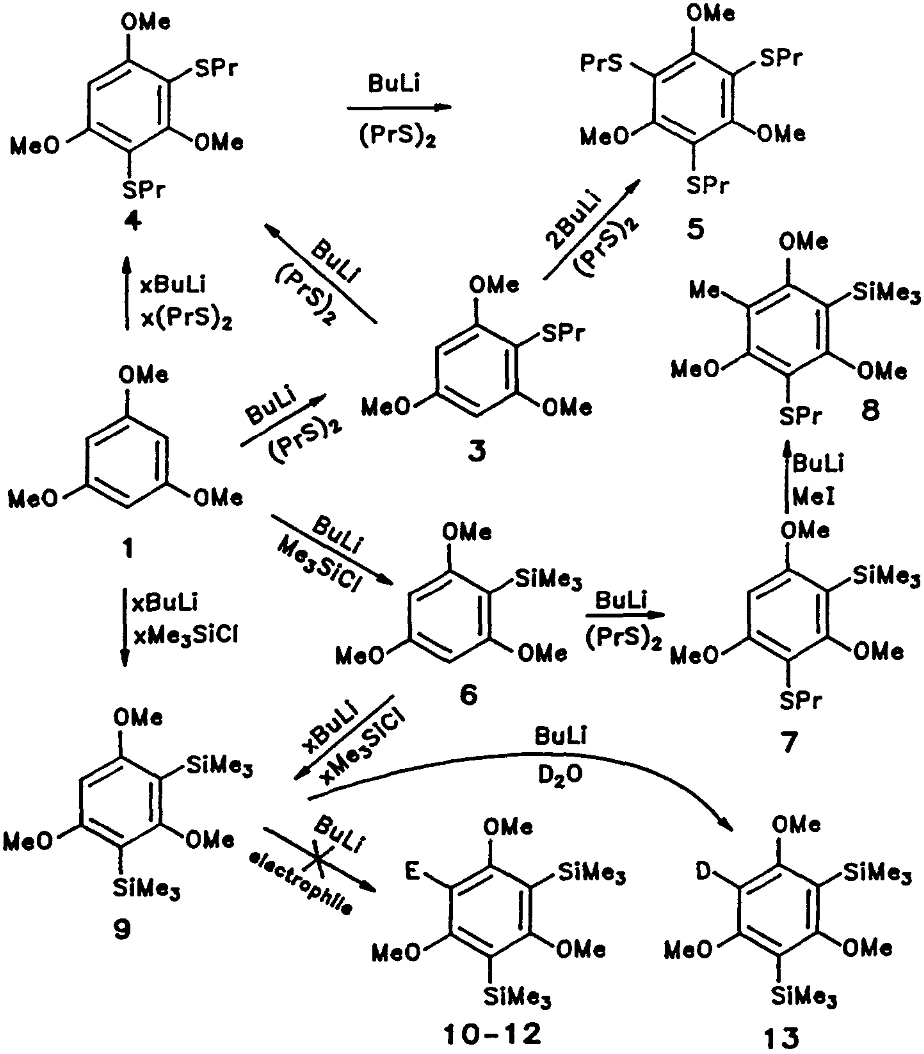
RESULTS AND DISCUSSION

All reactions were performed treating **1** and **2** with the *n*-butyllithium-*N,N,N',N'*-tetramethyl-1,2-ethanediamine (TMEDA) complex. Lithiation intermediates have never been isolated, but were revealed by their reaction with electrophiles. All products were identified on the basis of analytical and spectral data.

The reaction performed on compound **1** (Scheme 1) showed that only two lithium atoms can be introduced in a one-step procedure, even if **1** was treated with a considerable excess of BuLi (6 equiv of organolithium per mole of **1**). This was proved by the formation of **4**, as the only product, after treatment of the metalated species with dipropyldisulphide. However, the hexasubstituted derivative **5** can be obtained from **4** by successive monometalation and treatment with the electrophile. Compound **4** needs not to be isolated and the second step can be performed in the same flask immediately after the first one. Compound **5** was obtained through the synthesis of **3**, which was prepared *via* a monometalation/electrophile procedure on **1**; **3** was then bimetalated and treated with the same electrophile in a one-pot process. Alternatively, it is possible to repeat three monometalations, each one followed by treatment with the electrophile, in a one-pot process. The latter route allowed the substitution of the three arylic hydrogens with three different functional groups as proved by the attainment of **8** by the one-pot introduction of the electrophiles chlorotrimethylsilane, dipropyldisulphide and methyl iodide. On the other hand, attempts to prepare the tris-silylated compound **10** either from the bis-silylated **9** or from the monosilylated **6**, even using an excess of butyllithium, were unsuccessful. Analogous attempts to substitute the arylic hydrogen of **9** with a methyl or propylthio group to obtain **11** or **12** were also unsuccessful. With the aim to verify if the failure to introduce three bulky groups is due to steric hindrance of attack by the third electrophyle or to steric inhibition of the third lithiation, this reaction was repeated employing deuterium oxide as electrophile. The deuterated compound **13** was obtained.

