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SYNTHESIS OF 8-SUBSTITUTED 1-NAPHTHYLAMINE DERIVATIVES. EXCEPTIONAL REACTIVITY OF THE SUBSTITUENTS.

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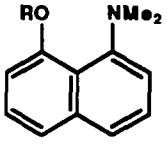
Abstract. *8-Lithio-1-N, N-dimethylaminonaphthalene has been prepared, and converted in good yield to the 8-CHO, $COCH_3$, $n\text{-}Bu_2B$ and OH derivatives. The peri-relationship confers special reactivity on both 1 and 8 substituents: the aldehyde (5) is largely ring-closed in acid, the borane (9) is inert to oxidation because of the B→N interaction, and the 8-methoxymethyl NMe_3^+ derivative is formed only with difficulty, and readily demethylated.*

Hetero-atom directed lithiation has been used for the construction of aromatic systems with otherwise difficult patterns of substitution.[1-3] In naphthalene systems lithiation of 1-substituted compounds allows both 2 and 8-regioproducts to be obtained, though - with one exception [4]- yields of the latter are poor. Some rationalisation of the observed regioselectivity is possible, in that strongly activating directing groups appear to favour kinetic lithiation.[2] Typical conditions involve the use of *n* or *sec*-BuLi in THF at low temperatures, often in the presence of TMEDA - thought to enhance reactivity by breaking up alkyllithium oligomers.[5] When *n* or *t*-BuLi is used in ether or hydrocarbon solvents at room temperature with long reaction times, 8-lithiation results. A good yield of 8-lithio-1-(N,N-dimethylamino)methyl naphthalene is obtained under these conditions.[4]

We needed the acetal **1** for use in another investigation. The parent aminonaphthol **2** has been prepared previously in very low yield,[6] by a method which failed repeatedly in this laboratory. We describe an improved and reproducible synthesis of **2**, and the special chemistry of a series of 8-substituted-1-naphthylamine derivatives prepared in the course of this work.



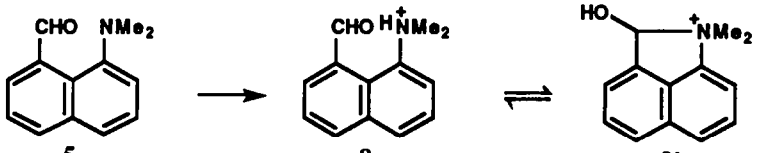
1, R = CH_3OCH_2
2, R = H

Results and Discussion.

We learned from Narasimhan[7] that N,N-dimethyl-1-naphthylamine can be lithiated regioselectively in the 8-position, and have confirmed this result by a ^{1}H NMR study. Irradiation of the N-CH_3 singlet of N,N-dimethyl-1-naphthylamine at 2.96 ppm resulted in positive nuclear Overhauser effects on signals at δ 8.35 - 8.11 (1H, m) and 7.14 (1H, dd, J 7.0 and 1.5Hz). These J-values are typical for $H_{2,3}$ and $H_{2,4}$ couplings in naphthalene systems,[8] and confirm the assignment [9] of the higher field proton as H(2) (cf. the reported chemical shift of 6.92 ppm.[9]) The lower field proton is thus H(8).

When treated with *n* -butyllithium (4.5 equivalents of a 1.7M solution in hexane) in diethyl ether, N,N-dimethyl-1-naphthylamine gave an anion, which was quenched with d_4-methanol to give a product in which the H(8) resonance was reduced to about 20% of its original intensity. We conclude that lithiation gives about 80% of the 8-Li compound **3**. Quenching with benzophenone is known to give the alcohol **4**.[7]

