PERKIN 1

The synthesis of some analogues of morphine 6-glucuronide through Wittig reactions upon dihydrocodeinone

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In preliminary studies to establish the biological role of the glucuronide unit in morphine 6-glucuronide, a number of codeine derivatives bearing alkyl side chains appended through C-6 have been synthesised using Wittig reactions between suitable ylides and dihydrocodeinone. During the course of this work some aldolisation type products of dihydrocodeinone were obtained. Attempts to introduce side chains by radical coupling reactions between bromocodides and allyltributyltin failed.

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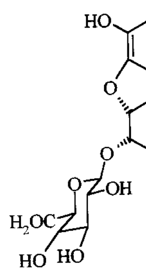
Introduction

Morphine 6-glucuronide, M6G **1**, a metabolite of morphine, is a potent analgesic, four times as active as morphine, with twice the duration of action.[1] It also causes fewer gastrointestinal and respiratory side effects than the aglycone.[2] That M6G is able to pass through the blood–brain barrier presents a puzzle. Some authors believe that the compound is a 'molecular chameleon', adopting a folded structure, which masks its polar nature when in association with a lipophilic membrane, and an extended structure when in a more polar environment.[3]

Since few analogues of M6G have been described, it is not clear whether a glucuronide unit is essential for activity, or whether a derivative with a bulky substituent in the 'SW corner' of morphine might prove equally useful as an analgesic. As a prelude to studies aimed at introducing a close mimic of the glucuronide unit we now describe some compounds in which the carbohydrate residue is replaced by an alkyl group.



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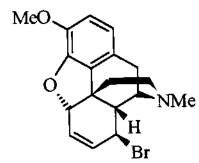

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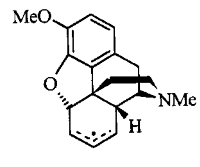

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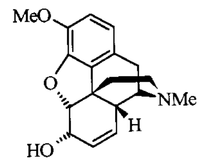

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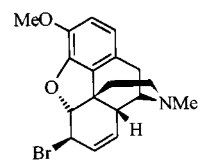

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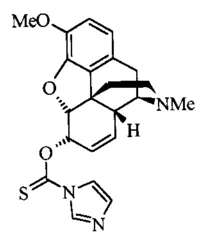

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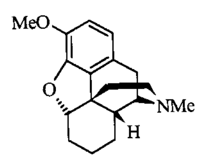

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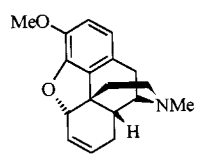

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Results and discussion

Initially, we attempted to couple 8β-bromocodide **2** with allyltributyltin in the presence of AIBN. Here we assumed that the delocalised radical **3** would form as an intermediate and that this would then undergo allylation at C-6 and/or C-8. Previous workers[4,5] have shown that treatment of codeine **4** with phosphorus tribromide leads to 8β-bromocodide **2** in 55% yield.[5] In our hands both this compound and 6β-bromocodide **5** were obtained as a mixture, in a ratio of 3 : 1 and an overall yield of 83%.

This mixture was reacted with allyltributyltin and AIBN in toluene at 80 °C,[6] giving a mixture of at least six compounds, all with very similar retention indices on silica. NMR Studies on the crude fractions showed that none of the components of this mixture contained allyl groups and further efforts to separate them were abandoned.

Next, the imidazolylthiocarbonyl derivative **6** of codeine[7] was prepared and an attempt was made to allylate it under comparable conditions. Once again a complex mixture was produced. This failure caused us to investigate similar coupling reactions with dihydrocodeines, where there is no double bond to reduce the reactivity of the intermediate radical. These reactions also failed, and a reaction between 8β-bromodihydrocodide and a 1.2 molar excess of tributyltin hydride and AIBN unexpectedly afforded deoxycodeine **8**, as well as the anticipated product dihydrodeoxycodeine D **7**.

These problems caused us to consider Wittig reactions upon dihydrocodeinone **16** in order to introduce an alkenyl side chain. Hahn and Fishman[8] have already described the synthesis of several 6-methylene derivatives (**9**–**12**) based upon naloxone and naltrexone prototypes by Wittig methodology, although these products were not reduced to the methyl analogues.

Our initial target was the aldehyde **14**, which could serve as the starting compound for a wide range of derivatives. Initial reaction between codeine and methoxymethyltriphenylphosphonium bromide gave the enol ether **13** as a 2.5 : 1 mixture of configurational isomers in 51% yield. However, all attempts to hydrolyse this precursor, under acidic conditions, led to ring-opening of the dihydrofuran ring and the formation of the phenol **15**.

Fortunately a Wittig reaction between dihydrocodeinone **16** and cyclohexylmethylphosphonium bromide worked well and

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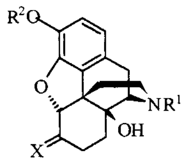
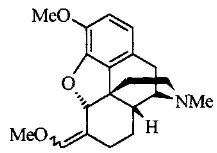
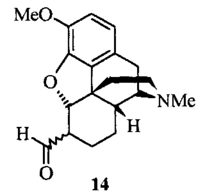



9 (R^1 = allyl, R^2 = Ac, X = CH_2) **13**
10 (R^1 = cyclopropylmethyl, R^2 = Ac, X = CH_2)
11 (R^1 = cyclopropylmethyl, R^2 = $O_2CCH{=}CHPh$, X = CH_2)
12 (R^1 = allyl, R^2 = H, X = $CHCO_2CH_3$)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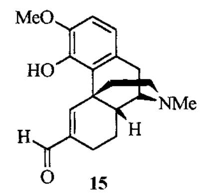
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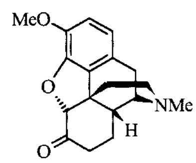
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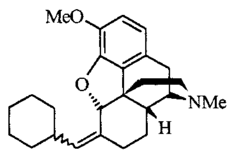
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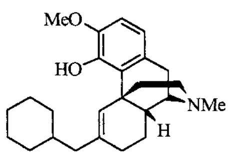
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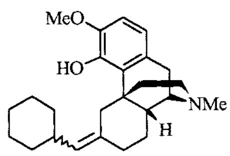
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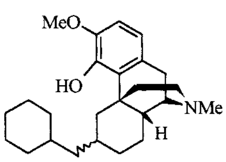
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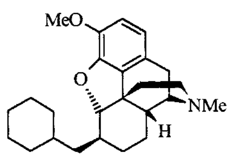
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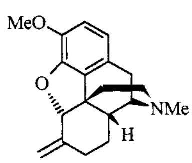
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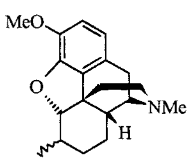
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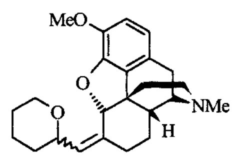
the alkene **17** was isolated in 91% yield, as a 1 : 1 mixture of *E*- and *Z*-isomers. Attempts to reduce this product by catalytic hydrogenation were unsatisfactory and, under severe conditions (40 atm of hydrogen over palladium on carbon), fission of the furanoid ring occurred with the formation of phenols **18** and **19** in 65 and 8% yields, respectively.