Analogous results were obtained from 1,2,4-trimethoxybenzene (**2**) (Scheme 2). Compound **16** can be obtained from **2** by a three-step one-pot lithiation-electrophile substitution sequence *via* **14** and **15**, or through a one-step bimetalation leading to **15**, followed by monometalation to **16**. The three-step one-pot sequence may be used to introduce three different electrophiles. We have prepared **19** from **2** by the sequential introduction of chlorotrimethylsilane, dipropyldisulphide and methyl iodide. Any attempt to prepare **21**, **22** and **23** upon lithiation of the bis-silylated prod-

Scheme 1



x = 2....6

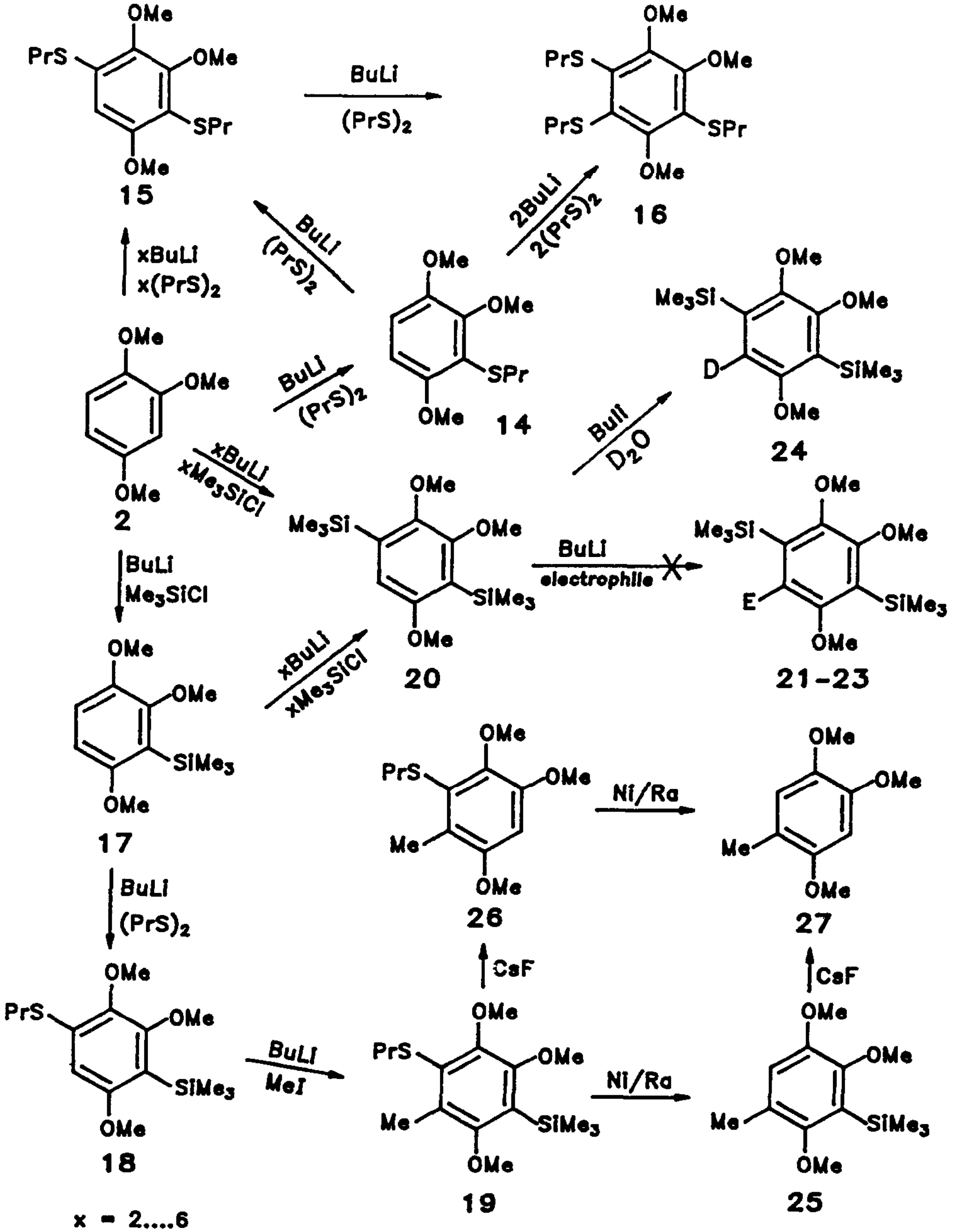
10: E = Me$_3$Si; 11: E = Me; 12: E = PrS.

