Synthesis of novel chromeno[3,4-*b*]pyridinones

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A concise synthesis of two novel chromeno[3,4-*b*]pyridin-9-ones (as their ethylene ketals) has been achieved using, as a key step, the reaction between a mixed cuprate derived from 6-methoxy-2-methyl-3-lithiopyridine and 4-*tert*-butyldimethylsiloxycyclohex-2-enone.

We are currently attempting to prepare huperzine A **1**, an inhibitor of the enzyme acetylcholine esterase, found in the club moss *Huperzia serrata*.[1] Four essentially linear syntheses have already been reported,[2] and there has also been some work with analogues.[3] Our approach to this interesting molecule is convergent and is illustrated in Fig. 1. This strategy required the construction of the key intermediate **2**, which we envisaged arising from the reaction between the higher order cuprate **3** and the quinone monoacetal **4**, or its equivalent, followed by an intramolecular organometallic or radical reaction.

The requisite higher order mixed cuprate **3** was prepared from 2-amino-6-methylpyridine **5** *via* diazotisation and bromination at −25 °C to produce 2-bromo-6-methylpyridine **6**[4] and thence 2-methoxy-6-methylpyridine **7** (NaH–MeOH) (Scheme 1). Selective bromination using ethanolic bromine provided 3-bromo-6-methoxy-2-methylpyridine **8** with all yields in excess of 80% on a medium (up to 30 gram) scale. Reaction of this bromide with *n*-butyllithium at −78 °C provided the 3-lithio-species and this was reacted with lithio-2-thienylcyanocuprate[5] at −40 °C to produce the buff-coloured mixed higher order cuprate **3**.

The quinonone monoacetals **4a,b** were prepared on the multigram scale by the routes shown in Scheme 2.[6,7] Reaction of the higher order cuprate **3** with monoacetal **4a** (at −40 °C in diethyl ether : THF 1 : 1) yielded the 1,4-adduct **9a** in 20% yield together with 4-methoxyphenol, also in around 20% yield (Scheme 3). This result should be compared with the result of Nillson and Ronlan[8] who reacted the homocuprate Me_2CuLi with the same acetal to produce only 4-methoxyphenol. It seems likely that the phenol is obtained by the one-electron process shown in Fig. 2, and the 1,4-adduct is obtained *via* the usually accepted oxidative addition–reductive elimination mechanism associated with cuprate reactions.[9]

Our results suggest that higher order cyanocuprates react *via* both pathways, which are in competition. Yamamoto *et al*. also obtained mixtures of products arising from 1,4-addition and reduction using trimethylcarbonylethylene as enone acceptor.[10] Almost exclusive 1,4-addition took place using $Me_2Cu(CN)Li_2$ while a 1 : 1 mixture of both addition and reduction products were obtained using Me_2CuLi. Taken together, these studies indicate that the electron transfer process is suppressed by the incorporation of a cyanide ligand into the cuprate cluster, although as yet there is no clear correlation between product ratio and cuprate structure.

In order to try to suppress this one electron process, we attempted the addition of **3** with the alternative acetal **4b** (prepared from **4a** by reaction with ethylene glycol in the presence of $BF_3 \cdot Et_2O$). Unfortunately, a similar result was obtained with around 20% yields of the 1,4-adduct **9b** and 4-hydroxyethoxyphenol. Although these results were disappointing, as far as we are aware, this is the first successful addition of a cuprate to a quinone monoacetal.

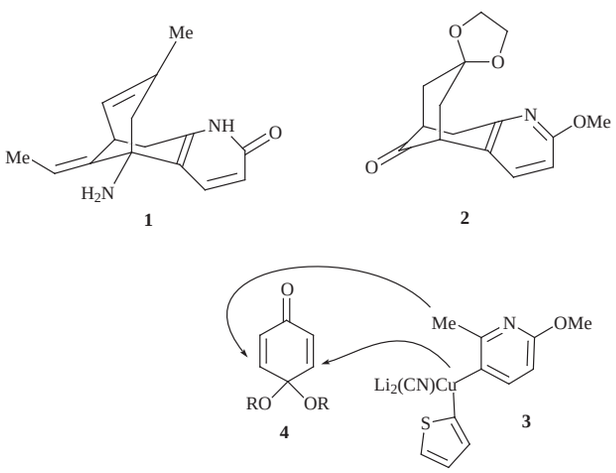
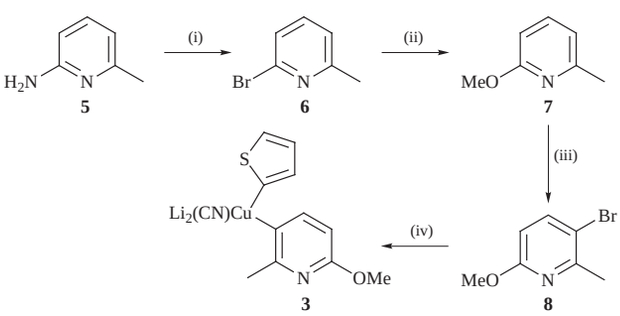


