

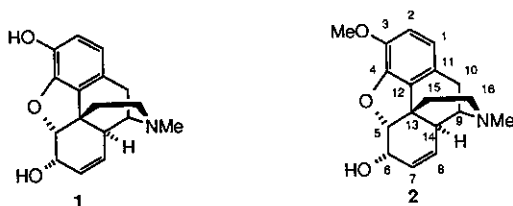
SYNTHESIS OF 1-SUBSTITUTED DERIVATIVES OF CODEINE FROM 1-BROMOCODEINE  
 via PALLADIUM CATALYSED COUPLING REACTIONS

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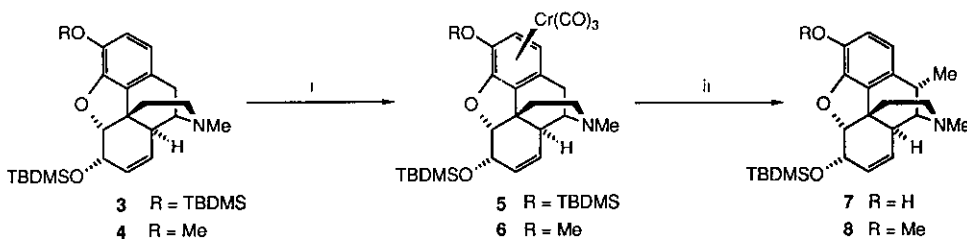
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**Abstract** - The 1-(methyl- $\beta$ -propenoate), 1- $\beta$ -styryl, 1-carboethoxy and 1-methyl derivatives of codeine have been prepared in good yields from 1-bromocodeine via palladium catalysed coupling reactions.

The morphine alkaloids are of considerable interest due to their analgesic properties.<sup>1</sup> The serious side effects exhibited by some of these alkaloids has resulted in intense long term interest in the synthesis of derivatives.<sup>2</sup> 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.



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.<sup>3</sup> More recently for codeine this methodology has been extended by Mathews and Sainsbury to yield 10-*S*-allyl- and 10-*S*-propylcodeine.<sup>4</sup>



i)  $\text{Cr}(\text{CO})_3$ ,  $n\text{Bu}_2\text{O}$

ii)  $(\text{Me}_3\text{Si})_2\text{NNa}$ , MeI; Pyridine;  $n\text{Bu}_4\text{NF} \cdot 3\text{H}_2\text{O}$

