Intermolecular silyl migration reactions

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Sodium hydride promoted *O*-alkylation of 2-[(4-*t*-butyldimethylsilyloxy)phenyl]ethan-1-ol with 1-bromo-2-(bromomethyl)-4,5-dimethoxybenzene depend on the solvent used in the coupling reaction. Mixtures of 2-[4-(2-bromo-4,5-dimethoxybenzyloxy)phenyl]-1-*t*-butyldimethylsilyloxyethane and 2-[4-(2-bromo-4,5-dimethoxybenzyloxy)phenyl] ethan-1-ol (in DMF), or 2-[4-(2-bromo-4,5-dimethoxybenzyloxy)phenyl]-1-*t*-butyldimethylsilyloxyethane and 4-[2-(2-bromo-4,5-dimethoxybenzyloxy)ethyl]phenol (in THF), were detected. These results can be explained by an unusual intermolecular silyl migration reaction.

Keywords: galanthamine analogues, benzyl bromide, alcohols, *O*-alkylation, silyl migration reactions, NaH

(-)-Galanthamine (**1**) (Fig. 1), an alkaloid isolated from different species of the *Amaryllidaceae* family,[1] is a selective, reversible, and competitive acetylcholinesterase (AChE) inhibitor.[2] Galanthamine is the most recently approved AChE inhibitor in Europe and in USA for the symptomatic treatment of Alzheimer's disease (AD).[3] Owing to the scarce supplies from botanical sources and the high cost of its isolation from daffodils (0.1–2% dry weight),[4] several total syntheses have been reported to produce this drug, and galanthamine analogues.[5] In this context, in this paper we report the results that we have found during the attempted preparation of the presumed useful intermediates **3**/**4** (Scheme 1) for the preparation of the unreported 11-oxanorgalanthamine (**2**) (Fig . 1).

Our retrosynthetic analysis for a compound of type **3** is shown in Scheme 1. This product should be the result of a phenol *o*-*p*-oxidative coupling reaction of diphenol **4** that could be prepared by simple *O*-alkylation reaction between benzylic bromide **5** and the conveniently protected alcohol **6** (Scheme 1).

Compound **5** can be prepared according to the method reported by Jordis *et al.*,[6] starting from 3,4-dimethoxybenzaldehyde (**7**) *via* aryl bromide **8** and alcohol **9** (Scheme 2).

Alcohol **6** has been synthesised from 2-(4-hydroxyphenyl)ethan-1-ol (**10**), after full silylation reaction followed by selective deprotection (Scheme 3).[7]

With compounds **5** and **6** in hand, we tested their coupling reaction mediated by NaH in dry DMF. Under these

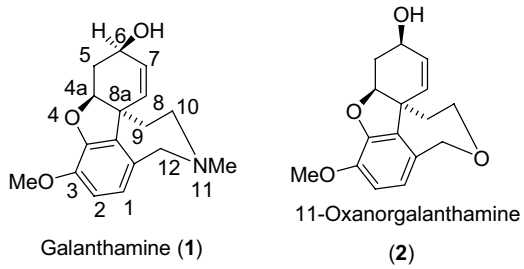


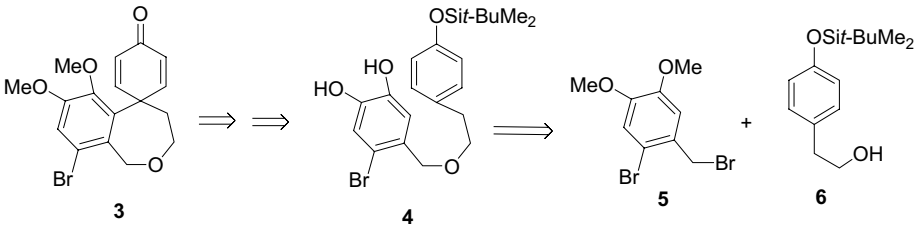
Fig. 1 Structure of galanthamine, and the target molecule 2.

experimental conditions we isolated compounds **11** and **12** in 14% and 84% yield, respectively (Scheme 4). Product **11** was a *O*-benzyl ether bearing a *t*-butyldimethylsilyl group, while ether **12** was devoid of the silyl protecting group.

