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Dilithiation of Aromatic Ethers

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The lithiations of anisole and of all the isomeric dimethoxy- and trimethoxybenzenes with 2–5 equiv of *n*-butyllithium/TMEDA complex have been investigated under a variety of reaction conditions. Anisole and *m*-dimethoxybenzene do not undergo dilithiation, but both *o*- and *p*-dimethoxybenzene give dilithio derivatives in synthetically useful yields. Among the trimethoxybenzenes, 1,3,5-trimethoxybenzene was dilithiated in >90% yield. 1,2,4-Trimethoxybenzene was dilithiated in up to 55% yield, but the 1,2,3-trimethoxy isomer did not undergo dilithiation to a synthetically useful extent.

The last decade has seen extraordinary growth in the use of organolithium compounds in organic synthesis.[1] Especially important advances have been made in the preparation of aryllithium reagents and they have become widely useful in the synthesis of organic and organometallic compounds.[1b] These advances have been based on the inclusion of new functional groups among those which support directed (ortho) lithiation,[2] the extension of halogen–lithium exchange reactions to various substituted aromatics,[3] and the development of routines for sequential or intramolecular processes which further extend the synthetic versatility of the reagents.[4] The variety of electrophiles available to react with the intermediate organolithiums has also increased.

Nearly all directed lithiations previously reported are monolithiations (*i.e.*, only one lithium on the ring), although dilithio intermediates involving relatively acidic functional groups are common.[5] *o*-,[6] *m*-,[7] and *p*-dilithiobenzene[8] have all been prepared by halogen-metal or metal–metal exchange and used occasionally in synthesis.[9] However, neither Gschwend's extensive review of the preparation of organolithium reagents by lithiation[1b] nor Wakefield's more general review[1c] indicate any comprehensive study of dilithiated intermediates prepared by lithiation. Worden and co-workers prepared 4,6-dimethoxyisophthalaldehyde in good yield *via* a dilithio intermediate prepared by halogen–metal exchange.[10] Dallacker and Schmets prepared 2,3-(methylenedioxy)-5,6-dimethoxyterephthalic acid by carboxylation of a dilithium intermediate prepared by lithiation of 5,6-dimethoxybenzo-1,3-dioxole.[11] These workers also prepared the dilithio derivative (meta orientation of lithiums) of 4,6-dimethoxybenzo-1,3-dioxole by halogen–metal exchange.

We became interested in determining the extent to which dilithiated intermediates could be prepared by direct lithiation adjacent to methoxy groups. The potential for directing ortho lithiation by the methoxy and related alkoxy groups is well-known.[1] Only two examples of dilithiation of aryl ethers could be located in the literature. 1,2-Dimethoxybenzene, when stirred in hexane–heptane at room temperature for 20 h with 2.5 equiv of *n*-butyllithium/TMEDA complex and then treated with iodine, gave a 2% yield of 2,3-dimethoxy-1,4-diiodobenzene.[12] Diphenyl ether, when heated at 38 °C with 2 equiv of *n*-butyllithium gives the 2,2′-dilithio intermediate which could be converted to carbonated or silylated products in 25–30% yields.[13]

Results

We report here the results of attempts to prepare the dilithium derivatives of anisole, and the isomeric di- and trimethoxy derivatives of benzene. We were primarily interested in preparing these intermediates by direct dilithiation, but in those cases where the dilithio intermediates could not be prepared directly or where there was some question concerning their stability or substitution pattern, halogen–lithium exchange was used.

In general, the methoxybenzenes were lithiated by employing 2.2 or more equiv of *n*-butyllithium–tetramethylethylenediamine (TMEDA) complex (1:1 molar ratio) in either diethyl ether or hydrocarbon solvents. Invariably the lithiated intermediates precipitated from solution[14] and elevated temperatures and/or long reaction times were often necessary to achieve dilithiation. The lithiation products were detected by trimethylsilylation and also in certain cases by deuteration or carbonation. The silylated reaction mixtures, after workup, were analyzed by gas chromatography. Product identities and ratios were determined by comparison with authentic

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(1) For general review see: (a) Seebach, D.; Geiss, K. H. *J. Organomet. Chem. Libr.* **1976**, *1*, 1–92. (b) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* (*N.Y.*) **1979**, *26*, 1–360. (c) Wakefield, B. J. "The Chemistry of Organolithium Compounds"; Pergamon Press: Oxford, 1974.

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(5) (a) A general review of di- and polyalkali metal derivatives: Kaiser, E. M.; Petty, J. D.; Knutson, P. L. A. *Synthesis* **1977**, 509. (b) Gilman and co-workers have observed di- and trilithiation of polyhalogenated aromatics: Haiduc, I.; Gilman, H. *J. Organomet. Chem.* **1968**, *12*, 394.

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(9) Zimmer, H.; Mosle, H. G. *Chem. Ber.* **1954**, *87*, 1255. Gilman, H.; Zuech, E. A. *Chem. Ind.* (*London*) **1960**, 120. Evleth, E. M.; Freeman, L. D.; Wagner, R. I. *J. Org. Chem.* **1962**, *27*, 2192. Bloomfield, R. R. Brit. Patent 904456; *Chem. Abstr.* **1963**, *58*, 6858. Hobin, T. P. Brit. Patent 1015501; *Chem. Abstr.* **1966**, *64*, 16013f. Kreisel, G.; Scholz, P.; Seidel, W. *Z. Anorg. Allg. Chem.* **1980**, *460*, 51.

(10) Worden, L. R.; Kaufman, K. D.; Smith, P. J.; Widiger, G. N. *J. Chem. Soc. C* **1970**, 227.

(11) Dallacker, F.; Schmets, G. *Chem. Ber.* **1971**, *104*, 2534.

(12) Pring, B. G. *Acta Chem. Scand.* **1973**, *27*, 3873.

(13) Oita, K.; Gilman, H. *J. Am. Chem. Soc.* **1957**, *79*, 339.

(14) Precipitation occurs during the monolithiation stage, even in the absence of excess lithiation reagent.

0022-3263/84/1949-4657$01.50/0

Table I. Summary of Direct Lithiation Results

no.	complex,^{a} equiv	solvent	time, h	temp,^{f} °C	product yield, %: monosilylation^b	disilylation^b
1	3.1	diethyl ether	12	RT	72 (53)	
4	5.0	diethyl ether	10	reflux	10	87
7	5.0	diethyl ether	36	reflux	72	0
	2.1	diethyl ether	11	RT	>95	<2
10	5.0	diethyl ether	24	reflux	10^c	90^c
	4.0	diethyl ether	71	RT	12	88
	3.0	hexanes	91	RT	5	94 (68)
13	2.2	hexanes	76	RT	49	8^d
16	3.0	diethyl ether	24	0	46	55
	3.0	hexanes	67.5	RT	31	49^e
	3.0	diethyl ether	8.0	0	52	48
	3.0	hexanes	96	RT	26	42
24	3.0	hexanes	71	RT	14	86
	3.0	diethyl ether	11	RT	14	86

[a] Complex = 1:1 *n*-butyllithium/TMEDA. [b] Isolated yields are in parenthesis; other yields by GC. [c] Very clean crude reaction mixture, with only traces of three other components present. [d] Results from the dilithiation were very inconsistent; yields of bis silylations (by VPC) varied from 0% to 40%, but the higher yields were not reproducible. In addition many unidentified components were present and the reaction mixtures decomposed with time. [e] The remaining material was not **16**, but four unidentified components. [f] RT = room temperature.