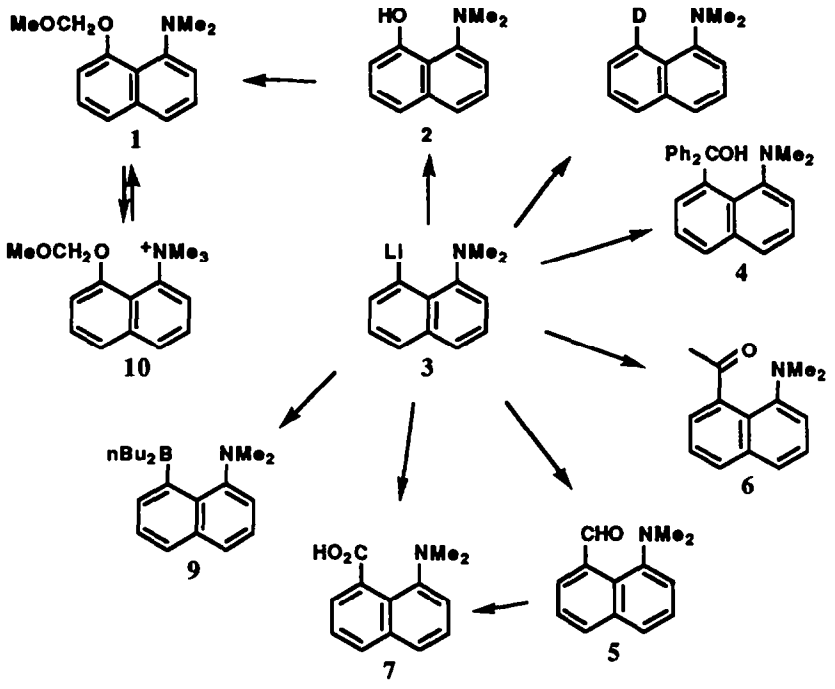
Our initial approach to **2** involved the introduction of an 8-substituent which could subsequently be oxidised to OH. Quenching the anion **3** with dimethylformamide or acetic anhydride gave the aldehyde **5** and the methyl ketone **6** in 76 and 70% yields, respectively. However, Baeyer-Villiger oxidation (*m*CPBA/CH_2Cl_2/reflux[10]) of **6** produced only the acid **7**. Dakin oxidation (H_2O_2/NaOH/MeOH[11]) of the aldehyde gave the same result. Methyl ketone oxidation under strongly acidic conditions ($CF_3CO_3H/CH_2Cl_2/H_2PO_4^-$ [12])was not followed up when we found that the aminoaldehyde **5** exists in acid (10% CF_3CO_3D in $CDCl_3$) predominantly as the cyclic aminal **8b** (*ca.* 2:1 mixture with the conjugate acid of **5**, as shown by NMR: see Figure). As discussed below, a major effect of *peri*-strain is a strong preference for sp^2 at the expense of sp^3-hybridised centres, making unfavourable addition of all but a neighbouring group nucleophile or electrophile. Ketone **6** and acid **7** have been prepared by Dunitz *et al.* by less direct routes.[13]



5 **8a** **8b**

We next attempted an organoborane-mediated conversion. Rapid addition of a solution of the anion **3** to BF_3-etherate (10 equivalents) at -78° unexpectedly gave the borane **9** in 17% yield. This compound proved totally inert to oxidation over long periods, even under forcing conditions. [14] The ^{1}H NMR chemical shift of the N-CH_3 signal (δ 2.90 in $CDCl_3$) is not consistent with a full N^+-B^- bond; but the ^{11}B NMR suggests significant coordination of N to B. The boron resonance in **9** appears at 9.13 ppm (downfield of BF_3 etherate), at much higher field than that in $PhBMe_2$ (77.6 ppm).[15] A conformation in which the nitrogen lone pair is directed at the boron will relieve *peri*-strain as well as allowing the Lewis acid-base

interaction shown (**9**). Unfortunately the crystals of **9** that we could obtain were not suitable for X-ray structural analysis.



Scheme

The target aminonaphthol **2** was eventually prepared quite simply, by Gilman oxidation of the 8-Mg derivative. Transmetallation of the Li derivative **3** with *n*-BuMgCl, followed by direct oxygenation (O_2 passed for 4h at -4 → 0°C)[16] gave **2** directly, in 51% yield.

The aminonaphthol was converted to the desired acetal (**1**, 67%) by refluxing with NaH and reacting the anion produced with methoxymethyl chloride. Kinetic studies on the hydrolysis of this compound are reported elsewhere.[17] It is notable for the exceptional efficiency of intramolecular general acid catalysis by the Me_2NH^+ group; and for its high pK_a (7.4) - evidence that the Me_2N group is twisted out of the plane of the aromatic ring.

In order to estimate the rate enhancement attributable to intramolecular general acid catalysis by the Me_2NH^+ group in the hydrolysis of **1**, we needed a comparison with an acetal lacking the NH^+ proton, but otherwise as close as possible in structure to **1**. The obvious model is the Me_3N^+ compound (**10**), so we attempted to quaternise the tertiary amino-group of **1**. The usual methods failed. Only after stirring in dichloromethane for 18h with trimethyloxonium tetrafluoroborate [18] did methylation occur. Removal of solvent gave a crystalline solid with the ^1H NMR expected for **10**. However, the desired comparison of reactivity was still not possible, because **10** is N-demethylated faster that its acetal group is

hydrolysed. Attempted purification, by dissolving **10** in water made weakly basic by adding triethylamine regenerated the starting aminoacetal **1** within 30 minutes.