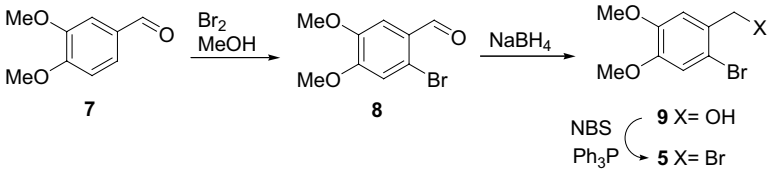
When we changed DMF by THF as solvent, we still isolated ether **11** in higher yield (61%), but we did not detect compound **12**; instead, we isolated a new ether with no *t*-butyldimethylsilyl group, in low yield, to whom structure **13** was assigned (Scheme 5).

Similar results were observed when we used an aqueous solution of sodium hydroxide as base in methylene chloride [**11** (58%) and **13** (13%)], or using the system K_2CO_3/DMF [unreacted starting material **5** (5%), and alcohols **9** (33%) (Scheme 2) and **10** (23%) (Scheme 3)].

Thus, according to their NMR data, compounds **12** and **13**



Scheme 1 Synthetic plan and retrosynthetic analysis.



Scheme 2

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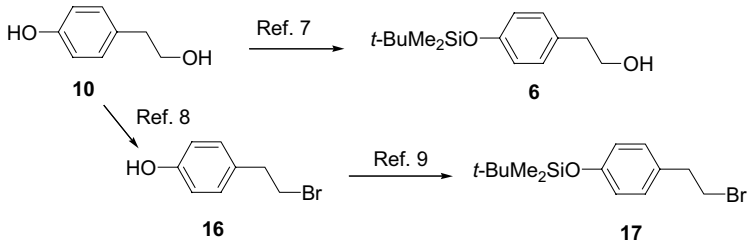
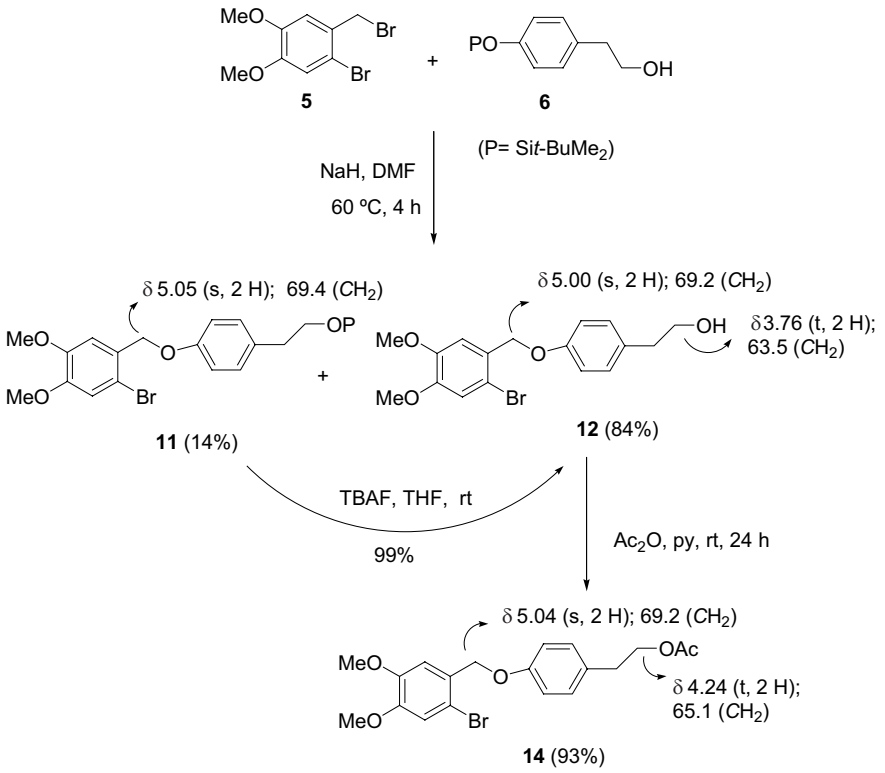
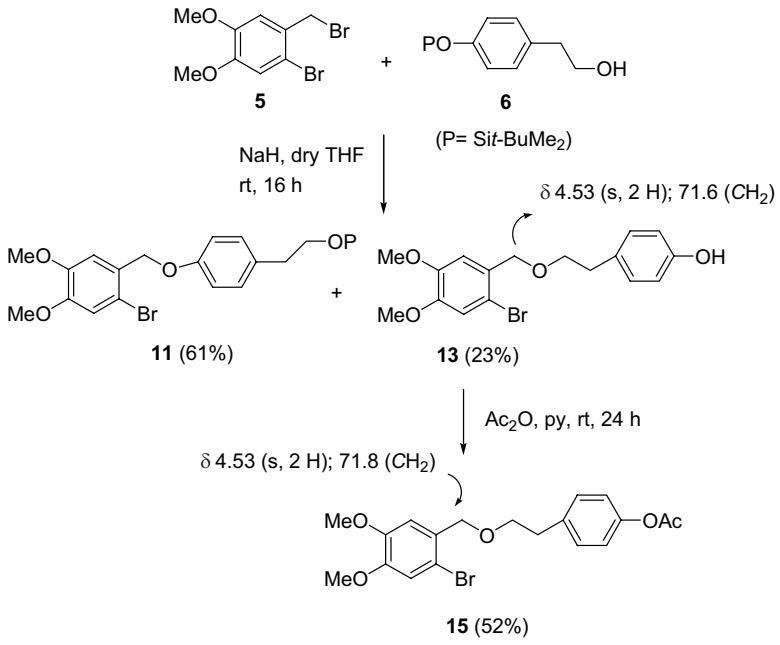