The first of these compounds also results when the mixed alkenes, in ethanol solution containing a few drops of hydrochloric acid, is hydrogenated at atmospheric pressure over palladium on charcoal. When triethylsilane,[9] in trifluoroacetic acid, is used as the reductant the phenol **18** and its dihydro derivative **20** are produced in yields of 23 and 48%, respectively.

This problem was partly solved by using dimide[10] as the reducing agent, and this, when reacted with the mixed alkenes, gave 49% of the reduced compound **21**, plus some of the unreacted *E*-alkene **17**. The stereochemistry of 6-methyldihydrodeoxycodeine **23**,[11] obtained by the hydrogenation of 6-methylenedihydrodeoxycodeine **23**,[11] obtained by the hydrogenation of 6-methylenedihydrodeoxycodeine **22**, was never established, although we now have evidence that the C-6 side chain in **21** is β-orientated. This configuration is, of course, the opposite of that of the 6-hydroxy group in morphine/codeine.

Our assignment agrees with an examination of the ^{1}H NMR spectrum of **21**, which shows, for example, a coupling constant $J_{5,6}$ 8.3. For dihydrocodeine $J_{5,6}$ 5.0. In addition, an NOE experiment indicates that for **21** H-5, H-15α and H-15β, but *not* H-6, lie within 2–4 Å of one another.

In order to test whether a closer mimic of M6G could be prepared in the same way, we sought to prepare the tetrahydropyran derivative **24** by a Wittig reaction between the ylide **25**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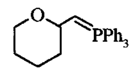
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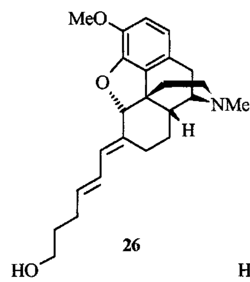
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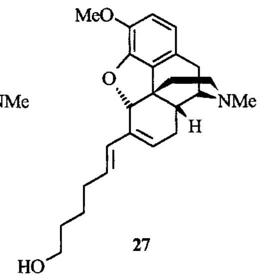
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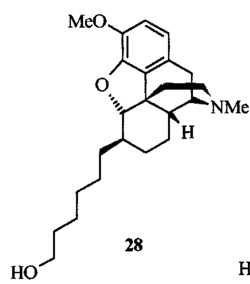
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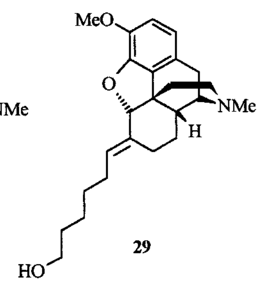
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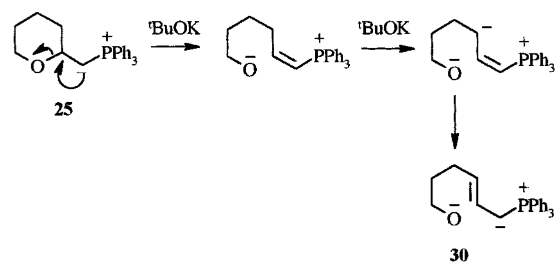
and dihydrocodeinone. In practice, however, this reaction gave an inseparable mixture of the dienes **26** and **27** in 97% yield. Dimide reduction of this product gave mainly the tetrahydro derivative **28** (21% yield), together with a small amount of the dihydro compound **29** (7% yield).

The configuration of the tetrahydro derivative **28** was confirmed by a single crystal X-ray analysis (see Fig. 1).

To account for the structures of the dienes **26** and **27** we assume that the ylide **25** undergoes ring-opening,[12] before reacting with dihydrocodeinone, perhaps as shown in Scheme 1.



Scheme 1

Further examples, prepared in two steps from dihydrocodeinone and the appropriate ylides, are the hexyl and 2-(*N*,*N*-dimethylamino)ethyl compounds **31** and **32**. The last compound

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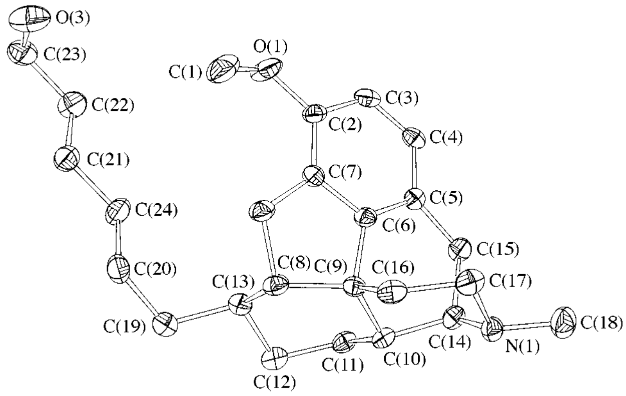
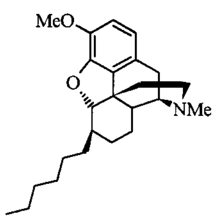


Fig. 1



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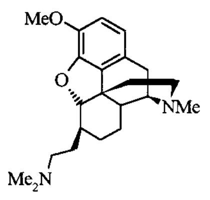

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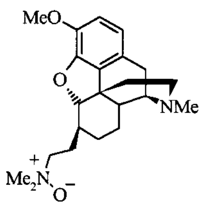

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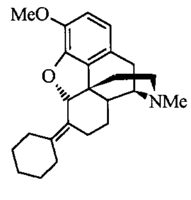
was accompanied by a minor amount of the *N*-oxide **33**. Undoubtedly, this impurity arises because of the presence of excess hydrogen peroxide used to generate diimide from hydrazine. Dimide was used in both syntheses as the reductant for the intermediates.

A Wittig reaction between cyclohexylphosphonium bromide and dihydrocodeinone failed to form the cyclohexylidene **34**, but gave instead the phenolic dimer **35** in 35–50% yield. We assume that this product is formed by a condensation between two dihydrocodeinone molecules, with perhaps the ylide acting as the base, followed by cyclisation and dehydration during work-up with aqueous acid (**36**→**37**→**35**). Interestingly, all attempts to prepare **35** by reacting dihydrocodeinone with potassium *tert*-butoxide alone failed and the starting material was recovered. We also found that when dihydrocodeinone is reacted with the ylide from isopropyltriphenylphosphonium iodide, an alternative product **38** is obtained. In this instance the dihydrofuran ring is not opened and dehydration does not occur during work-up in the presence of dilute acid. We did not detect the presence of the hydroxy ketone **38** in the reaction mixture which afforded the furan **35**.

Attack by carbanions upon morphine derivatives at C-5 has precedent[13,14] and, for example, dihydrothebaine **39** reacts with methylmagnesium iodide to give 5-methyldihydrothebainone **40**.[13] Similarly, Görlitzer has described the cyclisation of the diketone **41** to the 4*H*-pyran **42**.[15]

None of the new compounds described above exhibit significantly better results than codeine in tests for analgesic action.