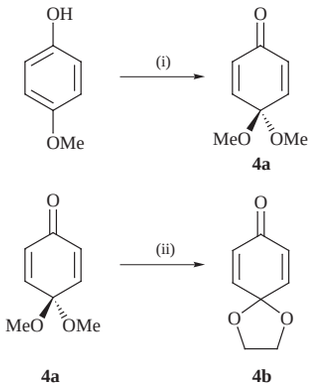
Fig. 1



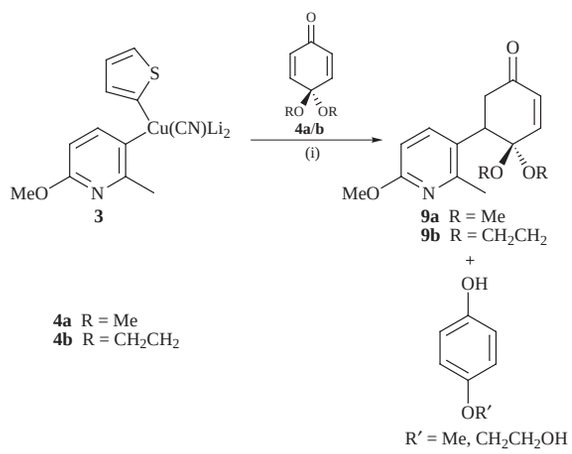
Scheme 1 *Reagents and conditions:* (i) HBr–Br_2, $NaNO_2$, −25 °C, 82%; (ii) MeOH–NaH, DMF, 150 °C, 80%; (iii) Br_2, EtOH, room temp., 80%; (iv) *a.* ^{n}BuLi, Et_2O, −78 °C; *b.* lithium 2-thienylcyanocuprate, Et_2O–THF (1 : 1), −40 °C.

In order to overcome the problems associated with the quinone monoacetals, the cuprate **3** was reacted with 4-*tert*-butyldimethylsiloxycyclohex-2-enone[11] **10** to provide the anticipated adduct **11** in 80% yield on the 10 gram scale (Scheme 4). It was clear from ^{1}H NMR that only one product had been produced and this was assigned the *trans*-stereochemistry, since $J_{3,4}$ for the cyclohexanone hydrogens was equal to 8.1 Hz, clearly suggestive of a diaxial relationship.[12] Protection of the ketone (ethylene glycol–*p*-TSA) yielded the expected ketal **12**.

With gram quantities of the ketal **12** in hand, we were able to embark upon the second stage of our planned approach to



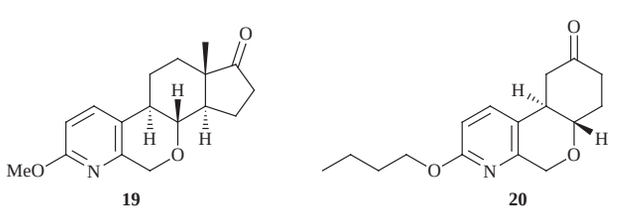
Scheme 2 *Reagents and conditions:* (i), Pt electrodes, $I = 1$A, 1% KOH–MeOH, room temp., 72%; (ii), $BF_3{\cdot}OEt_2$, ethylene glycol, DME, room temp., 82%.



Scheme 3 *Reagents and conditions:* (i), diethyl ether–THF (1:1), −40 °C.

huperzine A. To this end, ketal **12** was brominated with NBS to yield the expected bromide **13**, but upon removal of the TBDMS group (Bu_4NF–THF), nucleophilic displacement of the bromide occurred to produce chromenopyridinone ethylene acetal **14**. In an attempt to prevent this cyclisation, removal of the TBDMS group was carried out prior to bromination of the resultant alcohol **15** to produce bromo alcohol **16**. Finally, this was oxidised under Swern conditions[13] to yield the bromo ketone **17**. Reaction of this with LDA at −78 °C, with subsequent slow warming to room temperature, provided not the desired tricyclic product of intramolecular alkylation **2**, but the second novel chromenopyridinone ethylene acetal **18**.

Despite our failure to produce the desired, key intermediate **2**, it is worth noting that these chromeno[3,4-*b*]pyridinone systems are, as far as we are aware, novel, and could provide access to a range of interesting analogues of, *inter alia*, estrogens **19**



and cannabinoids **20**. We are pursuing these goals as well as trying to effect the synthesis of **2** by another route.

Experimental

IR spectra were recorded using a Perkin-Elmer 881 series double beam spectrophotometer, and samples were run as thin

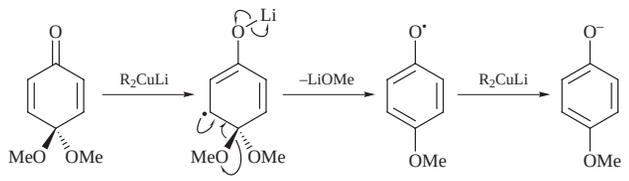
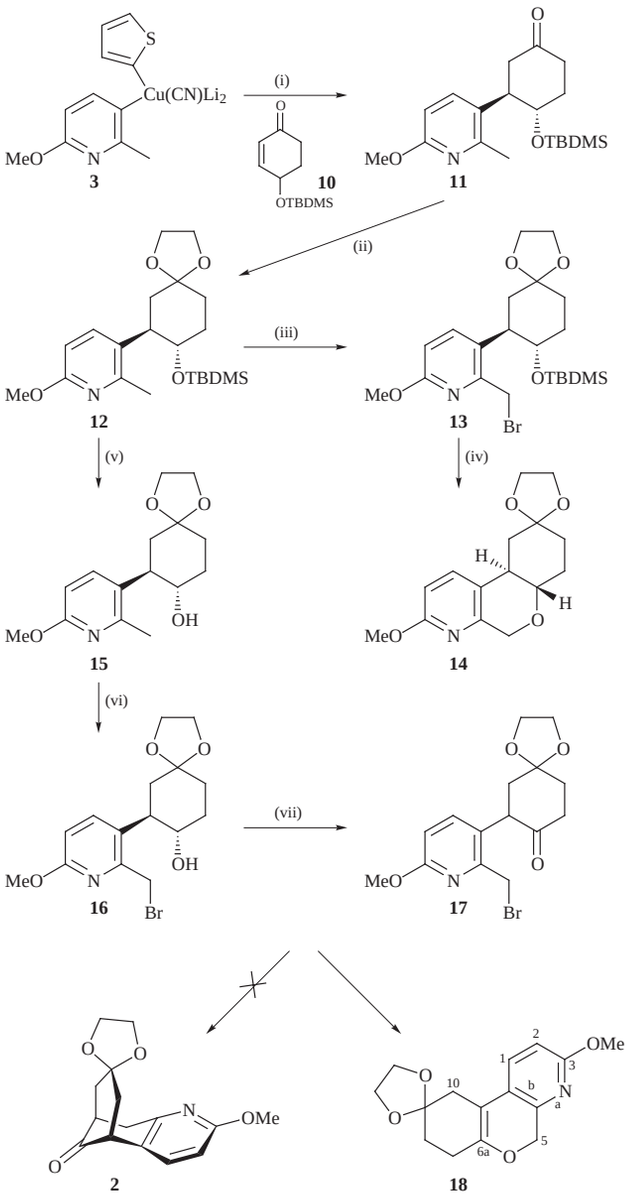