Scheme 3



Scheme 4



Scheme 5

are isomers with the expected *O*-benzyl moiety and a free hydroxyl group. The structure assignment was possible after their acetylation reaction. Compound **12** gave acetate **14** (Scheme 4), that showed in its ^{1}H NMR spectrum a triplet at 4.24 ppm, corresponding to a methylene substituted with an acetyloxy group, with the expected paramagnetic shift when compared with the same chemical shift for the same methylene group (3.76 ppm) in compound **12**. Analogously, compound **13** gave acetate **15** (Scheme 5). In good agreement with these structures, in the ^{1}H NMR of compounds **13** and **14**, no protons were directly bonded to carbons bearing the acetyloxy group, suggesting that compound **13** was a free phenol, while product **12** was an unprotected derivative of ethanol. Very interestingly, in products **11**, **12** and **14**, the benzylic methylene group resonated as a singlet around 5.00–5.05 ppm, while compounds **13** and **15**, the same protons appeared as a singlets at 4.53 ppm.

In view of these results, next we explored the *O*-alkylation of alcohol **9** (Scheme 2) with 4-(2-bromoethyl)phenol (**16**) (Scheme 3).[8] No reaction was observed using sodium hydroxide in methylene chloride; and when sodium hydride in THF was used as base a complex reaction mixture resulted from where we only could isolate aldehyde **8** (Scheme 2) (2%) and the expected phenol **13** (Scheme 5) albeit in low chemical yield (24%).

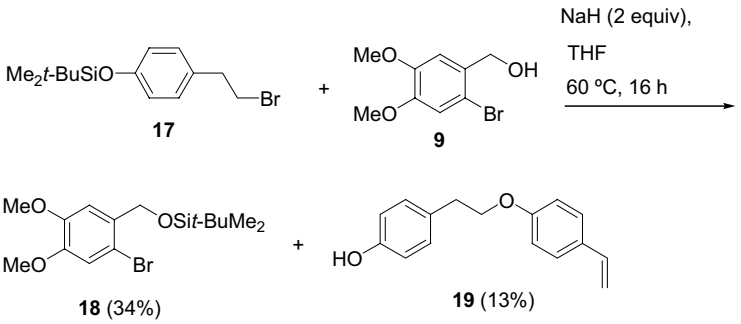
When we repeated the reaction, but with the *t*-butyldimethylsilyl derivative **17**,[9] we isolated only the silylated benzylic alcohol **18** and compound **19** (13%) (Scheme 6), the presumed result of the auto-coupling reaction of compound **17** with its deprotected form (**16**), followed by hydrogen bromide elimination.