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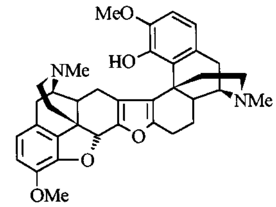

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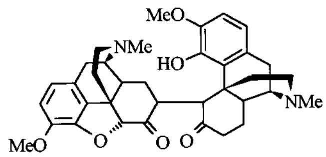

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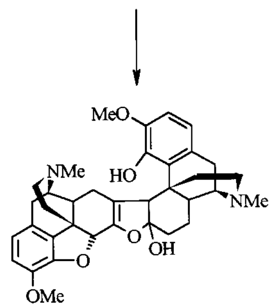

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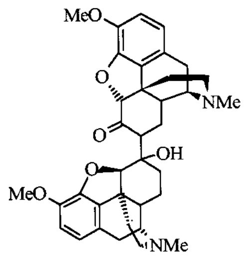

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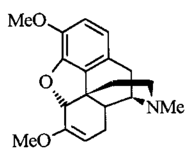

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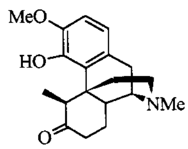

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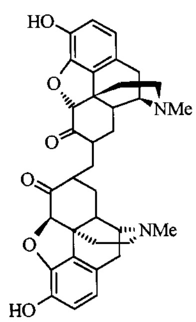

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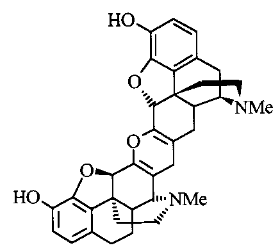

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Experimental

General

Unless stated otherwise, all solvents used were distilled and dried prior to use. Petrol refers to light petroleum, bp 60–80 °C. Solvents were removed by rotary evaporation at, or below, 45 °C. The drying agent used was anhydrous $MgSO_4$. Where necessary, the glass apparatus was dried in an oven and cooled under nitrogen. Most reactions were monitored by TLC on Whatman aluminium backed UV_{254} silica gel plates and visualised under UV light, or developed with iodine, or a $KMnO_4$ dip. Flash column chromatography was carried out under medium pressure on Amicon 60 Å silica gel. ^{1}H NMR Spectra were run in deuteriochloroform using tetramethylsilane as an internal standard, unless stated otherwise, these spectra were recorded at 270 or 400 MHz on JEOL instruments; *J* values are given in Hz. Mass spectra were determined on a VG Autospec instrument.

6-(Methoxymethylidene)-7,8-dihydro-6-deoxycodeine 13

To a stirred suspension of methoxymethyltriphenylphosphonium bromide (1.15 g, 3.34 mmol) in THF (14 cm^3), maintained at 20 °C was added potassium *tert*-butoxide (0.37 g, 3.34 mmol) in one portion. After 1 h, dihydrocodeinone (0.5 g, 1.67 mmol) was added to the deep red-coloured solution. The mixture was stirred for 1 h at 20 °C, heated at reflux for 11 h and then stirred overnight at room temperature. The solvent was removed, the residue diluted with water and then extracted

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into DCM (3×3 cm^3). The organic extracts were dried and solvent removed under reduced pressure. Purification by column chromatography using $CHCl_3$–MeOH (95:5) as eluent afforded the product as a mixture of E:Z isomers in the ratio 2.5:1 respectively. Overall yield 0.56 g (51%).

(*E*)-6-(Methoxymethylidene)-7,8-dihydro-6-deoxycodeine. R_f 0.43 ($CHCl_3$–MeOH 9:1); ν_{max}(neat)/cm^{-1} 1675 (C=CHOMe), 1633 (C=C), 1604 (ArC=C); δ_H 0.80–1.00 (1H, m, H-7), 1.45–1.55 (1H, m, H-7), 1.72 (1H, dd, J_{gem} 11.7, H-15eq), 1.76–1.90 (2H, m, H-8_{ax} and H-8_{eq}), 1.93 (1H, m, J_{gem} 11.7 and $J_{15ax,16eq}$ 5.2, H-15_{ax}), 2.12–2.35 (2H, m, H-16_{ax} and H-14), 2.37 (1H, dd, J_{gem} 18.5 and $J_{10\alpha,9}$ 5.9, H-10α), 2.41 (3H, s, N-CH_3), 2.53 (1H, dd, (J_{gem} 11.6 and $J_{16eq,15eq}$ 5.2, H-16_{eq}), 2.98 (1H, d, J_{gem} 18.5, H-10β), 3.09 (1H, dd, $J_{9,10\alpha}$ 5.9 and $J_{9,14}$ 2.7, H-9), 3.61 (3H, s, COOCH_3), 3.83 (3H, s, ArOCH_3), 5.37 (1H, d, $J_{5,19}$ 1.2, H-5), 5.86 (1H, d, $J_{19,5}$ 1.2, CHOCH$_3$), 6.58 (1H, d, $J_{1,2}$ 8.1, H-1), 6.70 (1H, d, $J_{2,1}$ 8.1, H-2); δ_C 20.2 (C-10), 22.7 (C-8), 23.0 (C-7), 35.7 (C-15), 39.5 (C-14), 41.1 (C-13), 42.8 (NCH$_3$), 46.9 (C-16), 56.8 (ArOCH$_3$), 59.7 (CHOCH$_3$), 60.1 (C-9) 87.1 (C-5), 111.7 (C-6), 114.1 (C-2), 118.3 (C-1), 127.2 (C-11), 129.9 (C-12), 142.2 (C-3), 144.9 (C-4), 146.2 (CHOCH$_3$) {Found [*m/z* (FAB)]: 328.1929. $C_{20}H_{26}NO_3$ ($M^+ + 1$) requires 328.1913}.

(*Z*)-6-(Methoxymethylidene)-7,8-dihydro-6-deoxycodeine. δ_H (selected signals) 3.53 (3H, s, CHOCH_3), 4.96 (1H, s, H-5), 6.29 (1H, s, CHOCH$_3$); δ_C (selected signals) 89.4 (C-5), 113.2 (C-6), 145.3 (CHOCH$_3$).