Fig. 2



Scheme 4 *Reagents and conditions:* (i) Et_2O–THF (1:1), −40 °C, 80%; (ii) ethylene glycol, oxalic acid, toluene, 110 °C, 92%; (iii) NBS, AIBN, CCl_4, room temp., 52%; (iv) TBAF, THF, room temp., 53%; (v) TBAF, THF, room temp., 77%; (vi) NBS, AIBN, CCl_4, room temp., 60%; (vii) oxalyl chloride, DMSO, Et_3N, DCM, −60 °C, 62%; (viii) LDA, THF, −78 °C to room temp., 50%.

films or in solution using NaCl plates. Low resolution and accurate mass data were recorded on a VG Autospec spectrometer. Elemental analyses were carried out by Medac Ltd., Brunel University on those compounds that were stable. All compounds for which exact mass data are provided were homogeneous by TLC in three different solvent systems, and exhibited no spurious signals in their ^1H NMR spectra at 400 MHz. NMR spectra were recorded using JEOL EX400, Bruker DPX 250 or Bruker WM250 spectrometers. Solvents were dried by distillation from calcium hydride (DCM, toluene, benzene,

acetonitrile) or from sodium–benzophenone (THF and diethyl ether). Light petroleum refers to the fraction with boiling range 40–60 °C; ether refers to diethyl ether.

2-Bromo-6-methylpyridine 6[4]

The title compound was prepared according to a modification of the literature procedure.[4] 2-Amino-6-methylpyridine **5** (12.9 g, 119 mmol) was dissolved in 60% aqueous HBr (10.2 cm^3, 815 mmol). The solution was cooled to −25 °C and sodium nitrite (19.3 g, 279 mmol) in water (30 cm^3) was added dropwise at this temperature. The reaction mixture was then warmed to room temperature over a period of 1 h and stirred for an additional hour before being recooled to −25 °C. A solution of sodium hydroxide (60.0 g) in water (150 cm^3) was added and the mixture warmed to room temperature and stirred overnight. The resulting oil in water dispersion was extracted with diethyl ether (3 × 200 cm^3) and the combined organic phases dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product as a red oil. Purification by distillation under reduced pressure [bp 95 °C/10 mmHg (lit.,[4] 80–90 °C/10 mmHg)] gave the title compound **6** as a colourless oil (16.8 g, 97.6 mmol, 82%); ν_{max} (film)/cm^{-1} 3051, 2956, 2923s, 1584s, 1559s, 1414s, 1420s; δ_H (400 MHz; $CDCl_3$) 2.46 (3H, s, Me), 7.00 (1H, m, 3-H), 7.18 (1H, m, 4-H).

2-Methoxy-6-methylpyridine 7

Sodium hydride as a 60% dispersion in mineral oil (6.10 g, 153 mmol) was washed with dry hexane (2 × 5 cm^3) under argon. DMF (70 cm^3) was added followed by the bromopicoline **6** (12.0 g, 70.0 mmol). Methanol (6.1 cm^3, 153 mmol) was added dropwise and the reaction mixture was stirred at 100 °C for 3 h, then cooled to room temperature. The solution was extracted with diethyl ether (3 × 100 cm^3) and the combined organic phases were washed with water (3 × 50 cm^3), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give a yellow oil. Purification by distillation under reduced pressure [bp 53 °C/10 mmHg (lit.,[14] 156 °C/759 mmHg)] gave the title compound as a colourless oil (9.80 g, 56.0 mmol, 80%); ν_{max} (film)/cm^{-1} 3066, 2949, 2924, 2854, 1578s, 1552s, 1467, 1409; δ_H (400 MHz; $CDCl_3$) 2.44 (3H, s, Me), 3.91 (3H, s, OMe), 6.52 (1H, d, *J* 8.2 Hz, 3-H), 7.03 (1H, d, *J* 7.0 Hz, 5-H), 7.33 (1H, dd, *J* 7.0, 8.2 Hz, 4-H).