uct 20 was unsuccessful. Even in this case it was possible to introduce only the small electrophile D^+ and the compound 24 was obtained.

The regiochemistry of the metalation was easily determined. In the symmetric molecule 1 the attack position was unambiguously identified. In the case of 2 it was known that initial lithiation occurs at 3-position, while the second lithium atom enters in 5-position.[13] Consequently the position of the third lithiation was easily assigned.

The here reported results show that it is possible to obtain various

Scheme 2

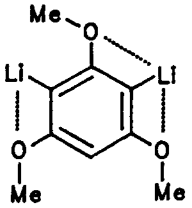


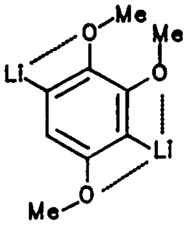
x = 2....6

20: E = Me_3Si; 21: E = Me; 22: E = PrS.

polysubstituted aromatics through metalation reactions by organolithium compounds. However, such processes are affected by steric factors. So, while linear chains such as SC_3H_7 (in compound **5** and **16**) can be easily introduced, it was impossible to introduce three trimethylsilyl groups, which have a large steric hindrance. Moreover, the presence of two such groups prevents the introduction of other, even though less hindered, groups, with the exception of the small deuterium atom. This was proved by the unsuccessful attempt to prepare **11-12**, **22-23** (see above). On the other hand it is possible to introduce in **1** and **2** three different groups if their steric hindrance does not interfere with the various lithiation/electrophilic introduction steps. This was demonstrated by the attainment of **8** and **19** by the three-step, one-flask introduction of the electrophiles chlorotrimethylsilane, propyldisulphide and methyl iodide, in this order. The results show that from **2** it is possible to obtain: i) hexasubstituted benzenes, ii) pentasubstituted derivatives with two new substituents in *ortho* to each other, after protodesilylation reaction; iii) pentasubstituted derivatives with two new substituents in *meta* to each other after removal of the alkylthio group; iv) tetrasubstituted derivatives with the new group in the place of the last substituted arylic hydrogen. Good examples are the preparation of **25** or **26**, obtained, respectively, after desulphuration or desilylation of **19**. Compounds **25** or **26** afforded **27** after desilylation or desulphuration, respectively.

The unsuccessful direct trimetalation of the examined compounds can be explained considering its mechanistic aspects. Metalation may be viewed as a three-step sequence:[1,3,17-25] i) coordination of organolithium reagent to the methoxylic oxygen atom; ii) deprotonation to give the coordinated *ortho*-lithiated species; iii) reaction with the electrophile to yield the product The coordination step limits the metalation to two sites only since three methoxy groups effectively interact with only two lithium ions, as shown in the figure:





Conversely one can say that each lithium atom coordinates two *ortho* oxygen atoms (if available) which are thus incapable of further coordination.[13] Only after substitution of the two metal atoms with electrophiles the methoxy oxygen atoms would be again free to coordinate another lithium atom. But, if the two first substituents have a large steric hindrance, the methoxy groups would take a conformation unsuitable for the attack by a third bulky electrophile.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage microscope and are uncorrected. ^1H NMR spectra were recorded on a Varian VXR-300 spectrometer with tetramethylsilane as internal reference. Mass spectra were recorded at 70 eV with a "Hitachi" Perkin-Elmer RMU-6D spectrometer, by use of the direct-inlet system. Microanalyses were carried out with a Carlo Erba (Model 1106) elemental analyzer.