The results obtained in the *O*-alkylation of alcohol **6** with benzyl bromide **5** were surprising and totally unexpected. We have no clear explanation for the different observed reactivity when changing the base system or the solvent used. However, it is clear that the formation of compound **11** should be the result of sequential process based on an intermolecular migration of the silyl group on the alkoxyde **6-A** -the equilibrium of this process being shifted to the preferred formation of the more stable sodium phenolate **6-B**-, the reactive intermediate for the final *O*-alkylation with benzyl bromide **5** (Scheme 7). The formation of the free-hydroxyl containing ethanol **12** should be also the result of a similar silyl migration process on compound **11** with the same alkoxyde **6-A** (Scheme 7). We are not aware of a similar, rare silyl migration process, although base-promoted oxygen–oxygen silyl migration reactions are well known rearrangement process in organic synthesis,[10] and related intramolecular migration reactions has been reported.[11]

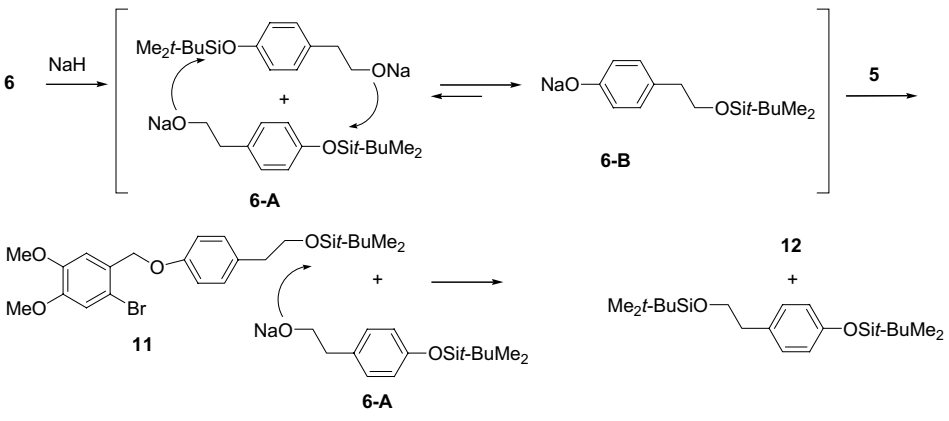
Experimental

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, at 300 and at 75 MHz (Bruker Avance-300), respectively. TLC was performed on Silica F254 (Merck) and detection by UV light at 254 nm or by charring with phosphomolybdic-H_2SO_4 reagent. Column chromatography was effected on Silica Gel 60 (Merck, 230 mesh).

2-[4-(2-Bromo-4,5-dimethoxybenzyloxy)phenyl]-1-t-butyldimethylsilyloxyethane (**11**)*/2-[4-(2-bromo-4,5-dimethoxybenzyloxy)-phenyl]ethan-1-ol* (**12**): To a stirred suspension of 60% NaH in mineral oil (35 mg, 0.71 mmol) in DMF (5 ml), under argon, 2-[(4-*t*-butyldimethylsilyloxy)phenyl]ethan-1-ol (**6**) (200 mg, 0.79 mmol) was added. This mixture was stirred until hydrogen evolution ceased and then treated with 1-bromo-2-(bromomethyl)-4,5-dimethoxybenzene (**5**) (268 mg, 0.86 mmol) and heated at 60°C for 4 h. The mixture was cooled, poured on to ice, and extracted with ether. The ether extract was washed with water, dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed on silica gel with hexane-ethyl acetate (6 : 1) as eluent to give 52 mg (14%) of product **11** as a colourless oil and 245 mg (84%) of product **12** as a yellow oil. **11**: IR ($CHCl_3$) ν_{max} 2925, 2853, 1606, 1510, 1463 cm^{-1}; ^{1}H NMR δ –0.02 (s, 6H, MeSi), 1.25 (s, 9H, t-BuSi), 2.76 (m, 2H, CH_2), 3.76 (m, 2H, CH_2–OTBS), 3.85 (s, 3H, OMe), 3.88 (s, 3H, OMe), 5.05 (s, 2H, CH_2–O), 6.90 (m, 2H, Ar), 7.05 (m, 2H, Ar), 7.13 (m, 2H, Ar); ^{13}C NMR δ 156.9 (C ipso), 149.1 (C–OMe), 148.6 (C–OMe), 131.9 (C–CHBr), 130.1 (CH meta), 128.4 (C para),