3-Bromo-6-methoxy-2-methylpyridine 8

Bromine (24.3 g, 152 mmol) was slowly added to methoxypicoline **7** (9.40 g, 76.0 mmol) in ethanol (100 cm^3) at 0 °C and the solution stirred at this temperature for 30 min. The mixture was neutralised by the addition of 2 M aqueous sodium hydroxide and the product extracted with diethyl ether (3 × 150 cm^3), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give a yellow oil purified by distillation under reduced pressure [bp 86 °C/10 mmHg] to give the title compound **8** as a colourless oil (12.3 g, 61 mmol, 80%); ν_{max} (film)/cm^{-1} 3071, 2980s, 2948s, 1580s, 1584s, 1461s; δ_H (400 MHz; $CDCl_3$) 2.54 (3H, s, Me), 3.88 (3H, s, OMe), 6.44 (1H, d, *J* 8.4 Hz, 5-H), 7.59 (1H, d, *J* 8.4 Hz, 4-H); *m/z* 201 (MH^+, 100%), 171 (12), 124 (8), 93 (5) [HRMS: found, 201.9941 (MH^+). C_7H_8BrNO requires 201.9868].

General procedure for the preparation of mixed higher order cuprate 3

Lithium 2-thienylcyanocuprate was prepared according to the literature procedure.[5] ^{n}BuLi (2.5 M) (1.0 cm^3, 2.50 mmol) was added to a solution of thiophene (0.21 g, 2.50 mmol) in THF (2.50 cm^3) at −30 °C under argon. The yellow solution was stirred for 30 min at −30 °C and added *via* cannula to a slurry of CuCN (0.23 g, 2.50 mmol) in THF (2.50 cm^3) at −78 °C. The mixture was warmed to room temperature to give a buff coloured solution of the mixed lower order cuprate.

Bromopyridine **8** (0.5 g, 2.50 mmol) was dissolved in diethyl ether (3 cm^3) and ^{n}BuLi (2.5 M) (1.0 cm^3, 2.5 mmol) added dropwise at −78 °C. The solution was stirred at this temperature under argon for 1 h and then warmed to −40 °C. The lower order cuprate was then added dropwise and the resulting buff coloured solution stirred at −40 °C for 30 min.

trans-4-*tert*-Butyldimethylsiloxy-3-(6′-methoxy-2′-methyl-3′-pyridyl)cyclohexan-1-one 11

A solution of mixed higher order cyanocuprate **3** (50.0 mmol) in Et_2O–THF (1:1) (200 cm^3) was prepared as outlined. The enone **10** (7.50 g, 33.0 mmol) was added neat at −40 °C and the mixture warmed to room temperature. The reaction was quenched with NH_4OH–NH_4Cl (9:1) (150 cm^3). Filtration through a pad of Celite® removed all solids and the mixture was extracted with diethyl ether (3 × 120 cm^3). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a yellow oil purified by column chromatography on silica gel using diethyl ether–light petroleum (3:7) as eluant to give the title compound **11** as a white solid (9.2 g, 26 mmol, 80%); mp 53–56 °C; ν_{max} (film)/cm^{-1} 3423, 2953, 2930, 1720s; δ_H (400 MHz; $CDCl_3$) −0.25 (3H, s, SiMe), 0.02 (3H, s, SiMe), 0.75 (9H, s, Si^{t}Bu), 1.80 (1H, m, 5-H), 2.11 (1H, m, 5-H), 2.62–2.89 (7H, m, 2, 6-H, 2′-Me) 3.32 (1H, m, 3-H), 3.85 (3H, s, OMe), 4.00 (1H, td, *J* 8.1, 3.7 Hz, 4-H), 6.55 (1H, d, *J* 8.8 Hz, 4′-H), 7.32 (1H, d, *J* 8.8 Hz, 5′-H); δ_C (100 MHz; $CDCl_3$) −5.3 (SiMe), −4.1 (SiMe), 18.2 (Si-C), 23.2 (C2′-Me), 25.9 (Bu^t), 38.2 (C5), 37.3 (C6), 43.7 (C2), 45.8 (C3), 54.3 (OMe), 73.2 (C4), 108.7 (C5′), 128.1 (C3′), 137.4 (C4′), 155.4 (C2′), 162.9 (C6′), 230.1 (C1) (Found: C, 65.5; H, 9.0; N, 4.0. $C_{19}H_{31}NO_3Si$ requires C, 65.3; H, 8.9; N, 4.0%); *m/z* 350 (MH^+, 47%), 292 (100), 218 (20), 136 (42), 75 (43)[HRMS: found, 350.2152 (MH^+). C_7H_8BrNO requires 350.2151].