This remarkably easy dealkylation is evidently driven by the relief of ground state strain: forcing conditions are usually necessary for the dealkylation of N-methylammonium compounds.[19-21] Strain is similarly a factor in the initial alkylation of **1**, as in other unusually difficult quaternisations.[22,23] *Peri*-strain has been recognised [24] in unsymmetrical 1,8-disubstituted naphthalenes as the cause of restricted rotation of the substituents, when one is sp^2 and the other sp^3-hybridised. When *both* are sp^3-hybridised (cf. **1** → **10**) the phenomenon is no longer observed: not because strain is reduced, but because the whole naphthalene nucleus has twisted to relieve the *peri*-interaction. *Peri* *t*-butyl groups, for example, are staggered by over 40°, one above and one below the mean plane of the ring system.[25] Presumably similar distortion occurs when the NMe_2 group of **1** is quaternised.

Experimental

8-Lithio-N,N-dimethyl-1-naphthylamine (3). *n*-Butyllithium (2.7 ml of a 1.7 M solution in hexane)was added in a continuous stream to a stirred solution of N,N-dimethyl-1-naphthylamine (*caution: possible carcinogen*, 0.17 g) in dry ether (2 ml) under argon at room temperature. After 48 hours lithiation was complete; details of quenching procedures are described below.

8-Deuterio-N,N-dimethyl-1-naphthylamine. d_4-Methanol (0.27 ml) was added to a solution of the anion (**3**,1 mmol) under argon at 0°C. After 15 min, deuterium oxide (0.2 ml) was added and the mixture allowed to warm to room temperature. The ethereal layer was removed with a pipette, passed through a short column of anhydrous sodium sulphate, and evaporated under reduced pressure. The yield of the deuteriated product was about 80%, as determined by ^1H NMR (see text).

8-Dimethylamino-1-naphthalenecarboxaldehyde (5). A solution of dry dimethylformamide (0.85 ml) in ether (5 ml) was added dropwise to a solution of the anion **3** (1.76 mmol) at -78°C. The mixture was allowed to warm to -20°C over 4 hours, then quenched with a solution of methanol (0.33 ml) in ether (1.7 ml) and allowed to warm to room temperature. The tan suspension was diluted further with ether (10 ml), washed with water (3 x 10 ml) and with brine (1 x 10 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed using 25% ether-hexane as eluant to afford the aldehyde (**5**, 0.27 g, 76%) which crystallised from hexane as plates, m.p. 86-87°C (Found: C, 78.5; H, 6.50; N, 7.0. $C_{13}H_{13}NO$ requires C, 78.4; H, 6.60; N, 7.05%). R_F (25% ether-hexane) 0.25, ν_{max} ($CHCl_3$) 1 660 cm^{-1}(C=O), δ_H(CD_2Cl_2) 10.69 (1H, s, CHO), 7.94-7.90 (1H, m), 7.68-7.65 (1H, m), 7.53-7.47 (3H, m), 7.37-7.33 (1H, m), 2.69 (6H, s, N-Me). Found: M^+, 199.0991. ($C_{13}H_{13}NO$ requires M^+, 199.0997), *m/z* 199 (60%, M^+), 170 (100, *M*-CHO).

1-Acetyl-8-dimethylaminonaphthalene (6). The ketone was prepared by the method described above except that a solution of acetic anhydride (1.05 ml) in ether (5 ml) was used to quench the anion. Column chromatography using 33% ether-hexane as eluant afforded the ketone (**6**, 0.27 g, 67%), which crystallised from hexane as plates, m.p. 107-108°C.[13] (Found:

C, 78.5; H, 7.30; N, 6.45%. $C_{14}H_{15}NO$ requires C, 78.8; H, 7.10; N, 6.55%). R_F (33% ether-hexane) 0.30, ν_{max} ($CHCl_3$) 1 720 cm^{-1}(C=O), δ_H($CDCl_3$) 7.81 (1H, dd, J 8.2 and 1 Hz), 7.64 (1H, dd, 10.6 and 1 Hz), 7.50-7.42 (2H, m), 7.31 (1H, dd, 7.4 and 1.1 Hz), 7.24 (1H, dd, 6.8 and 0.9 Hz), 2.64 (6H, v. broad peak resolving at 233 K into 2.79, 3H, s, and 2.29, 3H, s) and 2.34 (3H, s). (Found: M^+, 213.1140. $C_{14}H_{15}NO$ requires M^+, 213.1154), *m/z* 213 (100%, M^+), 198 (30, *M*-Me), 195 (40, *M*-H_2O).

