Palladium catalysed elaboration of codeine and morphine

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Palladium catalysed coupling reactions of 6-*O*-*tert*-butyldimethylsilyl-1-bromocodeine and 6-*O*-*tert*-butyldimethylsilyl-3-trifluoromethylsulfonylmorphine allow a range of substituted analogues of codeine in the 1-position and morphine in the 3-position to be efficiently and selectively prepared.

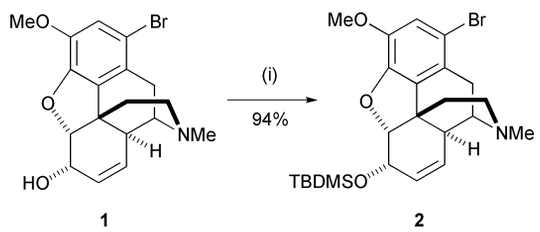
Introduction

The morphine alkaloids are of considerable pharmacological interest due to their potent analgesic properties.[1] The addiction associated with the administration of such analgesics has ensured that much effort has been devoted to the synthesis of potential non-addictive opioid derivatives.[2] As a result, the morphine skeleton has been functionalised in many positions, resulting in a qualitative understanding of the factors which affect opiate receptor binding. For instance, substituents on the nitrogen atom have been shown to have a dramatic effect on both the activity and the mode of action of the drug,[3] while neither the oxygen functionality nor unsaturation in the C ring is essential for activity.[4] Derivatisation of the aromatic A ring has received much less attention,[5] even though substitution of the aromatic ring has been shown to play an important role in binding to opioid receptors.[6] We wished to develop methodology which would allow systematic elaboration of the aromatic A ring of the morphine alkaloids, and now report herein that palladium catalysed coupling reactions enable the preparation of novel codeine and morphine derivatives. Part of this work has been previously communicated.[7]

Results and discussion

The synthesis of 1-substituted codeine derivatives

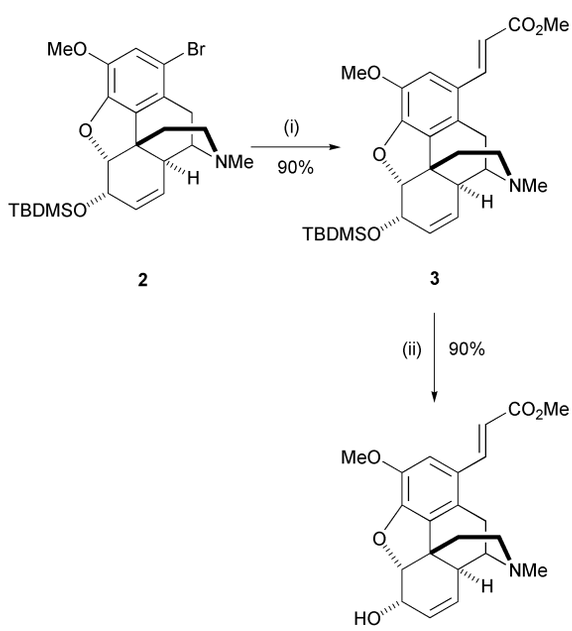
1-Bromocodeine **1** is readily prepared in multigram quantities[8] and seemed an attractive starting point for the functionalisation of the aromatic ring of codeine as aryl bromides have been shown to readily undergo palladium catalysed transformations.[9] The codeine skeleton of **1** offers a variety of synthetic challenges to explore the scope of these reactions. The functionalised aromatic halide contains a bulky *ortho*-group and electron donating substituents, both of which retard palladium insertion. The allylic ether moiety of **1** was also of some concern, as similar functionalities have been shown to be labile under palladium catalysis, notably to rearrangement to the corresponding vinyl ether[10] and to intermolecular Heck reactions.[11] To prevent such side reactions, the allylic alcohol of **1** was protected as its *tert*-butyldimethylsilyl ether by treatment with *tert*-butyldimethylsilyl chloride and imidazole, furnishing 6-*O*-*tert*-butyldimethylsilyl-1-bromocodeine **2** in 94% yield (Scheme 1).



1 **2**

Scheme 1 *Reagents and conditions*: (i) TBDMSCl (1.2 eq.), imidazole (1.2 eq.), DMF.

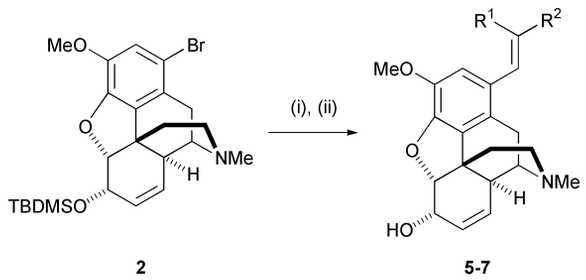
The susceptibility of 6-*O*-*tert*-butyldimethylsilyl-1-bromocodeine **2** to palladium catalysed coupling reactions was initially investigated through a Heck reaction with methyl acrylate to yield 6-*O*-*tert*-butyldimethylsilyl-1-[2-(methoxycarbonyl)ethenyl]codeine **3**, isolated as a single diastereoisomer in 90% yield. No indications of skeletal rearrangements or side reactions were seen in the crude reaction mixture, with the carbon–carbon double bond of **3** assigned the (*E*)-geometry due to the olefinic coupling constant of 15.9 Hz in the ^{1}H NMR analysis. Deprotection of the silyl protecting group with TBAF at RT afforded 1-[2-(methoxycarbonyl)ethenyl]codeine **4** in 90% yield (Scheme 2).



2 **3** **4**

Scheme 2 *Reagents and conditions*: (i) $Pd(OAc)_2$ (2 mol%), methyl acrylate (4 eq.), tri-*o*-tolylphosphine (8 mol%), NEt_3 (1.4 eq.), DMF, Δ; (ii) TBAF (2 eq.), THF, RT.

The scope of the Heck reaction and subsequent silyl deprotection for the synthesis of a range of 1-vinylogous codeine derivatives was extended to the use of styrene, methyl vinyl ketone and methyl methacrylate. In each case, a single diastereoisomer **5**–**7** with (*E*)-double bond geometry, on the basis of ^{1}H NMR spectroscopic analysis, was isolated after purification by column chromatography in good yield (Scheme 3).

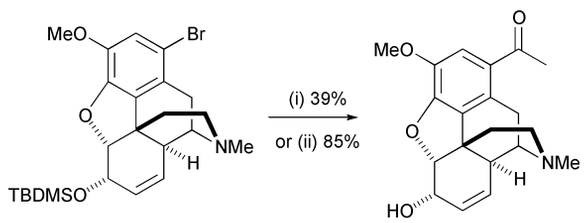


2 **5-7**

	R^1	R^2	Yield (%)
5	H	Ph	76
6	H	COMe	72
7	Me	CO_2Me	70

Scheme 3 *Reagents and conditions*: (i) $Pd(OAc)_2$ (2 mol%), vinyl acceptor (4 eq.), tri-*o*-tolylphosphine (8 mol%), NEt_3 (1.4 eq.), DMF, Δ; (ii) TBAF (2 eq.), THF, RT.

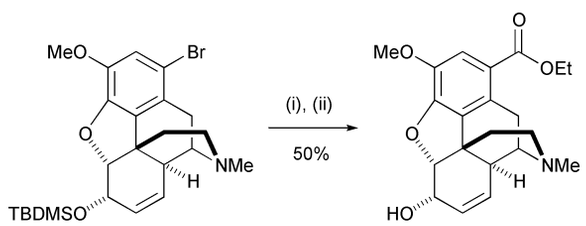
Attempted extension of this Heck methodology to the use of ethyl vinyl ether as the vinyl component in the coupling procedure afforded 1-acetylcodeine **8**, but in a disappointing 39% yield.[12] A more efficient synthesis of **8** was therefore followed, using (α-ethoxyvinyl)tributyltin[13] as a masked acetylating agent[14] which furnished 1-acetylcodeine **8** in 85% yield after hydrolysis and silyl deprotection (Scheme 4).



2 **8**

Scheme 4 *Reagents and conditions*: (i) $Pd(OAc)_2$ (2 mol%), ethyl vinyl ether (4 eq.), tri-*o*-tolylphosphine (8 mol%), NEt_3 (1.4 eq.), DMF, Δ then $HCl_{(aq)}$; (ii) $Pd(OAc)_2$ (2 mol%), (α-ethoxyvinyl)tributyltin (4 eq.), PPh_3 (8 mol%), NEt_3 (1.4 eq.), DMF, Δ then $HCl_{(aq)}$.

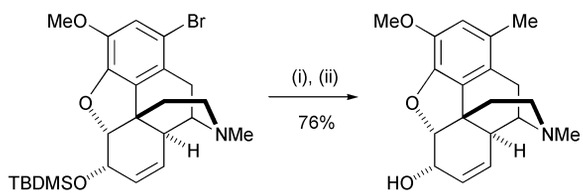
To extend the carbon functionality which can be directly incorporated in the 1-position of codeine and probe further the reactivity of 6-*O*-*tert*-butyldimethylsilyl-1-bromocodeine **2**, palladium catalysed carbonylation of **2** was attempted. Thus, **2** was subjected to carbonylation under 3 atmospheres of carbon monoxide with palladium(II) chloride catalysis. Subsequent silyl deprotection and purification by column chromatography gave 1-ethoxycarbonylcodeine **9** in 50% yield over two steps (Scheme 5).