Commercially available reagent-grade starting materials and solvents were used. Solutions of *n*-butyllithium in hexane were obtained from the Aldrich Chemical Company and were analyzed by the Gilman double titration method before use.[26] TMEDA was obtained from the Aldrich Chemical Company and distilled from calcium hydride before use. Commercial anhydrous ethyl ether was freshly distilled from lithium aluminum hydride before use. 1,3,5-Trimethoxy- (**1**) and 1,2,4-trimethoxybenzene (**2**) were purchased from the Aldrich Chemical Company. 1,2,4-Trimethoxy-5-methylbenzene (**27**) was prepared according to a published methods.[27]

1,3,5-Trimethoxy-2,4,6-tris(propylthio)benzene (5). - To a vigorously stirred solution of **1** (5 g, 30 mmol), anhydrous TMEDA (11.5 g, 99 mmol) and anhydrous ethyl ether (150 ml) an 1.2 M solution of *n*-butyllithium in hexane (83 ml, 99 mmol) was gradually added at room temperature under nitrogen and stirring was continued at room temperature for 24 h. The resulting solution was cooled at 10°C and a solution of dipropyldisulphide (14.8 g, 99 mmol) in dry ethyl ether (30 ml) was gradually added under nitrogen. When the addition was complete, the mixture was stirred for almost 4 h at room temperature and treated dropwise with a 1.2 M solution of *n*-butyllithium in hexane (27 ml, 32 mmol). The resulting solution was treated dropwise at 10°C with a solution of dipropyldisulphide (4.8 g, 32 mmol) in anhydrous ethyl ether (20 ml). Then the mixture was allowed to warm and left at room temperature for 10 h with stirring. The reaction mixture was poured into water, the organic layer separated and the aqueous layer extracted with ethyl ether. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was flash-chromatographed with hexane/ethyl acetate (5:1) to afford **5** as a yellow viscous oil. Yield 51%; ^1H NMR ($CDCl_3$) δ: 1.13 (9H, t, CH_3CH_2), 1.69 (6H, m, CH_3CH_2), 3.01 (6H, t, SCH_2), 4.04 (9H, s, OCH_3). *m/z*: 390 (M^+). (Found C, 55.15; H, 7.59; S, 24.49. $C_{18}H_{30}O_3S_3$ requires C, 55.34; H, 7.74; S, 24.62).

5 was also obtained with analogous yield by a sequence of monometalation/bimetalation or by three subsequent monometalations.

If we hydrolized a portion of the reaction mixture before the second treatment with *n*-butyllithium, *1,2,3-trimethoxy-2,4-bis(propylthio)benzene (**4**)* was obtained as a yellow viscous oil, which was purified by flash-chromatography using hexane/ethyl acetate (5:1) as eluent. ^{1}H NMR ($CDCl_3$) δ: 0.99 (6H, t, CH_3CH_2), 1.43 (4H, m, CH_3CH_2), 2.78 (4H, t, SCH_2), 3.83 (3H, s, OCH_3), 3.85 (6H, s, OCH_3), 6.18 (1H, s, Ar-*H*). *m/z*: 316 (M+). (Found: C, 56.80; H, 7.55; S, 20.14. $C_{15}H_{24}O_3S_2$ requires C, 56.93; H, 7.64; S, 20.26).

4 was also obtained performing the reaction with four, five or six mole equivalents of *n*-butyllithium.

1,3,5-Trimethoxy-2-methyl-4-trimethylsilyl-6-(propylthio)benzene (8). - A solution of **1** (5 g, 30 mmol), anhydrous TMEDA (3.8 g, 33 mmol) and anhydrous ethyl ether (100 ml) was treated dropwise at room temperature with *n*-butyllithium in hexane (28 ml, 33 mmol). The mixture was worked up as described above. The resulting solution was then cooled to 0°C, treated dropwise with chlorotrimethylsilane (3.6 g, 33 mmol) in dry ethyl ether (10 ml), allowed to warm and left at room temperature for 4 h with stirring. To this solution was added dropwise at 0°C *n*-butyllithium in hexane (28 ml, 33 mmol). The resulting mixture was cooled to 0°C, treated dropwise with dipropyldisulphide (4.9 g, 33 mmol) in anhydrous ethyl ether (10 ml), allowed to warm and left at room temperature for 4 h. The mixture was treated again dropwise at 10°C with *n*-butyllithium in hexane (28 ml, 33 mmol), then with iodomethane (4.7 g, 33 mmol) in anhydrous ethyl ether (10 ml) and left at room temperature overnight with stirring. The reaction mixture was poured into water, the organic layer separated and the aqueous layer extracted with ethyl ether. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was flash-chromatographed with petroleum ether (bp 40-70°C)/ethyl ether (20:1) to give **8** as a yellow oil. Yield 51%; ^{1}H NMR ($CDCl_3$) δ: 0.49 (9H, s, CH_3Si), 1.13 (3H, t, CH_3CH_2), 1.70 (2H, m, CH_3CH_2), 2.34 (3H, s, Ar-CH_3), 2.99 (2H, t, SCH_2), 3.83 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 4.00 (3H, s, OCH_3). *m/z*: 328 (M^+). (Found: C, 58.31; H, 8.55; S, 9.58. $C_{16}H_{28}O_3SSi$ requires C, 58.50; H, 8.59; S, 9.76).