Table II. Preparation of Authentic Trimethylsilyl Derivatives

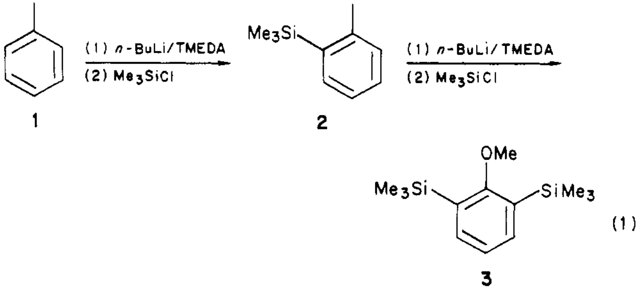
no.	*n*-BuLi/TMEDA complex, equiv	solvent	temp,^{a} °C	time, h	prod	% yield^a
1	1.2	hexanes	RT	29	**2**	71
2	2.0	ethyl ether	RT	31	**3**	72
4	1.1	ethyl ether	RT	46	**5**	86
5	1.1	hexanes	RT	28	**6**	73
7	1.1	ethyl ether	RT	26	**8**	83
8	1.1	hexanes	RT	30	**9**	47 (96)
10	1.1	hexanes	RT	71	**11**	75
11	1.1	hexanes	RT	25	**12**	18^b
13	1.1	ethyl ether	RT	27	**14**	84
14	1.1	ethyl ether	RT	22	**15**	(62)^c
34	3.1^d	ethyl ether	RT	1^f	**15**	(91)^c
16	1.1	hexanes	RT	16	**17**	80
17	1.1	ethyl ether	RT	27	**18**	82
24	1.1	ethyl ether	RT	26	**25**	76
25	1.1	hexanes	RT	14	**26**	(85)^b
35	4^d	ethyl ether	0	6^f	**26**	(82)^b

[a] Yields are isolated product except those in parenthesis which are by VPC analysis. [b] The bis-silylated products were more readily available from direct dilithiation and no attempts were made to isolate the products in better yields. [c] No individual isolated yields were obtained, instead these two reaction mixtures were combined and distilled for an analytical sample. [d] No TMEDA used in the bromine/lithium exchange. [e] RT = room temperature. [f] Time in minutes.

samples, which were prepared in separate reactions. A number of new methoxyarylsilanes have been synthesized. The results for each methoxy benzene derivative are summarized in the following paragraphs and are given in more detail in Tables I and II. Spectroscopic data and other physical constants are reported in the Experimental Section.

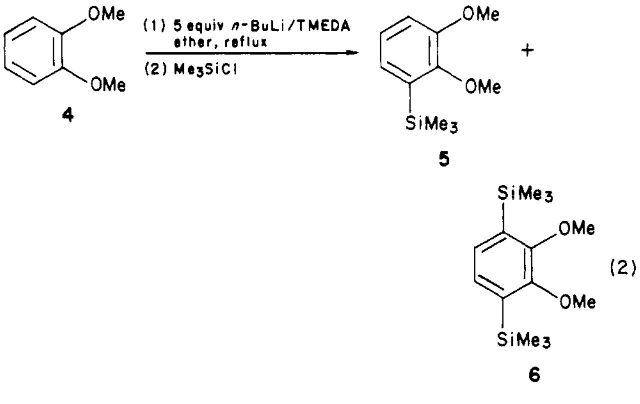
Anisole. The monolithiation of anisole is a well-established procedure, although the ortho-lithiated intermediate has not been reacted with chlorotrimethylsilane.[1b] In our hands not even a trace of any dilithiation of anisole was observed. For example, when anisole was treated with 3 equiv of *n*-butyllithium/TMEDA complex at ambient temperature for 12 h and quenched with chlorotrimethylsilane, no product resulting from the desired 2,6-dilithio intermediate could be detected in the reaction mixture. Instead the product mixture consisted of 72% of (2-methoxyphenyl)trimethylsilane, **2**, and 2% recovered anisole by VPC analysis.

The anticipated product resulting from dilithiation, 2-methoxy-1,3-bis(trimethylsilyl)benzene, **3**, was prepared by a stepwise monolithiation sequence as outlined in eq 1. Anisole was monolithiated and silylated to (2-methoxyphenyl)trimethylsilane, **2**, in 71% yield. The second monolithiation and silylation of **2** was accomplished in 72% to form the authentic bis(silyl) derivative, **3**, of anisole.

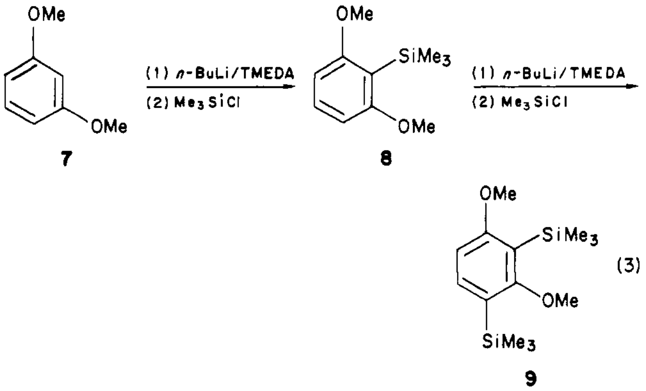


1,2-Dimethoxybenzene (Veratrole). The authentic monosilyl derivative of veratrole, (2,3-dimethoxyphenyl)trimethylsilane, **5**, was prepared in 70–86% yield. The authentic bis-silylated product, 1,4-bis(trimethylsilyl)-2,3-dimethoxybenzene, **6**, was prepared in 73% from **5** by repetition of the monolithiation and silylation sequence.

Direct dilithiation (eq 2) was examined under several sets of conditions. The highest yield of dilithiation, as determined by the formation of **6** after silylation, was obtained by using 5 equiv of *n*-butyllithium/TMEDA complex in refluxing ether for 10–12 h. The product mixture contained traces of recovered 1,2-dimethoxybenzene and about 10% of the monosilyl product, **5** and gave a 50–60% isolated yield of the bis-silylated product, **6**. Carbon dioxide was also used as an electrophile in this system, producing 2,3-dimethoxyterephthalic acid in 35–40% yield.

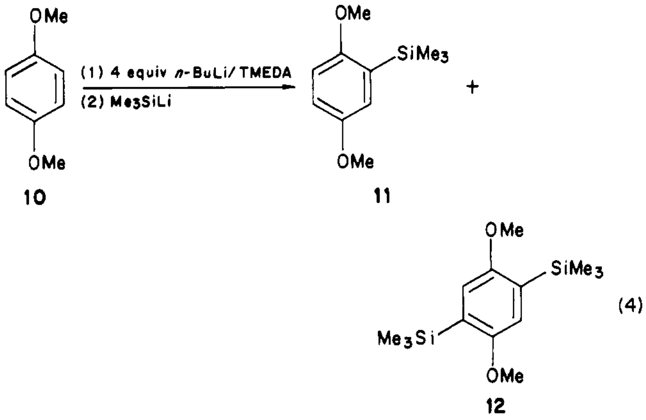


1,3-Dimethoxybenzene. When the same two-step sequential monolithiation–silylation procedure described above was followed, authentic (2,6-dimethoxyphenyl)trimethylsilane, **8**, was readily prepared in 83% yield; 1,3-bis(trimethylsilyl)-2,6-dimethoxybenzene, **9**, was then obtained from 8 in 47% yield (eq 3). Attempts at direct dilithiation of 1,3-dimethoxybenzene with 2 or 5 equiv of n-butyllithium/TMEDA complex were unsuccessful; the main product after silylation was the monosilyl derivative 8, which was isolated in 72% yield. VPC analysis of the reaction mixture from the 5 equiv run showed several other unidentified products, but none of them corresponded to the authentic bis-silylated material, 9.



