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FUNCTIONALISATION OF 2-METHOXY-6-METHYLPYRIDINE

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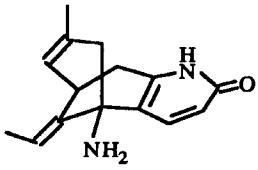
ABSTRACT : Selective bromination of 2-methoxy-6-methylpyridine **2** afforded 5-bromo-2-methoxy-6-methylpyridine **8**. Deprotonation of this pyridine derivative in benzylic position or lithium-bromine exchange allowed the regio-selective introduction of various electrophiles.

Introduction

Interest has recently been stimulated in the synthesis of the Lycopodium alkaloid, Huperzine A **1**, [1,2] a powerful acetylcholinesterase inhibitor, and analogues for structure-activity studies in the treatment of Alzheimer's disease. Novel methods of synthesis are therefore desired, one such approach is the functionalisation of 2-methoxy-6-methylpyridine **2**, the O-protected form of the 6-methyl-2-pyridone at its benzylic and C-5 positions.We describe in the present paper several approaches concerning the syntheses of compound **3**, a useful intermediate in the syntheses of Huperzine A **1** by Kozikowski [1] and by Quian[2], of the tricyclic compound **4**, a simplified analogue of Huperzine A **1**, and of its seco derivative **5**.



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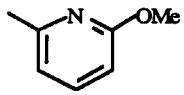

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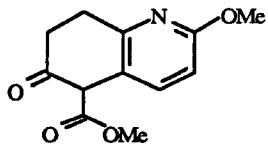

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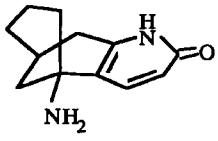

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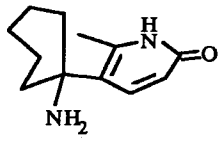
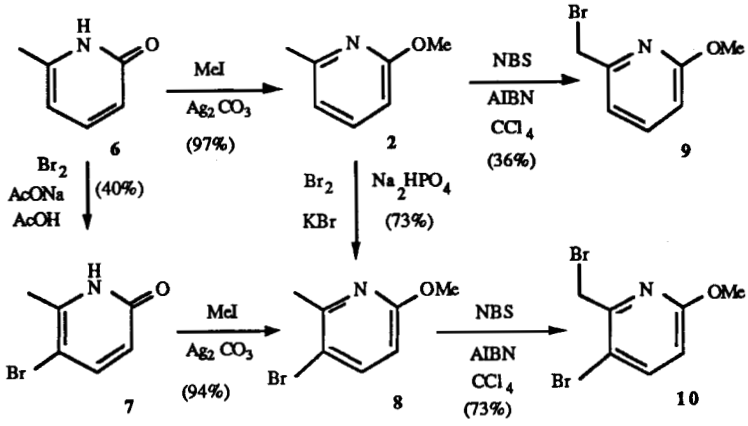


5

(i) Preparation of 5-bromo-2-methoxy-6-methylpyridine 8

Pyridine derivative **8** had been previously prepared from 2-amino-6-methylpyridine in 37% overall yield.[3,4] A more efficient preparation of **8** was required. In a first study, bromination of the commercially available 2-hydroxy-6-methylpyridine (Br_2, AcONa, AcOH, 25°C) gave a mixture of the 5-bromo-6-methyl-2-pyridone (40%), 3-bromo-6-methyl-2-pyridone (14%) and 3, 5-dibromo-6-methyl-2-pyridone (14%). O-Methylation of 5-bromo-6-methyl-2-pyridone afforded 5-bromo-2-methoxy-6-methylpyridine **8** (94%, 38% overall).[4] A more efficient alternative route was provided by initial O-methylation of 2-hydroxy-6-methylpyridine (97%) then bromination of **2** under controlled conditions to give; (a) in the presence of 1M KBr,[5] 5-bromo-2-methoxy-6-methylpyridine **8** (82%), along with 3,5-dibromo-2-methoxy-6-methylpyridine (7%), (b) in the presence of 0.15M Na_2HPO_4, 5-bromo-2-methoxy-6-methylpyridine **8** (73%) along with 3-bromo-2-methoxy-6-methylpyridine (5%).This modification suppressed the formation of the dibrominated product.