2 **9**

Scheme 5 *Reagents and conditions*: (i) $PdCl_2$ (2 mol%), PPh_3 (8 mol%), CO (3 atm), NEt_3–EtOH; (ii) TBAF (2 eq.), THF.

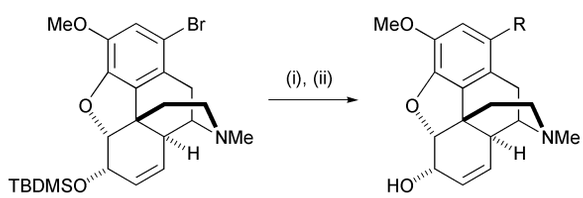
Having shown that both vinylic and carbonyl components can be efficiently utilised to prepare 1-substituted codeine analogues, the synthesis of 1-alkyl derivatives was attempted. The use of organotin derivatives to transmetallate an organic group to a palladium complex has been shown to provide a reliable and mild methodology for the formation of carbon–carbon bonds that is tolerated by many functional groups.[15] As a model system, utilisation of this methodology using a modified Stille procedure[16] enabled cross-coupling of 6-*O*-*tert*-butyldimethylsilyl-1-bromocodeine **2** with tetramethylstannane, furnishing 1-methylcodeine **10** in 76% yield after TBAF promoted silyl deprotection (Scheme 6).



2 **10**

Scheme 6 *Reagents and conditions*: (i) $Pd(OAc)_2$ (2 mol%), tri-*o*-tolylphosphine (8 mol%), Me_4Sn (1.2 eq.), NEt_3 (1.4 eq.), DMF; (ii) TBAF (2 eq.), THF, RT.

Extension of this coupling methodology to the use of a variety of alkyltributyltin species led to the preparation of a range of 1-alkylated codeines **11**–**14** in good yield (Scheme 7).



2 **11-14**

	R	Yield (%)
11	Ph	89
12	Vinyl	80
13	Allyl	73
14	Phenylethynyl	81

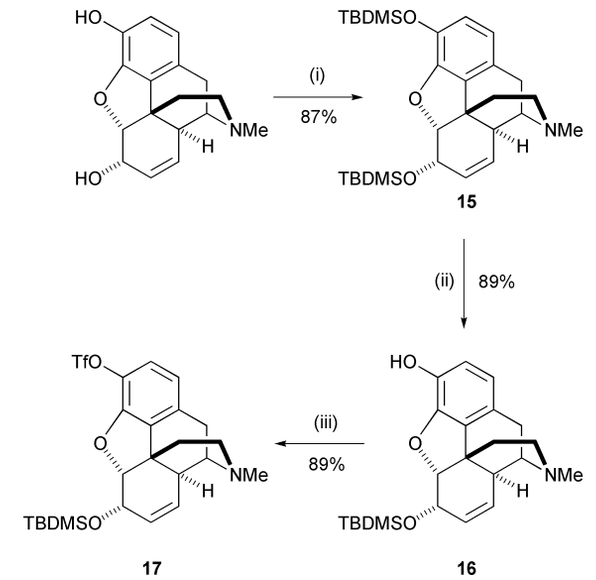
Scheme 7 *Reagents and conditions*: (i) $Pd(OAc)_2$ (2 mol%), PPh_3 (8 mol%), Bu_3SnR (1.2 eq.), NEt_3; (ii) TBAF (2 eq.), THF, RT.

Following the synthesis of a range of 1-substituted codeine derivatives prepared from 6-*O*-*tert*-butyldimethylsilyl-1-bromocodeine **2**, attention was turned to elaboration of the 3-position of morphine.

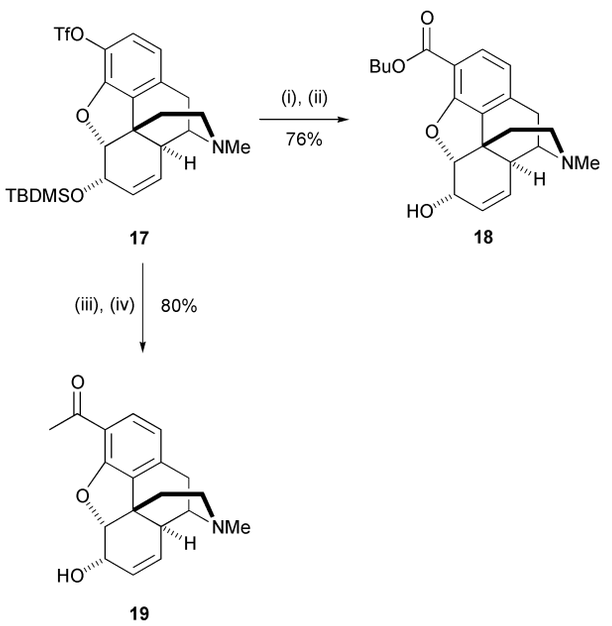
The synthesis of 3-substituted morphine derivatives

To elaborate upon the 3-position of morphine, we envisaged that the 3-hydroxy functionality could be derivatised using palladium catalysis *via* its aryl triflate. Thus, the 3- and 6-hydroxy functionalities were protected according to a literature procedure,[17] furnishing 3,6-di-*O*-*tert*-butyldimethylsilylmorphine **15** in 87% yield. Treatment of **15** with one equivalent of TBAF at 0 °C allowed selective mono-deprotection of the phenolic silyl protecting group, affording 6-*O*-*tert*-butyldimethylsilylmorphine **16** in 89% yield. 3-*O*-Trifluoromethylsulfonyl-6-*O*-*tert*-butyldimethylsilylmorphine **17** was subsequently prepared in 89% yield by addition of trifluoromethanesulfonic anhydride to a solution of **16** and 2,6-dimethylpyridine in DCM (Scheme 8).

Alkoxycarbonylation of the triflate **17** was successful under the palladium catalysed conditions described by Dolle *et al.*,[18] giving 3-deoxy-3-butoxycarbonylmorphine **18** in 76% yield. Similarly, tin cross-coupling of **17** with (α-ethoxyvinyl)tri-



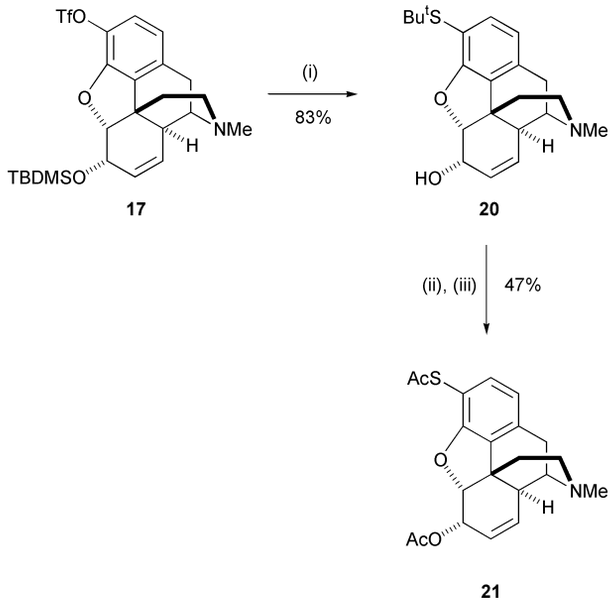
Scheme 8 *Reagents and conditions*: (i) TBDMSCl (3 eq.), imidazole (5.0 eq.), THF; (ii) TBAF (1 eq.), THF, 0 °C; (iii) trifluoromethanesulfonic anhydride (1.2 eq.), 2,6-dimethylpyridine (1 eq.), DCM, 0 °C.



Scheme 9 *Reagents and conditions*: (i) CO (3 atm), BuOH, $Pd(OAc)_2$ (4 mol%), 1,3-bis(diphenylphosphino)propane (4 mol%), Δ; (ii) TBAF, THF; (iii) (α-ethoxyvinyl)tributylstannane, $Pd(OAc)_2$ (4 mol%), PPh_3 (8 mol%), LiCl, DMF, Δ; (iv) $HCl_{(aq)}$, RT.

butylstannane gave 3-deoxy-3-acetylmorphine **19** in 80% yield (Scheme 9).

Having shown that aryl triflate **17** is susceptible to palladium catalysed coupling reactions, our attention turned to the preparation of 3-substituted sulfur derivatives of morphine. The replacement of the 3-hydroxy group of morphine with sulfur functionalities has previously been reported by Hori *et al.*,[19] who used the Newman–Kwart rearrangement[20] to replace the aromatic hydroxy group with a thio derivative. Our strategy toward this transformation was to utilise the palladium catalysed coupling of morphine triflate **17** with tributylstannyl *tert*-butyl sulfide. Initial attempts at using low catalyst loadings to this effect resulted, however, in >80% recovery of starting material. Good levels of conversion to the product could only be achieved with 0.5 equivalents of $Pd(PPh_3)_4$, giving 3-deoxy-3-*tert*-butylthiomorphine **20** in 83% yield. Mercuric acetate deprotection of the *tert*-butyl group in the presence of TFA and anisole, followed by treatment with hydrogen sulfide gas and trapping with acetic anhydride afforded 3-deoxy-3-acetylthio-6-acetylmorphine **21** in 47% yield (Scheme 10).



Scheme 10 *Reagents and conditions*: (i) $Pd(PPh_3)_4$ (0.5 eq.), tributylstannyl *tert*-butyl sulfide (2 eq.), LiCl (3 eq.), DMF, Δ; (ii) $Hg(OAc)_2$ (1.05 eq.), anisole, TFA, 0 °C then $SH_2(g)$; (iii) acetic anhydride, NEt_3, DMAP, DCM.