7 8 9 (3)

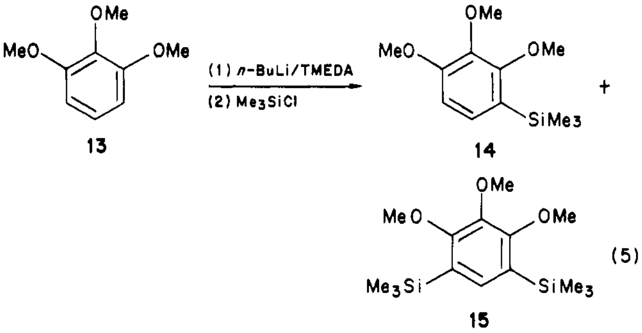
1,4-Dimethoxybenzene. (2,5-Dimethoxyphenyl)trimethylsilane, 11, and 1,4-bis(trimethylsilyl)-2,5-dimethoxybenzene, 12, were prepared by the stepwise monolithiation procedure in 75% and 18% yields, respectively. Direct dilithiation of 1,4-dimethoxybenzene proved to be exceptionally clean (eq 4). Lithiation in ether at room temperature with either 4 or 5 equiv of n-butyllithium/TMEDA complex, followed by silylation, gave a mixture of 11 and 12 in which the bis(silyl) product, 12, dominated by 8–9:1. The dilithiation also occurred readily in hexane, where 3 equiv of n-butyllithium/TMEDA complex gave a product mixture consisting of 94% bis product, 12, by VPC. The remainder of the reaction mixture was monosilyl product 11, a trace of 1,4-dimethoxybenzene, and a trace of an unidentified component. Product 12 could be isolated from this reaction mixture in 68% yield. Deuteration, after an 18-h reaction with 3 equiv of n-butyllithium/TMEDA complex, indicated 96% dideuteration (NMR analysis) and carbonation of the reaction mixture gave 2,5-dimethoxyterephthalic acid in good yield.



10 11 12 (4)

1,2,3-Trimethoxybenzene. Authentic (2,3,4-trimethoxyphenyl)trimethylsilane, 14, was prepared by the monolithiation–silylation procedure in 84% isolated yield. Since the second step of the sequential process, starting with 14, to form 1,5-bis(trimethylsilyl)-2,3,4-trimethoxybenzene, 15, initially failed in hexanes, the bis product was first obtained by halogen/lithium exchange on 1,5-dibromo-2,3,4-trimethoxybenzene, 34 (see Table II). When ether was used as solvent the second step of the sequential process gave a satisfactory yield of 15 (62% by VPC).

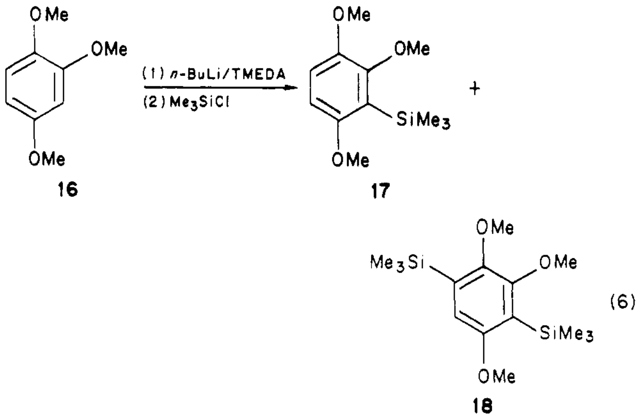
Direct dilithiation of 1,2,3-trimethoxybenzene with excess n-butyllithium/TMEDA complex, followed by reaction with chlorotrimethylsilane, gave mixtures containing varying amounts of monosilyl material, 14, and bis(silyl) material, 15, along with several unidentified products (eq 5). The maximum yield of 15 by VPC was about 20%. A dilithiation followed by deuteration showed only 16% incorporation of two deuteriums by NMR. Chromatography of the reaction mixture from deuteration showed a second component in addition to 1,2,3-trimethoxybenzene, but it was not identified.



13 14 15 (5)

1,2,4-Trimethoxybenzene. Authentic (2,3,6-trimethoxyphenyl)trimethylsilane, 17, and 1,4-bis(trimethylsilyl)-2,3,5-trimethoxybenzene, 18, were prepared by the usual two-step monolithiation–silylation sequence in 80% and 82% yields, respectively.

Dilithiation of 1,2,4-trimethoxybenzene under the best conditions found (see Table I) showed a maximum 55% yield of bis-silylated product 18 by VPC analysis (eq 6). Usually the remainder of the reaction mixture was mainly 17, but, depending upon the condition employed, additional unidentified components were present.



16 17 18 (6)

The bis-silylated compound 18 was the only product in this study whose structure could not be assigned from spectroscopic data or the assumption of normal regioselectivity for the ortho-lithiation. Although initial lithiation can be expected at the 3-position, the second lithium could conceivably have gone in the 5-position instead of the 6. VPC analysis established that the same bis-silylated product was obtained from the two-step sequential monolithiation–silylation procedure as from direct dilithiation–silylation. The structure of 18 was established as follows. 5-Bromo-1,2,4-trimethoxybenzene,[15] 19, was subjected to bromine/lithium exchange, followed by quenching with chlorotrimethylsilane to provide (2,4,5-trimethoxyphenyl)trimethylsilane, 20 (eq 7). This monosilyl derivative, 20, was then monolithiated–silylated to

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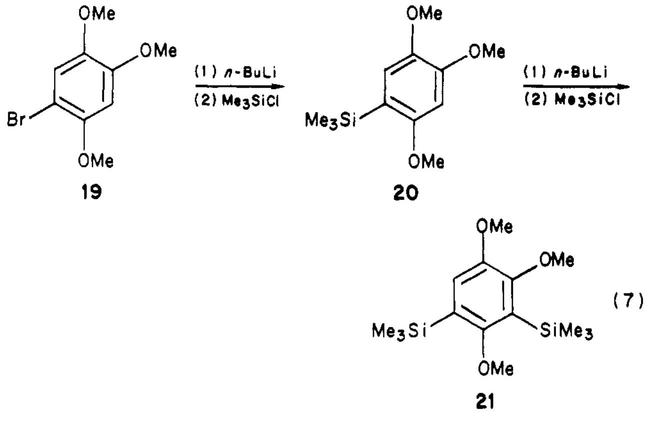
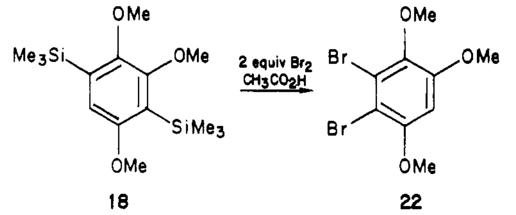
[15] Blatchly, J. M.; McOmie, J. F. W.; Searle, J. B. *J. Chem. Soc. C* 1969, 1350 and references therein.



