SYNTHESIS OF 1-SUBSTITUTED DERIVATIVES OF CODEINE FROM 1-BROMOCODEINE *via* PALLADIUM CATALYSED COUPLING REACTIONS

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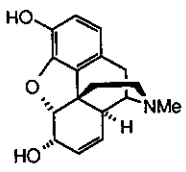
Abstract - The 1-(methyl-β-propenoate), 1-β-styryl, 1-carboethoxy and 1-methyl derivatives of codeine have been prepared in good yields from 1-bromocodeine *via* palladium catalysed coupling reactions.

The morphine alkaloids are of considerable interest due to their analgesic properties.[1] The serious side effects exhibited by some of these alkaloids has resulted in intense long term interest in the synthesis of derivatives.[2] Although many analogues of morphine **1** and codeine **2** have been prepared, 1-, 2- and 10-derivatives still present a synthetic challenge for selective elaboration.



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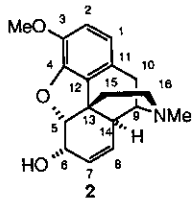

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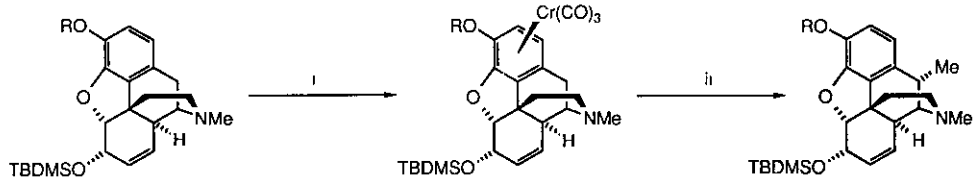
Barton *et al.* have demonstrated that the *t*-butyldimethylsilyl derivatives of morphine **3** and codeine **4** undergo stereoselective complexation to chromium tricarbonyl to give complexes **5** and **6** respectively. The chromium tricarbonyl moiety in **5** and **6** activates the 10-position towards stereoselective sequential deprotonation and methylation to yield after decomplexation and deprotection 10-S-methylmorphine **7** and 10-S-methylcodeine **8** respectively.[3] More recently for codeine this methodology has been extended by Mathews and Sainsbury to yield 10-S-allyl- and 10-S-propylcodeine.[4]



3 R = TBDMS
4 R = Me

5 R = TBDMS
6 R = Me

7 R = H
8 R = Me

i) $Cr(CO)_6$, nBu_2O

ii) $(Me_3Si)_2NNa$, MeI ; Pyridine ; $nBu_4NF.3H_2O$

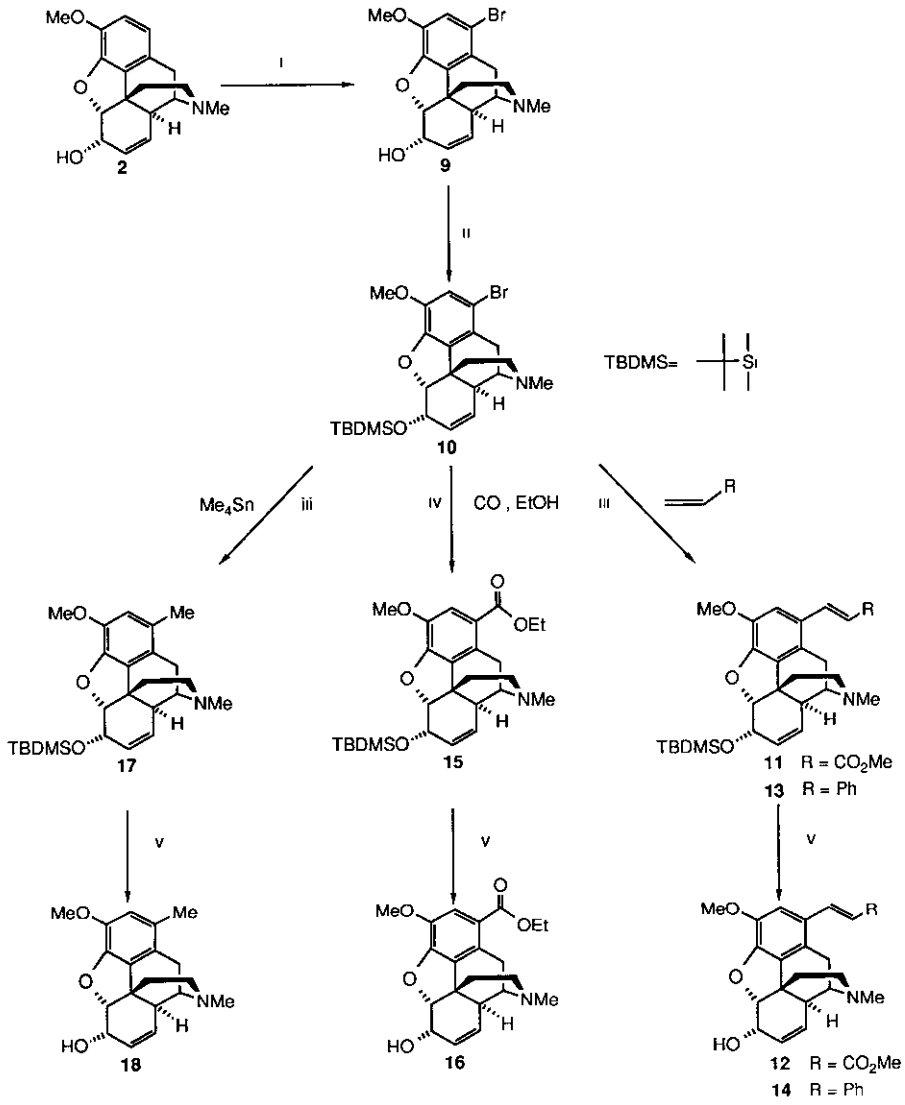
1-Bromocodeine **9** is readily available from codeine[5] and represents, therefore, an attractive starting material for the preparation of a variety of 1-substituted derivatives. Many synthetically useful substitution reactions of simple aryl bromides are known to be catalysed by palladium(0).[6] O-*t*-Butyldimethylsilyl-1-bromocodeine **10**, however, represents a challenge to explore the limits of the utility of palladium catalysed couplings: It contains a highly functionalised aromatic moiety with electron donating substituents which are known to retard the insertion reaction of palladium(0) into aryl bromine bonds,[6] an *ortho* methylene group renders the aryl bromine bond sterically less accessible and several heteroatom substituents have coordinating affinity for palladium. Furthermore, the allyl ether function within the skeleton of **10** is prone to palladium catalysed rearrangement to the corresponding vinyl ether[7] and to intermolecular Heck reactions.[8]