Scheme 6



Scheme 7

115.3 (CH o-Br), 114.7 (CH ortho), 112.5 (C–Br), 111.8 (CH *m*-Br), 69.4 (CH_2–O), 64.7 (CH_2–OTBS), 56.2 (OMe), 56.0 (OMe), 38.7 (CH_2), 29.7 (t-BuSi), 18.3 (C–Si), –5.41 (MeSi); MS (EI) m/z: 425 (M^+–57, 13), 231 (100). Found: C, 57.24; H, 6.87. Anal. Calcd. for $C_{23}H_{33}BrO_4Si$ (480.13): C, 57.37; H, 6.91. **12**: IR ($CHCl_3$) ν_{max} 3528, 2956, 2936, 1608, 1510 cm^{-1}; ^1H NMR δ 2.77 (m, 2H, CH_2), 3.76 (m, 2H, CH_2-OH), 3.82 (s, 3H, OMe), 3.84 (s, 3H, OMe), 5.00 (s, 2H, CH_2O), 6.92 (m, 2H, Ar), 7.02 (br s, 1H, Ar), 7.03 (br s, 1H, Ar), 7.12 (m, 2H, Ar); ^{13}C NMR: δ 156.9 (C ipso), 148.9 (C–OMe), 148.3 (C–OMe), 130.9 (C–CHBr), 129.8 (CH meta), 128.1 (C para), 115.1 (CH o-Br), 114.8 (CH ortho), 112.5 (C–Br), 111.8 (CH *m*-Br), 69.2 (CH_2–O), 63.5 (CH_2–OH), 56.0 (OMe), 55.8 (OMe), 38.1 (CH_2); MS (EI), m/z: 368 (M^+ +1, 2), 231 (100). Found: C, 55.47; H, 5.49. Anal. Calcd. for $C_{17}H_{19}BrO_4$ (366.05): C, 55.60; H, 5.21.

Compound **12** was obtained by desilylation of product **11** as follows: To a solution of ether **11** (277 mg, 0.58 mmol) in dry THF (10 ml) a tetrabutylammonium fluoride solution 1.0 M in tetrahydrofuran (0.84 ml, 0.92 mmol, 1.0 M in THF) was added. After being stirred at room temperature for 3 h, the reaction was quenched by addition of saturated $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated, to give pure product **12** (211 mg, 99%).

2-[4-(2-Bromo-4,5-dimethoxybenzyloxy)phenyl]-1-t-butyldimethylsilyloxyethane **(11)***/4-[2-(2-bromo-4,5-dimethoxybenzyloxy) ethyl]phenol* (**13**): A stirred suspension of 60% NaH in mineral oil (126 mg, 2.58 mmol) in dry THF (10 ml) was treated under argon with 2-[(4-*t*-butyldimethylsilyloxy)phenyl]-ethan-1-ol (**6**) (325 mg, 1.29 mmol). This mixture was stirred until hydrogen evolution ceased and then treated with 1-bromo-2-bromomethyl-4,5-dimethoxybenzene (**5**) (400 mg, 1.29 mmol) and TBAI (cat.) and heated at 60°C for 16 h. The mixture was cooled, neutralised with AcOH, poured on to ice, and extracted with AcOEt. The organic extract was washed with water, dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed on deactivated silica gel with hexane as eluent to give product **11** (77 mg, 61%) and product **13** (110 mg, 23%) as colourless oils. **13**: IR ($CHCl_3$) ν_{max} 3457, 2927, 2847, 1603, 1506 cm^{-1}; ^1H NMR δ 2.88 (m, 2H, CH_2), 3.71 (m, 2H, CH_2–OH), 3.79 (s, 3, OMe), 3.85 (s, 3H, OMe), 4.53 (s, 2H, CH_2–O), 6.75 (m, 2H, Ar), 6.90 (br s, 1H, Ar), 6.98 (br s, 1H, Ar), 7.11 (m, 2H, Ar); ^{13}C NMR δ 154.1 (C ipso), 148.7 (C–OMe), 148.4 (C–OMe), 130.8 (C–CHBr), 130.0 (CH meta), 129.6 (C para), 115.1 (CH o-Br), 115.1 (CH ortho), 112.6 (C–Br), 111.7 (CH *m*-Br), 71.7 (CH_2–O), 71.6 (CH_2–OH), 56.1 (OMe), 55.9 (OMe), 35.3 (CH_2); MS (EI), m/z: 368 (M^+ +1, 32), 367 (M^+, 6), 231 (100). Found: C, 55.87; H, 5.49. Anal. Calcd. for $C_{17}H_{19}BrO_4$ (366.05): C, 55.60; H, 5.21.