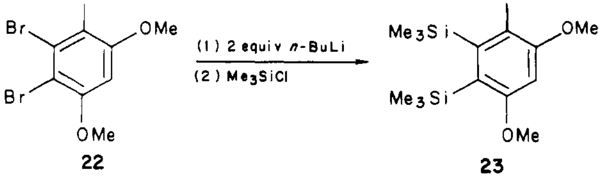
(7)

obtain a bis(silyl) derivative assigned structure **21**. The reaction mixture from the last step of eq 7 was compared, using GC–MS, to the bis-silylated product obtained by direct dilithiation. Both by retention times as well as single ion monitoring, there was none of the product assigned structure **18** in the reaction mixture from the monolithiation–silylation of **20**. This provided tentative evidence that the structure of **18** is as shown, but since the final step in eq 7 was not a completely clean conversion to bis-silylated product **21** we undertook another proof (eq 8). The bis-silylated product obtained from dilithiation (assigned structure **18**) was subjected to brominolysis. Since the trimethylsilyl group is an excellent *ipso* director and since all three possible dibromo isomers of 1,2,4-trimethoxybenzene are known, we anticipated the formation of the corresponding 3,6-dibromo isomer, which would be easily identifiable by melting point and ^{1}H NMR. However, the melting point of the product in eq 8 corresponded to the 5,6-dibromo isomer. Since a 5,6-disubstitution pattern is highly unlikely for the direct dilithiation–bis-silylation procedure, we repeated the synthesis[16] of 2,3-dibromo-1,4,5-trimethoxybenzene, **22** (mp 102–103 °C), and it proved to be identical with the product of the brominolysis in eq 8 (mp 97–98 °C (lit.[10,16] mp 97, mp 99–100 °C)). The infrared spectra of the two products were exactly superimposible.



(8)

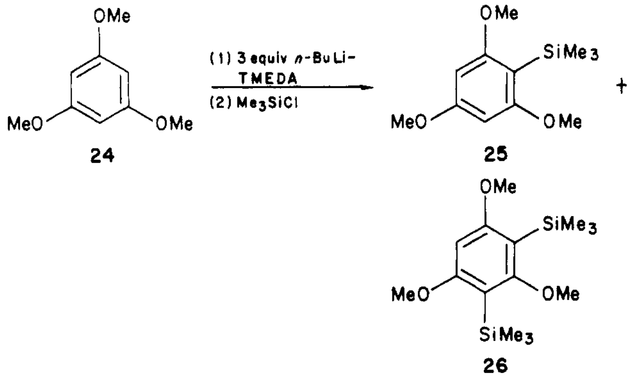
That both the trimethylsilyl groups of **18** had not been directly replaced by bromine was established by forming the bis-silylated derivatives **23** from **22** (eq 9). Dibromo isomer **22** was subjected to bromine/lithium exchange followed by quenching with chlorotrimethylsilane. The resulting reaction mixture was analyzed by GC–MS and found to contain none of the bis-silylated product **18** obtained by either direct dilithiation–silylation or the two-step sequence. The formation of **22** in the brominolysis of **18** (eq 8) evidently resulted from initial bromination in the unsubstituted 5-position, followed by protodesilylation in the 3-position, and *ipso* substitution of the remaining silyl substituent at the 6-position. Although *ipso* electrophilic substitution in aryltrimethylsilanes is usually more rapid than substitution for hydrogen, Wilbur,[17] Eaborn,[18] and others have shown that in highly activated systems, *ipso* substitution does not compete with substitution for hydrogen. The HBr formed by the bromination would be expected to effect protodesilylation preferentially at the more activated 3-position.



(9)

1,3,5-Trimethoxybenzene. Authentic (2,4,6-trimethoxyphenyl)trimethylsilane, **25**, was prepared by monolithiation–silylation in 76% yield. Authentic 2,4-bis(trimethylsilyl)-1,3,5-trimethoxybenzene, **26**, was readily prepared both from **25** by monolithiation–silylation or from 2,4-dibromo-1,3,5-trimethoxybenzene, **35**, by bromine/lithium exchange followed by reaction with chlorotrimethylsilane.

Dilithiation of **24** gave 85–95% yield of **26** when 3 equiv of *n*-butyllithium/TMEDA complex were used in either ether or hexanes (eq 10). The dilithiation in hexanes was slow, requiring 71 h to achieve good results. Nevertheless, the reaction mixture was very clean; the remainder of the material was **25**. Quenching the dilithiated mixture with deuterium oxide and ^{1}H NMR analysis of the recovered 1,3,5-trimethoxybenzene indicated 97% dideuteration.



Discussion

The results reported here represent the first examples of substituent-directed dilithiations of methoxybenzenes in preparatively useful yields.[19] The relative ease of achieving dilithiation in the methoxybenzene series is summarized in Chart I. The dilithio compounds **27** and **28** are readily formed in excellent yields and **29** is nearly as satisfactory. Formation of **30** and **31** under the conditions we investigated was incomplete and competition with other reactions occurred. Although **30** could be useful synthetically, **31**, is formed to the extent of only 20% or less. Neither **32** nor **33** could be detected after lithiation.

In a broad sense it appears these results can be interpreted in terms of the kinetics of the lithiation process.

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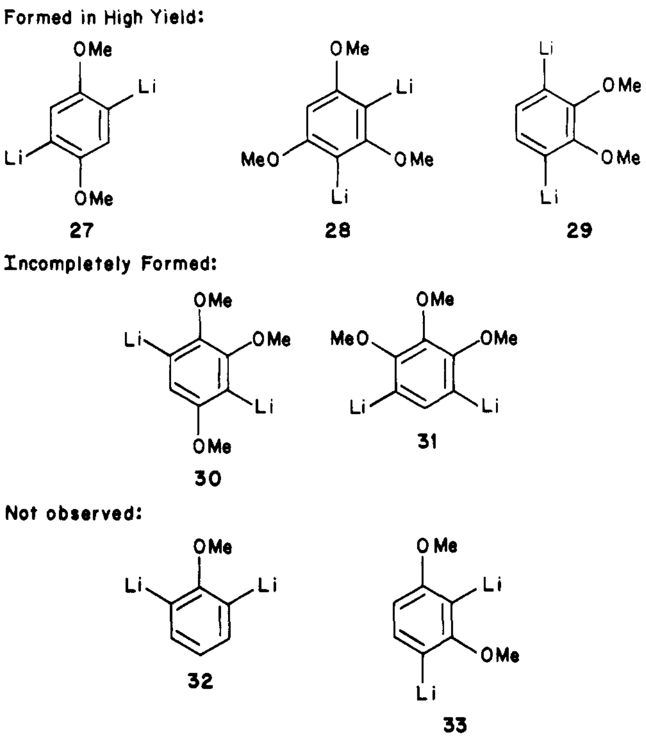
(16) Dorn, H. W.; Warren, W. H.; Bullock, J. L. *J. Am. Chem. Soc.* **1939**, *61*, 144.

(17) Wilbur, D. S.; Stone, W. E.; Anderson, K. W. *J. Org. Chem.* **1983**, *48*, 1542.

