Factors influencing prenylation of an aromatic organolithium

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An apparently routine metal–halogen exchange (MHE) reaction gave variable low yields under typical conditions. ^{13}C and ^{7}Li NMR studies suggested a diversity of organolithiums were formed in the MHE reaction leading to a plethora of products on subsequent electrophilic aromatic substitution with geranyl bromide. A reversal of reagent addition simplified the ^{7}Li NMR spectrum and the product distribution, in addition to increasing the isolated yield of the desired product from a variable 5–40% to a consistent 65%.

Keywords: toluhydroquinones, metal–halogen exchange, ^{7}Li NMR, organolithium

Ortho-polyprenylated toluquinones and toluhydroquinones, *e.g.* **1** and **2**, are an important class of bioactive secondary metabolites regularly isolated from Southern African marine invertebrates.[1-3] The *in vitro* anti-proliferative activity of **2** against oesophageal cancer cells[4] recently prompted us to synthesise the related marine natural product analogues; 5-methyl-2-[(2'*E*, 6'*E*)-3',7', 11'-trimethyl-2',6',10'-dodecatrienyl]-2,5-cyclohexadiene-1,4-dione (**3**) and 5-methyl-2-[(2'*E*,6'*E*)-3,7,11-trimethyl-2',6',10'-dodecatrienyl]-1,4-benzenediol (**4**).[5] A number of strategies are available for the regioselective synthesis of *ortho*-prenylated phenols including Claisen rearrangements, directed *ortho*-metallation (D*o*M), metal-mediated coupling and metal–halogen exchange (MHE).[6,7] Of these, butyllithium-mediated MHE provided access to **5** (the methylated precursor of **3**) from **6** and farnesyl bromide, in relatively low and frustratingly variable isolated yield (5–40%).[5] Given the apparent vagaries of the prenylation of bromodimethoxytoluene substrates using MHE methodology, we present here our attempt to shed light on the factors that may be influencing this reaction.

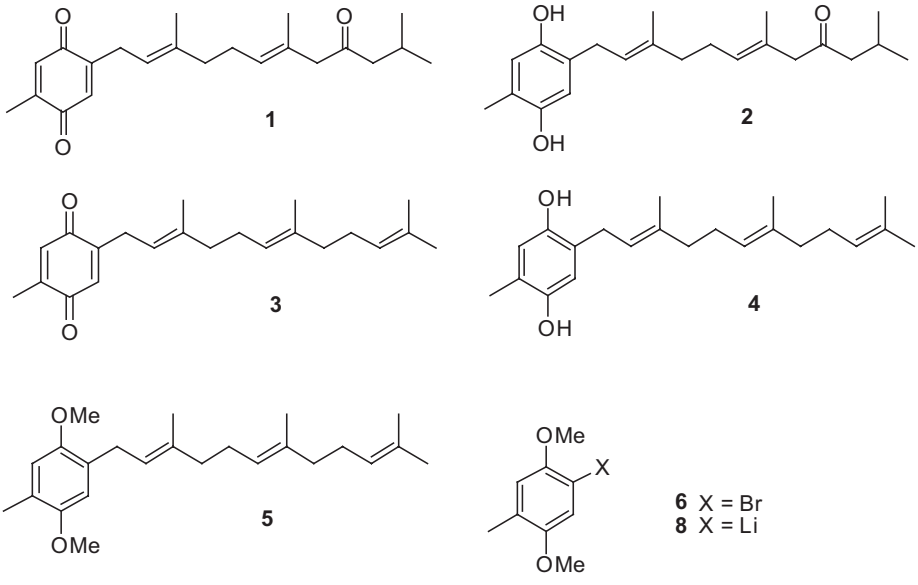
The *n*-BuLi-mediated MHE reaction between **6** and geranyl bromide (**9a**), in the absence and presence of TMEDA, was monitored by ^{13}C and ^{7}Li NMR spectroscopy. HPLC analysis of the product mixture consistently suggested that the same five components (Table 1 and Scheme 1) were being formed in variable amounts in each experiment. It was also noted that a reversal in the order in which the reactants were added by Scheepers *et al.*[5] reduced the number of side-products and improved the yield of the desired prenylated product. The possible rationale behind our observations is discussed here.