8-Dimethylamino-1-naphthalenecarboxylic acid (7). A solution of the anion (**3**, 1 mmol) was transferred via a double-ended needle into a mechanically-stirred slurry of solid carbon dioxide (20 g) in ether (50 ml) in a continuous stream. Upon completion of the transfer, the slurry was allowed to warm to room temperature and evaporated under reduced pressure. The residue was taken up in dichloromethane (20 ml) and washed with a buffer of pH 4 (3 x 20 ml). The pH of the aqueous phase was adjusted to 3, extracted with dichloromethane (3 x 10 ml) and the organic extracts dried ($MgSO_4$), and evaporated. The residue was flash-chromatographed with ethyl acetate as eluant to remove unreacted starting material; changing the eluant to 25% methanol-ethyl acetate allowed the isolation of the acid (**7**, 0.1 g, 47%) which was crystallised (with extreme difficulty) from 50% ether-hexane as needles, m.p. 100-101°C,[13] R_F (25% MeOH-EtOAc) 0.60, ν_{max}(CCl_4) 3 300- 2 400 (O-H), 1 680 cm^{-1}(C=O), δ_H($CDCl_3$, 90 MHz) 16.0 (1H, br. s, exchanged with D_2O, COOH), 8.73 (1H, dd, J 9 and 1.5 Hz), 8.06 (1H, dd, 9 and 1.5 Hz), 7.95 (1H, dd, 6 and 3 Hz), 7.80-7.50 (3H, m) and 2.93 (6H, s). (Found: M^+, 215.0928. $C_{13}H_{13}NO_2$ requires 215.0946), *m/z* 215 (100%, M^+) 170 (80, *M*-CO_2, H^+).

(**7**) was also the major product from the following reactions.

Baeyer-Villiger oxidation of (5). *m*-Chloroperbenzoic acid (0.865 g) was added to a solution of the aldehyde (**5**, 0.199 g) in dichloromethane (10 ml) under nitrogen at reflux; after 1 hour, TLC analysis showed the consumption of starting material was complete. The mixture was washed with phosphate buffer (pH 6.5), the organic phase dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed with 25% methanol-chloroform containing 1% triethylamine as eluant to yield the acid (**7**, 0.14 g, 65%).

Dakin oxidation of (5). Hydrogen peroxide (0.08 ml of a 30% w/v solution) was added to a solution of the aldehyde (0.04 g) in deuteriomethanol (0.5 ml) containing aqueous sodium hydroxide (0.06 ml of a 3M solution) in an NMR tube. After 30 min at room temperature, consumption of the aldehyde was indicated by TLC and by the NMR spectrum of the mixture which contained resonances identical to those in a spectrum of pure (**7**).

Attempted preparation of the trifluoroacetate salt (8a). Trifluoroacetic acid (1 ml) was added to a solution of the aldehyde (**5**, 0.116g) in ether (15 ml) containing chloroform (3 ml). After 15 min, the solvent was evaporated under reduced pressure to afford an oil, (0.183 g, 100%), δ_H ($CDCl_3$, 60 MHz) 12.2 (1H, br.s, exchanged with D_2O), 7.9-7.3 (6H, m), 7.0 (1H, br.s) and 3.4 (6H, br.s). When the aldehyde (**5**) was dissolved in 10% d_1-TFA/$CDCl_3$ and the spectrum recorded at 250 MHz, a different result was obtained, indicating a mixture of (**8a**) and (**8b**). This spectrum is shown in the Figure.