(18) Eaborn, C. *J. Organomet. Chem.* **1975**, *100*, 43.

(19) We believe that the deuteration and carbonation experiments preclude the possibility that the disilylated products could be formed by a sequential lithiation process occurring after the addition of chlorotrimethylsilane. Furthermore, since both anisole and 1,3-dimethoxybenzene can be disilylated by the separate stepwise sequence, there is no reason they should not also be subject to disilylation if it were occurring sequentially. Although the reaction between aryllithiums and chlorotrimethylsilane is not instantaneous, it appears to be considerably faster than the directed lithiation of either the ethers or the trimethysilyl derivatives; see also: Smith, W. N. *Adv. Chem.* **1974**, *130*, 23.

Chart I



Thus 1,2- and 1,4-dimethoxybenzene react fairly rapidly and cleanly with *each* methoxy group directing the lithiation of an adjacent position. On the other hand in anisole and 1,3-dimethoxybenzene, the first lithiation evidently diminishes the effectiveness of the methoxy groups (which are now associated with an ortho lithium) for directing lithiation and no dilithiation is observed. In this context the dilithiation of 1,3,5-trimethoxybenzene can be understood as being directed by the "free" methoxy group. There is no evidence that the dilithio compounds which can not be formed by lithiation are less stable than those that can be. In several cases these species were prepared readily by halogen–metal exchange, although the much milder conditions of the halogen–metal exchange leaves the issue of stability to more vigorous conditions open. Within this broad context, however, the situation with 1,2,3- and 1,2,4-trimethoxybenzene is puzzling. It is not obvious why the former compound should not undergo dilithiation, but it is clear from the numerous experiments tried, that there is serious competition from other processes. The borderline effectiveness of the 1,2,4-isomer is also somewhat surprising. In particular, it is not clear why this compound should be less effectively dilithiated than 1,2-dimethoxybenzene.

Hart[8b] has recently reported an exclusive preference for *p*-dilithio intermediates over meta in the bromine/lithium exchange of tetrabromoaromatics. He ascribed this preference to the minimization of charge repulsion between the two lithiums However, other workers[10] have reported facile formation of *m*-dilithio intermediates in bromine/lithium exchange reactions and in two of our syntheses (that of the bis-silylated product in the 1,2,3-trimethoxy series, **15**, and the bis-silylated product in the 1,3,5-trimethoxy series, **26**) we were able to readily accomplish the formation of *m*-dilithio intermediates. Each of the dilithio derivatives of benzene has been reported in the literature[6–8] and from existing, albeit limited, data it appears that the stability of the various isomers is comparable.

It should be emphasized that nearly all the lithiations described in this paper were conducted under heterogeneous conditions. Except for the lithiation of (2-methoxyphenyl)trimethylsilane, **2**, which remains a clear solution throughout the course of the lithiation, all of the methoxy aromatics discussed begin to form precipitates as the lithiation proceeds. The dilithiations therefore may be taking place either as heterogeneous reactions or by lithiation of the fraction of monolithiated products which is still in solution. since we have frequently used several equivalents of *n*-butyllithium/TMEDA complex, the ratio of lithiating reagent to the monolithium intermediate remaining in solution must considerably exceed the stoichiometric ratio. It seems likely that in those cases where dilithiation is slow, there may be substantial competing attack on solvent and also possibly on the methoxy substituents. Such reactions are the likely cause of the unidentified products which arise in the cases which are most resistant toward dilithiation. It is also possible that precipitation of both the mono and dilithio intermediates is beneficial in the sense of retarding the total rate of subsequent decomposition by the excess butyllithium that is present in solution. Clearly, one could expect additives, which might partially solubilize the mono- and dilithiated intermediates, to have a major impact on the outcome of the reaction. We intend to examine this point and to extend these reactions to other electrophiles in future studies.

Our results extend previous studies in which dilithiated aromatic rings have been used as synthetic intermediates. The preparation of dilithio intermediates by direct lithiation appears to be less general than by halogen–metal exchange and requires more vigorous reaction conditions. Nevertheless, it can be useful with apropriate substrates, since the intermediate bromination step is avoided. The two processes can be complementary in cases where the regioselectivity of the bromination is different from that of lithiation.

Experimental Section

General Methods. Analytical gas–liquid chromatography (VPC) was performed on a Varian Model 2400 with a flame-ionization detector with a 5 ft × 0.25 in. 5% FS 1265 on 50/60 mesh Anakrom ABS, a Perkin Elmer Model 3920 with a flame-ionization detector with a 10 ft × 0.125 in 10% OV-101 on 100–120 mesh Chromosorb W, or a Gow-Mac Series 550 with a thermal conductivity detector with a 6 ft. × 0.25 in. 15% DC 200 on 60/80 Chromasorb P.

^{1}H NMR spectra were recorded on a Varian EM-390 or a Hitachi/Perkin Elmer R-24 spectrometer. Unless otherwise noted the solvent was $CDCl_3$. Chemical shifts are reported relative to tetramethylsilane internal standard. ^{1}H NMR data are listed in the following order: δ value (multiplicity, coupling constants in Hz, number of protons). IR spectra were determined on a Nicolet MX-1 Fourier Transform spectrophotometer in the programmed mode which selects the 10 most intense bands. IR data are listed in the following order: cm^{-1} (% transmittance).

Elemental analyses were performed by Atlantic Microlab, Inc. GC-MS were mainly recorded on a Hewlett-Packard Model 5992 with a 3 ft. × 0.25 in. OD (1.8 mm ID) glass column packed with 2% OV-101 on 100–120 mesh ultrabond 20M. Several reaction mixtures were also checked on a Finigan 4600 GC-MS. Mass spectral data are listed in the following order: m/z (intensity relative to the base peak).

The substrate aryl ethers were obtained from Aldrich, checked by VPC, and used without further purification. The hexanes, diethyl ether, and tetrahydrofuran solvents were purified prior to use by distillation from sodium/benzophenone ketyl. Tetramethylethylenediamine (TMEDA, Aldrich) was distilled from CaH_2, kept in small containers, and carefully protected from the atmosphere by the use of septa in all transfers. The chlorotrimethylsilane (Aldrich) was treated with a *tertiary* amine (either triethylamine or TMEDA) to form a solution which was 80% (v/v) chlorotrimethylsilane and which was kept under refrigeration between uses. The desired amount of clear supernatant solution was carefully syringed away from the precipitated amine hydrochloride for each use.

All glassware used in the lithiations was dried at 110 °C prior to assembly. Lithiations were run under a positive pressure of N_2. TMEDA, *n*-butyllithium, and the chlorotrimethylsilane solution were all transferred with syringes and septa.

Typical Lithiation Procedure. The substrate (usually 10–20 mmol) was weighed into a 100-mL one-necked round-bottomed flask and 60–70 mL of solvent (usually diethyl ether or hexanes) was added. The flask was fitted with a Claisen adapter having a septum and nitrogen inlet. The TMEDA was added and the mixture, stirred magnetically, was chilled with an ice bath (0 °C). *n*-Butyllithium (2–5 equiv) was added slowly over 1–2 min. The lithiation mixture was stirred at the temperatures and for the times specified in Tables I and II. During this metalation period a tannish-yellow precipitate formed which was assumed to be the intermediate lithio salts.