3-(2′-Methyl-6′-methoxy-3′-pyridyl)-4,4-dimethoxycyclohex-5-en-1-one 9a

A solution of mixed higher order cyanocuprate **3** (2.50 mmol) in diethyl ether–THF (1:1) (10 cm^3) was prepared as outlined. Quinone monoacetal **4a** (0.36 g, 2.40 mmol) was then added at −40 °C and the mixture stirred at this temperature for 2 h. The reaction was quenched by the addition of NH_4Cl–NH_4OH (9:1) (5 cm^3) and filtered through a pad of Celite®. The mixture was then extracted with diethyl ether (3 × 10 cm^3) and the combined organic phases dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a yellow oil. Purification by flash column chromatography on silica gel with ethyl acetate–dichloromethane (1:9) as eluant afforded two products; *p*-methoxyphenol isolated as a white solid (0.06 g, 0.50 mmol, 20%) and the title compound **9a** isolated as a pale yellow solid (0.13 g, 0.50 mmol, 20%); mp 73–75 °C; ν_{max} (film)/cm^{-1} 2942, 2832, 1688s, 1597, 1579, 1542; δ_H (400 MHz; $CDCl_3$) 2.49 (3H, s, Me), 2.79 (1H, dd, *J* 16.8, 6.6 Hz, 2-H), 2.80 (1H, dd, *J* 16.8, 5.2 Hz, 2-H), 3.16 (3H, s, OMe), 3.21 (3H, s, OMe), 3.80 (1H, dd, *J* 6.6, 5.2 Hz, 3-H), 3.88 (3H, s, py-OMe), 6.17 (1H, d, *J* 10.3 Hz, 6-H), 6.48 (1H, d, *J* 8.4 Hz, 5′-H), 6.97 (1H, d, *J* 10.3 Hz, 5-H), 7.59 (1H, d, *J* 8.4 Hz, 4′-H); δ_C (100 MHz; $CDCl_3$) 22.6 (Me), 42.1 (C2), 43.6 (C3), 48.8 (OMe), 50.0 (OMe), 53.1 (py-OMe), 97.9 (C4), 107.2 (C5′), 125.1 (C3′), 131.2 (C6′), 138.9 (C5), 148.7 (C4′), 153.8 (C2′), 162.0 (C6′), 198.0 (C1); *m/z* 277 (M^+, 8%), 246 (23), 214 (6), 148 (12), 128 (100), 99 (36) [HRMS: found, 277.1309 (M^+). $C_{15}H_{19}NO_4$ requires 277.1314].

3-(2′-Methyl -6′-methoxy-3′-pyridyl)cyclohex-5-ene-1,4-dione 4-ethylene acetal 9b

A solution of mixed higher order cyanocuprate **3** (2.50 mmol)

in diethyl ether–THF (1:1) (10 cm^3) was prepared as outlined. Quinone monoacetal **4b** (0.36 g, 2.40 mmol) was then added at −40 °C and the mixture stirred at this temperature for 2 h. The reaction was quenched by the addition of NH_4Cl–NH_4OH (9:1) (5 cm^3) and filtered through a pad of Celite®. The mixture was extracted with diethyl ether (3 × 10 cm^3) and the combined organic phases dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give a yellow oil. Purification by flash column chromatography on silica gel with ethyl acetate–light petroleum (1:1) as eluant afforded acetal **9b**, isolated as a yellow solid (0.07 g, 0.25 mmol, 10%); mp 123–126 °C; ν_{max} (film)/cm^{-1} 2977, 2895, 1681s, 1598, 1581, 1559; δ_H (400 MHz; $CDCl_3$) 2.53 (3H, s, Me), 3.11 (1H, m, 2-H), 3.24 (1H, m, 2-H), 3.56 (1H, m, 3-H), 3.86 (4H, m, acetal), 3.91 (3H, s, OMe), 6.07 (1H, d, *J* 10.3 Hz, 6-H), 6.48 (1H, d, *J* 8.4 Hz, 5′-H), 6.67 (1H, d, *J* 10.3 Hz, 5-H), 7.57 (1H, d, *J* 8.4 Hz, 4′-H); δ_C (100 MHz; $CDCl_3$) 22.6 (Me), 42.1 (C2), 43.5 (C3), 48.8 (OCH_2), 50.0 (OCH_2), 53.2 (py-OMe) 97.9 (C4), 107.2 (C5′), 125.1 (C3′), 131.2 (C6), 138.9 (C5), 148.7 (C4′), 153.8 (C2′), 162.0 (C6′), 197.9 (C1); *m*/*z* 276 (MH^+, 30%), 231 (27), 126 (100), 98 (24) [HRMS: found, 276.1223 (MH^+). $C_{15}H_{18}NO_4$ requires 276.1236].

trans-4-*tert*-Butyldimethylsiloxy-3-(6′-methoxy-2′-methyl-3′-pyridyl)cyclohexan-1-one ethylene acetal 12

The ketone **11** (4.30 g, 12.3 mmol) and oxalic acid dihydrate (0.30 g, 2.40 mmol) were both dissolved in toluene (200 cm^3) and anhydrous ethylene glycol (12.6 g, 117 mmol) was added. A Dean–Stark apparatus was fitted for continuous removal of water and the mixture was stirred under reflux for 24 h. Saturated aqueous sodium hydrogen carbonate (200 cm^3) was added and the mixture was extracted with diethyl ether (3 × 150 cm^3). The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give a yellow oil, purified by flash column chromatography on silica gel with ether–light petroleum (3:7) as eluant to give the title compound **12** as a colourless oil, which solidified on standing to give a colourless, crystalline solid (4.72 g, 11.3 mmol, 92%); mp 57–60 °C; ν_{max} (film)/cm^{-1} 3050, 2950, 2856, 1599, 1478s, 1444, 1426; δ_H (400 MHz; $CDCl_3$) −0.40 (3H, s, SiMe), −0.14 (3H, s, SiMe), 0.66 (9H, s, Si^tBu), 1.73–1.90 (6H, m, 2, 5, 6-H), 2.50 (3H, s, Me), 3.12 (1H, m, 3-H), 3.58 (1H, m, 4-H), 3.90 (3H, s, OMe), 4.04 (4H, m, acetal), 6.54 (1H, d, *J* 8.4 Hz, 4′-H), 7.34 (1H, d, *J* 8.4 Hz, 5′-H); δ_C (100 MHz; $CDCl_3$) −5.1 (SiMe), −3.9 (SiMe), 18.2 (Si-C), 22.2 (C2′-Me), 25.9 (Bu^t), 33.1 (C6), 33.2 (C2), 40.0 (C5), 43.1 (C3), 53.4 (OMe), 64.4 (acetal), 75.3 (C4), 107.1 (C1), 108.2 (C5′), 129.5 (C3), 136.4 (C4′), 154.9 (C2), 161.3 (C6) (Found: C, 64.2; H, 8.9; N, 3.5. $C_{21}H_{35}NO_4Si$ requires C, 64.1; H, 9.0; N, 3.6%); *m*/*z* 394 (MH^+, 100%), 336 (54), 218 (57), 136 (46) [HRMS: found, 394.2432 (MH^+). $C_{21}H_{35}NO_4Si$ requires 394.2414].