Conclusion

The transformation of 6-*O*-*tert*-butyldimethylsilyl-1-bromocodeine **2** and 6-*O*-*tert*-butyldimethylsilyl-3-trifluoromethylsulfonylmorphine **17** to a range of acyl, alkyl and vinyl derivatives has been successfully achieved using palladium catalysis.

Experimental

General

All reactions involving organometallic or other moisture sensitive reagents were performed under an atmosphere of nitrogen *via* standard vacuum line techniques. All glassware was flame-dried and allowed to cool under vacuum. THF was distilled under an atmosphere of dry nitrogen from sodium–benzophenone ketyl. Water was distilled. All other solvents and reagents were used as supplied (Analytical or HPLC grade), without prior purification. All organometallic reagents were used as supplied. Reactions were dried with $MgSO_4$. Thin layer chromatography (tlc) was performed on aluminium sheets coated with 60 F_{254} silica. Sheets were visualised using iodine, UV light or 1% aqueous $KMnO_4$ solution. Flash chromatography was performed on Kieselgel 60 silica. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker WH300 (^{1}H: 300 MHz and ^{13}C: 75 MHz), a Bruker DPX 400 (^{1}H: 400 MHz and ^{13}C: 100.6 MHz) or, where stated, on a Bruker AMX 500 (^{1}H: 500 MHz and ^{13}C: 125.3 MHz) spectrometer in the deuterated solvent stated. All chemical shifts (δ) are quoted in ppm and coupling constants (J) in Hz. Coupling constants are quoted twice, each being recorded as observed in the spectrum without averaging. Residual signals from the solvents were used as an internal reference. ^{13}C Multiplicities were assigned using a DEPT sequence. In all cases, the reaction diastereoselectivity was assessed by peak integration of the ^{1}H NMR spectrum of the crude reaction mixture. Infrared spectra were recorded on a Perkin-Elmer 1750 IR Fourier Transform spectrophotometer using thin films on NaCl plates (film) or KBr discs (KBr) as stated. Only the characteristic peaks are quoted. Low resolution mass spectra

(*m*/*z*) were recorded on VG MassLab 20-250 or Micromass Platform 1 spectrometers and high resolution mass spectra (HRMS) on a Micromass Autospec 500 OAT spectrometer or on a Waters 2790 Micromass LCT Exact Mass Electrospray Ionisation Mass Spectrometer. Techniques used were chemical ionisation (CI, NH_3), atmospheric pressure chemical ionisation (APCI) or electrospray ionisation (ESI) using partial purification by HPLC with methanol–acetonitrile–water (40 : 40 : 20) as eluent. Specific optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell and are given in units of 10^{-1} deg cm^2 g^{-1}. Concentrations are quoted in g per 100 ml. Melting points were recorded on a Gallenkamp apparatus and are uncorrected. Elemental analyses were performed by the microanalysis service of the Dyson Perrins Laboratory, Oxford.

Representative procedure 1

DMF, NEt_3 and the appropriate olefin were added to a stirred mixture of the palladium catalyst, phosphine ligand and aryl halide in a Fischer–Porter bottle. The mixture was frozen, degassed and filled with N_2. The vessel was sealed, allowed to warm to RT and the pressure vented. The freeze–pump–thaw process was repeated twice, before the vessel was sealed and heated to 100 °C for 4 hours. After cooling, the mixture was diluted with Et_2O, filtered and concentrated *in vacuo* before purification.

Representative procedure 2

A solution of TBAF (2 eq.) in THF was added to the *tert*-butyldimethylsilyl ether in THF and stirred at RT for 2 hours. The solution was diluted with DCM, washed with H_2O, dried, filtered and concentrated *in vacuo* before purification by column chromatography (DCM–MeOH 12 : 1) to give the corresponding alcohol.

Preparation of 6-*O*-*tert*-butyldimethylsilyl-1-bromocodeine 2

tert-Butyldimethylsilyl chloride (2.2 g, 15 mmol) in THF (15 ml) was added to a stirred solution of **1** (5.0 g, 13 mmol) and imidazole (1 g, 15 mmol) in THF (15 ml) at RT. After twenty hours, the solution was diluted with Et_2O (100 ml), washed with H_2O (2 × 50 ml), dried and concentrated *in vacuo*. The residue was recrystallised (EtOH) to give **2** (6.1 g, 94%) as a white solid; mp 103 °C; $C_{24}H_{34}BrNO_3Si$ requires C, 58.5, H, 7.0, N, 2.8%; found C, 58.3, H, 7.0, N, 2.8%; $[\alpha]_D^{24}$ −153.8 (*c* 1.0, $CHCl_3$); ν_{max} (film) 2929, 2854 (C–H), 1472, 1438, 1129 (C–O); δ_H (400 MHz, $CDCl_3$) 0.13, 0.15 (2 × 3H, s, Si(*Me*)$_2$^{t}Bu), 0.93 (9H, s, Si(Me)$_2$^{t}*Bu*), 1.83–1.88 (1H, m, C(15)H_B), 2.01 (1H, td, $J_{15A,15B;15A,16A}$ 12.5, $J_{15A,16B}$ 5.1, C(15)H_A), 2.17 (1H, dd, *J* 18.9, *J* 6.2, C(10)H_A), 2.34 (1H, td, $J_{16A,16B;16A,15A}$ 12.5, $J_{16A,15B}$ 3.6, C(16)H_A), 2.45 (3H, s, N*Me*), 2.57 (1H, dd, $J_{16B,16A}$ 12.5, $J_{16B,15B}$ 4.6, C(16)H_B), 2.61–2.64 (1H, m, C(14)*H*), 2.89 (1H, d, *J* 18.9, C(10)H_B), 3.39 (1H, dd, $J_{9,10A}$ 6.1, $J_{9,14}$ 3.0, C(9)*H*), 3.84 (3H, s, O*Me*), 4.23–4.27 (1H, m, C(6)*H*), 4.72 (1H, dd, $J_{5,6}$ 6.1, $J_{5,7}$ 0.9, C(5)*H*), 5.24–5.28 (1H, m, C(8)*H*), 5.64–5.68 (1H, m, C(7)*H*), 6.83 (1H, s, C(2)*H*); δ_C (100 MHz, $CDCl_3$) −4.8, −4.6, 18.4, 22.0. 25.9, 35.9, 40.8, 43.1, 43.7, 46.2, 57.0, 58.8, 68.3, 92.5, 111.8, 117.0, 126.5, 127.8, 132.5, 134.1, 142.9, 147.2; *m*/*z* (CI$^+$) 492.1 (MH$^+$, 100%).

Preparation of 6-*O*-*tert*-butyldimethylsilyl-1-[2-(methoxycarbonyl)ethenyl]codeine 3

Following representative procedure 1, **2** (500 mg, 1 mmol), methyl acrylate (0.36 ml, 4 mmol), $Pd(OAc)_2$ (5 mg, 2 mol%), tri-*o*-tolylphosphine (25 mg, 8 mol%), NEt_3 (0.2 ml, 1.4 mmol) and DMF (1.5 ml) gave, after purification by column chromatography and recrystallisation (EtOH), **3** (430 mg, 90%) as a white solid; mp 151 °C; $C_{28}H_{39}NO_5Si$ requires C, 67.6, H, 7.9, N, 2.8%; found C, 67.5, H, 7.9, N, 2.7%; $[\alpha]_D^{24}$ −81.2 (*c* 0.58, $CHCl_3$); ν_{max} (film) 2930, 2856 (C–H), 1715 (C=O), 1160 (C–O); δ_H (400 MHz, $CDCl_3$) 0.13, 0.15 (2 × 3H, s, Si(*Me*)$_2$^{t}Bu), 0.93 (9H, s, Si(Me)$_2$^{t}*Bu*), 1.83–1.87 (1H, m, C(15)H_B), 2.03 (1H, td, $J_{15A,15B;15A,16A}$ 12.3, $J_{15A,16B}$ 5.0, C(15)H_A), 2.31–2.39 (2H, m, C(10)H_A and C(16)H_A), 2.47 (3H, s, N*Me*), 2.59 (1H, dd, $J_{16B,16A}$ 12.0, $J_{16B,15B}$ 4.1, C(16)H_B), 2.63–2.66 (1H, m, C(14)*H*), 3.14 (1H, d, *J* 18.7, C(10)H_B), 3.39 (1H, dd, $J_{9,10A}$ 5.3, $J_{9,14}$ 2.9, C(9)*H*), 3.80, 3.88 (2 × 3H, s, O*Me* and CO_2*Me*), 4.27–4.30 (1H, m, C(6)*H*), 4.77 (1H, dd, $J_{5,6}$ 6.2, $J_{5,7}$ 0.9, C(5)*H*), 5.26–5.28 (1H, m, C(8)*H*), 5.66–5.69 (1H, m, C(7)*H*), 6.21 (1H, d, *J* 15.9, HC=C*H*CO$_2$Me), 6.97 (1H, s, C(2)*H*), 7.81 (1H, d, *J* 15.9, *H*C=CHCO$_2$Me); δ_C (100 MHz, $CDCl_3$) −4.3, −4.2, 18.8, 19.7, 26.3, 36.4, 41.0, 43.7, 43.8, 46.7, 52.1, 57.2, 59.0, 68.8, 93.5, 112.5, 115.5, 124.7, 128.4, 132.1, 134.5, 141.5, 143.0, 150.9, 168.4; *m*/*z* (CI$^+$) 498.3 (MH$^+$, 100%).