6-Formyl-4-hydroxy-3-methoxy-*N*-methylmorphin-5-ene 15

A mixture of toluene-*p*-sulfonic acid (49 mg, 0.24 mmol), water (4 cm^3), 1,4-dioxane (10 cm^3) and **13** (390 mg, 1.19 mmol) was heated at reflux for 16 h. The pH of the cooled mixture was adjusted to 9 by the addition of NH_4OH and it was then extracted with DCM (3×3 cm^3). The combined organic extracts were dried and solvent removed under reduced pressure. Crystallisation of the resultant colourless residue from diethyl ether yielded pure **15** as prisms (285 mg, 76%); R_f 0.30 ($CHCl_3$–MeOH–NH_3 90:9:1), mp 177–178 °C; *m/z* (FAB) 314.2 ($M^+ + 1$, 100%); ν_{max}(Nujol)/cm^{-1} 3189 (OH), 2810, 2715 (CHO), 1676 (C=O), 1631 (C=C), 1606 (ArC=C), 1274 (Ar–O–CH$_3$); δ_H 1.52 (1H, m, H-8_{ax}), 1.59–171 (1H, m, H-8_{eq}), 1.78 (1H, dd, J_{gem} 11.4 and $J_{15ax,16eq}$ 4.7, H-15_{ax}), 1.90 (1H, br d, $J_{14,8ax}$ 12.6, H-14), 2.04 (1H, dd, J_{gem} 11.4 and $J_{15eq,16eq}$ 3.0, H-15_{eq}), 2.10–2.30 (2H, m, H-16_{ax} and H-7_{eq}), 2.31 (1H, br dd, J_{gem} 18.2 and $J_{7ax,8eq}$ 6.7, H-7_{ax}), 2.40 (3H, s, NCH_3), 2.58 (1H, m, J_{gem} 11.9 and $J_{16eq,15eq}$ 3.0, H-16_{eq}), 2.69 (1H, dd, J_{gem} 18.3 and $J_{10\alpha,9}$ 5.5, H-10α), 3.00 (1H, d, $J_{9,10\alpha}$ 5.5, H-9), 3.01 (1H, d, J_{gem} 18.3, H-10β), 3.83 (3H, s, O–CH_3), 6.63 (1H, d, $J_{1,2}$ 8.2, H-1), 6.70 (1H, d, $J_{2,1}$ 8.2, H-2), 7.69 (1H, s, H-5), 9.55 (1H, s, CHO); δ_C 21.8 (C-7), 22.7 (C-8), 23.4 (C-10), 35.7 (C-15), 38.6 (C-13), 42.4 (N–CH$_3$), 43.1 (C-14), 47.5 (C-16), 55.9 (OCH$_3$), 57.4 (C-9), 108.75 (C-2), 118.7 (C-1), 125.1 (C-11), 129.3 (C-12), 138.5 (C-6), 143.8 (C-3), 144.85 (C-4), 158.55 (C-5), 195.6 (C=O) {Found [*m/z* (FAB)]: 314.1756. $C_{19}H_{24}NO_3$ ($M^+ + 1$) requires 314.1772}.

Cyclohexylmethyltriphenylphosphonium bromide

A mixture of triphenylphosphine (10 g, 38.1 mmol) and cyclohexylmethyl bromide (5.32 cm^3, 38.1 mmol) in toluene (20 cm^3) were heated at reflux for 28 h. After cooling, the resultant solid was collected and then washed with toluene to afford the title compound as a colourless powder, mp 130–131 °C (lit.,[16] mp 130–131 °C) (42.6 g, 26%) {Found [*m/z* (FAB)]: 359.1929. Calc. for $C_{25}H_{28}P$ ($M^+ +$ Br) 359.1929}.

(*E*- and *Z*-)-6-(Cyclohexylmethylidene)-7,8-dihydro-6-deoxycodeine 17

To a suspension of cyclohexylmethyltriphenylphosphonium bromide (1.19 g, 3.34 mmol) in THF (29 cm^3) at 20 °C was added potassium *tert*-butoxide (0.37 g, 3.34 mmol) in one portion. After 90 min, dihydrocodeinone (0.50 g, 1.67 mmol) was added to the deep orange-coloured solution. The mixture was stirred for 15 min at 20 °C, before heating it at reflux for 6 h. After standing overnight at room temperature, THF was removed from the mixture and the residue was dissolved in DCM and washed with water (3×5 cm^3). The organic extract was dried and the solvent removed under reduced pressure. Purification of the residue by column chromatography using $CHCl_3$–MeOH (9:1) as eluent afforded the title compound as a 1:1 mixture of E:Z isomers. Overall yield 0.58 g (91%).

(*Z*)-6-(Cyclohexylmethylidene)-7,8-dihydro-6-deoxycodeine. R_f 0.49 ($CHCl_3$–MeOH–NH_3 95:5:1); ν_{max}(Nujol)/cm^{-1} 1636 (C=C), 1607 (ArC=C), 1503 (C–N), 1275 (ArCOCH$_3$); δ_H(400 MHz) 0.89–1.03 (3H, m, H-8 and CH_2-cyclohexyl), 1.09–1.18 (1H, m, CH_2-cyclohexyl), 1.29–1.43 (3H, m, CH_2-cyclohexyl), 1.45–1.52 (1H, m, H-8), 1.61–1.76 (6H, m, H-15_{eq} and CH_2-cyclohexyl), 1.89 (1H, td, J_{gem} 12.2 and $J_{15ax,16eq}$ 4.9, H-15_{ax}), 2.00–2.03 (2H, m, H-7_{ax} and H-7_{eq}), 2.13–2.19 (1H, m, H-14), 2.14 (1H, td, J_{gem} 12.2, $J_{16ax,15eq}$ 3.4, H-16_{ax}), 2.34 (1H, dd, J_{gem} 18.6 and $J_{10\alpha,9}$ 5.9, H-10α), 2.40 (3H, s, NCH_3), 2.51 (1H, dd, J_{gem} 12.2 and $J_{16eq,15ax}$ 3.9, H-16_{eq}), 2.68–2.78 (1H, m, cyclohexyl), 2.98 (1H, d, J_{gem} 18.6, H-10β), 3.07 (1H, dd, $J_{9,10\alpha}$ 5.9 and $J_{9,14}$ 2.9, H-9), 3.84 (3H, s, OCH_3), 5.11 (1H, d, J 9.8, CH-cyclohexyl), 5.20 (1H, d, J 1.5, H-5), 6.59 (1H, d, $J_{1,2}$ 8.3, H-1), 6.70 (1H, d, $J_{2,1}$ 8.3, H-2); δ_C 20.0 (C-10), 24.6 (C-8), 25.8, 25.9 and 26.2 (cyclohexyl), 31.7 (C-7), 33.4 and 33.7 (cyclohexyl), 36.5 (C-15), 37.3 (cyclohexyl), 41.6 (C-14), 43.0 (NCH$_3$), 43.9 (C-13), 47.1 (C-16), 56.4 (OCH$_3$), 59.9 (C-9), 89.6 (C-5), 113.3 (C-2), 118.4 (C-1), 127.3 (C-11), 129.9 (C-12), 131.75 (C-6), 137.9 (CH-cyclohexyl), 142.4 (C-3), 145.6 (C-4) {Found [*m/z* (FAB)]: 380.2608. $C_{25}H_{34}NO_2$ ($M^+ + 1$) requires 380.2590}.