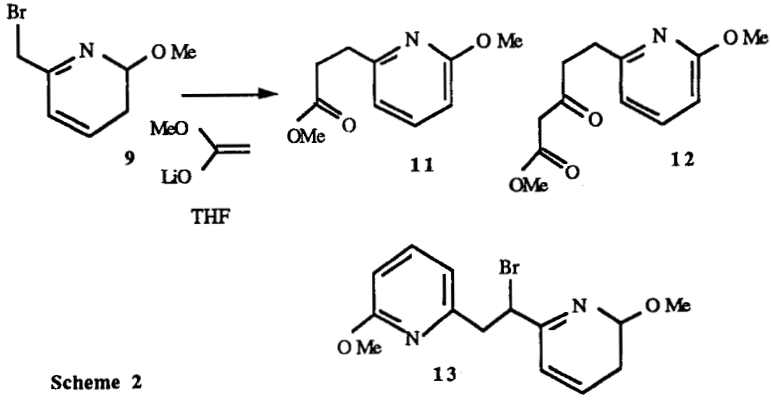
Bromination of 2-methoxy-6-methylpyridine **2** using NBS in CCl_4 gave a mixture of 6-bromomethyl-2-methoxypyridine **9** (36%) and 6-dibromomethyl-2-methoxypyridine (15%).[6] Similarly bromination of 5-bromo-2-methoxy-6-methylpyridine **8** under the same conditions gave a mixture of 5-bromo-6-bromomethyl-2-methoxypyridine **10** (73%) and 5-bromo-6-dibromomethyl-2-methoxypyridine (8%).(Scheme 1)



Scheme 1

(ii) Nucleophilic functionalisation of 6-bromomethyl-2-methoxypyridine 9

Reaction of 6–bromomethyl-2-methoxypyridine **9** with the anion of methyl acetate gave ester **11** (46%) and keto-ester **12** (25%), the latter is of interest as cyclisation would provide a key intermediate **3** in the synthesis of Huperzine A .[1,2] Use of excess anion (4eq) gave keto-ester **12** (31%) and coupling product **13** (37%). Surprisingly, treatment of 5-bromo-6-bromomethyl-2-methoxy-6-methylpyridine **10** with the anion of methyl acetate gave none of the analogous products to **9**.(Scheme 2)



Scheme 2

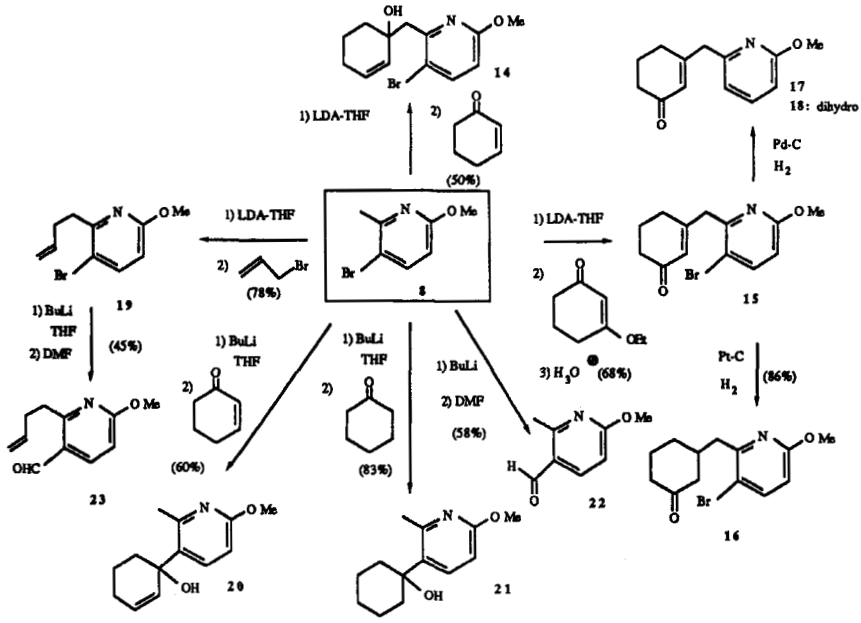
(iii) Electrophilic benzylic and aromatic functionalisation of 5-bromo-2-methoxy-6-methylpyridine 8

Deprotonation of **8** with two equivalents of LDA at -78°C in THF allowed the formation of the benzylic anion; thus treatment of the latter with 2-cyclohexen-1-one gave only the product of 1,2-addition, **14** in 50% yield.