2-[4-(2-Bromo-4,5-dimethoxybenzyloxy)phenyl]ethyl acetate (**14**): Alcohol **12** (211 mg, 0.57 mmol) was acetylated with Ac_2O and pyridine at rt for 24 h. The solvents were removed *in vacuo*, and the crude, submitted to chromatography on silica gel eluting with hexane/AcOEt (5: 1) afforded product **14** (219 mg, 93%): IR ($CHCl_3$) ν_{max} 3011, 2936, 2848, 1737, 1607 cm^{-1}; ^1H NMR δ 2.03 (s, 3H, Me), 2.88 (m, 2H, CH_2), 3.85 (s, 3H, OMe), 3.87 (s, 3H, OMe), 4.24 (m, 2H, CH_2–OAc), 5.04 (s, 2H, CH_2–O), 6.93 (m, 2H, Ar), 7.04 (br s, 2H, Ar), 7.14 (m, 2H, Ar); ^{13}C NMR δ 171.0 (OC=O), 157.2 (C ipso), 149.1 (C–OMe), 148.5 (C–OMe), 130.4 (C–CHBr), 129.9 (CH meta), 128.2 (C para), 115.3 (CH *o*-Br), 114.9 (CH ortho), 112.6 (C–Br), 111.9 (CH *m*-Br), 69.4 (OCH_2), 65.1 (CH_2OAc), 56.2 (OMe), 56.0 (OMe), 34.2 (CH_2), 21.0 (Me); MS (EI) *m/z*: 410 (M^+ +1, 1), 229 (100). Found: C, 55.49; H, 5.34. Anal. Calcd. for $C_{19}H_{21}BrO_5$ (408.06): C, 55.76; H, 5.17.

4-[2-(2-Bromo-4,5-dimethoxybenzyloxy)ethyl]phenyl acetate (**15**): Phenol **13** (40 mg, 0.11 mmol) was acetylated with Ac_2O and piridine as above to give after chromatography on silica gel eluting with hexane/AcOEt (5 : 1) afforded product **15** (23 mg, 52%) isolated as a colourless oil: IR ($CHCl_3$) ν_{max} 2933, 2852, 1760, 1603, 1507 cm^{-1}; ^1H NMR δ 2.29 (s, 3H, Me), 2.94 (m, 2H, CH_2), 3.74 (m, 2H, CH_2), 3.80 (s, 3H, OMe), 3.85 (s, 3H, OMe), 4.53 (s, 2H, CH_2–O), 6.90 (s, 1H, Ar), 6.99 (s, 1H, Ar), 7.00 (m, 2H, Ar), 7.25 (m, 2H, Ar); ^{13}C NMR δ 169.5 (OC=O), 149.0 (C ipso), 148.7 (C–OMe), 148.4 (C–OMe), 136.6 (C), 129.9 (CH meta OAc), 129.6 (C para), 121.3 (CH ortho OAc), 115.2 (CH *o*-Br), 112.5 (C–Br), 111.7 (CH meta Br), 71.8 (OCH_2), 71.2 (OCH_2), 56.1 (OMe), 56.0 (OMe), 35.7 (CH_2), 21.1 (Me); MS (EI), *m/z*: 410 (M^+ + 1, 31), 409 (M^+, 7), 366 (M^+ –43, 15), 229 (100). Found: C, 55.62; H, 5.28. Anal. Calcd for $C_{19}H_{21}BrO_5$ (408.06): C, 55.76; H, 5.17.