(*E*)-6-(Cyclohexylmethylidene)-7,8-dihydro-6-deoxycodeine. R_f 0.42 ($CHCl_3$–MeOH–NH_3 95:5:1); δ_H 0.77–1.00 (2H, m, cyclohexyl), 1.03–1.40 (4H, m, cyclohexyl), 1.52–1.76 (8H, m, H-7_{ax}, H-7_{eq}, H-8, H-15_{eq} and cyclohexyl), 1.88 (1H, td, J_{gem} 12.2 and $J_{15ax,16eq}$ 4.9, H-15_{ax}), 2.01–2.13 (1H, m, CH-cyclohexyl), 2.17 (1H, td, J_{gem} 12.2, $J_{16ax,15eq}$ 3.4, H-16_{ax}), 2.20–2.27 (1H, m, H-14), 2.30 (1H, dd, J_{gem} 18.6 and $J_{10\alpha,9}$ 5.4, H-10α), 2.38–2.44 (1H, m, H-8), 2.40 (3H, s, NCH_3), 2.53 (1H, dd, J_{gem} 12.2 and $J_{16eq,15ax}$ 3.4, H-16_{eq}), 2.97 (1H, d, J_{gem} 18.6, H-10β), 3.05 (1H, dd, $J_{9,10\alpha}$ 5.4 and $J_{9,14}$ 2.9, H-9), 3.89 (3H, s, OCH_3), 4.84 (1H, s, H-5), 5.60 (1H, d, J 8.8, CH-cyclohexyl), 6.56 (1H, d, $J_{1,2}$ 8.2, H-1), 6.68 (1H, d, $J_{2,1}$ 8.2, H-2); δ_C 20.2 (C-10), 24.9 (C-8), 25.7, 25.8, 25.9 and 26.2 (C-7 and cyclohexyl), 33.2 and 33.3 (cyclohexyl), 35.9 (C-15), 36.0 (CH-cyclohexyl), 42.8 (C-14), 42.9 (NCH$_3$), 44.2 (C-13), 47.5 (C-16), 57.21 (OCH$_3$), 59.9 (C-9), 91.5 (C-5), 114.4 (C-2), 118.65 (C-1), 127.3 (C-11), 130.05 (C-12), 132.1 (CH-cyclohexyl), 133.1 (C-6), 142.9 (C-3), 145.6 (C-4).

Catalytic hydrogenation of mixed alkenes 17

(i) At RT and 40 atm pressure. Hydrogenation of **17** (133 mg, 0.35 mmol) in dimethylformamide (7 cm^3) using palladium on charcoal (31 mg) as catalyst was performed at room temperature and 40 atmospheres pressure. The disappearance of starting material was monitored by TLC and on complete reaction the reaction mixture was filtered over Celite and washed thoroughly with excess DMF. The filtrate was concentrated and the residue dissolved in EtOAc and washed with water (3×5 cm^3). After drying, the organic solvent was removed under reduced pressure. Purification by column chromatography using $CHCl_3$–MeOH–NH_3 (97:3:1) as eluent afforded **18** (87 mg, 65%) and **19** (16 mg, 8%) as colourless oils.

(ii) Acid catalysed. To a mixture of the alkenes **17** (540 mg, 1.42 mmol) and palladium on charcoal (80 mg) in absolute ethanol (20 cm^3) was added conc. HCl (1 drop). The reaction mixture was hydrogenated at room temperature and atmospheric pressure. After 3 h the mixture was filtered through Celite and then washed through with excess ethanol (2×20 cm^3). The solvent was removed under reduced pressure and the

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residue purified by column chromatography using $CHCl_3$–MeOH–NH_3 (97 : 3 : 1) as eluent to give starting material **17** (430 mg, 80%) and **18** (77 mg, 14%) as a colourless oil.

6-Cyclohexylmethyl-5,6-didehydro-4-hydroxy-3-methoxy-*N*-methylmorphinan 18

R_f 0.37 ($CHCl_3$–MeOH–NH_3 95 : 5 : 1); ν_{max}(neat)/cm^{-1} 3526 (OH), 1724 (C=C), 1606, 1581 (ArC=C), 1483 (C–N), 1278 (ArC–OCH_3); δ_H(400 MHz) 0.76–0.90 (2H, m, cyclohexyl-axial), 1.11–1.19 (3H, m, cyclohexyl-axial), 1.37–1.45 (1H, m, cyclohexyl), 1.48–1.54 (2H, m, H-8$_{ax}$ and H-8$_{eq}$), 1.62–1.72 (6H, m, H-15 and cyclohexyl-equatorial), 1.79–1.90 (5H, m, H-7, H-14, H-15, H-19$_{ax}$ and H-19$_{eq}$), 2.02–2.22 (2H, m, H-7 and H-16$_{ax}$), 2.39 (3H, s, N–CH_3), 2.52 (1H, m, J_{gem} 10.7 and $J_{16eq,15}$ 2.9, H-16$_{eq}$), 2.65 (1H, dd, J_{gem} 18.1 and $J_{10\alpha,9}$ 5.6, H-10α), 2.92 (1H, br s, H-9), 2.95 (1H, d, J_{gem} 18.1, H-10β), 3.82 (3H, s, OCH_3), 5.95 (1H, br s, OH), 6.23 (1H, s, H-5), 6.57 (1H, d, $J_{1,2}$ 8.3, H-1), 6.64 (1H, d, $J_{2,1}$ 8.3, H-2); δ_C 23.8 (C-10), 24.35 (C-8), 26.0, 26.3 and 26.7 (cyclohexyl), 28.9 (C-7), 32.8 and 33.7 (cyclohexyl), 35.5 (C-13), 35.7 (cyclohexyl), 37.4 (C-15), 42.5 (NCH_3), 43.95 (C-14), 45.95 (cyclohexyl), 48.05 (C-16), 55.95 (OCH_3), 57.9 (C-9), 108.05 (C-2), 118.15 (C-1), 127.8 (C-6), 129.7 (C-11), 130.9 (C-5), 134.1 (C-12), 144.3 (C-3), 144.8 (C-4) {Found [*m*/*z* (FAB)]: 382.2733. $C_{25}H_{36}NO_2$ (M^+ + 1) requires 382.2746}.