Ketone **16** was required for studies of the synthesis of the [3,3,1] ring system present in Huperzine A **1** and in the tricyclic analogue **4**. The problem of the sought after 1,4-addition to 2-cyclohexen-1-one was overcome by reaction with 3-ethoxy-2-cyclohexen-1-one, followed by acidic work up to give the enone **15** (68%). Selective hydrogenation in the presence of Pt/C in MeOH gave the desired ketone **16** (86%). As an indication of regioselective reduction, hydrogenation in the presence of Pd/C gave the debrominated enone **17** (54%) and on continuation the ketone **18** (22%). When allyl bromide was used as an electrophile **19** was obtained in 78% yield. It is of interest that in the presence of LDA (1eq) no alkylation products were observed with electrophiles.(Scheme 3)

Unexpectedely, reaction of 3,5-dibromo-2-methoxy-6-methylpyridine with various amounts of LDA, followed by addition of electrophiles gave no addition products. Treatment of 2-methoxy-6-methylpyridine **2** with LDA or ^{n}BuLi (1eq), followed by electrophiles also gave no alkylation. In some cases on using more than 1eq of base a small amount of addition product was obtained (5-10%). In this later case, the unexpected poor reactivity of 2-methoxy-6-methylpyridine can be due to the absence bromine substituant in position 5 and by the presence of a methoxy group in position 2.

Treatment of 5-bromo-2-methoxy-6-methylpyridine **8** with ^{n}BuLi (1eq) at -78°C THF led to rapid lithium-bromine exchange, then addition of an electrophile gave 5-substituted products[7,8]. Thus addition of 2-cyclohexen-1-one gave the 1,2-addition product **20** (60%) and cyclohexanone afforded **21** (83%). Use of DMF as the electrophile gave 5-formyl-2-methoxy-6-methylpyridine **22** (58%). Protection of the aldehyde **22** as the dioxolane and attempted alkylation at the 6-methyl position proved unsuccessful. Treatment of 5-bromo-6-(3-butenyl)-2-methoxy-pyridine **19** with ^{n}BuLi (1eq) at -78°C in THF, followed by DMF (2eq) gave 5-formyl-6-(3-butenyl)-2-methoxypyridine **23** (45%) in better yield than by reacting **19** with lithium and DMF in THF under ultrasonic conditions (17%).



Scheme 3

Conclusion

5-Bromo-2-methoxy-6-methylpyridine **8** proved to be a versatile synthon in the synthesis of various intermediates designed for the synthesis of Huperzine A **1** and analogues. Peculiarly combination of deprotonation at the benzylic carbon and of lithium-bromine exchange at position 5 showed it to be a powerful equivalent of 6-methyl-2-pyridone **6**, a well known ambident nucleophile.[10]

Experimental

2-Methoxy-6-methylpyridine 2

2-Hydroxy-6-methylpyridine (2.96g, 0.0271mol), silver carbonate (10.1g, 0.366mol) and iodomethane (17.4ml, 0.279mol) were stirred in chloroform (100ml) protected from light for 40h (until all the starting material was consumed). The mixture was filtered through a silica pad and washed(Et_2O). The solvent was removed (rotary evaporator <20°C) to give 2-methoxy-6-methylpyridine[9] **2**

(3.24g, 97%) as a colourless oil ; ν_{max} (film) 1585m, 1462s, 1420w, 1295m, 1040w and 800m; ^{1}H nmr (200MHz, $CDCl_3$) 7.43 (1H, d J=8.3, 8.3Hz, Ar-H), 6.69 (1H, d J=8.3Hz, Ar-H), 6.51 (1H, d J=8.3Hz, Ar-H), 3.89 (3H, s, OCH_3) and 2.40 (3H, s, CH_3); ^{13}C nmr (62.9MHz, $CDCl_3$) 159.1, 148.4, 138.7, 115.7, 107.0, 53.2 and 24.1; m/z 123 (M^+, 67%), 122(100), 93 (95), 66 (43), 53 (15) and 39 (50).