Preparation of 1-[2-(methoxycarbonyl)ethenyl]codeine 4

Following representative procedure 2, **3** (500 mg, 1 mmol) and TBAF (0.64 g, 2 mmol) in THF gave, after purification by column chromatography and recrystallisation (EtOH), **4** (350 mg, 90%) as a white solid; mp 134 °C; $C_{22}H_{25}NO_5$ requires C, 68.9, H, 6.6, N, 3.65%; found C, 69.0, H, 6.5, N, 3.4%; $[\alpha]_D^{24}$ −1.82 (*c* 1.0, $CHCl_3$); ν_{max} (film) 3392 (OH), 2948, 2908 (C–H), 1708 (C=O), 1594 (C=C), 1165 (C–O); δ_H (400 MHz, $CDCl_3$) 1.85–1.89 (1H, m, C(15)H_B), 2.09 (1H, td, $J_{15A,15B;15A,16A}$ 12.4, $J_{15A,16B}$ 5.2, C(15)H_A), 2.31–2.39 (2H, m, C(10)H_A and C(16)H_A), 2.47 (3H, s, N*Me*), 2.61 (1H, dd, $J_{16B,16A}$ 12.3, $J_{16B,15B}$ 4.4, C(16)H_B), 2.68–2.70 (1H, m, C(14)*H*), 3.17 (1H, d, *J* 18.8, C(10)H_B), 3.39 (1H, dd, $J_{9,10A}$ 6.9, $J_{9,14}$ 3.0, C(9)*H*), 3.81, 3.87 (2 × 3H, s, O*Me* and CO_2*Me*), 4.21–4.23 (1H, m, C(6)*H*), 4.95 (1H, dd, $J_{5,6}$ 6.5, $J_{5,7}$ 1.0, C(5)*H*), 5.29–5.32 (1H, m, C(8)*H*), 5.71–5.75 (1H, m, C(7)*H*), 6.25 (1H, d, *J* 15.8, HC=C*H*CO$_2$Me), 6.96 (1H, s, C(2)*H*), 7.82 (1H, d, *J* 15.8, *H*C=CHCO$_2$Me); δ_C (100 MHz, $CDCl_3$) 19.2, 35.7, 40.4, 43.2, 46.2, 51.7, 56.1, 58.5, 66.5, 92.2, 110.4, 115.8, 125.1, 127.9, 128.3, 131.6, 133.5, 140.8, 142.7, 148.8, 167.8; *m*/*z* (CI$^+$) 384.3 (MH$^+$, 100%).

Preparation of 1-(α-styryl)codeine 5

Following representative procedure 1, **2** (500 mg, 1 mmol), styrene (0.14 ml, 1.2 mmol), $Pd(OAc)_2$ (5 mg, 2 mol%), tri-*o*-tolylphosphine (25 mg, 8 mol%), NEt_3 (0.2 ml, 1.4 mmol) and DMF (1.5 ml) gave, after treatment with TBAF (0.64 g, 2 mmol) in THF (10 ml) according to representative procedure 2, **5** (300 mg, 76%) as a pale yellow solid; mp 173 °C, $C_{26}H_{27}NO_3$ requires C, 77.8, H, 6.8, N, 3.5%; found C, 78.1, H, 6.95, N, 3.4%; $[\alpha]_D^{22}$ −36.6 (*c* 1.05, $CHCl_3$); ν_{max} 3392 (OH), 1592 (C=C), 1499, 1446, 1121 (C–O); δ_H (300 MHz, $CDCl_3$) 1.88–1.93 (1H, m, C(15)H_B), 2.09 (1H, td, $J_{15A,15B;15A,16A}$ 12.2, $J_{15A,16B}$ 5.0, C(15)H_A), 2.34–2.48 (2H, m, C(10)H_A and C(16)H_A), 2.50 (3H, s, N*Me*), 2.61 (1H, dd, $J_{16B,16A}$ 12.3, $J_{16B,15B}$ 4.3, C(16)H_B), 2.70–2.72 (1H, m, C(14)*H*), 3.12 (1H, d, *J* 18.4, C(10)H_B), 3.39 (1H, dd, $J_{9,10A}$ 5.9, $J_{9,14}$ 3.1, C(9)*H*), 3.92 (3H, s, O*Me*), 4.19–4.23 (1H, m, C(6)*H*), 4.92–4.94 (1H, m, C(5)*H*), 5.25–5.34 (1H, m, C(8)*H*), 5.66–5.76 (1H, m, C(7)*H*), 6.91 (1H, d, *J* 16.1, HC=C*H*Ph), 7.00 (1H, s, C(2)*H*), 7.18 (1H, d, *J* 16.1, *H*C=CHPh), 7.26–7.51 (5H, m, Ph); δ_C (50 MHz, $CDCl_3$) 19.3, 35.7, 40.4, 43.1, 46.3, 56.2, 58.8, 66.4, 91.6, 108.9, 124.7, 125.1, 126.3, 126.7, 127.4, 127.7, 128.4, 128.6, 128.7, 131.4, 133.5, 137.6, 142.6, 146.4; *m*/*z* (CI$^+$) 402.3 (MH$^+$, 100%).

Preparation of 1-(2-acetylethenyl)codeine 6

Following representative procedure 1, **2** (500 mg, 1 mmol), methyl vinyl ketone (0.10 ml, 1.2 mmol), $Pd(OAc)_2$ (5 mg, 2 mol%), tri-*o*-tolylphosphine (25 mg, 8 mol%), NEt_3 (0.2 ml, 1.4 mmol) and DMF (1.5 ml) gave, after treatment with TBAF (0.64 g, 2 mmol) in THF (10 ml) according to representative procedure 2, **6** (260 mg, 72%) as a yellow solid; mp 161 °C,

$C_{22}H_{25}NO_4$ requires C, 71.9, H, 6.9, N, 3.8%; found C, 71.7, H, 7.1, N, 3.7%; $[\alpha]_D^{22}$ −34.0 (*c* 0.15, $CHCl_3$); ν_{max} 3500 (OH), 1690 (C=O), 1585 (C=C); δ_H (300 MHz, $CDCl_3$) 1.84–1.89 (1H, m, C(15)H_B), 2.09 (1H, td, $J_{15A,15B;15A,16A}$ 12.2, $J_{15A,16B}$ 5.0, C(15)H_A), 2.32–2.45 (2H, m, C(10)H_A and C(16)H_A), 2.37 (3H, s, CO*Me*), 2.48 (3H, s, N*Me*), 2.61 (1H, dd, $J_{16B,16A}$ 12.3, $J_{16B,15B}$ 3.8, C(16)H_B), 2.69–2.71 (1H, m, C(14)*H*), 3.15 (1H, d, *J* 18.7, C(10)H_B), 3.43 (1H, dd, $J_{9,10A}$6.2, $J_{9,14}$3.2, C(9)*H*), 3.88 (3H, s, O*Me*), 4.20–4.23 (1H, m, C(6)*H*), 4.94–4.97 (1H, m, C(5)*H*), 5.28–5.33 (1H, m, C(8)*H*), 5.71–5.75 (1H, m, C(7)*H*), 6.56 (1H, d, *J* 16.0, HC=C*H*COMe), 6.99 (1H, s, C(2)*H*), 7.67 (1H, d, *J* 16.0, *H*C=CHCOMe); δ_C (50 MHz, $CDCl_3$) 19.1, 27.7, 35.4, 40.0, 42.9, 45.9, 56.0, 58.3, 66.6, 92.6, 110.6, 125.0, 125.1, 128.2, 128.4, 131.9, 133.7, 139.4, 142.8, 149.7, 198.6; *m*/*z* (CI^+) 368.2 (MH^+, 100%).

Preparation of 1-[2-(methoxycarbonyl)propenyl]codeine 7

Following representative procedure 1, **2** (500 mg, 1 mmol), methyl methacrylate (0.13 ml, 1.2 mmol), $Pd(OAc)_2$ (5 mg, 2 mol%), tri-*o*-tolylphosphine (25 mg, 8 mol%), NEt_3 (0.2 ml, 1.4 mmol) and DMF (1.5 ml) gave, after treatment with TBAF (0.64 g, 2 mmol) in THF (10 ml) according to representative procedure 2, **7** (260 mg, 72%) as a yellow solid; mp 168 °C; $C_{23}H_{27}NO_5$ requires C, 69.5, H, 6.85, N, 3.5%; found C, 69.3, H, 6.95, N, 3.4%; $[\alpha]_D^{22}$ −51.3 (*c* 0.15, $CHCl_3$); ν_{max} (film) 2930, 2842 (C–H), 1705 (C=O), 1597 (C=C), 1111 (C–O); δ_H (400 MHz, $CDCl_3$) 1.88–1.91 (1H, m, C(15)H_B), 2.04–2.10 (1H, m, C(15)H_A), 2.08 (3H, d, *J* 1.2, HC=C(*Me*)CO_2Me), 2.24 (1H, dd, $J_{10A,10B}$ 18.8, $J_{10A,9}$ 6.2, C(10)H_A), 2.37 (1H, td, $J_{16A,16B;16A,15A}$ 12.3, $J_{16A,15B}$ 3.5, C(16)H_A), 2.46 (3H, s, N*Me*), 2.61 (1H, dd, $J_{16B,16A}$ 12.0, $J_{16B,15B}$ 4.3, C(16)H_B), 2.84–2.88 (1H, m, C(14)*H*), 3.15 (1H, d, *J* 18.8, C(10)H_B), 3.43 (1H, dd, $J_{9,10A}$ 6.2, $J_{9,14}$ 2.7, C(9)*H*), 3.83, 3.86 (2 × 3H, s, O*Me* and CO_2*Me*), 4.20–4.22 (1H, m, C(6)*H*), 4.93–4.95 (1H, m, C(5)*H*), 5.27–5.32 (1H, m, C(8)*H*), 5.71–5.74 (1H, m, C(7)*H*), 6.71 (1H, s, C(2)*H*), 7.65 (1H, d, *J* 1.2, *H*C=C(Me)CO_2Me); δ_C (100 MHz, $CDCl_3$) 14.3, 19.6, 35.8, 40.5, 43.1, 46.3, 52.0, 56.4, 58.7, 66.6, 91.8, 113.9, 126.7, 127.1, 127.4, 128.2, 131.3, 133.4, 136.1, 141.9, 146.8, 169.1; *m*/*z* (CI^+) 398.3 (MH^+, 100%).