Earlier studies of the structure of 2-lithioanisole indicated that probable internal coordination between the oxygen of the methoxy group and the lithium renders the anisole almost unreactive to electrophiles.[8] TMEDA and other strongly coordinating solvent additives are therefore often used to moderate aggregation and internal coordination as an aid to enhance reactivity.[9] This was borne out by the low ratios of desired product **7** to unreacted geranyl bromide (4 : 5) obtained in our small scale prenylation studies of **6** when TMEDA was omitted (Table 1). Conversely, the addition of one equivalent

Table 1 Product ratios as determined from HPLC analysis of reaction mixtures (using a differential refractometer)[a]

Fraction	Compound	Without TMEDA	1 equiv. TMEDA	2 equiv. TMEDA
A	**9a,b**	5	1	1
B	**7**	4	6	6
C	**7,10**	0.6	1	1
D	**6,11**	0.6	0.8	1

[a]There were also traces of unidentified products.



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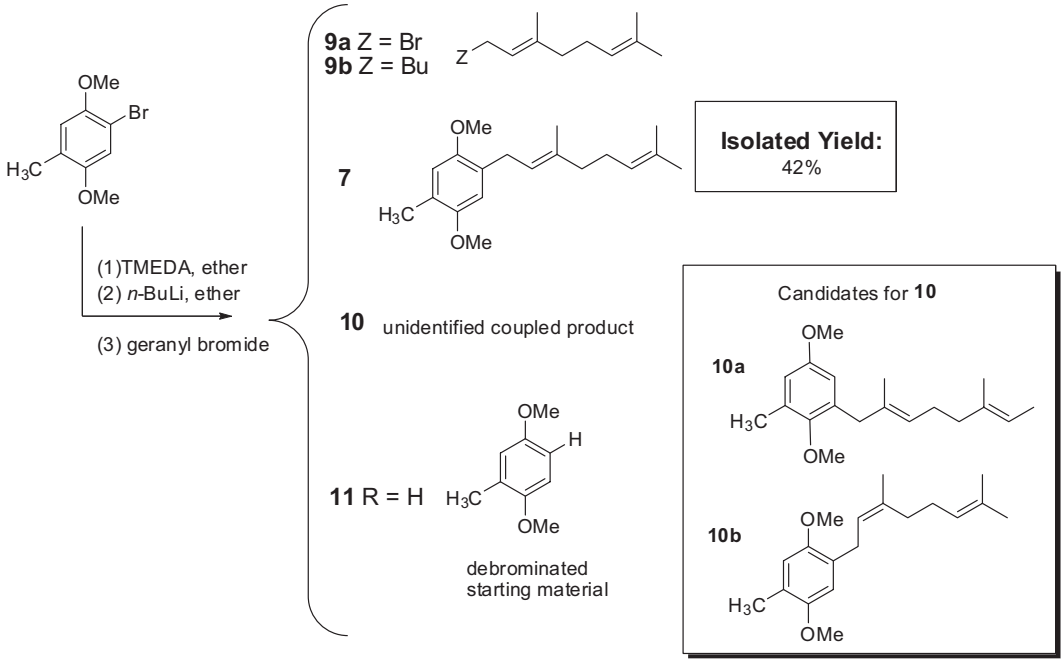

Scheme 1 Prenylation of **6** (following method of Scheepers *et al.*).[5]

of TMEDA to the ether solution of **6** and *n*-BuLi resulted in an increase in the proportion of **7** obtained with the proportion of geranyl bromide dramatically reduced. We observed that there was no added advantage gained by increasing the amount of TMEDA from one to two equivalents (see Table 1), which suggests that no more than one TMEDA is involved in the rate-determining step.[10] Frustratingly, the favourable ratio of **7** suggested from HPLC analysis of the product mixture obtained from the addition of TMEDA could not be extrapolated to give a comparable isolated yield of **7** when the reaction was scaled up. A closer investigation of the nuances of this MHE reaction was thus required.

In order to gain a better understanding of the reaction and its mechanism, we first attempted to identify the major by-product (**10**) which appeared to be an alternative coupling product. Mass spectrometric (*m/z* 288) and ^{1}H NMR data (Fig. 2) suggested that the unknown component **10** of the intractable mixture obtained from semi-preparative HPLC (fraction **C** from Table 1) is an isomer (**10a** or **10b**) of the major product **7** (Scheme 1). The structures of the starting materials (**6** and **9a**) and the by-products (**9b** and **11**) in the reaction product mixture were similarly determined from NMR data.