5-Bromo-2-methoxy-6-methylpyridine 8

(i) 2-Methoxy-6-methylpyridine **2** (1.02g, 8.29mmol), potassium hydroxide (0.232g, 4.14mmol) and Et_4NCl (20mg) in 1M aqueous KBr (50ml) was treated dropwise over 1h with bromine (1.33g, 8.29mmol) in 1M aqueous KBr (50ml) and was stirred for 20h (yellow colouration dissipated). The mixture was extracted (CH_2Cl_2), the organic phase dried ($MgSO_4$) and the solvent was removed (<25°C) to give a colourless oil. Flash column chromatography (2.5% EtOAc/pentane) gave a *5-bromo-2-methoxy-6-methylpyridine* **8** (1.09g, 65% (isolated); 1.37g, 82% (by ^{1}H nmr)) as a colourless oil; [4] m.p. just below room temperature ; ν_{max} (film) 2950w, 1581s, 1467s, 1423s, 1315s, 1254m, 1127w, 1044m, 995w and 650m; ^{1}H nmr (200MHz, $CDCl_3$) 7.57 (1H, d J=8.8Hz, Ar-H), 6.43 (1H, d J=8.8Hz, Ar-H), 3.86 (3H, s, OCH_3) and 2.52 (3H, s, CH_3); ^{13}C nmr (62.9MHz, $CDCl_3$) 162.5, 154.4, 144.1, 142.1, 111.9, 109.6, 53.7 and 24.7; m/z 202/200 (M^+, 100/99%), 174/172 (26/22) and 92 (9) as well as 3,5-dibromo-2-methoxy-6-methylpyridine (165mg, 7%)

(ii) 2-Methoxy-6-methylpyridine **2** (4.75g, 0.0386mol) in 0.15M aqueous Na_2HPO_4 (80ml) was treated dropwise with bromine (1.99ml, 0.0386mol) in 0.15M aqueous Na_2HPO_4 (80ml) after the yellow colouration had been dissipated the mixture was extracted (CH_2Cl_2), the organic phase dried ($MgSO_4$) and the solvent was removed (<25°C). Flash column chromatography (2.5% EtOAc/pentane) gave a colourless oil which was a mixture of 5-bromo-2-methoxy-6-methylpyridine **8** (5.69g, 73%) and 3-bromo-2-methoxy-6-methylpyridine (0.390g, 5%)

6-Bromomethyl-2-methoxypyridine 9

2-Methoxy-6-methylpyridine **2** (2.99g, 0.0243mol), NBS (4.32g, 0.0243mol), AIBN (150mg), AcOH (1.75ml) in CCl_4 (60ml) at 45-60°C under Ar was irradiated (150W, Hg lamp) and the reaction was monitored by ^{1}H nmr.

CH_2Cl_2 (60ml) was added and the organic phase was washed (saturated aqueous $NaHCO_3$, then saturated aqueous NaCl, dried ($MgSO_4$) and the solution concentrated (rotary evaporator, <25°C) then filtered, the filtrate had the solvent removed (as above). Flash column chromatography (50% Et_2O/pentane) gave as a pale yellow liquid *6-bromomethyl-2-methoxypyridine* **9** (2.24g, 46%); ^1H nmr (200MHz, $CDCl_3$) 7.55 (1H, dd J=7.4, 8.1Hz, Ar-H), 6.98 (1H, d J=7.4Hz, Ar-H), 6.66 (1H, d J=8.1Hz, Ar-H), 4.45 (2H, s, CH_2) and 3.94 (3H, s, OCH_3); ^{13}C (62.9MHz, $CDCl_3$) 163.7, 154.1, 139.1, 115.9, 110.3, 53.4 and 34.0; m/z 203 (M+, 32%), 202 (46), 201 (32), 200 (43), 174 (8), 173 (7), 172 (9), 171 (6), 122 (100), 121 (13), 107 (12), 92 (33), 91 (25), 79 (37), 77 (24), 65 (47), 52 (20) and 39 (37) and *6-dibromomethyl-2-methoxypyridine* (0.414g, 6%)

5-Bromo-6-bromomethyl-2-methoxypyridine 10

5-Bromo-2-methoxy-6-methylpyridine **8** (122mg, 0.605mmol), NBS (108mg, 0.605mmol), AIBN (15mg), AcOH (0.175ml) in CCl_4 (6ml) under Ar was irradiated (150W, Hg lamp) and the reaction was monitored by ^1H nmr. Filtration through a silica pad (20% EtOAc/pentane) and removal of solvent gave a mixture of *5-bromo-6-bromomethyl-2-methoxypyridine* **10** (124mg, 73%); ν_{max} (film) 2940m, 2865w, 1588s, 1473s, 1424m, 1335m, 1273m, 1024w and 834w; ^1H nmr (200MHz, $CDCl_3$) 7.68 (1H, d J=9.3Hz, Ar-H), 6.60 (1H, d J=9.3Hz, Ar-H), 4.61 (2H, s, CH_2) and 3.93 (3H, s, OCH_3); m/z 283 (13%), 282 (12), 281 (28), 280 (22), 279 (14), 202 (100), 200 (96), 106 (12), 93 (20), 91 (11), 90 (21), 78 (62), 63 (36) and 51 (34) and *5-bromo-6-dibromomethyl-2-methoxypyridine* (8%).