6-Cyclohexylmethylidene-4-hydroxy-3-methoxy-*N*-methylmorphinan 19

R_f 0.22 ($CHCl_3$–MeOH–NH_3 97 : 3 : 1), mp 217–218 °C; ν_{max}(neat)/cm^{-1} 3519 (OH), 1721, 1646, 1608; δ_H 0.66–0.82 (1H, m, CH_2), 0.88–1.29 (6H, m, H-8, 5 × CH_2), 1.46–1.72 (6H, m, H-8, H-15$_{ax}$, 4 × CH_2), 1.74–1.92 (4H, m, H-5, H-7, H-14, H-15$_{eq}$), 1.94–2.06 (1H, m, cyclohexyl), 2.05 (1H, dt, J_{gem} 12.3 and $J_{16ax,15}$ 3.5, H-16$_{ax}$), 2.37 (3H, s, NCH_3), 2.42–2.54 (2H, m, H-16$_{eq}$, H-7), 2.60 (1H, dd, J_{gem} 18.3 and $J_{10\alpha,9}$ 5.5, H-10α), 2.82 (1H, dd, $J_{9,10\alpha}$ 5.6 and $J_{9,14}$ 3.0, H-9), 2.91 (1H, d, J_{gem} 18.3, H-10β), 3.83 (1H, dd, J_{gem} 19.5 and $J_{5,19}$ 1.5, H-5), 3.84 (3H, s, OCH_3), 5.09 (1H, d, J_{gem} 9.0, H-19), 5.94 (1H, s, OH), 6.55 (1H, d, $J_{1,2}$ 8.2, H-1), 6.66 (1H, d, $J_{2,1}$ 8.1, H-2); δ_C 24.05 (C-10), 25.9 (C-8), 26.0 and 26.15 and 28.4 (cyclohexyl-CH_2), 28.8 (C-7), 33.4 and 33.8 (cyclohexyl-CH_2), 35.95 (cyclohexyl-*C*H), 37.95 (C-15), 40.1 (C-13), 42.8 (NCH_3), 45.5 (C-5), 47.0 (C-14), 47.7 (C-16), 56.5 (OCH_3), 57.7 (C-9), 108.4 (C-2), 118.0 (C-1), 125.8 (C-11), 129.0 (C-19), 131.7 (C-12), 134.2 (C-6), 144.5 (C-4), 144.6 (C-4) {Found [*m*/*z* (FAB)]: 382.2749. $C_{25}H_{36}NO_2$ (M^+ + 1) requires: 382.2746}.

Reduction of the mixed alkenes 17 with triethylsilane and trifluoroacetic acid [17]

To a stirred solution of the alkenes **17** (699 mg, 1.84 mmol) in trifluoroacetic acid (4 cm^3) was added triethylsilane (0.3 cm^3, 1.88 mmol). After stirring at room temperature for 48 h, the pH of the reaction mixture was adjusted to 9 by the addition of saturated $NaHCO_3$ and extracted with DCM (3 × 5 cm^3). The combined organic extracts were dried and the solvent removed. Purification of the residue using $CHCl_3$–MeOH–NH_3 (95 : 5 : 1) as eluent afforded a mixture of **18** (160 mg, 23%) and **20** (340 mg, 48%) as colourless oils.

6-Cyclohexylmethyl-4-hydroxy-3-methoxy-*N*-methylmorphinan 20

R_f 0.29 ($CHCl_3$–MeOH–NH_3 95 : 5 : 1); ν_{max}(Nujol)/cm^{-1} 3522 (OH), 1603 (ArC=C), 1592, 1280 (ArCOCH_3); δ_H 0.71–0.90 (3H, m, H-5 and CH_2), 0.93–1.55 (10H, m, H-6, H-8$_{ax}$, H-8$_{eq}$, C*H*, H-19$_{ax}$, H-19$_{eq}$ and 4 × CH_2), 1.59–1.74 (9H, m, H-7$_{ax}$, H-7$_{eq}$, H-14, H-15$_{ax}$, H-15$_{eq}$, 4 × CH_2), 2.08 (1H, td, J_{gem} 12.2 and $J_{16ax,15}$ 3.4, H-16$_{ax}$), 2.40 (3H, s, NCH_3), 2.47 (1H, dd, J_{gem} 12.2 and $J_{16eq,15}$ 2.9, H-16$_{eq}$), 2.67 (1H, dd, J_{gem} 18.1 and $J_{10\alpha,9}$ 5.9, H-10α), 2.81 (1H, br s, $J_{9,10\alpha}$ 5.9, H-9), 2.93 (1H, d, J_{gem} 18.1, H-10β), 3.36 (1H, d, J_{gem} 12.7, H-5), 3.84 (3H, s, OCH_3), 5.95 (1H, br s, OH), 6.60 (1H, d, $J_{1,2}$ 8.3, H-1), 6.68 (1H, d, $J_{2,1}$ 8.3, H-2); δ_C 24.1 (C-10), 26.5 (C-8), 26.5, 26.85 and 27.3 (CH_2), 30.7 (*C*H), 33.8 (CH_2), 33.95 (C-7), 34.0 (CH_2), 34.4 (C-6), 37.9 (C-13), 38.2 (C-15), 42.7 (NCH_3), 43.95 (C-5, 45.6 (CH_2-cyclohexyl), 46.7 (C-14), 47.6 (C-16), 56.3 (O–CH_3), 57.9 (C-9), 108.3 (C-2), 118.3 (C-1), 121.9 (C-11), 126.1 (C-12), 131.9 (C-3), 144.5 (C-4) {Found [*m*/*z* (FAB)]: 384.2906. $C_{25}H_{38}NO_2$ (M^+ + 1) requires 384.2903}.

Diimide reduction of the mixed alkenes 17

To a mixture of **17** (475 mg, 1.25 mmol), hydrazine hydrate (1.17 cm^3, 35.7 mmol) and 95% ethanol (6 cm^3) maintained at ~40 °C was added hydrogen peroxide [27.5% (2.32 cm^3, 18.8 mmol)] dropwise. The warm reaction mixture was stored for 60 h, then cooled, diluted with saturated NaCl and extracted with EtOAc (3 × 10 cm^3). The combined organic extracts were washed with saturated NaCl, 2 M $FeSO_4$, saturated $NaHCO_3$, and saturated NaCl solutions, before being dried and evaporated to dryness. Purification of the residue by column chromatography eluting with $CHCl_3$–MeOH (9 : 1) afforded **21** as a pale yellow oil (233 mg, 49%).

6β-(Cyclohexylmethyl)-7,8-dihydro-6-deoxycodeine 21

R_f 0.51 ($CHCl_3$–MeOH 9 : 1); ν_{max}(neat)/cm^{-1} 1634, 1607 (ArC=C, 1276 (ArOCH_3); δ_H 0.72–0.96 (4H, m, H-7, H-8 and 2 × CH_2-cyclohexyl), 1.09–1.25 (4H, m, 1 × CH_2 bridge and 3 × CH_2-cyclohexyl), 1.28–1.46 (2H, m, H-6 and C*H*-cyclohexyl), 1.47–1.69 (9H, m, H-7, H-8, H-15$_{eq}$, 1 × CH_2 bridge and 5 × CH_2-cyclohexyl), 1.76 (1H, td, J_{gem} 12.9 and $J_{15,16}$ 4.9, H-15$_{ax}$), 2.10–2.16 (1H, m, H-14), 2.16 (1H, td, J_{gem} 12.2 and $J_{16,15}$ 3.9, H-16$_{ax}$), 2.35 (1H, dd, J_{gem} 18.6 and $J_{10\alpha,9}$ 5.4, H-10α), 2.39 (3H, s, NCH_3), 2.50 (1H, dd, *J* 12.2 and $J_{16eq,15}$ 4.9, H-16$_{eq}$), 3.00 (1H, d, J_{gem} 18.6, H-10β), 3.05 (1H, dd, $J_{9,10\alpha}$ 4.9 and $J_{9,14}$ 2.9, H-9), 3.88 (3H, s, O–CH_3), 4.11 (1H, d, $J_{5,6}$ 8.3, H-5), 6.59 (1H, d, $J_{1,2}$ 8.1, H-1), 6.64 (1H, d, $J_{2,1}$ 8.1, H-2); δ_C 19.8 (C-10), 24.8 (C-8), 25.9, 26.0 and 26.3 (cyclohexyl), 27.9 (C-7), 32.9 and 33.8 (CH_2-cyclohexyl), 34.3 (cyclohexyl), 35.4 (C-15), 36.6 (C-6), 42.3 (C-13), 42.6 (CCH_3), 43.1 (cyclohexyl), 43.2 (C-14), 47.2 (C-16), 56.7 (OCH_3), 59.4 (C-9), 96.1 (C-5), 113.9 (C-2), 118.0 (C-1), 126.8 (C-11), 130.7 (C-12), 143.1 (C-3), 144.2 (C-4) {Found [*m*/*z* (FAB)]: 392.2750. $C_{25}H_{36}NO_2$ (M^+ + 1) requires 382.2746}.