Attempts to prepare 1,3,5-trimethoxy-2,4,6-tris(trimethylsilyl)benzene (10), 1,3,5-trimethoxy-2-methyl-4,6-bis(trimethylsilyl)benzene (11) and 1,3,5-trimethoxy-2-(propylthio)-4,6-bis(trimethylsilyl)benzene (12)

A solution of **1** (5 g, 30 mmol), anhydrous TMEDA (11.5 g, 99 mmol) and anhydrous ethyl ether (150 ml) was treated with 1.2 M solution of *n*-butyllithium in hexane (83 ml, 99 mmol) in the same manner described for the preparation of **5**. The resulting solution was cooled to -10°C and a solution of chlorotrimethylsilane (10.8 g, 99 mmol) in anhydrous ethyl ether (30 ml) was gradually added under nitrogen. When the addition was complete the mixture was treated again with *n*-butyllithium in hexane (27 ml, 33 mmol), then, at -10°C, with a solution of chlorotrimethylsilane (3.6 g, 33 mmol) in anhydrous ethyl ether (10 ml) and worked-up in the same manner described for the preparation of **5**. The crude product was crystallized from ethanol and identified as *1,3,5-trimethoxy-2,4-bis(trimethylsilyl)benzene (9)*. Yield 86%; mp 95-96°C (lit.[13] mp 95-97°C).

Unreacted starting material was recovered after treatment of **9** with one or two or three mole equivalents of n-butyllithium and chlorotrimethylsilane or iodomethane or dipropyldisulphide.

1,3,5-Trimethoxy-2,4-bis(trimethylsilyl)-5-deuterobenzene (13). A solution of **9** (2 g, 6.4 mmol), anhydrous TMEDA (0.8 g, 7 mmol) and anhydrous ethyl ether (50 ml) was treated with 1.2 M solution of *n*-butyllithium in hexane (6 ml, 7 mmol) in the same manner described for the preparation of **5**. The resulting solution was cooled to 0°C, hydrolized with deuterium oxide and worked-up in the same manner above described. The crude product was flash-chromatographed with hexane/ethyl acetate (10:1) to afford **13** as white crystals Yield 85%; mp 99-100°C; ^{1}H NMR (CDCl$_3$) δ: 0.34 (18H, s, CH_3Si), 3.54 (3H, s, OCH_3), 3.84 (6H, s, OCH_3); *m/z*: 313 (M^+).

1,2,4-Trimethoxy-3,5,6-tris(propylthio)benzene (16). - A solution of **2** (5 g, 30 mmol), anhydrous TMEDA (11.5 g, 99 mmol) and anhydrous ethyl ether (150 ml) was worked up in the same manner described for the preparation of **5**. The crude product was flash-chromatographed with hexane/ethyl acetate (4:1) to afford **16** as a yellow viscous oil. Yield 55%; ^{1}H NMR (CDCl$_3$) δ: 1.15 (9H, t, CH_3CH_2), 1.75 (6H, m, CH_3CH_2), 2.98 (4H, t, SCH_2), 3.01 (2H, t, SCH_2), 3.99 (3H, s, OCH_3), 4.04 (6H, s, OCH_3). *m/z*: 390 (M^+). (Found C, 55.20; H, 7.36; S, 24.45. $C_{18}H_{30}O_3S_3$ requires:C, 55.34; H, 7.74; S, 24.62).

The same compound **16** was obtained after a sequence of monometalation/bimetalation or after three subsequent monometalations.