A combination of carbon and lithium NMR spectroscopy has been shown to provide an insight into the mechanistic details of lithium-mediated reactions.[11] There was clear evidence from an analysis of the ^{13}C and ^{7}Li NMR spectra and the structures proposed for the products formed in this reaction that the MHE had taken place. The signal corresponding to the brominated carbon (δ_C 108) disappeared and two broad signals (δ_C 122

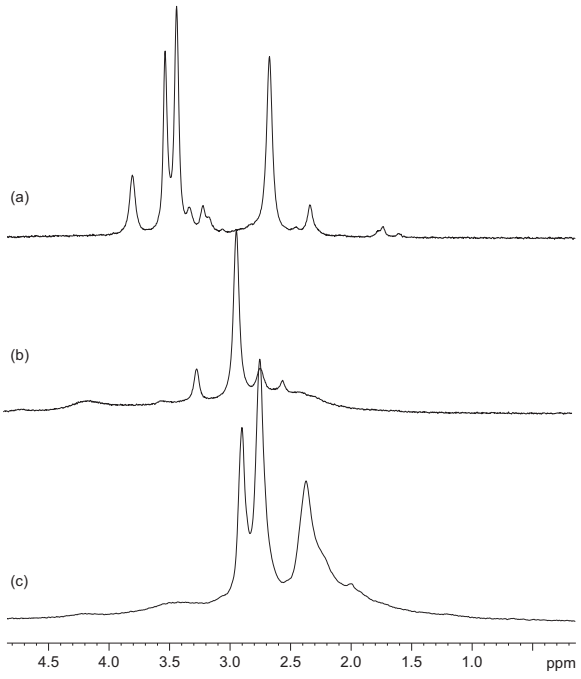

Fig. 1 ^{7}Li spectra (155.5 MHz, δ_{Li} 0–5.5, LiBr) of (a) *n*-BuLi added to 6 (b) *n*-BuLi and TMEDA added to **6** and (c) **6** added to *n*-BuLi and TMEDA.

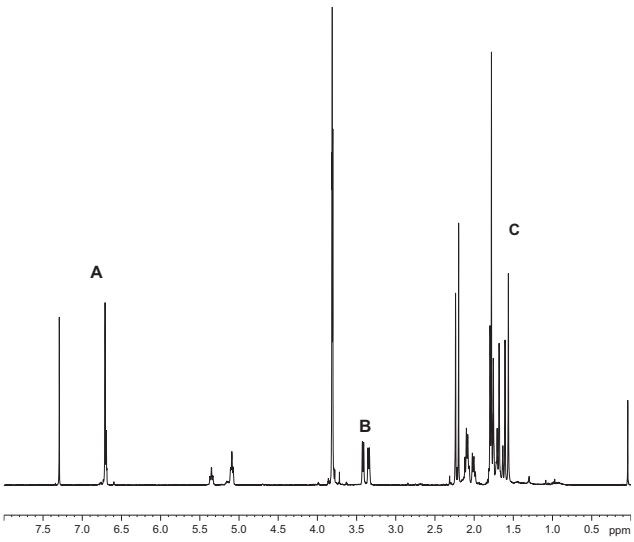

Fig. 2 ^{1}H NMR (400 MHz) spectrum of fraction C obtained from HPLC. Signals indicated by **A**, **B** and **C** refer to the aromatic, benzylic methylene, and methyl signals respectively.

and 108) consistent with lithiated carbon were observed. The chemical shift of the lithiated aromatic carbon signals normally appear in the region 110–200 ppm, *e.g.* phenyllithium (dimer, δ_C 188)[12] and *ortho*-lithio-anisole (δ_C 115).[13] The quadrupolar broadening of the lithiated carbon resonances observed in the ^{13}C NMR spectra of the mélange of mixed aggregates is typical of a system unsymmetrical around ^7Li.[14,15] In our case, we also propose that competitive coordination between Li and the ether, TMEDA and aromatic methoxy groups contributed to quadrupolar broadening.[16] Additional broadening of the NMR signals could be attributed to solvent exchange processes around ^7Li.[13] The signal broadening observed in the ^{13}C NMR spectrum was corroborated by similar broadening of the signals in the ^7Li NMR spectra (Fig. 1b).