1-Bromocodeine **9** was synthesised by the method of Speyer and Rosenfeld[5] by bubbling hydrogen bromide through a solution of codeine in dichloromethane/diethyl ether. Evaporation gave codeine hydrobromide salt quantitatively. Treatment of a formic acid (30%) solution of this salt with hydrogen peroxide (30%) gave, after addition of base (2M NaOH) to >pH 11, a precipitate of 1-bromocodeine **9** (69%). The 1-position of the bromine substituent was unambiguously confirmed by n.O.e. difference spectroscopy: Irradiation of the methoxyl methyl singlet in codeine gave a 16% enhancement of the proton on C-2 and no enhancement of the proton on C-1 whereas irradiation of the methoxyl methyl singlet in 1-bromocodeine gave a 22% enhancement of the single remaining aromatic proton. 1-Bromocodeine **9** was converted into its *t*-butyldimethylsilyl ether **10** by treatment with *t*-butyldimethylsilyl chloride and imidazole(94%).

The Heck reaction[9] of **10** with methyl acrylate in the presence of catalytic amounts of $Pd(OAc)_2$ and P(*o*-tolyl)$_3$ in DMF/Et_3N proceeded cleanly to give **11** (90%). ^{1}H-Nmr spectroscopy indicated the exclusive formation of a single diastereoisomer assigned as E-**11** on the basis of the olefinic proton coupling J = 15Hz. The 1-position of the β-propenoate group was confirmed by n.O.e difference spectroscopy. Deprotection of the allylic alcohol function with tetrabutylammonium fluoride in THF gave 1-(methyl-β-propenoate)codeine **12** (90%) in an overall yield of 76% from 1-bromocodeine **9**.

A similar Heck reaction of **10** with styrene gave, *via* the intermediate **13**, 1-β-styrylcodeine **14** in 71% overall yield from 1-bromocodeine **9**.

Carbonylation[10] of **10** in ethanol with Et_3N (1.2 equiv), $PdCl_2$ (0.1 equiv.) and PPh_3 (0.2 equiv.) under 3 atmospheres of carbon monoxide at 100°C was slow and had not gone to completion after 24hrs. However, carbonylation gave **15** as the only product, which, after separation from starting material **10** and deprotection gave



i) HBr , CH_2Cl_2/Et_2O ; HCO_2H , H_2O_2

ii) TBDMSCl , Imidazole , THF

iii) $Pd(OAc)_2$ (2%) , P(*o*-tolyl)$_3$ (8%) , DMF , Et_3N

iv) $PdCl_2$ (10%) , PPh_3 (20%)

v) nBu$_4$NF $3H_2O$, THF

1-carboethoxycodeine **16** in 50% yield.

1-Bromocodeine was converted to 1-methylcodeine using a modified Stille procedure.[11] Reaction of **10** with tetramethyltin utilising $Pd(OAc)_2/P(o\text{-tolyl})_3$ as catalyst in DMF/Et_3N as solvent gave **17** (90%). Deprotection of **17** as before yielded 1-methylcodeine **18** (87%).

The above reactions demonstrate the usefulness of palladium chemistry for the preparation of 1-substituted derivatives of codeine *via* the selective substitution of 1-bromocodeine. All novel codeine derivatives were fully characterised by spectroscopy and elemental microanalysis.

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