Esters 11 and 12

Diisopropylamine (0.560ml, 4.00mmol) and ^nBuLi in hexanes (1.2M, 3.66ml, 4.40mmol) in THF (3ml) were stirred at 0°C for 25min then cooled to -78°C. Methyl acetate (0.302ml, 3.80mmol) was added and the reaction stirred at -78°C for 25min. 6-Bromomethyl-2-methoxypyridine **9** (81%, 0.250g, 1.00mmol) in THF (3ml) and HMPA (0.3ml) at -78°C was slowly added and the reaction was warmed to room temperature and stirred for 22h. AcOH was added, extraction (Et_2O), drying of the organic phase ($MgSO_4$) and removal of the solvent gave a yellow oil. Flash column chromatography (20% EtOAc/pentane) afforded *Ester* **11** (90mg, 46%) as a pale yellow oil; ν_{max} (film) 2960m, 1740s, 1605s, 1584m,

1470s, 1445m, 1420, 1365w, 1295m, 1265w, 1165w, 1085w, 1043m, 990w, 895w, 841w, 815m and 740w; ^{1}H nmr (200MHz, $CDCl_3$) 7.47 (1H, dd J=7.3, 8.5Hz, Ar-H), 6.73 (1H, d J=7.3Hz, Ar-H), 6.54 (1H, d J=8.5Hz, Ar-H), 3.88 (3H, s, OCH_3); 3.68 (3H, s, CO_2CH_3), 3.04 (2H, t J=7.1Hz, CH_2) and 2.80 (2H, t J=7.1Hz, CH_2) and *keto-ester* **12** (59mg, 25%) as a pale yellow oil; ν_{max} (film) 2980w, 1765s, 1735s, 1615w, 1595m, 1485s, 1455m, 1430w, 1305m, 1165w, 1093w, 1055m and 815w; ^{1}H nmr (250MHz, $CDCl_3$) 7.42 (1H, dd J=7.3, 8.6Hz, Ar-H), 6.69 (1H, d J=7.3Hz, Ar-H), 6.51 (1H, d J=8.6Hz, Ar-H), 3.85 (3H, s, OCH_3); 3.68 (3H, s, CO_2CH_3), 3.51 (2H, s, CH_2) and 2.97 (4H, s, $2CH_2$); ^{13}C nmr (62.9MHz, $CDCl_3$) 202.1, 167.6, 163.6, 157.3, 138.8, 115.4, 107.8, 53.2, 52.5, 49.0, 41.4 and 31.0; m/z 237 (M^+, 10%), 206 (7), 178 (5), 164 (13), 136 (100), 104 (19), 93 (17), 77 (15), 59 (20) and 39 (18).

Alcohol 14

Diisopropylamine (0.540ml, 3.86mmol) and ^{n}BuLi in hexanes (1.5M, 2.60ml, 3.86mmol) in THF (4ml) were stirred at 0°C for 20min then cooled to -78°C. 5-Bromo-2-methoxy-6-methylpyridine **8** (0.325g, 1.61mmol) in THF (3ml) at -78°C was slowly added (deep-red colouration developed) and the reaction was stirred for 25min. 2-cyclohexen-1-one (187µl, 1.93mmol) in THF (2ml) was slowly added (dissipation of some of the colouration) and after stirring for 3.5h at -78°C the reaction was warmed to room temperature. Saturated aqueous NH_4Cl was added, extraction (Et_2O), drying of the organic phase ($MgSO_4$) and removal of the solvent gave a yellow oil. Flash column chromatography (20% EtOAc/pentane) afforded *alcohol* **14** (237mg, 50%) as a pale yellow oil; ν_{max} (film) 3390s, 1660w, 1575s, 1457s, 1415s, 1061m, 820s and 735m; ^{1}H nmr (200MHz, $CDCl_3$) 7.97 (1H, d J=9.4Hz, Ar-H), 6.83 (1H, d J=9.4Hz, Ar-H), 6.07 (1H, m, CH=C), 5.87 (1H, m J=10.6Hz, CH=C), 4.15 (3H, s, OCH_3), 3.37 (2H, s, CH_2) and 2.46-1.84 (6H, m, CH_2); ^{13}C nmr (62.9MHz, $CDCl_3$) 161.9, 154.6, 143.2, 132.0, 129.4, 112.9, 110.8, 70.3, 53.7, 45.0, 36.0, 25.1 and 19.1; m/z 299/297 (M^+, 1/1%), 280, 278 (100/94), 264 (15), 251 (47), 238 (12), 203/201 (64/58), 184 (22), 167 (14), 154 (14), 128 (12) and 97 (27).