In the case of D*o*M in anisole, the reaction is perceived to be a simple two step process: coordination of the butyllithium dimer to the methoxy/electron-rich aromatic ring followed by metal proton exchange.[13, 17-19] The resulting complex includes a mixed dimer of butyllithium and aryllithium.[13, 20] Assuming that the same process is followed for MHE in **6**, then we expected to see evidence of a mixed dimer product in the ^{13}C and ^7Li NMR spectra of the reaction mixture. Unfortunately, despite several attempts, it was neither possible to conclusively identify a mixed dimer, nor to establish the structure of any of the aryllithium aggregates.

It is also significant that several signals were observed in both the ^{13}C NMR and ^7Li NMR spectra, indicating the presence of more than one aggregate (Fig. 1). In accordance with a general medium effect, both the TMEDA (methyl and methylene ^{13}C resonances) and organolithium (^7Li) signals were shifted (Fig. 3). The ^7Li NMR spectrum of **8**, acquired in the absence of TMEDA, suggested three major aggregates (δ_{Li} 3.6, 3.5, 2.7, Fig. 1a) and several minor aggregates. Interestingly, addition of TMEDA simplified the ^7Li NMR spectrum in which a single new aggregate (δ_{Li} 2.9) was dominant (Fig. 1b).

In a dynamic NMR study of the TMEDA/organolithium sample, the ^7Li signals were observed to coalesce at or around 257 K suggesting that they exist in various dynamic equilibria with one another[21] (Fig. 4). Several possible structures have been proposed for aggregates involving lithiated anisoles with various combinations of TMEDA and ether[22] and similar opportunities for aggregation are envisaged for **8**.

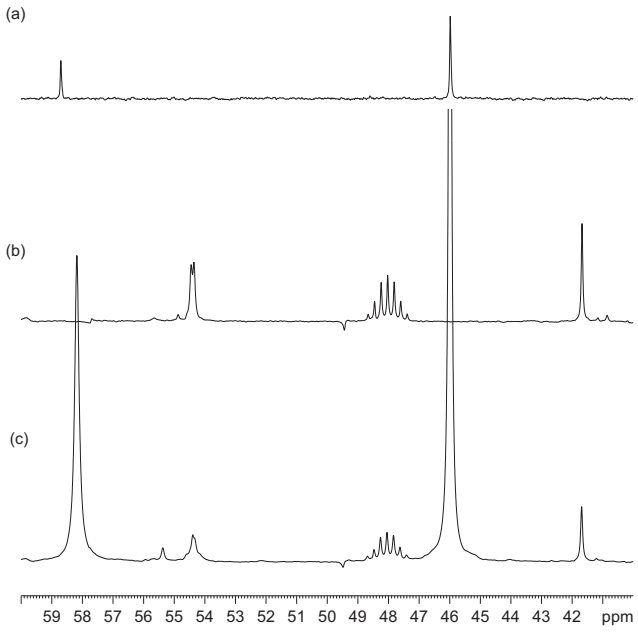

Fig. 3 Comparison of ^{13}C NMR spectra (100 MHz, δ_C 40–80, $CDCl_3$) of (a) TMEDA, (b) **8** without TMEDA and (c) **8** with TMEDA.

The addition of geranyl bromide to the mixed aggregates of **8** at 194 K resulted in the immediate appearance of a new signal (δ_{Li} 2.7) in the ^7Li NMR spectrum, accompanied by the disappearance of at least one other smaller species and a slight reduction in the major aggregate. As the temperature was increased (at 20 minute intervals), the broad signal at δ_{Li} 4.3 shifted upfield and then disappeared, while the major aggregate (δ_{Li} 2.9) was completely consumed by the time 222K was reached. It was not clear whether this was a result of reaction of **8** with the geranyl bromide taking place gradually over the intervening time period or as a result of the temperature increase (Fig. 5).

During the course of this study we were still unable to obtain **7** in reproducible and satisfactory yields. This therefore prompted us to investigate the possible influence of adventitious water despite our previous efforts to work under strictly anhydrous conditions. In order that any traces of water would react with excess butyllithium prior to the addition of **6** the order of reagents was reversed, *i.e. n*-BuLi was initially combined with TMEDA in diethyl ether and cooled to –10 °C, after which a solution of **6** in ether was added dropwise. Removal of any traces of water would consequently decrease the loss of **8** due to protonation. The previous NMR studies indicated that the MHE was rapid, so there would be very little of **6** remaining in the presence of excess *n*-BuLi/TMEDA.