Reaction of compounds **9** *and* **16**: A stirred suspension of 60% NaH in mineral oil (312 mg, 6.37 mmol) in dry THF (10 ml) was treated under argon with (2-bromo-4,5-dimethoxyphenyl)methanol (**9**) (524 mg, 2.12 mmol). This mixture was stirred until hydrogen evolution ceased and then treated with 4-(2-bromoethyl)phenol (**16**) (427 mg, 2.12 mmol) and refluxed for 16 h. The mixture was cooled, poured on to ice, and extracted with ether. The ether extract was washed with water, dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed on silica gel with hexane–dichloromethane–ethyl acetate (7 : 7 : 1) as eluent to give products **13** (190 mg, 24%) and 2-bromo-4,5-dimethoxybenzaldehyde (**8**) (10 mg, 2%).

[(2-Bromo-4,5-dimethoxybenzyl)oxy]-t-butyldimethylsilane **(18)***/4-[2-(4-vinylphenoxy)ethyl]phenol* (**19**): A stirred suspension of 60% NaH in mineral oil (48 mg, 0.98 mmol) in dry THF (10 ml) was treated under argon with [4-(2-bromoethyl)phenoxy] (*t*-butyl)dimethylsilane (**17**) (155 mg, 0.49 mmol). This mixture was stirred until hydrogen evolution ceased and then treated with (2-bromo-4,5-dimethoxyphenyl)methanol (**9**) (122 mg, 0.49 mmol) and heated at 60°C for 16 h. The mixture was cooled, poured on to ice, and extracted with AcOEt. The organic extract was washed with water, dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed on silica gel with hexane–ethyl acetate (15 : 1) as eluent to give product **18** (62 mg, 34%), and compound **19** (15 mg, 13%) as a colourless oils. **18**: IR ($CHCl_3$) ν_{max} 3427, 2949, 2930, 2856, 1603, 1505 cm^{-1}; ^1H NMR δ 0.14 (s, 6H, MeSi), 0.97 (s, 9H, *t*-BuSi), 3.86 (s, 3H, OMe), 3.88 (s, 3H, OMe), 4.68 (s, 2H, CH_2), 6.98 (s, 1H, Ar), 7.13 (s, 1H, Ar); ^{13}C NMR δ 148.4 (C–OMe), 148.2 (C–OMe), 132.4 (*C*–CH_2), 115.0 (CH Ar), 110.6 (CH Ar), 110.5 (C–Br), 64.2 (CH_2), 56.2 (OMe), 55.8 (OMe), 25.9 (*t*-BuSi), 18.3 (C–Si), –5.3 (2 CH_3Si); MS (EI) *m/z*: 361 (M^+, 95), 246 (M^+-115, 31), 75 (100). Found: C, 49.57; H, 7.03. Anal. Calcd. for $C_{15}H_{25}BrO_3Si$ (360.08): C, 49.86; H, 6.97. **19**: IR ($CHCl_3$) ν 3369, 2929, 1606, 1510 cm^{-1}; ^1H NMR δ 3.05 (m, 2H, CH_2), 4.15 (m, 2H, CH_2), 5.14 (dd, 1H, *J* = 1.0, 10.9 Hz, =CHH), 5.63 (dd, 1H, *J* = 1.0, 17.6 Hz, =CH*H*), 6.68 (dd, 1H, *J* = 10.9, 17.6 Hz, CH=CH_2), 6.81 m, 2H, Ar), 6.87 (m, 2H Ar), 7.18 (m, 2H Ar), 7.36 (m, 2H Ar); ^{13}C NMR δ 158.6 (C–O), 154.1 (C–OH), 136.2 (*CH*=*CH*$_2$), 130.5 (C), 130.3 (C), 130.1 (CH ortho OH), 127.4 (CH meta O), 115.3 (CH ortho O), 114.5 (CH meta OH), 111.5 (=CH_2), 68.9 (OCH_2), 34.8 (CH_2); MS (EI) *m/z*: 240 (M^+, 12), 121 (100). Found: C, 79.72; H, 6.68. Anal. Calcd. for $C_{16}H_{16}O_2$ (240.12): C, 79.97; H, 6.71.

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