At the end of the metalation period the mixture was again chilled to 0 °C and quenched by slowly syringing in a 10% molar excess (over *n*-butyllithium) of the 80% (v/v) of chlorotrimethylsilane/amine solution. The precipitate became more dense and turned white. After stirring for at least 15 min (often longer) the quenched mixture was worked up by pouring onto a mixture of crushed ice with 150% molar equiv excess of NH_4Cl (over total base present). The pH of the resulting aqueous layer was usually slightly basic and the ether layer was extracted with 15–20-mL portions of saturated NH_4Cl until the aqueous washes tested neutral or slightly acidic. A final extraction with saturated $NaHCO_3$ was performed and the ether layer dried with $MgSO_4$. The dried ether layer was either concentrated for isolation or subjected to VPC analysis.

(2-Methoxyphenyl)trimethylsilane (2) was obtained by distillation as a clear oil (bp 88–90 °C (15 mm)) from the monolithiation/silylation of anisole: ^{1}H NMR δ 0.24 (s, 9.1 H), 3.7 (s, 2.8 H), 6.7–7.5 (m, 4.1 H); IR (liquid film) 1588 (20), 1475 (15), 1462 (18), 1430 (6), 1236 (1), 1128 (20), 851 (2), 839 (2), 755 (9), 719 (17); MS 180 (M^+, 14), 165 (32), 135 (100), 59 (11). Anal. Calcd for $C_{10}H_{16}OSi$: C, 66.66; H, 8.94. Found: C, 66.70; H, 8.95.

2-Methoxy-1,3-bis(trimethylsilyl)benzene (3) was obtained after distillation as a clear oil (bp 55–58 °C (0.05 mm)) from the monolithiation/silylation of **2**. The oil solidified and was sublimed for analysis: ^{1}H NMR δ 0.31 (s, 17.0 H), 3.66 (s, 3.5 H), 6.8–7.5 (m, 3.6 H); IR (liquid film) 2954 (10), 1371 (2), 1249 (2), 1212 (4), 1016 (17), 849 (dbt 0.5), 776 (14), 754 (26), 743 (16), 621 (25); MS 252 (M^+, 17), 237 (11), 208 (24), 207 (100), 163 (16), 149 (26), 133 (28), 89 (15), 73 (53), 59 (29). Anal. Calcd for $C_{13}H_{24}OSi_2$: C, 61.84; H, 9.58. Found: C, 61.99; H, 9.61.

(2,3-Dimethoxyphenyl)trimethylsilane (5) was obtained after distillation as a clear oil (bp 54–55 °C (0.1 mm)) from the monolithiation/silylation of 1,2-dimethoxybenzene: ^{1}H NMR δ 0.32 (s, 8.97 H), 3.8–4.0 (m, 6.04 H), 6.93 (m, 2.99 H); IR (liquid film) 1457 (0.7), 1416 (0.9), 1261 (0.7), 1246 (4), 1224 (7), 1205 (2), 1154 (6), 876 (2), 835 (0.5 dbt), 757 (1); MS 210 (M^+, 45), 195 (68), 165 (100), 135 (43), 121 (57), 59 (24). Anal. Calcd for $C_{11}H_{18}O_2Si$: C, 62.81; H, 8.62. Found: C, 62.71; H, 8.67.

1,4-Bis(trimethylsilyl)-2,3-dimethoxybenzene (6) was obtained as a clear oil, which quickly solidified (bp 64–65 °C (0.1 mm), mp 47–51 °C), from the stepwise monolithiation/silylation of **5**: ^{1}H NMR δ 0.25 (s, 18.6 H), 3.73 (s, 5.78 H), 6.92 (s, 1.6 H); IR (liquid film) 2954 (7), 1377 (0), 1366 (3), 1246 (1), 1229 (4), 1160 (9), 1021 (3), 881 (8), 837 (0, dbt), 759 (7); MS 282 (M^+, 40), 237 (66), 193 (100), 133 (24), 89 (22), 73 (43), 59 (28). Anal. Calcd for $C_{14}H_{26}O_2Si_2$: C, 59.52; H, 9.28. Found: C, 59.39; H, 9.29.

(2,6-Dimethoxyphenyl)trimethylsilane (8) was obtained by distillation as a clear oil (bp 51–52 °C (0.1 mm)) which slowly solidified, from the monolithiation/silylation of 1,3-dimethoxybenzene: ^{1}H NMR δ 0.25 (s, 8.46), 3.68 (s, 6.42), 6.42 (d, J = 8.7 Hz, 2.13 H), 7.20 (t, J = 8.7 Hz, 0.99 H); IR (liquid film) 2953 (34), 1585 (4), 1461 (0.5), 1427 (5), 1239 (0.03), 1105 (0.6), 854 (6), 845 (6, dbt), 782 (14), 714 (31); MS 210 M^+, 17), 195 (35), 165 (19), 135 (100), 91 (11), 59 (14). Anal. Calcd for $C_{11}H_{18}O_2Si$: C, 62.81; H, 8.62. Found: C, 62.65; H, 8.65.

1,3-Bis(trimethylsilyl)-2,6-dimethoxybenzene (9) was obtained by distillation as a clear oil (bp 83–87 °C (0.15 mm)) from the stepwise monolithiation/silylation of **8**. The oil readily solidified and was sublimed for analysis: ^{1}H NMR δ 0.27 and 0.33 (both s, 18.4 H), 3.6 (s, 2.6 H), 3.74 (s, 3.2 H), 6.6 (d, J = 8.2 Hz, 0.91 H), 7.4 (d, J = 8.2 Hz, 0.88 H); IR (liquid film) 2953 (9), 1566 (0.5), 1355 (2), 1274 (6), 1247 (0.5), 1217 (7), 1114 (1), 1082 (2), 914 (11), 849 (dbt, 0.05); MS 282 (M^+, 22), 237 (100), 207 (78), 193 (21), 133 (25), 89 (25), 73 (50), 59 (41.6). Anal. Calcd for $C_{14}H_{26}O_2Si_2$: C, 59.52; H, 9.28. Found: C, 59.65; H, 9.40.

(2,5-Dimethoxyphenyl)trimethylsilane (11) was obtained by distillation as an oil [bp 55–57 °C (0.5 mm) [lit.[20] bp 70 °C (0.1 mm)]] from the monolithiation/silylation of 1,4-dimethoxybenzene: ^{1}H NMR δ 0.34 (s, 9.1 H), 3.77 (s, 6.0 H), 6.7–7.1 (m, 2.9 H) [lit.[20] ^{1}H NMR δ 0.23 (s, 9 H), 3.65 and 3.68 (2s, 6 H), 6.61 (m, 2 H), 6.75 (m, 1 H); IR (liquid film): 2952 (19), 1480 (5), 1464 (10), 1400 (14), 1273 (6), 1245 (13), 1222 (2), 1048 (14), 884 (9), 837 (2); MS 210 (M^+, 46), 195 (32), 180 (10), 165 (100), 135 (17), 121 (73), 59 (18).