It was evident upon examination of the ^7Li NMR spectrum, acquired from the experiment in which the addition of reagents had been reversed (Fig. 1c), that several of the lesser aggregates had been eliminated, thus indicating that the effect of the revised reagent addition method served to control the number and nature of the organolithium species in solution

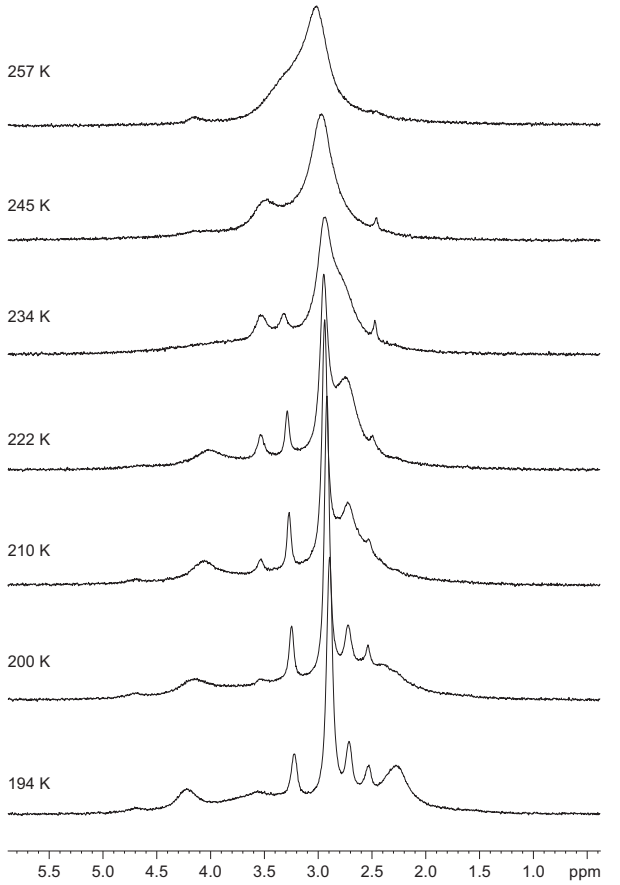

Fig. 4 Dynamic NMR study of **8** in TMEDA (155.5 MHz, δ_{Li} 0–5.5, LiBr) showing dynamic relationship between several less populated aggregates and the sustained dominance of a single species.

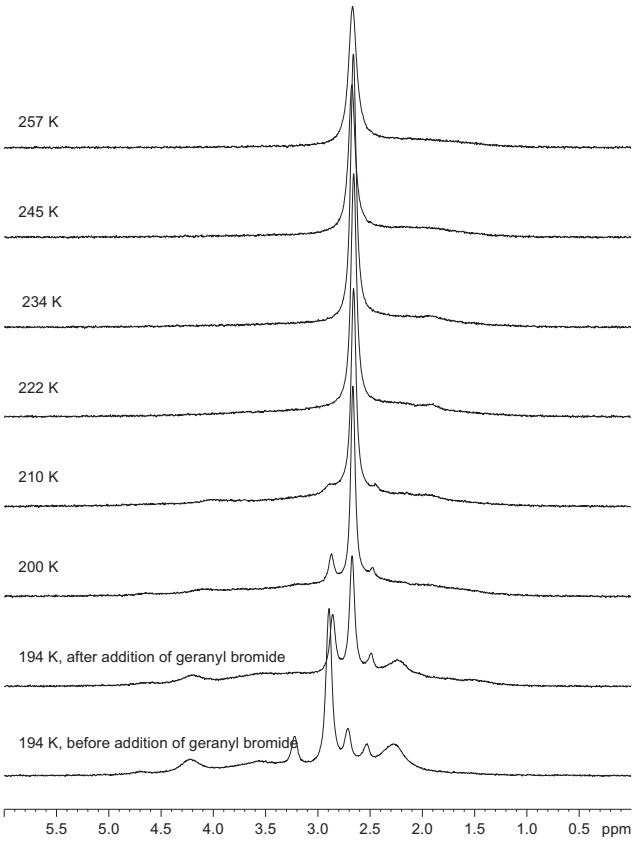

Fig. 5 Variable temperature NMR study of **8** in TMEDA following the addition of geranyl bromide (155.5 MHz, δ_{Li} 0–5.5, LiBr) showing the effect of increased temperature on the progress of the reaction.