Preparation A of 1-acetylcodeine 8

Following representative procedure 1, **2** (1.5 g, 3 mmol), ethyl vinyl ether (1.2 ml, 13 mmol), $Pd(OAc)_2$ (15 mg, 2 mol%), tri-*o*-tolylphosphine (75 mg, 8 mol%), NEt_3 (0.6 ml, 4.2 mmol) and DMF (4.5 ml) were heated for 4 hours. The crude product was dissolved in Et_2O (2 × 50 ml), washed with 1 M $HCl_{(aq)}$ (50 ml), the aqueous layer basified to pH 11 with 2 M $NaOH_{(aq)}$, extracted with Et_2O (2 × 50ml), dried, filtered and concentrated *in vacuo*. Purification by column chromatography (DCM–MeOH 12 : 1) gave **8** (400 mg, 39%) as a white solid; mp 141 °C, $C_{20}H_{23}NO_4$ requires C, 70.4, H, 6.8, N, 4.1%; found C, 70.3, H, 6.85, N, 3.9%; $[\alpha]_D^{22}$ −124.5 (*c* 0.97, $CHCl_3$); ν_{max} (film) 2936, 2842 (C–H), 1663 (C=O), 1590 (C=C), 1307, 1200 (C–O); δ_H (400 MHz, $CDCl_3$) 1.84–1.88 (1H, m, C(15)H_B), 2.13 (1H, td, $J_{15A,15B;15A,16A}$ 12.5, $J_{15A,16B}$ 4.9, C(15)H_A), 2.35 (1H, td, $J_{16A,16B;16A,15A}$ 12.3, $J_{16A,15B}$ 3.4, C(16)H_A), 2.48 (3H, s, CO*Me*), 2.55 (3H, s, N*Me*), 2.58–2.65 (2H, m, C(16)H_B and C(10)H_A), 2.70–2.72 (1H, m, C(14)*H*), 3.43 (1H, dd, $J_{9,10A}$ 5.8, $J_{9,14}$ 3.0, C(9)*H*), 3.52 (1H, d, *J* 20.2, C(10)H_B), 3.91 (3H, s, O*Me*), 4.22–4.26 (1H, m, C(6)*H*), 4.96–4.98 (1H, m, C(5)*H*), 5.32–5.36 (1H, m, C(8)*H*), 5.70–5.74 (1H, m, C(7)*H*), 7.26 (1H, s, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 22.0, 28.8, 35.7, 39.9, 42.9, 43.0, 46.0, 56.5, 58.4, 66.6, 92.4, 116.7, 128.0, 128.6, 130.8, 132.1, 133.3, 141.3, 150.4, 198.5; *m*/*z* (CI^+) 342.2 (MH^+, 100%).

Preparation B of 1-acetylcodeine 8

Following representative procedure 1, **2** (500 mg, 1 mmol), (α-ethoxyvinyl)tributyltin (433 mg, 1.2 mmol), $Pd(OAc)_2$ (5 mg, 2 mol%), PPh_3 (21 mg, 8 mol%) and NEt_3 (2 ml) were heated for 4 hours. The crude product was dissolved in Et_2O (2 × 50 ml) and washed with 1 M $HCl_{(aq)}$ (50 ml), the aqueous layer basified to pH 11 with 2 M $NaOH_{(aq)}$, extracted with Et_2O (2 × 50 ml), dried, filtered and concentrated *in vacuo*. Purification by column chromatography (DCM–MeOH 12 : 1) gave **8** (290 mg, 85%) as a white solid identical to that prepared previously.

Preparation of 1-ethoxycarbonylcodeine 9

EtOH (3 ml) and NEt_3 (0.5 ml) were added to a mixture of **2** (500 mg, 1 mmol), $PdCl_2$ (19 mg, 10 mol%) and PPh_3 (56 mg, 20 mol%) in a Fischer–Porter bottle. The reaction vessel was flushed with CO, and pressurised to 3 atm before heating for 48 hours. After filtering through Celite (eluent EtOH), and concentration *in vacuo*, the crude reaction mixture was treated with TBAF (0.64 g, 2 mmol) in THF (10 ml) according to representative procedure 2 to give **9** (200 mg, 50%) as a white solid; mp 152 °C, $C_{21}H_{25}NO_5$ requires C, 67.9, H, 6.8, N, 3.8%; found C, 67.7, H, 7.0, N, 3.6%; $[\alpha]_D^{22}$ −98.5 (*c* 0.54, $CHCl_3$); ν_{max} (film) 2934, 2843 (C–H), 1704 (C=O), 1592 (C=C), 1200 (C–O); δ_H (400 MHz, $CDCl_3$) 1.40 (3H, t, *J* 7.0, OCH_2CH_3), 1.85–1.89 (1H, m, C(15)H_B), 2.08 (1H, td, $J_{15A,15B;15A,16A}$ 12.3, $J_{15A,16B}$ 5.1, C(15)H_A), 2.36 (1H, td, $J_{16A,16B;16A,15A}$ 12.3, $J_{16A,15B}$ 3.5, C(16)H_A), 2.47 (3H, s, N*Me*), 2.54–2.66 (2H, m, C(16)H_B and C(10)H_A), 2.66–2.68 (1H, m, C(14)*H*), 3.38 (1H, dd, $J_{9,10A}$ 6.2, $J_{9,14}$ 3.1, C(9)*H*), 3.50 (1H, d, *J* 20.0, C(10)H_B), 3.89 (3H, s, O*Me*), 4.20–4.23 (1H, m, C(6)*H*), 4.33 (2H, q, *J* 7.0, OCH_2CH_3), 4.95–4.97 (1H, m, C(5)*H*), 5.32–5.36 (1H, m, C(8)*H*), 5.71–5.75 (1H, m, C(7)*H*), 7.48 (1H, s, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 14.4, 21.6, 36.0, 40.2, 43.1, 46.0, 56.2, 58.5, 60.4, 66.6, 92.3, 115.8, 120.6, 128.7, 131.3, 131.7, 133.3, 141.7, 150.3, 166.5; *m*/*z* (CI^+) 372.2 (MH^+, 100%).

Preparation of 1-methylcodeine 10

Following representative procedure 1, **2** (500 mg, 1 mmol), tetramethyltin (0.17 ml, 1.2 mmol), $Pd(OAc)_2$ (5 mg, 2 mol%), tri-*o*-tolylphosphine (25 mg, 8 mol%), NEt_3 (0.2 ml, 1.4 mmol) and DMF (1.5 ml) gave, after treatment with TBAF (0.64 g, 2 mmol) in THF (10 ml) according to representative procedure 2, **10** (240 mg, 76%) as a white solid; mp 161 °C; $C_{19}H_{23}NO_3$ requires C, 72.8, H, 7.4, N, 4.5%; found C, 73.1, H, 7.6, N, 4.3%; $[\alpha]_D^{22}$ −114.4 (*c* 0.13, $CHCl_3$); ν_{max} (film) 2920, 2890 (C–H), 1504, 1123 (C–O); δ_H (400 MHz, $CDCl_3$) 1.86–1.89 (1H, m, C(15)H_B), 2.05 (1H, td, $J_{15A,15B;15A,16A}$ 12.3, $J_{15A,16B}$ 5.0, C(15)H_A), 2.10–2.12 (1H, m, C(10)H_A), 2.16 (3H, s, C(1)*Me*), 2.37 (1H, td, $J_{16A,16B;16A,15A}$ 12.0, $J_{16A,15B}$ 3.5, C(16)H_A), 2.46 (3H, s, N*Me*), 2.60 (1H, dd, $J_{16B,16A}$ 12.1, $J_{16B,15B}$ 4.5, C(16)H_B), 2.66–2.67 (1H, m, C(14)*H*), 2.88 (1H, d, *J* 18.6, C(10)H_B), 3.41 (1H, dd, $J_{9,10A}$ 6.0, $J_{9,14}$ 3.1, C(9)*H*), 3.84 (3H, s, O*Me*), 4.17–4.19 (1H, m, C(6)*H*), 4.87–4.89 (1H, m, C(5)*H*), 5.28–5.32 (1H, m, C(8)*H*), 5.71–5.74 (1H, m, C(7)*H*), 6.52 (1H, s, C(2)*H*); δ_C (100 MHz, $CDCl_3$) 17.8, 19.3, 35.8, 40.5, 42.9, 43.1, 46.4, 56.2, 58.8, 66.2, 91.1, 113.6, 125.1, 128.0, 128.2, 130.8, 133.4, 135.9, 141.8, 144.1; *m*/*z* (CI^+) 314.2 (MH^+, 100%).