Bromoenone 15

Diisopropylamine (1.16ml, 8.27mmol) and ^{n}BuLi in hexanes (1.6M, 5.17ml, 8.27mmol) in THF (10ml) were stirred at 0°C for 20min then cooled to

-78°C. 5-Bromo-2-methoxy-6-methylpyridine **8** (0.669g, 3.31mmol) in THF (3ml) at -78°C was slowly added (deep-red colouration developed) and the reaction was stirred for 40min. 3-Ethoxy-2-cyclohexen-1-one (1.20ml, 8.27mmol) in THF (2ml) was slowly added (dissipation of some of the colouration) and after stirring for 2h at -78°C the reaction was warmed to room temperature. 2M HCl (3ml) was added and the reaction stirred for a further 30min. Neutralisation ($NaHCO_3$), extraction (Et_2O), drying of the organic phase ($MgSO_4$) and removal of the solvent gave a yellow oil. Flash column chromatography (20% EtOAc/pentane) afforded *Bromo-enone* **15** (665mg, 68%) as a colourless solid; ν_{max} (film) 1673s, 1575s, 1460m, 1425m, 1320m, 1018m and 825m; ^1H nmr (250MHz, $CDCl_3$) 7.62 (1H, d J=8.5Hz, Ar-H), 6.50 (1H, d J=8.5Hz, Ar-H), 5.74 (1H, s, CH=C), 3.84 (3H, s, OCH_3), 3.74 (2H, s, $ArCH_2$), 2.41-2.31 (4H, m, $2CH_2$), 2.04-1.91 (2H, m, CH_2); ^{13}C nmr (62.9MHz, $CDCl_3$) 199.6 (C=O), 162.4, 162.2, 152.6, 142.4, 127.0, 112.1, 110.7, 53.5, 44.9, 37.1, 29.7 and 22.4; m/z 297 (18%), 296 (17), 295 (18), 294 (14), 269 (52), 267 (53), 254 (19), 252 (22), 241 (100), 239 (82), 226 (47), 224 (54), 203 (11), 201 (13), 117 (18), 90 (13), 78 (17), 65 (25) and 39 (47).

Bromo-ketone 16

Bromoenone **15** (350mg, 1.18mmol), Pt/C (10%, 35mg) and MeOH (15ml) were degassed (Ar) and then stirred under an atmosphere of H_2 until all the starting material was consumed. The mixture was filtered through celite and the solvent removed. Diethylether (15ml) was added and the solution of *dimethoxyketal* (tlc, Rf=0.77 (20% EtOAc/pentane)) was treated with 2M HCl (5ml) and stirred for 1h (until all the ketal was hydrolysed). Neutralisation ($NaHCO_3$), extraction (Et_2O), drying the organic phases ($MgSO_4$) the removal of the solvent gave a colourless oil. Flash column chromatography (14% EtOAc/pentane) gave *bromo-ketone* **16** (0.302g, 86%) as a colourless oil; ν_{max} (film) 2895s, 1692s, 1557s, 1445s, 1400s, 1110m, 1025m, 1000m and 810s; ^1H nmr (200MHz, $CDCl_3$) 7.63 (1H, d J=8.6Hz, Ar-H), 6.48 (1H, d J=8.6Hz, Ar-H), 3.86 (3H, s, OCH_3), 2.87 (2H, m, $ArCH_2$) and 2.47-1.41 (9H, m, CH/CH_2); ^{13}C nmr (62.9MHz, $CDCl_3$) 211.8(C=O), 162.3, 155.2, 112.2, 110.2, 53.8, 47.9, 43.3, 41.6, 38.5, 31.3 and 25.3; m/z 299/297 (M^+, 6/6%), 242/240 (5/5), 228/226 (8/7), 216/214 (5/5), 203/201(92/100) and 41 (44).

Enone 17

Bromoenone **15** (70mg, 0.236mmol), Pd/C (10%, 4mg) and MeOH (7ml) were degassed (Ar) and then stirred under an atmosphere of H_2 for 5-10min. The mixture was filtered through celite and the solvent removed. Flash column chromatography (14% EtOAc/pentane) gave *enone* **17** (28mg, 54%) as a colourless oil; ν_{max} (film) 1620s, 1581m, 1525s, 1412s, 1370s, 1278m, 1145w, 970w and 778m; ^{1}H nmr (250MHz, $CDCl_3$) 7.48 (1H dd J=7.8, 8.9Hz, Ar-H), 6.69 (1H, d J=7.8Hz, Ar-H), 6.53 (1H, d J=8.9Hz, Ar-H), 5.86 (1H, s, CH=C), 3.86 (3H, s, OCH_3), 3.56 (2H, m, Ar-CH_2), 2.39-2.29 (4H, m, $2CH_2$) and 2.04-1.88 (2H, m, CH_2); m/z 216 (24 %), 189 (66), 174 (23), 161 (100) and 146 (48).