1,4-Bis(trimethylsilyl)-2,5-dimethoxybenzene (12) was obtained from either stepwise monolithiation/silylation of **11** or by direct dilithiation. After concentration of the organic extract, **12** was isolated as a solid (mp 99–100 °C (petroleum ether)). No attempt was made to maximize the low yield from the stepwise process since **12** was more readily available by direct dilithiation: ^{1}H NMR δ 0.23 (s, 17.4 H), 3.74 (s, 6.46 H), 6.83 (s, 2.1 H); IR (KBr pellet) 1476 (27), 1463 (10), 1345 (3), 1239 (10), 1208 (5), 1106 (18), 1045 (7), 837 (dbt, 0.9), 768 (17), 637 (19); MS 282 (M^+, 63), 237 (58), 193 (100), 163 (11), 133 (17), 89 (17), 73 (40), 59 (29). Anal. Calcd for $C_{14}H_{26}O_2Si_2$: C, 59.52; H, 9.28. Found: C, 59.57; H, 9.38.

(2,3,4-Trimethoxyphenyl)trimethylsilane (14) was obtained after distillation as an oil (bp 67–70 °C (0.05 mm)) from the monolithiation/silylation of 1,2,3-trimethoxybenzene: ^{1}H NMR δ 0.23 (s, 9.12 H), 3.78 and 3.85 (both s, 9.06 total H), 6.60 and 6.97 (both d, J = 8.7 Hz, 1.82 total H); IR (liquid film) 1585 (10), 1487 (9), 1453 (13), 1397 (2), 1291 (6), 1270 (14), 1230 (5), 1097 (0), 1021 (16), 837 (2); MS 240 (M^+, 35), 225 (55), 195 (100), 165 (13), 151 (39), 135 (11), 93 (16), 89 (17), 73 (13), 59 (20). Anal. Calcd for $C_{12}H_{20}O_3Si$: C, 59.96; H, 8.39. Found: C, 59.86; H, 8.41.

1,5-Bis(trimethylsilyl)-2,3,4-trimethoxybenzene (15) was obtained after distillation as an oil (bp 68–72 °C (0.075 mm)) from the stepwise monolithiation/silylation of **14**. The oil solidified on standing and the solid (mp <36 °C) was sublimed for analysis. The same product, **15**, could also be obtained by bromine/lithium exchange with 1,5-dibromo-2,3,4-trimethoxybenzene, **34**, followed by silylation: ^{1}H NMR δ 0.26 (s, 17.4 H), 3.78 (s, 3.3 H), 3.86 (s, 6.1 H), 6.98 (s, 1.2 H); IR (KBr pellet) 2955 (19), 1451 (24), 1411 (25), 1378 (9), 1245 (17), 1229 (20), 1072 (12), 1013 (24), 852 (15), 836 (8); MS 312 (M^+, 57), 297 (34), 276 (100), 223 (27), 209 (26), 93 (30), 89 (42), 73 (61), 59 (48). Anal. Calcd for $C_{15}H_{28}O_3Si_2$: C, 57.64; H, 9.03. Found: C, 57.59; H, 9.07.

(2,3,6-Trimethoxyphenyl)trimethylsilane (17) was obtained by distillation as an oil (bp 65–70 °C (0.05 mm)) which showed some decomposition with time, from the monolithiation/silylation of 1,2,4-trimethoxybenzene: ^{1}H NMR δ 0.31 (s, 9.2 H), 3.70 and 3.77 (both s, 8.9 total H), 6.5 (d, J = 9.0 Hz, 0.98 H), 6.86 (d, J = 9.0 Hz, 0.89 H); IR (liquid film) 2951 (31), 1463 (4), 1427 (15), 1398 (24), 1249 (4), 1210 (30), 1150 (23), 1090 (7), 859 (10), 843 (9); MS 240 (M^+, 48), 225 (65), 210 (12), 195 (51), 165 (100), 151 (27), 135 (29), 121 (83), 59 (30). Anal. Calcd for $C_{12}H_{20}O_3Si$: C, 59.96; H, 8.39. Found: C, 60.01; H, 8.39.

1,4-Bis(trimethylsilyl)-2,3,5-trimethoxybenzene (18) was obtained by distillation as an oil (bp 78.5–79 °C (0.1 mm)) from the stepwise monolithiation/silylation of **17**. The oil olidified: mp 40–45 °C; ^{1}H NMR δ 0.31 (s, 17.3 H), 3.69 and 3.73 (both s, 9.6 total H), 6.51 (s, 1.1 H); IR (KBr pellet) 2952 (9), 1456 (8), 1358 (2), 1248 (4), 1225 (10), 1199 (14), 1151 (11), 1097 (4), 1020 (8), 838 (2); MS 312 (M^+, 57), 297 (12), 237 (40), 193 (100), 133 (23), 89 (32), 73 (54), 59 (32). Anal. Calcd for $C_{15}H_{28}O_3Si_2$: C, 57.64; H, 9.03. Found: C, 57.46; H, 9.05.

(2,4,6-Trimethoxyphenyl)trimethylsilane (25) was obtained by distillation as an oil (bp 93–94 °C (0.1 mm)) from the monolithiation/silylation of 1,3,5-trimethoxybenzene. Distillation caused considerable decomposition; **25** also decomposed when the injection port was 250 °C; column injection showed the sample

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to be bery pure. The oil solidified: mp 79–80 °C; ^{1}H NMR δ 0.27 (s, 9.1 H), 3.72 and 3.80 (both s, 9.0 total H), 6.07 (s, 1.8 H); IR (KBr pellet) 1599 (14), 1578 (16), 1398 (19), 1220 (8), 1207 (13), 1155 (23), 1123 (11), 1092 (18), 848 (19), 809 (21); MS 240 (M$^+$, 15), 225 (35), 202 (20), 165 (100), 121 (20), 95 (14), 93 (34), 73 (13), 59 (23). Anal. Calcd for $C_{12}H_{20}O_3Si$: C, 59.96; H, 8.39. Found: C, 59.95; H, 8.43.

2,4-Bis(trimethylsilyl)-1,3,5-trimethoxybenzene (26) was obtained as a solid, mp 95–97 °C, from the double bromine/lithium exchange with 2,4-dibromo-1,3,5-trimethoxybenzene, **35**, followed by silylation: ^{1}H NMR δ 0.28 (s, 18.0 H), 3.49 (s, 3.0 H), 3.74 (s, 6.0 H), 6.16 (s, 1.0); IR (KBr pellet) 1572 (4), 1348 (3), 1246 (11), 1241 (12), 1202 (7), 1120 (5), 1099 (5), 1092 (7), 855 (7), 840 (5); MS 312 (M$^+$, 22), 267 (33), 259 (16), 237 (100), 199 (24), 193 (38), 141 (18), 133 (19), 95 (30), 93 (75), 89 (32), 75 (18), 73 (64), 59 (53). Anal. Calcd for $C_{15}H_{28}O_3Si_2$: C, 57.64; H, 9.03. Found: C, 57.79; H, 9.09.

Bromo Derivatives of Methoxybenzenes. The bromo derivatives used in the bromine/lithium exchanges were prepared following standard procedures which used 1 or 2 equiv of Br_2 in either chloroform, carbon tetrachloride, or acetic acid.