Preparation of 1-phenylethynylcodeine 14

Following representative procedure 1, **2** (500 mg, 1 mmol), phenylethynyltributyltin (470 mg, 1.2 mmol), $Pd(OAc)_2$ (5 mg, 2 mol%), PPh_3 (25 mg, 8 mol%) and NEt_3 (2 ml) gave, after treatment with TBAF (0.64 g, 2 mmol) in THF (10 ml) according to representative procedure 2, **14** (325 mg, 81%) as a pale yellow solid; mp 148 °C; $C_{26}H_{25}NO_3$ requires C, 78.2, H, 6.3, N, 3.5%; found C, 78.5, H, 6.4, N, 3.3%; $[\alpha]_D^{22}$ −81.3 (*c* 0.97, $CHCl_3$); ν_{max} (film) 3363 (OH), 2934, 2911 (C–H), 2195 (C≡C), 1498, 1440, 1357, 1121 (C–O); δ_H (400 MHz, $CDCl_3$) 1.89–1.92 (1H, m, C(15)H_B), 2.11 (1H, td, $J_{15A,15B;15A,16A}$ 12.4, $J_{15A,16B}$ 5.0, C(15)H_A), 2.39–2.48 (2H, m, C(10)H_A and C(16)H_A), 2.51 (3H, s, N*Me*), 2.65 (1H, dd, $J_{16B,16A}$ 12.3, $J_{16B,15B}$ 3.8, C(16)H_B), 2.72–

2.74 (1H, m, C(14)*H*), 3.15 (1H, d, *J* 19.3, C(10)H_B), 3.47–3.50 (1H, m, C(9)*H*), 3.87 (3H, s, O*Me*), 4.20–4.22 (1H, m, C(6)*H*), 4.94–4.96 (1H, m, C(5)*H*), 5.30–5.34 (1H, m, C(8)*H*), 5.71–5.74 (1H, m, C(7)*H*), 6.89 (1H, s, C(2)*H*), 7.32–7.39 (3H, m, *Ph*), 7.51–7.54 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.3, 35.5, 40.5, 43.0, 43.1, 46.2, 56.2, 58.7, 66.5, 87.3, 91.9, 92.5, 113.9, 115.7, 123.4, 128.1, 128.2, 128.4, 131.1, 131.4, 133.4, 141.6, 142.2, 147.2; *m*/*z* (CI^+) 400.2 (MH^+, 100%).

Preparation of 1-phenylcodeine 11

Following representative procedure 1, **2** (500 mg, 1 mmol), phenyltributyltin (440 mg, 1.2 mmol), $Pd(OAc)_2$ (5 mg, 2 mol%), PPh_3 (25 mg, 8 mol%) and NEt_3 (2 ml) gave, after treatment with TBAF (0.64 g, 2 mmol) in THF (10 ml) according to representative procedure 2, **11** (330 mg, 89%) as a white solid; mp 162 °C; $C_{24}H_{25}NO_3$ requires C, 76.8, H, 6.7, N, 3.4%; found C, 76.6, H, 7.0, N, 3.7%; δ_H (300 MHz, $CDCl_3$) 1.94–1.98 (1H, m, C(15)H_B), 2.11–2.17 (2H, m, C(15)H_A and C(10)H_A), 2.45 (3H, s, N*Me*), 2.56 (1H, dd, $J_{16B,16A}$ 12.2, $J_{16B,15B}$ 3.4, C(16)H_A), 2.68–2.74 (2H, m, C(14)*H* and C(16)H_B), 3.05 (1H, d, *J* 19.0, C(10)H_B), 3.33 (1H, m, C(9)*H*), 3.87 (3H, s, O*Me*), 4.21–4.24 (1H, m, C(6)*H*), 4.94–4.96 (1H, m, C(5)*H*), 5.30–5.34 (1H, m, C(8)*H*), 5.75–5.79 (1H, m, C(7)*H*), 6.64 (1H, s, C(2)*H*), 7.32–7.45 (5H, m, *Ph*); δ_C (75 MHz, $CDCl_3$) 20.4, 35.6, 40.2, 43.3, 46.6, 56.3, 59.0, 66.3, 91.4, 114.4, 124.1, 126.8, 128.0, 128.3, 129.1, 131.2, 133.6, 134.1, 140.7, 142.0, 148.5; *m*/*z* (EI^+) 375 (M^+, 100%).

Preparation of 1-allylcodeine 13

Following representative procedure 1, **2** (500 mg, 1 mmol), allyltributyltin (397 mg, 1.2 mmol), $Pd(OAc)_2$ (5 mg, 2 mol%), PPh_3 (25 mg, 8 mol%) and NEt_3 (2 ml) gave, after treatment with TBAF (0.64 g, 2 mmol) in THF (10 ml) according to representative procedure 2, **13** (250 mg, 73%) as a colourless oil; $C_{21}H_{25}NO_3$ requires C, 74.3, H, 7.4, N, 4.1%; found C, 74.1, H, 7.6, N, 3.8%; δ_H (300 MHz, $CDCl_3$) 1.86–1.90 (1H, m, C(15)H_B), 2.11 (1H, td, $J_{15A,15B;15A,16A}$ 12.2, $J_{15A,16B}$ 5.0, C(15)H_A), 2.21 (1H, dd, *J* 18.7, *J* 6.3, C(10)H_A), 2.38 (1H, td, $J_{16A,16B;16A,15A}$ 12.2, $J_{16A,15B}$ 3.5, C(16)H_A), 2.47 (3H, s, N*Me*), 2.64 (1H, dd, $J_{16B,16A}$ 12.2, $J_{16B,15B}$ 4.1, C(16)H_B), 2.73–2.75 (1H, m, C(14)*H*), 2.92 (1H, d, *J* 18.7, C(10)H_B), 3.17–3.31 (2H, m, CH_2CH=CH$_2$), 3.42 (1H, dd, $J_{9,10}$ 6.3, $J_{9,8}$ 3.1, C(9)*H*), 3.83 (3H, s, O*Me*), 4.16–4.20 (1H, m, C(6)*H*), 4.88 (1H, dd, $J_{5,6}$ 6.3, $J_{5,7}$ 3.1, C(5)*H*), 4.95 (1H, dq, *J* 17.2, *J* 1.6, CH$_2$CH=CHH_{trans}), 5.05 (1H, dq, *J* 10.1, *J* 1.6, CH$_2$CH=CHH_{cis}), 5.24–5.29 (1H, m, C(8)*H*), 5.69–5.74 (1H, m, C(7)*H*), 5.85–5.99 (1H, m, CH$_2$C*H*=CH$_2$), 6.51 (1H, s, C(2)*H*); δ_C (66 MHz, $CDCl_3$) 19.0, 35.4, 36.1, 40.0, 42.8, 46.5, 56.4, 59.0, 66.2, 91.1, 113.9, 115.3, 124.8, 127.6, 129.8, 130.9, 133.6, 136.6, 142.1, 148.8; *m*/*z* (EI^+) 339 (M^+, 100%).

Preparation of 1-vinylcodeine 12

Following representative procedure 1, **2** (500 mg, 1 mmol), vinyltributyltin (378 mg, 1.2 mmol), $Pd(OAc)_2$ (5 mg, 2 mol%), PPh_3 (25 mg, 8 mol%) and NEt_3 (2 ml) gave, after treatment with TBAF (0.64 g, 2 mmol) in THF (10 ml) according to representative procedure 2, **12** (260 mg, 73%) as a white solid; mp 175 °C; δ_H (300 MHz, $CDCl_3$) 1.85–1.90 (1H, m, C(15)H_B), 2.07 (1H, td, $J_{15A,15B;15A,16A}$ 12.5, $J_{15A,16B}$ 5.1, C(15)H_A), 2.27 (1H, dd, *J* 18.7, *J* 6.2, C(10)H_A), 2.39 (1H, td, $J_{16A,16B;16A,15A}$ 12.1, $J_{16A,15B}$ 3.6, C(16)H_A), 2.46 (3H, s, N*Me*), 2.60 (1H, dd, $J_{16B,16A}$ 12.3, $J_{16B,15B}$ 4.2, C(16)H_B), 2.67–2.69 (1H, m, C(14)*H*), 3.03 (1H, d, *J* 18.7, C(10)H_B), 3.41 (1H, dd, $J_{9,10}$ 6.2, $J_{9,8}$ 3.2, C(9)*H*), 3.87 (3H, s, O*Me*), 4.17–4.20 (1H, m, C(6)*H*), 4.90 (1H, dd, $J_{5,6}$ 6.5, $J_{5,7}$ 1.1, C(5)*H*), 5.19 (1H, dd, *J* 11.1, *J* 1.1, CH=CHH_{cis}), 5.27–5.32 (1H, m, C(8)*H*), 5.54 (1H, dd, *J* 17.4, *J* 1.1, CH=CHH_{trans}), 5.70–5.74 (1H, m, C(7)*H*), 6.78 (1H, dd, *J* 17.4, *J* 11.1, C*H*=CH$_2$), 6.88 (1H, s, C(2)*H*); δ_C (66 MHz, $CDCl_3$) 19.4, 35.7, 40.3, 43.0, 46.3, 56.3, 58.8, 66.4, 91.6, 109.7, 112.9, 124.9, 128.2, 128.7, 131.0, 133.0, 133.5, 142.5, 146.6; *m*/*z* (EI^+) 325 (M^+, 100%); HRMS (EI^+) $C_{20}H_{23}NO_3$ requires 325.1678, found 325.1677.