Ketone 18

Bromoenone **15** (58mg, 0.196mmol), Pd/C (10%, 4mg) and EtOH (8ml) were degassed (Ar) and then stirred under an atmosphere of H_2 for 1h. The mixture was filtered through celite and the solvent removed. Flash column chromatography (14% EtOAc/pentane) gave *ketone* **18** (10mg, 22%) as a colourless oil; ν_{max} (film) 1695s, 1595m, 1537s, 1460s, 1290m, 1045m and 797w; ^{1}H nmr (200MHz, $CDCl_3$) 7.44 (1H dd J=7.9, 8.6Hz, Ar-H), 6.63 (1H, d J=7.9Hz, Ar-H), 6.53 (1H, d J=8.6Hz, Ar-H), 3.87 (3H, s, OCH_3), 2.65 (2H, m, Ar-CH_2) and 2.41-1.33 (9H, m, CH/CH_2); m/z 219 (M^+, 7%), 176 (3), 162 (7), 148 (8), 123 (100), 108 (5), 91 (6), 80 (5) and 65 (6).

Pyridine 19

Diisopropylamine (0.940ml, 6.72mmol) and ^{n}BuLi in hexanes (1.6M, 4.20ml, 6.72mmol) in THF (10ml) were stirred at 0°C for 20min then cooled to -78°C. 5-Bromo-2-methoxy-6-methylpyridine **8** (0.617g, 3.05mmol) in THF (5ml) at -78°C was slowly added (deep-red colouration developed) and the reaction was stirred for 40min. Allyl bromide (0.580ml, 6.72mmol) in THF (2ml) was slowly added (dissipation of some of the colouration) and after stirring for 30min at -78°C the reaction was slowly warmed to room temperature. Saturated aqueous NH_4Cl was added then extraction (Et_2O), drying of the organic phase ($MgSO_4$) and removal of the solvent gave a yellow oil. Flash column chromatography (2% EtOAc/pentane) afforded **19** (579mg, 78%) as a colourless oil; ν_{max} (film) 3060w,

2820s, 1637m, 1575s, 1560s, 1413s, 1305s, 1250s, 1130m, 1040s, 913s and 825s; ^{1}H nmr (200MHz, $CDCl_3$) 7.59 (1H, d J=8.3Hz, Ar-H), 6.45 (1H, d J=8.3Hz, Ar-H), 5.92 (1H, m, CH=C), 5.14-4.93 (2H, m, CH=C), 3.89 (3H, s, OCH_3), 2.91 (2H, m, CH_2) and 2.50 (2H, m, CH_2); m/z 243 (40%), 242 (35), 241 (49), 240 (37), 228 (52), 226 (59), 214 (22), 212 (22), 187 (10), 162 (23), 160 (20), 147 (47), 132 (20), 117 (36), 103 (21), 91 (26), 78 (49) and 39 (100).

Formylpyridine 23

Pyridine **19** (0.236g, 0.975mmol) in THF (5ml) was treated with ^{n}BuLi (1.6M, 0.790ml, 1.27mmol) at -78°C under Ar. The reaction mixture was stirred at -78°C for 20min then DMF (0.151ml, 1.95mmmol) was added and after stirring for 1h at -78°C was slowly warmed to room temperature. Saturated aqueous NH_4Cl was added, extraction (Et_2O) followed by drying ($MgSO_4$) and the solvent removed to give a colourless oil. Flash column chromatography (5%EtOAc/pentane) afforded **23** (83mg, 45%) as a colourless oil; ν_{max} (film) 1650s, 1540s, 1427m, 1270m, 981w, 865w and 786w; ^{1}H nmr ($CDCl_3$) 10.21 (1H, s, CHO), 7.99 (1H, d J=8.6Hz, Ar-H), 6.66 (1H, d J=8.6Hz, Ar-H), 5.82 (1H, m, CH=C), 5.11-4.94 (2H, m, CH=C), 4.01 (3H, s, OCH_3), 3.20 (2H, m, CH_2) and 2.55 (2H, m, CH_2); m/z 191 (M^+, 100%), 176 (M^+-CH_3, 49), 162 (M^+-CHO, 39), 148 (34), 130 (17), 124(19), 107 (11), 77 (14) and 56 (14).