2-(Methyltriphenylphosphonium)tetrahydro-2*H*-pyran bromide

A mixture of 2-(bromomethyl)tetrahydro-2*H*-pyran (7.16 cm^3, 56 mmol), triphenylphosphine (14.7 g, 56 mmol) and toluene (25 cm^3) were heated at reflux for 28 h. After cooling, the resultant solid was collected and then washed with toluene to afford the title compound as a colourless powder (17 g, 69%), mp 233–235 °C; *m*/*z* (FAB) 361.1 (M − Br, 100%); δ_H 1.35–1.61 (4H, m), 1.80 (1H, br d, *J* 5.3), 2.23 (1H, br d, *J* 12.8), 2.85 (1H, dt, *J* 11.4 and *J* 1), 3.46–3.65 (3H, m), 4.45 (1H, t, *J* 13.4), 7.63–7.85 (15H, m, ArC*H*); δ_C 22.7 (CH_2), 24.8 (CH_2), 30.55 (d, *J* 51.7, CH–CH_2–P^+), 32.3 (d, *J* 14.7, CH_2–CH–CH_2–P^+), 68.0 (−CH–CH_2O), 72.5 (d, *J* 5.5, CH), 119.2 (d, *J* 86.4, CH_2–P^+–Ar*C*), 129.7, 129.9, 130.1, 133.8, 133.9, 134.0, 134.1, 134.4 (Ar*C*H) (Found: C, 65.3; H, 5.9. $C_{24}H_{26}BrOP$ requires C, 65.3; H, 5.9%).

Wittig reaction between 2-(methyltriphenylphosphonium)-tetrahydro-2*H*-pyran bromide and dihydrocodeinone

To a cooled, stirred suspension of 2-(methyltriphenylphosphonium)tetrahydro-2*H*-pyran bromide (3.3 g, 7.52 mmol) in THF (60 cm^3) was added potassium *tert*-butoxide (0.71 g, 6.33 mmol) in one portion. After 1 h, dihydrocodeinone (1.50 g, 5.01 mmol) was added to the deep red-coloured solution. The mixture was stirred for a further 15 min at 20 °C, heated at reflux for 8 h and then stirred overnight at room temperature. After

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removal of the solvent the resultant purple-coloured residue was purified by column chromatography using $CHCl_3$–MeOH–NH_3 (97 : 3 : 1) as eluent to afford an inseparable 1 : 1 mixture of **26** and **27**. Overall yield 1.86 g (97%).

6-(6-Hydroxyhex-2-enylidene)-7,8-dihydro-6-deoxycodeine 26

R_f 0.28 ($CHCl_3$–MeOH–NH_3 97 : 3 : 1); ν_{max}(Nujol)/cm^{-1} 3712 (OH), 1634 (ArC=C), 1602 (C=C–C=C), 1257 ($ArOCH_3$) (Found: C, 75.4; H, 8.2; N, 3.6. $C_{24}H_{31}NO_3$ requires C, 75.6; H, 8.2; N, 3.7%).

6-(6-Hydroxyhex-1-enyl)-6-dehydro-8-hydro-6-deoxycodeine 27

R_f 0.22 ($CHCl_3$–MeOH–NH_3 97 : 3 : 1); ν_{max}(neat)/cm^{-1} 3384 (OH), 1634, 1607 (ArC=C), 1503 (C–N), 1445, 1372 (ArC–O–CH_3); δ_H 0.84–0.94 (1H, m, H-8), 1.55–1.66 (3H, m, H-8, H-23_{ax}, H-23_{eq}), 1.70–1.81 (2H, br q, H-15_{eq}, H-22), 1.89 (1H, td, J_{gem} 12.2 and $J_{15ax,16}$ 4.9, H-15_{ax}), 2.12–2.15 (2H, q, H-7_{ax}, H-7_{eq}), 2.18 (1H, td, J_{gem} 12.2 and $J_{16,15}$ 3.9, H-16_{ax}), 2.30 (1H, dd, J_{gem} 18.6 and $J_{10\alpha,9}$ 4.9, H-10α), 2.27–2.33 (1H, m, H-14), 2.38 (3H, s, NCH_3), 2.52 (1H, dd, J_{gem} 12.2 and $J_{16eq,15}$ 4.4, H-16_{eq}), 2.66 (1H, m, J_{gem} 11.2, H-22), 2.82 (1H, br s, OH), 2.98 (1H, d, J_{gem} 18.6, H-10β), 3.05 (1H, dd, $J_{9,10\beta}$ 4.9 and $J_{9,14}$ 2.4, H-9), 3.60 (2H, t, J 6.6, CH_2OH), 3.88 (3H, s, OCH_3), 4.90 (1H, s, H-5), 5.70 (1H, dt, $J_{21,20}$ 14.7, $J_{21,22}$ 7.3, H-21), 6.20 (1H, dd, $J_{20,21}$ 14.7, $J_{20,19}$ 11.2, H-20), 6.37 (1H, d, $J_{19,20}$ 10.7, H-19), 6.58 (1H, d, $J_{1,2}$ 8.3, H-1), 6.68 (1H, d, $J_{2,1}$ 8.3, H-2); δ_C 20.0 (C-10), 25.25 (C-8), 25.4 (C-22), 29.1 (C-7), 32.1 (C-23), 35.4 (C-15), 42.7 (NCH_3), 42.75 (C-14), 44.05 (C-13), 47.4 (C-16), 56.7 (OCH_3), 59.5 (C-9), 61.9 (CH_2OH), 90.5 (C-5), 113.7 (C-2), 118.6 (C-1), 124.7 (C-10), 125.6 (C-20), 126.8 (C-11), 129.45 (C-12), 134.4 (C-21), 135.6 (C-6), 142.8 (C-3), 145.0 (C-4) {Found (*m/z* FAB): 382.2367. $C_{24}H_{32}NO_3$ (M^+ + 1) requires 382.2382}.