1,2,4-Trimethoxy-5-methyl-3-trimethylsilyl-6-(propylthio)benzene (19). - A solution of **2** (5 g, 30 mmol), anhydrous TMEDA (3.8 g, 33 mmol) and anhydrous ethyl ether (100 ml) was worked up in the same manner described for the preparation of **8**. The crude product was flash-chromatographed with hexane-ethyl acetate (10:1) to afford **19** as a yellow oil. Yield 48%;

^{1}H NMR ($CDCl_3$) δ: 0.47 (9H, s, CH_3Si), 1.14 (3H, t, CH_3CH_2), 1.72 (2H, m, CH_3CH_2), 2.44 (3H, s, $ArCH_3$), 2.82 (2H, t, SCH_2), 3.89 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 3.98 (3H, s, OCH_3). *m/z*: 328 (M^+). Found C, 58.35; H, 8.51; S, 9.62. $C_{16}H_{28}O_3SSi$ requires C, 58.50; H, 8.59; S, 9.76).

Attempts to prepare 1,2,4-trimethoxy-3,5,6-tris(trimethylsilyl)benzene (21), 1,2,4-trimethoxy-5-methyl-3,6-bis(trimethylsilyl)benzene (22) and 1,2,4-trimethoxy-5-(propylthio)-3,6-bis(trimethylsilyl)benzene (23).

A solution of **2** (5 g, 30 mmol), anhydrous TMEDA (11.5 g, 99 mmol) and anhydrous ethyl ether (150 ml) was worked up in the same manner described for the attempt to prepare **10**. The crude product was purified by flash-chromatography using hexane/ethyl acetate (10:1) as eluent and identified as *1,2,4-trimethoxy-3,6-bis(trimethylsilyl)benzene (20)*. Yield 58%; mp 51-53°C (lit.[13] mp 40-45°C).

Unreacted starting material was recovered after treatment of **20** with one or two or three mole equivalents of *n*-butyllithium and chlorotrimethylsilane or iodomethane or dipropyldisulphide.

Only **20** was obtained also after a sequence of three monometalations/silylations.

1,2,4-Trimethoxy-3,6-bis(trimethylsilyl)-5-deuterobenzene (24). This compund was prepared in the same manner described for the preparation of **13**. Yield 83%; mp 48-49°C; ^{1}H NMR ($CDCl_3$) δ: 0.30 (18H, s, CH_3Si), 3.61 (3H, s, OCH_3), 3.92 (6H, s, OCH_3): *m/z*: 313 (M^+).

1,2,4-Trimethoxy-3-trimethylsilyl-5-methylbenzene (25). - A mixture of **19** (3.3 g, 10 mmol) in 95% ethanol was refluxed 2 h with Raney nickel (2 g).[28] The mixture was filtered and evaporated. The yellow oil was not purified further and was used as such in the next step. Yield 81%; ^{1}H NMR ($CDCl_3$) δ: 0.40 (9H, s, CH_3Si), 2.41 (3H, s, $ArCH_3$), 3.90 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 6.81. (1H, s, Ar-*H*).

1,2,4-Trimethoxy-5-methylbenzene (27). - A mixture of **25** (1 g, 3.8 mmol), cesium fluoride (11.6 g, 76 mmol), dimethylformamide (45 ml) and water (2 ml) was refluxed for 24 h. The mixture was then poured into water and extracted with ethyl ether. The extracts was carefully washed with water, dried (Na_2SO_4) and evaporated. The crude product was purified by flash-chromatography using petroleum ether (bp 40-70°C)/ethyl ether (30:1) as eluent. Yield 78%; mp 49-51°C (lit.[27] mp 50-50.5°C).

1,2,5-Trimethoxy-3-(propylthio)-4-methylbenzene (26). - A mixture of **19** (2 g, 6.1 mmol), cesium fluoride (18.5 g, 122 mmol), dimethylformamide

(70 ml) and water (3 ml) was refluxed for 24 h and worked up in the same manner described for **27**. The yellow oil was not further purified and was used as such in the next step. Yield 75%; ^{1}H NMR ($CDCl_3$) δ: 1.17 (3H, t, CH_3CH_2), 1.75 (2H, m, CH_3CH_2), 2.32 (3H, s, $ArCH_3$), 3.85 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 4.02 (3H, s, OCH_3), 6.94 (1H, s, Ar-*H*).

This compound, after desulphuration, gave **27** in 78% yield.

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