trans-4-*tert*-Butyldimethylsiloxy-3-(6′-methoxy-2′-bromomethyl-3′-pyridyl)cyclohexan-1-one ethylene acetal 13

The ketal **12** (1.50 g, 3.80 mmol) was dissolved in carbon tetrachloride (30 cm^3). *N*-Bromosuccinimide (0.68 g, 3.80 mmol) and AIBN (0.09 g, 0.60 mmol) were added and the mixture irradiated with a 150 W mercury lamp for 10 h. The mixture was filtered to remove solids and concentrated under reduced pressure to give an orange oil. Purification by flash column chromatography on silica gel with diethyl ether–light petroleum (3:7) as eluant returned starting material as a yellow solid (0.26 g, 0.66 mmol) and gave the title compound **13** as a pale yellow solid (0.94 g, 1.99 mmol, 52%); mp 84–86 °C; ν_{max} (film)/cm^{-1} 3056, 2932, 2866, 1597, 1472s, 1440s; δ_H (400 MHz; $CDCl_3$) −0.43 (3H, s, SiMe), −0.11 (3H, s, SiMe), 0.63 (9H, s, Si^tBu), 1.71–1.96 (6H, m, 2, 5, 6-H), 3.21 (1H, m, 3-H), 3.58 (1H, m, 4-H), 3.90 (3H, s, OMe), 3.98 (4H, m, acetal), 4.36 (1H, d, *J* 9.5 Hz, CH_2Br), 4.94 (1H, d, *J* 9.5 Hz, CH_2Br), 6.64 (1H, d, *J* 8.4 Hz, 4′-H), 7.34 (1H, d, *J* 8.4 Hz, 5′-H); δ_C (100 MHz; $CDCl_3$) −5.3 (SiMe), −3.3 (SiMe), 18.2 (Si-C), 22.2 (C2′-Me), 25.9 (Bu^t), 33.4 (C6), 33.6 (C2), 39.7 (C5), 43.6 (C3), 46.4 (CH_2Br), 53.4 (OMe), 64.4 (acetal), 75.5 (C4), 107.3 (C1), 107.9 (C5′), 129.7 (C3), 136.1 (C4′), 155.3 (C2), 160.2 (C6); *m*/*z* 473 (MH^+, 44%), 429 (20), 393 (100) [HRMS: found, 473.1510 (MH^+). $C_{21}H_{34}BrNO_4Si$ requires 473.1514].

3-Methoxy-6a,7,8,9,10,10a-hexahydro-5*H*-chromeno[3,4-*b*]-pyridin-9-one ethylene acetal 14

The silyl ether **13** (0.55 g, 1.16 mmol) was dissolved in THF (10 cm^3) and tetrabutylammonium fluoride (1.0 M in THF) (2.30 cm^3, 2.30 mmol) was added. The solution was stirred at room temperature for 12 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using diethyl ether–light petroleum (1:1) as eluant to give the title compound **13** as a colourless gum (0.16 g, 1.15 mmol, 50%); mp 99–100 °C; ν_{max} (film)/cm^{-1} 3020, 2948, 2878, 2838, 1601s, 1578, 1480; δ_H (400 MHz; $CDCl_3$) 1.79–1.91 (4H, m, 7, 8-H), 2.03 (1H, m, 10-H) 2.30 (1H, m, 10-H), 2.89 (1H, td, *J* 3.7, 9.9 Hz, 6a-H), 3.31 (1H, td, *J* 4.0, 9.9 Hz, 10a-H), 3.87 (3H, s, OMe), 4.03 (4H, m, acetal), 4.79 (2H, s, 5-H), 6.56 (1H, d, *J* 8.4 Hz, 2-H), 7.38 (1H, d, *J* 8.4 Hz, 1-H); δ_C (100 MHz; $CDCl_3$) 29.1 (C10a), 33.4 (C8), 35.8 (C7), 37.4 (C6a), 53.3 (OMe), 63.6 (acetal), 69.3 (C5), 106.5 (C9), 108.4 (C2), 128.3 (C10b), 133.4 (C1), 147.4 (C5a), 161.9 (C3); *m*/*z* 278 (MH^+ 100%), 219 (9), 99 (18) [HRMS: found, 278.1387 (MH^+). $C_{15}H_{19}NO_4$ requires 278.1392].

trans-4-Hydroxy-3-(6′-methoxy-2′-methyl-3′-pyridyl)cyclohexan-1-one ethylene acetal 15