(8-Dimethylamino-1-naphthyl)-di-n-butylborane (9).
Boron trifluoride etherate (2.84 g) was added rapidly to a solution of **3**, (2 mmol) at -78°C. After 15 min. effervescence and precipitation of lithium fluoride had ceased, and the resulting clear solution was allowed to warm to room temperature. Aqueous sodium hydroxide (5 ml of a 3M solution) was added, followed by water (100 ml), and the mixture extracted with ether (3 x 50 ml). The combined extracts were washed with water (50 ml), dried ($MgSO_4$) and evaporated under reduced pressure. Baseline material was removed on a short column with 33% ether-hexane as eluant, affording a mixture of two close-running spots, which were separated by multiple-elution PTLC with hexane as eluant. The faster-running band was recrystallised from aqueous ethanol to yield the borane (**9**) as needles (0.099 g, 17%), m.p. 67-68°C. (Found: C, 81.5; H, 10.15; N, 4.75%. $C_{20}H_{30}BN$ requires C, 81.3; H, 10.25; N, 4.75%). R_F (33% ether-hexane) 0.45, ν_{max} ($CHCl_3$) 1 610, 1 590, 1 460 cm^{-1}(all Ar-H bending), δ_H($CDCl_3$) 9.13 (broad signal), 7.72-7.18 (6H, m), 2.90 (6H, s, N-Me), and 1.31-0.44 (18H, m, *n*-Bu), *m/z* (FAB), 296 (M^++1), 238, 182, 167, *m/z* (EI) 238 (80%, M-C_4H_9), 182(100, $C_{12}H_{14}BN$).

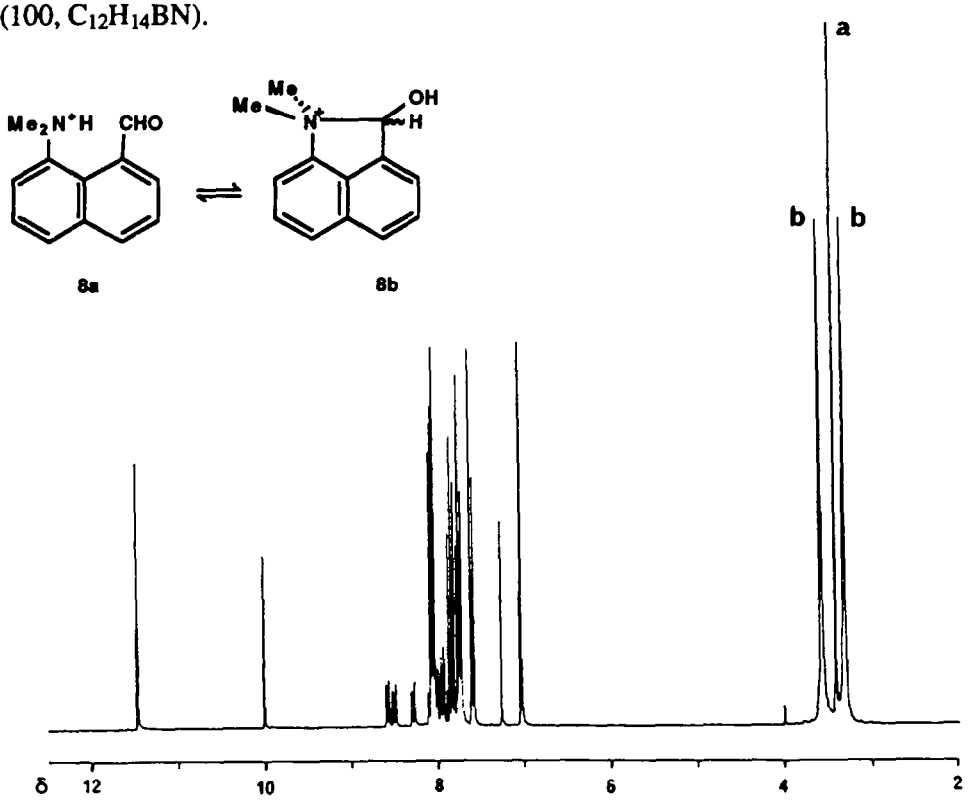


Figure. 250 MHz ^1H NMR spectrum of **5** in trifluoroacetic acid. Note: (a) the single N-methyl peak for **8a**, (b) the two diastereotopic methyls of **8b**; the aldehyde proton of **8a** at δ 10, and the methine proton of the cyclic carbinolamine **8b** at δ 7.0.