Alcohol 21

5-Bromo-2-methoxy-6-methylpyridine **8** (0.868g, 4.30mmol) in THF (10ml) at -50°C was treated with ^{n}BuLi in hexanes (1.6M, 3.22ml, 5.15mmol) and the orange reaction was stirred at -50°C for 40min. Cyclohexanone (0.56ml, 5.40mmol) was added and the reaction was decolourised and was warmed to room temperature. Saturated aqueous NH_4Cl was added and after extraction (Et_2O) the organic phase was dried ($MgSO_4$) and the solvent removed to give a pale-yellow oil. Flash column chromatography gave *alcohol* **21** (0.793g, 83%) as a colourless, crystalline solid; m.p. 84°C; ν_{max} (nujol) 3490s, 1585s, 1290s, 1140m, 1045w and 830m; ^{1}H nmr (200MHz,$CDCl_3$) 7.61 (1H, d J=8.8Hz, Ar-H), 6.47 (1H, d, J=8.8Hz, Ar-H), 3.88 (3H, s, OCH_3), 2.68 (3H, s, CH_3), 1.95-1.52 (10H, m, CH_2); m/z 221(M^+, 17%), 204 (15), 203 (100), 202 (85), 188 (17), 179 (7), 178 (63), 175 (19), 174 (44), 173 (11), 165 (16), 160 (25), 150 (57), 146 (10), 91 (13), 79 (13), 77 (17), 65 (15), 56 (24) and 55 (13).

Alcohol 20

5-Bromo-2-methoxy-6-methylpyridine **8** (130mg, 0.642mmol) in THF (2ml) at -78°C under Ar was treated with ^{n}BuLi in hexanes (1.6M, 0.514ml, 0.771mmol) (yellow anion formation) and the reaction mixture was stirred for 25min. 2-Cyclohexen-1-one (62µl, 0.642mmol) was added and the colour of the anion was dissipated, the reaction was stirred at -78°C for 2.5h then warmed to room temperature. Saturated aqueous NH_4Cl was added, the mixture extracted (Et_2O), the organic phase dried (Na_2SO_4) and the solvent removed to yield a colourless oil (0.184g). Flash column chromatography (20% EtOAc/pentane) afforded *alcohol* **20** (84mg, 60%) as a colourless oil; ν_{max} (film) 3390s, 2920s, 1585s, 1467s, 1301s, 1043m, 960w, 823w and 739w; ^{1}H nmr (200MHz, $CDCl_3$) 7.82 (1H, d J=8.8Hz, Ar-H), 6.55 (1H, d J=8.8Hz, Ar-H), 6.03(1H, m, CH=C), 5.78 (1H, m, CH=C), 3.91 (3H, s, OCH_3), 2.58 (3H, s, CH_3) and 2.26-1.24 (6H, m, CH_2); m/z 219 (M^+, 7%), 201 (M^+-H_2O, 100), 186 (31), 171 (11), 136 (19), 115 (22), 91 (12), 77 (18) and 65 (13).

5-Formyl-2-methoxy-6-methylpyridine 22

5-Bromo-2-methoxy-6-methylpyridine **8** (1.00g, 4.95mmol) in THF (5ml) was treated with ^{n}BuLi (1.6M, 3.40ml, 5.45mmol) at -78°C under Ar. The reaction mixture was stirred at -78°C for 20min then DMF (0.760ml, 9.90mmol) was added and after stirring for 40min at -78°C was slowly warmed to room temperature. Saturated aqueous NH_4Cl was added, extraction (Et_2O) followed by drying ($MgSO_4$) and the solvent removed to give a colourless oil. Flash column chromatography (10%EtOAc/pentane) afforded *5-formyl-2-methoxy-6-methylpyridine* **22** (0.434mg, 58%) as a colourless crystalline solid, m.p.59°C; ν_{max} (nujol) 1685m, 1590s, 1315m, 1040w and 830w; ^{1}H nmr (200MHz, $CDCl_3$) 10.25 (1H, s, CHO), 8.02 (1H, d J=8.6Hz, Ar-H), 6.72 (1H, d J=8.6Hz, Ar-H), 4.05 (3H, s, OCH_3) and 2.83 (3H, s, CH_3); m/z 151 (M^+, 77%), 150 (100), 121 (26), 107 (14), 92 (11), 65 (20) and 56 (33).

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