The silyl ether **12** (1.40 g, 3.60 mmol) was dissolved in THF (100 cm^3) and tetrabutylammonium fluoride (1.0 M in THF) (14.4 cm^3, 14.4 mmol) was added. The mixture was stirred at room temperature for 12 h and then concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel with diethyl ether as eluant to give the title compound **15** as a colourless gum (0.54 g, 2.77 mmol, 77%); ν_{max} (film)/cm^{-1} 3448s, 3044, 2950, 2884, 1599, 1582, 1476, 1472; δ_H (400 MHz, $CDCl_3$) 1.58–1.81 (5H, m, 2, 5, 6-H), 2.05 (1H, m, 5-H), 2.47 (3H, s, Me), 3.06 (1H, td, *J* 3.7, 10.3 Hz, 3-H), 3.67 (1H, td, *J* 3.7, 10.3 Hz, 4-H), 3.86 (3H, s, OMe), 3.88–3.97 (4H, m, acetal), 6.53 (1H, d, *J* 8.4 Hz, 5′H), 7.39 (1H, d, *J* 8.4 Hz, 4′H); δ_C (100 MHz, $CDCl_3$) 23.2 (Me), 32.3 (C5), 34.2 (C6), 40.1 (C2), 43.7 (C3), 54.4 (OMe), 64.2 (acetal), 74.1 (C4), 107.1 (C1), 107.3 (C5′), 127.1 (C3′), 136.4 (C4′), 154.6 (C2′), 161.9 (C6′); *m*/*z* 280 (MH^+, 100%), 222 (34), 136 (21) [HRMS: found, 280.1554 (MH^+). $C_{15}H_{21}NO_4$ requires 280.1549].

trans-4-Hydroxy-3-(6′-methoxy-2′-bromomethyl-3′-pyridyl)-cyclohexan-1-one 16

The silyl ether **15** (0.54 g, 2.30 mmol) was dissolved in carbon tetrachloride (10 cm^3). *N*-Bromosuccinimide (0.41 g, 2.30 mmol) and AIBN (0.05 g, 0.33 mmol) were added and the mixture irradiated with a 150 W mercury lamp for 2 h. The mixture was filtered to remove solids and concentrated under reduced pressure to give an orange oil purified by flash column chromatography on silica gel with diethyl ether as eluant to give a white solid (0.55 g, 1.77 mmol, 77%); mp 97–98 °C; ν_{max} (film)/cm^{-1} 3445, 3011, 2946, 2885, 1600s, 1575, 1479; δ_H (400 MHz; $CDCl_3$) 1.81–2.14 (5H, m, 2, 5, 6-H), 2.13 (1H, m, 5-H) 3.53 (1H, td, *J* 9.9, 3.3 Hz, 3-H), 3.77 (1H, td, *J* 9.9, 4.0 Hz, 4-H), 3.97 (3H, s, OMe), 4.08 (4H, m, acetal), 4.53 (1H, d, *J* 9.5 Hz, CH_2Br), 4.80 (1H, d, *J* 9.5 Hz, CH_2Br), 6.76 (1H, d, *J* 8.4 Hz, 5′-H), 7.55 (1H, d, *J* 8.4 Hz, 4′-H); δ_C (100 MHz; $CDCl_3$) 28.9 (C5), 33.1 (C6), 37.0 (C2), 37.8 (C3), 45.3 (CH_2Br), 53.5 (OMe), 64.6 (acetal), 78.5 (C4), 108.2 (C5′), 108.8

(C1), 125.9 (C3′), 135.5 (C4′), 151.3 (C2′), 162.2 (C6′); *m*/*z* 358 (MH^+, 52%), 314 (27), 278 (100) [HRMS: found, 365.0642 (MH^+). $C_{15}H_{20}BrNO_4$ requires 358.0654].

3-(6′-Methoxy-2′-bromomethyl-3′-pyridyl)cyclohexane-1,4-dione 4-ethylene acetal 17

DMSO (0.46 g, 5.50 mmol) was added to a solution of oxalyl chloride (0.43 g, 3.40 mmol) in dichloromethane (10 cm^3) at −60 °C under argon. The mixture was stirred for 2 min then bromo alcohol **16** (1.0 g, 2.80 mmol) was added in dichloromethane (2 cm^3) at −60 °C. The mixture was stirred for 15 min then triethylamine (1.40 g, 13.8 mmol) was added and the mixture stirred for a further 15 min before being warmed to room temperature. Water (20 cm^3) was added and the mixture extracted with DCM (2 × 50 cm^3) and the organic extract was dried and concentrated. Purification by silica gel chromatography with diethyl ether–light petroleum (7:3) as eluant to give the title compound **17** as a white solid (0.60 g, 1.68 mmol, 60%); mp 108–109 °C; ν_{max} (film)/cm^{-1} 3009, 2931, 2894, 2855, 1721s, 1605s, 1485; δ_H (400 MHz, $CDCl_3$) 2.05–2.15 (4H, m, 2, 6-H), 2.55 (1H, m, 5-H), 2.90 (1H, m, 5-H), 3.90 (3H, s OMe), 4.00–4.15 (4H, m, acetal), 4.30 (1H, dd, 5.9, 13.0 Hz, 3-H), 4.58 (1H, d, *J* 11.0 Hz, CH_2Br), 4.62 (1H, d, *J* 11.0 Hz, CH_2Br), 6.78 (1H, d, *J* 8.4 Hz, 5′-H), 7.43 (1H, d, *J* 8.4 Hz, 4′-H); δ_C (100 MHz, $CDCl_3$) 35.1 (C2), 38.9 (C5), 41.9 (C6), 46.2 (CH_2Br), 47.7 (C3), 54.6 (OMe), 63.4 (acetal), 64.1 (acetal), 108.4 (C1), 112.2 (C5′), 124.9 (C3′), 139.8 (C4′), 151.1 (C2′), 162.1 (C6′), 207.1 (C4); *m*/*z* 356 (MH^+, 5%), 324 (16), 312 (100), 276 (90), 99 (70) [HRMS: found 356.0511 (MH^+). $C_{15}H_{20}BrNO_4$ requires 356.0500].