Preparation of 3,6-di-*O*-*tert*-butyldimethylsilylmorphine 15[7]

tert-Butyldimethylsilyl chloride (8.0 g, 53 mmol) was added to a stirred solution of morphine (4.2 g, 14 mmol) and imidazole (4.8 g, 71 mmol) in DMF (25 ml) and heated to 90 °C for four hours. After cooling, the solution was diluted with DCM (200 ml), washed with H_2O (2 × 100 ml), dried and concentrated *in vacuo*. The residue was purified by column chromatography (DCM–MeOH 25 : 1) to give **15** (6.2 g, 87%) as a white solid; δ_H (300 MHz, $CDCl_3$) 0.11, 0.14, 0.15, 0.22 (4 × 3H, s, Si(*Me*)$_2$^{t}Bu), 0.94, 0.98 (2 × 9H, s, Si(Me)$_2$^{t}*Bu*), 1.82–1.87 (1H, m, C(15)H_B), 2.13 (1H, td, $J_{15A,15B;15A,16A}$ 12.2, $J_{15A,16B}$ 3.5, C(15)H_A), 2.31 (1H, dd, *J* 18.6, *J* 6.1, C(10)H_A), 2.46 (3H, s, N*Me*), 2.38–2.48 (1H, m, C(16)H_A), 2.54–2.65 (2H, m, C(16)H_B and C(14)*H*), 3.03 (1H, d, *J* 18.6, C(10)H_B), 3.34 (1H, dd, $J_{9,10A}$ 6.1, $J_{9,14}$ 3.3, C(9)*H*), 4.19–4.25 (1H, m, C(6)*H*), 4.69 (1H, dd, *J* 6.6, *J* 1.1, C(5)*H*), 5.24–5.28 (1H, m, C(8)*H*), 5.48–5.57 (1H, m, C(7)*H*), 6.42, 6.58 (2 × 1H, d, *J* 8.1, C(1)*H* and C(2)*H*).

Preparation of 6-*O*-*tert*-butyldimethylsilylmorphine 16

TBAF (1.5 g, 4.7 mmol) in THF (5 ml) was added to a stirred solution of **15** (2.4 g, 4.7 mmol) in THF (10 ml) at 0 °C and stirred for one hour. The solution was diluted with DCM (100 ml), washed with H_2O (2 × 30 ml), dried, and concentrated *in vacuo*. The residue was purified by column chromatography (DCM–MeOH 12 : 1) to give **16** (1.6 g, 89%) as a white solid; mp 206 °C; $C_{23}H_{33}NO_3Si$ requires C, 69.1, H, 8.3, N, 3.5%; found C, 69.1, H, 8.7, N, 3.1%; ν_{max} (KBr) 3421 (OH), 2920, 2852 (C–H), 1248, 1126 (C–O); $[\alpha]_D^{22}$ −158.5 (*c* 0.53, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 0.13, 0.15 (2 × 3H, s, Si(*Me*)$_2$^{t}Bu), 0.95 (2 × 9H, s, Si(Me)$_2$^{t}*Bu*), 1.83–1.88 (1H, m, C(15)H_B), 2.13 (1H, td, $J_{15A,15B;15A,16A}$ 12.3, $J_{15A,16B}$ 5.1, C(15)H_A), 2.31 (1H, dd, *J* 18.5, *J* 6.1, C(10)H_A), 2.45 (3H, s, N*Me*), 2.38–2.48 (1H, m, C(16)H_A), 2.58–2.67 (2H, m, C(16)H_B and C(14)*H*), 3.03 (1H, d, *J* 18.6, C(10)H_B), 3.34 (1H, dd, $J_{9,10A}$ 6.2, $J_{9,14}$ 3.2, C(9)*H*), 4.23–4.27 (1H, m, C(6)*H*), 4.71 (1H, dd, *J* 5.9, *J* 1.2, C(5)*H*), 5.23–5.31 (1H, m, C(8)*H*), 5.59–5.63 (1H, m, C(7)*H*), 6.47, 6.63 (2 × 1H, d, *J* 8.0, C(1)*H* and C(2)*H*); δ_C (100 MHz, $CDCl_3$) −4.8, 18.4, 20.6, 25.9, 35.2, 40.5, 42.5, 43.6, 46.2, 58.5, 69.1, 92.6, 117.7, 119.0, 125.4, 128.3, 130.6, 133.7, 138.9, 147.3; *m*/*z* (CI^+) 400 (MH^+, 70%).

Preparation of 3-*O*-trifluoromethylsulfonyl-6-*O*-*tert*-butyldimethylsilylmorphine 17

Trifluoromethanesulfonic anhydride (0.8 ml, 4.8 mmol) was added dropwise to a stirred solution of **16** (1.6 g, 4.0 mmol) and 2,6-dimethylpyridine (0.46 ml, 4.0 mmol) in DCM (10 ml) at 0 °C and warmed to RT. After twenty hours, the solution was diluted with DCM (100 ml), washed with H_2O (2 × 30 ml), dried, and concentrated *in vacuo*. The residue was purified by column chromatography (DCM–MeOH 30 : 1) to give **17** (1.9 g, 89%) as a white solid; mp 75 °C; $C_{24}H_{32}NF_3O_5SSi$ requires C, 54.2, H, 6.1, N, 2.6%; found C, 54.2, H, 6.3, N, 2.4%; ν_{max} (KBr) 2960, 2852 (C–H), 1417, 1225, 1205, 1137 (C–O); $[\alpha]_D^{22}$ −127.7 (*c* 1.02, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 0.12, 0.15 (2 × 3H, s, Si(*Me*)$_2$^{t}Bu), 0.94 (2 × 9H, s, Si(Me)$_2$^{t}*Bu*), 1.84–1.89 (1H, m, C(15)H_B), 2.06 (1H, td, $J_{15A,15B;15A,16A}$ 12.3, $J_{15A,16B}$ 5.0, C(15)H_A), 2.27–2.41 (2H, m, C(10)H_A and C(16)H_A), 2.44 (3H, s, N*Me*), 2.59 (1H, dd, $J_{16B,16A}$ 12.2, $J_{16B,15B}$ 4.5, C(16)H_B), 2.66–2.68 (1H, m, C(14)*H*), 3.07 (1H, d, *J* 19.0, C(10)H_B), 3.34 (1H, dd, $J_{9,10A}$ 6.0, $J_{9,14}$ 3.2, C(9)*H*), 4.25–4.28 (1H, m, C(6)*H*), 4.81–4.83 (1H, m, C(5)*H*), 5.23–5.28 (1H, m, C(8)*H*), 5.61–5.64 (1H, m, C(7)*H*), 6.57, 6.90 (2 × 1H, d, *J* 8.4, C(1)*H* and C(2)*H*); δ_C (100 MHz, $CDCl_3$) −4.9, −4.7, 21.2, 25.7, 35.6, 40.9, 43.0,

43.9, 46.1, 58.6, 68.4, 94.2, 116.2, 119.1, 121.6, 127.8, 130.6, 133.5, 134.1, 135.2, 150.6; *m/z* (CI^+) 532 (MH^+, 100%).

Preparation of 3-deoxy-3-butoxycarbonylmorphine 18

Butanol (1 ml), NEt_3 (1 ml) and DMF (2 ml) were added to a mixture of **17** (170 mg, 0.3 mmol), $Pd(OAc)_2$ (5 mg, 4 mol%) and 1,3-bis(diphenylphosphino)propane (10 mg, 4 mol%) in a Fischer–Porter bottle. The reaction vessel was flushed with CO and pressurised to 3 atm before heating to 70 °C for 48 hours. After cooling, the crude mixture was concentrated *in vacuo*, and treated with TBAF (135 mg, 0.45 mmol) in THF (5 ml) according to representative procedure 2 to give **18** (92 mg, 76%) as a white solid; mp 95 °C; $C_{22}H_{27}NO_4$ requires C, 71.5, H, 7.4, N, 3.8%; found C, 71.2, H, 7.6, N, 3.5%; ν_{max} (film) 3411 (OH), 1690 (C=O); $[\alpha]_D^{22}$ −18.4 (*c* 1.02, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.20 (3H, t, *J* 7.0, $OCH_2CH_2CH_2CH_3$), 1.47 (1H, sx, *J* 7.0, $OCH_2CH_2CH_2CH_3$), 1.73 (1H, qu, *J* 7.0, $OCH_2CH_2CH_2CH_3$), 1.85–1.89 (1H, m, C(15)H_B), 2.10 (1H, td, $J_{15A,15B;15A,16A}$ 12.4, $J_{15A,16B}$ 5.0, C(15)H_A), 2.31–2.38 (2H, m, C(10)H_A and C(16)H_A), 2.45 (3H, s, N*Me*), 2.62 (1H, dd, $J_{16B,16A}$ 12.4, $J_{16B,15B}$ 3.8, C(16)H_B), 2.71–2.74 (1H, m, C(14)*H*), 3.10 (1H, d, *J* 19.4, C(10)H_B), 3.37 (1H, dd, $J_{9,10A}$ 6.0, $J_{9,14}$ 3.3, C(9)*H*), 4.21–4.27 (2H, m, C(6)*H* and $OCH_AH_BCH_2CH_2CH_3$), 4.31–4.36 (1H, m, $OCH_AH_BCH_2CH_2CH_3$), 5.01 (1H, dd, $J_{5,6}$ 6.6, $J_{5,7}$ 1.1, C(5)*H*), 5.27–5.30 (1H, m, C(8)*H*), 5.69–5.72 (1H, m, C(7)*H*), 6.65, 7.60 (2 × 1H, d, *J* 8.0, C(1)*H* and C(2)*H*); δ_C (66 MHz, $CDCl_3$) 13.7, 19.3, 21.7, 30.8, 35.5, 40.6, 41.8, 43.0, 46.2, 58.5, 64.5, 66.2, 91.5, 111.1, 119.4, 127.9, 129.8, 131.5, 133.8, 140.6, 159.3, 165.3; *m/z* (CI^+) 370 (MH^+, 100%).