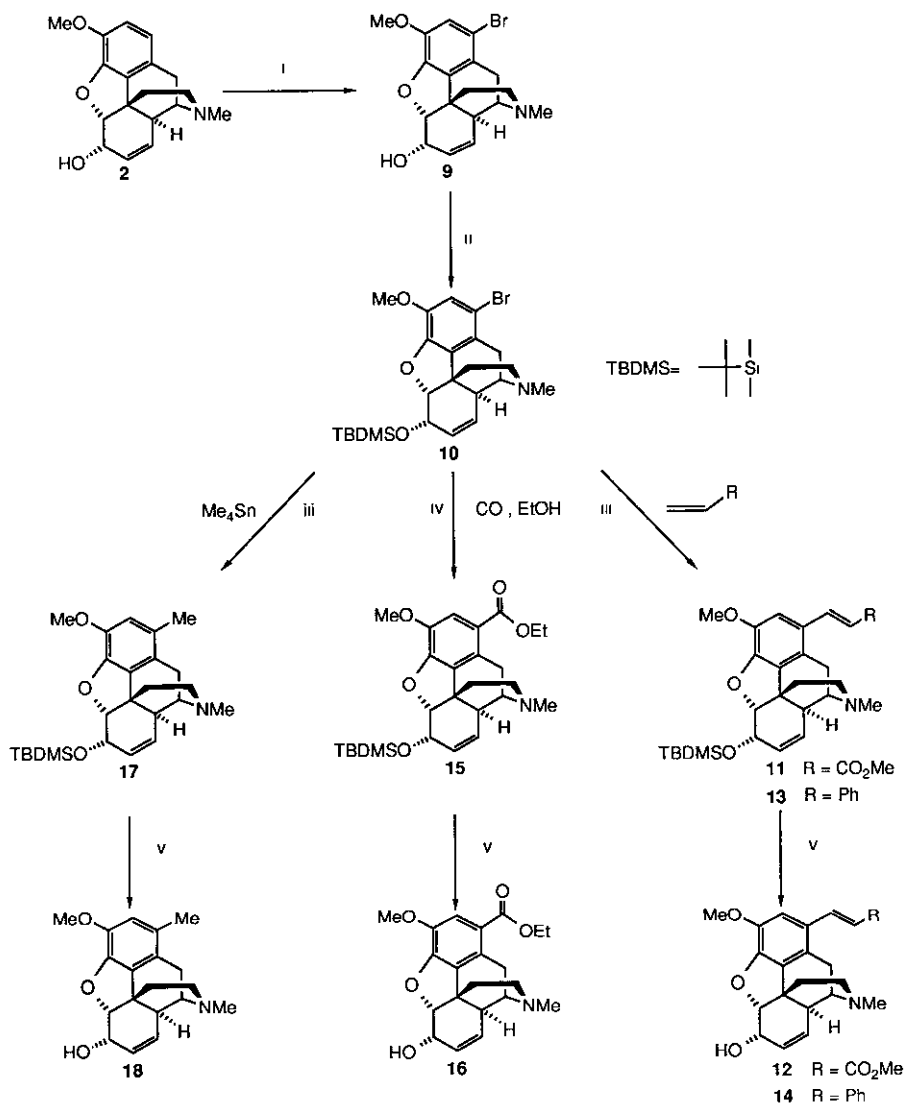
1-Bromocodeine **9** is readily available from codeine<sup>5</sup> and represents, therefore, an attractive starting material for the preparation of a variety of 1-substituted derivatives. Many synthetically useful substitution reactions of simple aryl bromides are known to be catalysed by palladium(0).<sup>6</sup> *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,<sup>6</sup> 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<sup>7</sup> and to intermolecular Heck reactions.<sup>8</sup>

1-Bromocodeine **9** was synthesised by the method of Speyer and Rosenfeld<sup>5</sup> 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<sup>9</sup> of **10** with methyl acrylate in the presence of catalytic amounts of Pd(OAc)<sub>2</sub> and P(*o*-tolyl)<sub>3</sub> in DMF/Et<sub>3</sub>N proceeded cleanly to give **11** (90%). <sup>1</sup>H-Nmr spectroscopy indicated the exclusive formation of a single diastereoisomer assigned as *E*-**11** on the basis of the olefinic proton coupling  $J = 15\text{Hz}$ . The 1-position of the  $\beta$ -propenoate group was confirmed by n.O.e difference spectroscopy. Deprotection of the allylic alcohol function with tetrabutylammonium fluoride in THF gave 1-(methyl- $\beta$ -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- $\beta$ -styrylcodeine **14** in 71% overall yield from 1-bromocodeine **9**.

Carbonylation<sup>10</sup> of **10** in ethanol with Et<sub>3</sub>N (1.2 equiv), PdCl<sub>2</sub> (0.1 equiv.) and PPh<sub>3</sub> (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)  $\text{HBr}$ ,  $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ ;  $\text{HCO}_2\text{H}$ ,  $\text{H}_2\text{O}_2$   
 ii)  $\text{TBDMSCl}$ ,  $\text{Imidazole}$ ,  $\text{THF}$   
 iii)  $\text{Pd}(\text{OAc})_2$  (2%),  $\text{P}(o\text{-tolyl})_3$  (8%),  $\text{DMF}$ ,  $\text{Et}_3\text{N}$   
 iv)  $\text{PdCl}_2$  (10%),  $\text{PPh}_3$  (20%)  
 v)  $n\text{Bu}_4\text{NF} \cdot 3\text{H}_2\text{O}$ ,  $\text{THF}$

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

1-Bromocodeine was converted to 1-methylcodeine using a modified Stille procedure.<sup>11</sup> Reaction of **10** with tetramethyltin utilising Pd(OAc)<sub>2</sub>/P(*o*-tolyl)<sub>3</sub> as catalyst in DMF/Et<sub>3</sub>N 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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