(and thereby reduce the potential for side reactions) The gratifying outcome was a significant increase in the isolated yield (65%), accompanied by an elimination of the alternative coupling product (**10**). Furthermore, this method yields the reproducible results absent when using the earlier method.[5]

In conclusion, we have established firstly, that even in the presence of TMEDA, MHE-mediated prenylation reactions of bromodimethoxytoluene substrates give rise to multiple Li aggregates in the reaction mixture, ultimately resulting in a complex cohort of products. Secondly, the low recovery of unreacted **6** and the absence of corresponding signals (such as C–Br) in the ^{13}C NMR suggest that MHE is almost quantitative in the presence of TMEDA and the low yields often encountered in this reaction cannot be attributed to the initial MHE step but rather to the electrophilic addition step. Thirdly, competition between geranyl bromide and trace amounts of water, gives rise to protonation of **8** and the formation of dimethoxytoluene (**11**) as a significant side product. Finally, we have established that alteration of the sequence in which the reactants are added has improved the yields of this reaction from a variable 5–40% to a consistent 65%.

Experimental

Melting points were determined using a Reichert hot stage microscope and are uncorrected. IR spectra were recorded on a Perkin Elmer Spectrum 2000 FT-IR spectrometer with the compounds as films (neat) on NaCl discs. NMR spectra were acquired on Bruker 400 MHz Avance and 600 MHz Avance II spectrometers using standard pulse sequences. Chemical shifts are reported in ppm, referenced to residual solvent resonances ($CDCl_3$ δ_H 7.25, δ_C 77.0), and coupling constants are reported in Hz. HRFABMS data were obtained on a JEOL SX102 spectrometer. Reactions where exclusion of water was necessary were performed using glassware dried in a 150 °C oven overnight or dried at 600 °C with a heatgun and flushed with dry Ar to remove air and moisture. All reactions were performed under an atmosphere of dry Ar. Immediately prior to their use Et_2O and THF were distilled from sodium metal/benzophenone ketyl. General laboratory solvents were distilled before use. Reactions were monitored by thin layer chromatography (DC-Plastikfolien Kieselgel 60 F_{254} plates). Plates were visualised under UV light and developed by spraying with either 10% conc. H_2SO_4 in methanol or by exposure to iodine. Kieselgel 60 (230–400 mesh) was used for initial flash chromatographic separations. Semi-preparative HPLC was performed using a Whatman's Magnum 9 Partisil 10 column (10 mm i.d., length 50 cm) and a Waters 410 Differential Refractometer. All reagents were commercially available, except 1-bromo-2,5-dimethoxy-4-methylbenzene (**6**) which was prepared as described below.

General procedure for the preparation of NMR samples

Method A: The organolithium samples were prepared by reaction of **6** with *n*-BuLi. The samples of **6** (28 mg, 0.12 mmol) were weighed into oven-dried 5 mm NMR tubes fitted with a screw cap and a $CDCl_3$ insert and flushed with argon. After dilution with ether and cooling in a dry ice/acetone bath, each sample was treated with a stoichiometric amount of *n*-BuLi (~1.5 equiv. of 1.5 M solution) and 0, 1 or 2 equivalents of TMEDA and mixed by shaking and applying a vortex. The resulting organolithium samples were then inserted into the NMR probe precooled to 198 K. After a short time for temperature equilibration, the field was locked and shimmed. This was followed by acquisition of a ^{13}C (proton decoupled) spectrum (referenced to $CDCl_3$) and a ^{7}Li NMR spectrum (referenced to an external standard of 1M LiBr in D_2O at 303 K). Additional lithium spectra were subsequently obtained at intervals as the temperature was increased. The temperature of the NMR probe was calibrated using a 4% MeOH in d_4-methanol sample.