Preparation of 3-deoxy-3-acetylmorphine 19

Following representative procedure 1, **17** (510 mg, 1 mmol), (α-ethoxyvinyl)tributyltin (433 mg, 1.2 mmol), $Pd(OAc)_2$ (10 mg, 4 mol%), PPh_3 (25 mg, 8 mol%), LiCl (130 mg, 3 mmol) and DMF (3 ml) were combined and heated. The crude reaction mixture was dissolved in Et_2O (50 ml), washed with 1 M $HCl_{(aq)}$ (20 ml), basified to pH 11 with 1 M $NaOH_{(aq)}$, extracted with Et_2O (3 × 100 ml) to give, after purification by column chromatography (DCM–MeOH 12 : 1), **19** (250 mg, 80%) as a buff coloured solid; mp 168 °C; $C_{19}H_{21}NO_3$ requires C, 73.3, H, 6.8, N, 4.5%; found C, 73.1, H, 7.05, N, 4.3%; ν_{max} (film) 2960, 2852 (C–H), 1417, 1225, 1205, 1137 (C–O); $[\alpha]_D^{22}$ −24.0 (*c* 0.52, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 1.87–1.89 (1H, m, C(15)H_B), 2.11 (1H, td, $J_{15A,15B;15A,16A}$ 12.3, $J_{15A,16B}$ 5.0, C(15)H_A), 2.31–2.40 (2H, m, C(10)H_A and C(16)H_A), 2.45, 2.60 (2 × 3H, s, N*Me* and CO*Me*), 2.61–2.65 (1H, m, C(16)H_B), 2.72–2.74 (1H, m, C(14)*H*), 3.10 (1H, d, *J* 19.5, C(10)H_B), 3.38 (1H, dd, $J_{9,10A}$ 6.0, $J_{9,14}$ 3.2, C(9)*H*), 4.26–4.28 (1H, m, C(6)*H*), 5.01 (1H, dd, $J_{5,6}$ 6.4, $J_{5,7}$ 1.1, C(5)*H*), 5.31–5.35 (1H, m, C(8)*H*), 5.68–5.72 (1H, m, C(7)*H*), 6.68, 7.40 (2 × 1H, d, *J* 8.1, C(1)*H* and C(2)*H*); δ_C (125 MHz, $CDCl_3$) 21.7, 30.1, 35.5, 40.5, 41.9, 42.8, 45.9, 58.3, 66.7, 92.1, 118.3, 119.2, 128.3, 131.1, 133.3, 141.0, 159.3, 195.8; *m/z* (CI^+) 312 (MH^+, 100%).

Preparation of 3-deoxy-3-(*tert*-butylthio)morphine 20

DMF (15 ml) was added to a mixture of **17** (330 mg, 0.62 mmol), $Pd(PPh_3)_4$ (360 mg, 0.32 mmol) and LiCl (80 mg, 1.8 mmol), which was degassed and heated to 70 °C to ensure reaction homogeneity. A solution of tributylstannyl *tert*-butyl sulfide (470 mg, 1.2 mmol) in DMF was added *via* syringe and heated at 70 °C for 35 hours. The crude reaction mixture was filtered through Celite, dissolved in Et_2O (50 ml), washed with 1 M $HCl_{(aq)}$ (20 ml), basified to pH 11 with 1 M $NaOH_{(aq)}$ and reextracted with DCM (3 × 100 ml). After concentration *in vacuo*, the crude reaction mixture was purified by column chromatography (DCM–MeOH 12 : 1) to give **20** (185 mg, 83%) as a yellow solid; mp 145 °C; $C_{21}H_{27}NO_2S$ requires C, 70.55, H, 7.6, N, 3.9%; found C, 70.6, H, 7.7, N, 3.75%; $[\alpha]_D^{22}$ −127.6 (*c* 0.5, $CHCl_3$); ν_{max} (film) 2920, 2798 (C–H), 1420; δ_H (300 MHz, $CDCl_3$) 1.30 (9H, s, S*t*Bu), 1.82–1.87 (1H, m, C(15)H_B), 2.10 (1H, td, $J_{15A,15B;15A,16A}$ 12.4, $J_{15A,16B}$ 5.1, C(15)H_A), 2.32–2.42 (2H, m, C(10)H_A and C(16)H_A), 2.47 (3H, s, N*Me*), 2.62 (1H, dd, $J_{16B,16A}$ 12.4, $J_{16B,15B}$ 4.2, C(16)H_B), 2.71–2.73 (1H, m, C(14)*H*), 3.10 (1H, d, *J* 19.2, C(10)H_B), 3.39 (1H, dd, $J_{9,10A}$ 6.0, $J_{9,14}$ 3.2, C(9)*H*), 4.18–4.23 (1H, m, C(6)*H*), 4.89 (1H, dd, $J_{5,6}$ 6.4, $J_{5,7}$ 1.1, C(5)*H*), 5.29–5.34 (1H, m, C(8)*H*), 5.65–5.70 (1H, m, C(7)*H*), 6.61, 7.11 (2 × 1H, d, *J* 7.8, C(1)*H* and C(2)*H*); δ_C (125 MHz, $CDCl_3$) 21.4, 31.0, 35.7, 40.8, 42.8, 43.0, 46.3, 46.9, 58.6, 66.8, 90.8, 109.8, 119.4, 128.3, 129.9, 133.6, 136.7, 138.1, 161.9; *m/z* (CI^+) 358.2 (MH^+, 100%).

Preparation of 3-deoxy-3-acetylthio-6-acetylmorphine 21

Mercuric acetate (305 mg, 0.95 mmol) was added to a stirred solution of **20** (325 mg, 0.91 mmol) and anisole (0.2 ml) in TFA (10 ml) at 0 °C. After 1.5 hours, the reaction was concentrated *in vacuo*, the residue dissolved in acetone and $H_2S_{(g)}$ bubbled through the solution for 10 minutes. The resultant black precipitate was removed by filtration through Celite and the filtrate concentrated *in vacuo*. The residue was dissolved in DCM (10 ml) prior to the addition of NEt_3 (0.55 ml, 4 mmol), acetic anhydride (0.39 ml, 4 mmol) and DMAP (10 mg) and stirred at RT. After 24 hours, the resulting solution was diluted with DCM (100 ml), washed with H_2O (50 ml), dried and concentrated *in vacuo* before purification by column chromatography (DCM–MeOH 12 : 1) to give **21** (170 mg, 47%) as a white solid; mp 145 °C; $C_{21}H_{23}NO_4S$ requires C, 65.7, H, 6.15, N, 3.95%; found C, 65.4, H, 6.0, N, 3.65%; ν_{max} (film) 2920, 2847 (C–H), 1739, 1712 (C=O), 1425, 1234; $[\alpha]_D^{22}$ −153.7 (*c* 0.21, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.85–1.89 (1H, m, C(15)H_B), 2.08 (1H, td, $J_{15A,15B;15A,16A}$ 12.4, $J_{15A,16B}$ 5.2, C(15)H_A), 2.15 (3H, s, CO*Me*), 2.33–2.41 (2H, m, C(10)H_A and C(16)H_A), 2.37 (3H, s, CO*Me*), 2.47 (3H, s, N*Me*), 2.62 (1H, dd, $J_{16B,16A}$ 12.0, $J_{16B,15B}$ 4.3, C(16)H_B), 2.77–2.79 (1H, m, C(14)*H*), 3.10 (1H, d, *J* 19.2, C(10)H_B), 3.39 (1H, dd, $J_{9,10A}$ 5.6, $J_{9,14}$ 3.3, C(9)*H*), 5.13–5.19 (2H, m, C(6)*H* and C(5)*H*), 5.44–5.47 (1H, m, C(8)*H*), 5.62–5.65 (1H, m, C(7)*H*), 6.67, 7.02 (2 × 1H, d, *J* 7.9, C(1)*H* and C(2)*H*); δ_C (125 MHz, $CDCl_3$) 21.3, 21.6, 30.3, 35.6, 41.1, 43.2, 43.4, 46.8, 59.2, 68.6, 88.7, 105.8, 120.4, 129.1, 129.9, 130.6, 135.0, 160.4, 170.9; *m/z* (CI^+) 386 (MH^+, 100%).

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