Attempted oxidation of the borane (9). After the method of Hawthorne,[14] the crude product from the reaction between boron trifluoride etherate (2.84 g) and the anion (**3**, 2 mmol), was evaporated under reduced pressure and taken up in methanol (10 ml) under an atmosphere of nitrogen. The solution was treated with aqueous sodium hydroxide (1.2 ml of a 3M solution) and aqueous hydrogen peroxide (1.6 ml of a 30% solution) at 0°C, upon which no visible reaction occurred. The solution was allowed to warm to room temperature and stirred for 1 hour, refluxed for a further hour, then poured into water (40 ml), extracted with dichloromethane (4 x 70 ml) and the combined organic extracts washed with water (100 ml) and dried ($MgSO_4$). Removal of solvent under reduced pressure yielded an oil from which crystals of boric acid were obtained upon trituration with hexane. Organic products were separated as described above.

8-Dimethylamino-1-naphthol (2). After the method of Campaigne *et al.*,[16] a solution of the anion (**3**, 0.016 mol) was cooled to 0°Cand *n*-butylmagnesium chloride (34 ml of a 2M solution in ether) added so that the temperature remained constant. After 20 min, the solution was cooled further to -5°C and maintained at this temperature for 4 hours while dry oxygen was passed with stirring. The mixture was poured into water (100 ml) containing glacial acetic acid (10 ml) and zinc powder (1 g) and the two phases stirred until effervescence had ceased, by which time the aqueous phase was neutral. The flocculated zinc was filtered off, the phases separated and the ethereal layer washed with saturated sodium hydrogen carbonate solution (3 x 50 ml) and then with water (50 ml) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to yield an oil which was chromatographed using 17% ether-hexane as eluant (after pre-absorbing the crude product mixture onto silica) to yield the aminonaphthol (**2**, 1.52 g, 51%). Recrystallisation from methanol gave plates, m.p. 58-59°C (lit.[6] 57-58°C), R_F (33% ether-hexane) 0.32, ν_{max} ($CHCl_3$) 3 500-2 200 (O-H), 1 610, 1 600 and 1 590 cm^{-1} (all Ar-H), δ_H ($CDCl_3$) 14.39 (1H, br.s, slow exchange with D_2O), 7.66 (1H, dd, 7.8 and 1.6 Hz), 7.41-7.26 (4H, m), 6.86 (1H, dd, 7.5 and 1.3 Hz) and 2.83 (6H, s). Irradiation of the N-Me resonance at 2.83 ppm results in a positive nOe on signals at 14.39 ppm and on a signal in the four proton multiplet, allowing the 6.86 ppm resonance to be assigned as H(2). (Found: M^+, 187.0993. $C_{12}H_{13}NO$ requires *M*, 187.0997), *m/z* 187 (100%, M^+), 172 (40, *M*-Me).

8-Methoxymethoxy-N,N-dimethyl-1-naphthylamine (1).

A solution of the aminonaphthol (**2**, 0.374 g) in THF (2 ml) was added to a suspension of sodium hydride (0.12 g of a 60% dispersion in mineral oil, washed once with dry pentane) in THF (8 ml) at reflux under argon. After 18 hours, chloromethyl methyl ether (*caution*: *carcinogen*, 0.242 g) was added dropwise and the mixture stirred at reflux for 1 hour, allowed to cool and poured into dilute sodium hydrogen carbonate solution (20 ml). The mixture was extracted with dichloromethane (4 x 10 ml) and the combined extracts dried (K_2CO_3) and evaporated under reduced pressure. The residue was chromatographed on alumina (UG1) with 33% ether-hexane as eluant to afford the acetal (**1**, 0.308 g, 67%), R_F (33% ether-hexane.) 0.37, ν_{max}($CDCl_3$) 1 610, 1 590 and 1 570 cm^{-1} (all Ar-H), δ_H ($CDCl_3$, 90 MHz) 7.70-7.10 (6H, m), 5.25 (2H, s), 3.65 (3H, s) and 2.90 (6H, s). (Found: M^+, 231.1263. $C_{14}H_{17}NO_2$ requires M^+, 231.1259), *m/z* 231 (60%, M^+), 199 (100, *M*-Me).

8-Methoxymethoxy-N,N,N-trimethyl-1-naphthylammonium tetrafluoroborate (10).

Trimethyloxonium tetrafluoroborate (0.032 g) was added to a solution of the acetal (**1**) (0.050 g) in dichloromethane (2 ml) and the mixture stirred for 18 hours in the dark at room temperature. Evaporation of the solvent under reduced pressure afforded the salt (**10**), $\delta_H(CDCl_3\text{-}CD_3OD)$ 8.20-7.95 (2H, m), 7.85-7.50 (4H, m), 5.70 (2H, s), 3.65 (3H, s) and 3.50 (9H, s).

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