Method B: The *n*-BuLi aliquots were transferred into oven-dried 5 mm NMR tubes fitted with a screw cap and a $CDCl_3$ insert and flushed with argon. After dilution with ether, each sample was treated with a stoichiometric amount of TMEDA and mixed by shaking and applying a vortex before cooling in a dry ice/acetone bath. The solution of **6** (28 mg, 0.12 mmol) in ether (0.2 mL) was added dropwise and the resulting solution mixed carefully using a vortex mixer. The resulting organolithium samples were then inserted into the NMR probe precooled to 198 K. After a short time for temperature equilibration, the field was locked and shimmed. This was followed by acquisition of a ^{13}C (proton decoupled) spectrum (referenced to $CDCl_3$) and a ^{7}Li NMR spectrum (referenced to an external standard of 1M LiBr in D_2O at 303 K). Further lithium spectra were then acquired at intervals as the temperature was increased.

Synthesis of 1-bromo-2,5-dimethoxy-4-methylbenzene (**6**)[23]

N-bromosuccinimide (4.40 g, 24.8 mmol) was added to a solution of 1,4-dimethoxy-2-methylbenzene (3.15 g, 20.7 mmol) in MeCN (200 mL) and stirred overnight at room temperature. The solvent was then removed under reduced pressure and the residue taken up in CH_2Cl_2 (50 mL), washed with sodium sulfite solution (50 mL) and water (50 mL) dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a white solid (8.56 g). Flash chromatography of the crude product in 9:1 hexane: EtOAc yielded pure **6** (3.94 g, 17.0 mmol, 82%) as white plates from hexane; m.p 82–86 °C, lit.[24] 81–82 °C; IR ν_{max} 2945, 2833, 1505, 1217, 1037, 866 cm^{-1}; δ_H (600 MHz, $CDCl_3$) 6.98 (1H, s, H-3), 6.73 (3H, s, H-6), 3.83 (3H, s, OMe), 3.77 (3H, s, OMe), 2.17 (3H, s, H-7). δ_C (150 MHz, $CDCl_3$) 152.2, 149.7, 126.8, 115.4, 115.2, 108.0, 57.0, 56.1, 16.3. Calcd for $C_9H_{11}O_2{}^{79}Br$ $[M^+]$ 229.9942. Found 229.9943.

Synthesis of 1-[(2E)-3,7-dimethylocta-2',6'-dienyl]-2,5-dimethoxy-4-methyl-benzene (**7**)

TMEDA (1.01 g, 8.65 mmol, 2.0 equiv.) followed by 1.6 M *n*-BuLi (5.4 mL, 8.65 mmol) was added to dry Et_2O (1 mL) at –10 °C and allowed to stir for 15 min before a solution of **6** (1.0 g, 4.33 mmol, 1.0 equiv.) in dry Et_2O (5 mL) was added. The resulting mixture was stirred at –10 °C for 15 min before geranyl bromide (1.88 g, 8.65 mmol, 2.0 equiv.) was added dropwise and the mixture was allowed to stir overnight at room temperature. The reaction was thereafter quenched with sat. NH_4Cl (10 mL) and the aqueous solution extracted with Et_2O (3 × 5 mL). The combined ethereal extracts were washed with water and sat. brine and dried over anhydrous $MgSO_4$. Concentration *in vacuo* afforded the crude mixture (1.97 g) as a brown oil. Purification using NP HPLC (96:4 hexane: EtOAc) yielded **7** (810 mg, 2.8 mmol, 65%) as a pale yellow oil. IR ν_{max} 2915, 2849, 1506, 1400, 1211, 857;

δ_H (600 MHz, $CDCl_3$) 6.67 (1H, s, H-6), 6.65 (1H, s, H-3), 5.30 (1H, t, J = 7.3 Hz, H-2'), 5.10 (1H, t, J = 6.8 Hz, H-6'), 3.77 (3H, s, OMe-1), 3.76 (3H, s, OMe-4), 3.30 (2H, d, J = 7.3 Hz, H-1'), 2.18 (3H, s, H-7), 2.10 (2H, dd, J = 14.4, 6.8 Hz, H-5'), 2.04 (2H, m, H-4'), 1.70 (3H, s, H-10'), 1.67 (3H, s, H-8'), 1.59 (3H, s, H-8'). δ_C (150 MHz, $CDCl_3$) 151.6, 151.0, 136.1, 131.4, 128.0, 124.4, 124.3, 122.7, 114.0, 112.4, 56.3, 56.1, 39.8, 28.2, 26.8, 25.7, 17.7, 16.1. Calcd for $C_{19}H_{28}O_2$ [M^+] 288.2089. Found 288.2090

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