3-Methoxy-7,8,9,10-tetrahydro-5*H*-chromeno[3,4-*b*]pyridin-9-one ethylene acetal 18. A solution of LDA was prepared by the addition of ^{n}BuLi (2.5 M in hexanes) (0.30 cm^3, 0.73 mmol) to a solution of diisopropylamine (0.08 g, 0.73 mmol) in THF (5 cm^3) at 0 °C under argon. The mixture was stirred for 30 min at 0 °C and then ketone **17** (0.26 g, 0.73 mmol) was added in THF (1 cm^3) at −78 °C. The mixture was stirred at this temperature for 2 h then warmed to room temperature and stirred for a further 2 h. The reaction was then quenched with water (10 cm^3) and the mixture extracted with diethyl ether (3 × 15 cm^3). The combined organic phases were dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a yellow oil. This was purified by flash column chromatography on silica gel with diethyl ether–light petroleum (7:3) as eluant to give the title compound **18** as a white solid (0.10 g, 0.37 mmol, 50%); ν_{max} (film)/cm^{-1} 3053, 2952, 1604s, 1581, 1480; δ_H (400 MHz; $CDCl_3$) 1.89 (2H, m, 7-H), 2.43 (2H, m, 8-H), 2.54 (1H, s, 10-H), 3.88 (3H, s, OMe), 4.03 (4H, m, acetal), 5.04 (2H, s, 5-H), 6.58 (1H, d, *J* 8.4 Hz, 2-H), 7.55 (1H, d, *J* 8.4 Hz, 1-H); δ_C (100 MHz; $CDCl_3$) 25.8 (C7), 30.9 (C8), 33.5 (C10), 53.9 (OMe), 64.6 (acetal), 64.9 (C5), 108.1 (C9), 109.4 (C10a), 129.5 (C11), 131.2 (C6a), 136.9 (C1), 150.1 (4a), 162.9 (C3); *m*/*z* 276 (MH^+, 100%), 189 (28) [HRMS: found, 276.1228 (MH^+). $C_{15}H_{17}NO_4$ requires 276.1236].

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References

1 J.-S. Liu, Y.-L. Zhu, C.-M. Yu, Y.-Z. Zhou, Y.-Y. Han, F.-W. Wu and B.-F. Qi, *Can. J. Chem.*, 1986, **64**, 837.
2 Y. Xia and A. P. Kozikowski, *J. Am. Chem. Soc.*, 1989, **111**, 4116; L. Qian and R. Ji, *Tetrahedron Lett.*, 1989, **30**, 2089; G. Campiani, Li-Q. Sun, A. P. Kozikowski, P. Aaagard and M. J. McKinney, *J. Org. Chem.*, 1993, **58**, 7660.
3 A. P. Kozikowski, W. Tuckmantel, A. Saxena and B. P. Doctor, *Helv. Chim. Acta*, 1994, **77**, 1256; S. Kaneko, N. Nakajima, M. Shikano, S. Katoh and S. Terashima, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 1927; A. P. Kozikowski, G. Campiani, V. Nacci, A. Saxena and B. P. Doctor, *J. Chem. Soc.*, *Perkin Trans. 1*, 1996, 1287; A. P. Kozikowski, G. Campiani, L.-Q. Sun, S. Wang, A. Saxena and B. P. Doctor, *J. Am. Chem. Soc.*, 1996, **118**, 11357; S. Keneko, N. Nakajima, M. Shikano, T. Katoh and S. Terashima, *Tetrahedron*, 1998, **54**, 5471.
4 L. C. Craig, *J. Am. Chem. Soc.*, 1934, **56**, 231.
5 B. H. Lipshutz, J. A. Kozlowski, D. A. Parker, S. L. Nguyen and K. E. McCarthy, *J. Organomet. Chem.*, 1985, **285**, 437.
6 D. R. Henton, K. Anderson, M. J. Manning and J. S. Swenton, *J. Org. Chem.*, 1980, **45**, 3422.
7 E. C. L. Gautier, N. J. Lewis, A. Mc.Killop and R. J. K. Taylor, *Synth. Commun.*, 1994, **24**, 2989.
8 A. Nillson, A. A. Ronlan and V. D. Parker, *Tetrahedron Lett.*, 1975, **16**, 1107.
9 R. A. J. Smith, in *Organocopper Reagents* (ed. R. J. K. Taylor), OUP, 1994, pp. 293–306.
10 Y. Chounan, T. Ibuka and Y. Yamamoto, *J. Chem. Soc.*, *Chem. Commun.*, 1994, 2003.
11 S. J. Danishefsky and B. Simoneau, *J. Am. Chem. Soc.*, 1989, **111**, 2599.
12 We have now obtained a crystal structure of cuprate adduct **11**, as its methyl ether rather than TBDMS ether and this confirmed the *anti*-stereochemistry.
13 M. J. Mancuso and D. Swern, *Synthesis*, 1981, 165.
14 G. R. Clemo, B. W. Fox and R. Raper, *J. Am. Chem. Soc.*, 1954, **76**, 2693.

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