1,5-Dibromo-2,3,4-trimethoxybenzene (34) was obtained as an oil: bp 100–110 °C (0.5 mm) (lit.[10] bp 157–161 °C (12 mm)); ^{1}H NMR δ 3.85 and 3.89 (both s, 9.1 total H), 7.43 (s, 0.94 H); IR (liquid film) 2938 (19), 1459 (0.07), 1412 (0.1) 1398 (0.08), 1272 (18), 1218 (4), 1066 (2), 1004 (0.7), 873 (19), 726 (16); MS 328 (M$^+$, 45), 326 (100), 324 (48), 313 (16), 311 (35), 309 (18), 270 (16), 268 (32), 266 (20), 204 (26), 202 (33), 77 (40), 53 (37).

2,4-Dibromo-1,3,5-trimethoxybenzene (35) was obtained as a solid: mp 131–132 °C (lit.[21] mp 132 °C; ^{1}H NMR δ 3.93 and 3.95 (both s, 9.03 total H), 6.32 (s, 0.97 H); IR (KBr pellet) 1573 (32), 1468 (47),1458 (48), 1429 (42), 1387 (36), 1340 (42), 1211 (25), 1107 (21), 1098 (42), 691 (49); MS 328 (M$^+$, 42), 326 (100), 324 (50), 217 (50), 215 (51), 189 (22), 187 (30), 166 (35), 138 (24).

5-Bromo-1,2,4-trimethoxybenzene (19) was obtained as a solid: mp 52–55 °C (lit.[15] mp 54–55.5 °C); ^{1}H NMR δ 3.75, 3.78, and 3.80 (all s, 8.8 total H), 6.47 (s, 1.1 H), 6.95 (s, 1.1 H); ^{1}H NMR (lit.[15]) δ 3.75 (s, 3 H), 3.78 (s, 6 H), 6.43 (s, 1 H), 6.93 (s, 1 H); IR (KBr pellet) 1507 (26), 1472 (49), 1452 (48), 1439 (44), 1379 (44), 1280 (52), 1213 (20), 1169 (45), 1025 (34), 801 (44). MS: 248 (M$^+$, 79), 246 (84), 233 (58), 231 (70), 205 (55), 203 (47), 159 (23), 124 (100), 109 (44), 53 (46).

1-Bromo-2,3,5-trimethoxybenzene was obtained by following the procedure of Dorn:[16] ^{1}H NMR δ 3.74, 3.78 and 3.82 (all s, 9.08 total H), 6.31 (d, $J = 2.6$ Hz, 0.97 H), 6.61 (d, $J = 2.6$ Hz, 0.95 H); ^{1}H NMR (lit.[15]) δ 3.60, 3.67, and 3.68 (all s), 6.22 (d, $J = 2.8$ Hz), 6.42 (d, $J = 2.8$ Hz).

2,3-Dibromo-1,4,5-trimethoxybenzene (22) was obtained by following the procedure of Dorn,[16] who incorrectly assigned the structure: ^{1}H NMR δ 3.75 (s, 2.9 H), 3.85 (s, 6.2 H), 6.5 (s, 0.96 H) [lit.[15] ^{1}H NMR δ 3.70 (s, 3 H), 3.78 (s, 3 H), 3.79 (s, 3 H), 6.38 (s, 1 H)]; IR (KBr pellet) 1582 (46), 1478 (44), 1430 (30), 1373 (27), 1320 (39), 1226 (32), 1205 (32), 1032 (25), 1009 (39), 818 (41); MS 328 (M$^+$, 35), 326 (76), 324 (45), 313 (45), 311 (100), 309 (49), 259 (33), 189 (35), 187 (39).

General Bromine/Lithium Exchange Conditions. The best results were obtained by following a procedure similar to that used by Worden.[10] The intermediate aryllithium derivatives were allowed to form for 1 min at 0 °C in diethyl ether and then quenched with chlorotrimethylsilane/*tertiary* amine solution.

(2,4,5-Trimethoxyphenyl)trimethylsilane (20) was obtained by distillation as an oil (bp 83–84 °C (0.1 mm)) from bromine/lithium exchange and silylation of 5-bromo-1,2,4-trimethoxybenzene, **19**. The oil solidified: mp 40.5–43 °C; ^{1}H NMR δ 0.26 (s, 8.84 H), 3.74, 3.80, and 3.84 (all s, 9.14 total H), 6.45 (s, 1.01 H), 6.84 (s, 1.01 H); IR (KBr pellet) 1371 (62), 1239 (56), 1211 (51), 1100 (37), 1077 (60), 1034 (58), 936 (38), 903 (25), 853 (63), 838 (59). MS: 240 (M$^+$, 52), 225 (22), 195 (100), 151 (69), 105 (10), 89 (12), 75 (11), 59 (19).

Carbonation Experiments. The lithiation reaction mixture (heterogeneous suspension) was poured onto solid dry ice and the mixture opened to the atmosphere and allowed to evaporate overnite. The reaction mixture was then acidified. In the case of 2,3-dimethoxyterephthalic acid (from 1,2-dimethoxybenzene), the acid was extracted into ether and then into $NaHCO_3$ solution, from which it was reextracted after acidification. The solvent was evaporated to yield crude product which was washed with cold benzene and dried to give 2,3-dimethoxyterephthalic acid, mp 214 °C dec (lit.[22] mp 219 °C. In the case of 2,5-dimethoxyterephthalic acid (from 1,4-dimethoxybenzene), the crude product was obtained by filtering the acidified reaction mixture then recrystallized from hot water, mp 265 °C, lit.[23] mp 263–264 °C.

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Registry No. 1, 100-66-3; **2**, 877-68-9; **3**, 92669-90-4; **4**, 91-16-7; **5**, 92669-91-5; **6**, 92669-92-6; **7**, 151-10-0; **8**, 92669-93-7; **9**, 92669-94-8; **10**, 150-78-7; **11**, 72054-75-2; **12**, 92669-95-9; **13**, 634-36-6; **14**, 92669-96-0; **15**, 92669-97-1; **16**, 135-77-3; **17**, 92669-98-2; **18**, 92669-99-3; **19**, 20129-11-7; **20**, 92670-00-3; **21**, 92670-01-4; **22**, 23149-34-0; **23**, 92670-02-5; **24**, 621-23-8; **25**, 36086-05-2; **26**, 92670-03-6; **27**, 92670-04-7; **28**, 92670-05-8; **29**, 92670-06-9; **30**, 92670-07-0; **31**, 92670-08-1; **34**, 92670-09-2; **35**, 5876-90-4; 1-bromo-2,3,5-trimethoxybenzene, 23030-39-9; 2,3-dimethoxyterephthalic acid, 7168-95-8; 2,5-dimethoxyterephthalic acid, 21004-11-5.

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Synthesis of Cis Vicinally Disubstituted Cyclopentanes by Fragmentation of Bicyclo[3.2.0]heptan-6-ols. Total Synthesis of (±)-Multifidene[1a]

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A fragmentation–olefination process has been developed for the conversion of bicyclo[3.2.0]heptan-6-ols bearing anion stabilizing functions at C-7 into cyclopentanes with vicinal and functionalized methyl substituents. Under appropriate conditions reasonable stereoselectivity in favor of the cis isomers can be achieved as in the **3** → **4c** and **16** → **17c** transformations. This methodology is applied to a total synthesis of (±)-multifidene (**1c**), the gamete-attracting substance of the brown algae *Cutleria multifida*.

Several years ago we became interested in methodology for the stereoselective synthesis of cis-1,2-disubstituted cyclopentanes. Existing methods for the construction of vicinally substituted cyclopentanes have arisen primarily

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