Diimide reduction of the dienes 26 and 27

To a warm (40 °C) mixture of the dienes (541 mg, 1.42 mmol) in hydrazine hydrate (0.88 cm^3, 28 mmol) and 95% ethanol (7 cm^3) was added 27.5% aqueous hydrogen peroxide (1.76 cm^3, 14 mmol) dropwise. The reaction mixture was maintained at 40 °C for a further 8 h and then stirred at room temperature overnight. The solution was diluted with saturated aqueous NaCl and extracted with EtOAc (3 × 5 cm^3). The combined organic extracts were washed with saturated aqueous NaCl, 2 M $FeSO_4$, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl before being dried and evaporated to dryness. Purification of the residue by column chromatography eluting with $CHCl_3$–MeOH (9 : 1) afforded **28** as a colourless crystalline solid (115 mg, 21%) and **29** (36 mg, 7%) as a colourless oil.

6β-(6-Hydroxyhexyl)-7,8-dihydro-6-deoxycodeine 28

R_f 0.33 ($CHCl_3$–MeOH 9 : 1), mp 118–119 °C; *m/z* (FAB) 380.2 (M^+ + 1, 100%); ν_{max}(neat)/cm^{-1} 3378 (OH), 1633, 1606 (ArC=C), 1276 ($ArCOCH_3$); δ_H 0.85–0.98 (2H, m, CH_2), 1.24–1.45 (8H, m), 1.49–1.66 (5H, m), 1.69 (1H, dd, J_{gem} 12.2 and $J_{15eq,16eq}$ 3.9, H-15_{eq}), 1.85 (1H, dt, J_{gem} 12.2 and $J_{15ax,16eq}$ 4.9, H-15_{ax}), 2.22 (1H, dt, J_{gem} 12.2 and $J_{16ax,15eq}$ 3.4, H-16_{ax}), 2.20–2.30 (1H, m, H-14), 2.43 (1H, dd, J_{gem} 18.1 and $J_{10\alpha,9}$ 5.4, H-10α), 2.45 (3H, s, NCH_3), 2.59 (1H, dd, J_{gem} 12.2 and $J_{16eq,15ax}$ 4.4, H-16_{eq}), 3.00 (1H, d, J_{gem} 18.1, H-10β), 3.13 (1H, br s, H-9), 3.62 (2H, t, J_{gem} 6.4, CH_2OH), 3.87 (3H, s, OCH_3), 4.16 (1H, d, J_{gem} 7.8, H-5), 6.62 (1H, d, $J_{1,2}$ 8.3, H-1), 6.72 (1H, d, $J_{2,1}$ 8.3, H-2); δ_C 20.3 (C-10), 25.1 (C-8), 25.6, 26.65 and 27.6 (3 × CH_2), 29.5 (C-7), 32.8 and 34.6 (2 × CH_2), 35.35 (C-15), 40.0 (C-6), 42.45 (C-13), 42.7 (N–CH_3), 43.0 (C-14), 47.7 (C-16), 56.8 (O–CH_3), 59.95 (C-9), 63.0 (CH_2–OH), 95.45 (C-5), 113.9 (C-2), 118.5 (C-1), 126.4 (C-11), 130.6 (C-12), 143.6 (C-3), 144.5 (C-4) (Found: C, 74.9; H, 9.2; N, 3.55. $C_{24}H_{35}NO_3$ requires C, 74.8; H, 9.15; N, 3.6%).

6-(6-Hydroxyhexylidene)-7,8-dihydro-6-deoxycodeine 29

R_f 0.28 ($CHCl_3$–MeOH 9 : 1), ν_{max}(neat)/cm^{-1} 3378 (OH), 1715 (C=C), 1635, 1609 (ArC=C), 1276 ($ArCOCH_3$); δ_H 0.79–0.94 (1H, m, CH_2), 1.11–1.17 (2H, m, H-8_{ax} and H-8_{eq}), 1.24–1.32 (2H, m, CH_2), 1.44 (2H, q, C-6=CH–CH_2), 1.51–1.81 (3H, m, H-7, H-15_{eq} and CH_2), 1.90 (1H, dt, J_{gem} 12.7 and $J_{15ax,16}$ 4.9, H-15_{ax}), 1.91–2.00 (2H, m, CH_2), 2.04 (1H, s, OH), 2.20 (1H, td, J_{gem} 12.2 and $J_{16,15eq}$ 3.9, H-16_{ax}), 2.28–2.30 (1H, m, H-14), 2.32 (1H, dd, J_{gem} 18.1 and $J_{10\alpha,9}$ 5.4, H-10α), 2.40 (3H, s, NCH_3), 2.45 (1H, td, J_{gem} 14.2 and $J_{7,8}$ 3.4, H-7), 2.54 (1H, dd, J_{gem} 12.2 and $J_{16eq,15ax}$ 4.4, H-16_{eq}), 2.98 (1H, d, J_{gem} 18.6, H-10β), 3.07 (1H, dd, $J_{9,10\alpha}$ 5.4, H-9), 3.53 (1H, t, J 6.4, C-6=CHCH_2), 3.62 (1H, t, J 6.4, C-6=CHCH_2), 3.89 (3H, s, OCH_3), 4.87 (1H, s, H-5), 5.74 (1H, t, J 7.3, C-6=CH), 6.59 (1H, d, $J_{1,2}$ 8.3, H-1), 6.69 (1H, d, $J_{2,1}$ 8.3, H-2); δ_C 20.1 (C-10), 24.8 (C-7), 24.9 (C-8), 25.55, 26.7 and 29.2 (CH_2), 32.6 (CHCH_2), 35.6 (C-15), 42.5 (NCH_3), 42.85 (C-14), 44.2 (C-13), 47.5 (C-16), 56.9 (OCH_3), 59.7 (C-9), 62.8 (CH_2OH), 91.15 (C-5), 113.8 (C-2), 118.65 (C-1), 125.6 (CHCH$_2$), 127.1 (C-11), 129.9 (C-12), 134.5 (C-6), 142.9 (C-3), 145.3 (C-4) {Found (*m/z* FAB): 384.2543. $C_{24}H_{34}NO_3$ (M^+ + 1) requires 384.2539}.

Catalytic reduction of 6-(6-hydroxyhex-2-enylidene)-7,8-dihydro-6-deoxycodeine using palladium on charcoal

6-(6-Hydroxyhex-2-enylidene)-7,8-dihydro-6-deoxycodeine (219 mg, 0.57 mmol) in 95% ethanol (20 cm^3) was hydrogenated at room temperature at atmospheric pressure using palladium on charcoal (36 mg) as catalyst. The disappearance of starting material was monitored by TLC and on completion the mixture was filtered through Celite and the residue washed thoroughly with excess ethanol. The filtrate was concentrated under reduced pressure to afford a colourless oil. Purification by column chromatography $CHCl_3$–MeOH (97 : 3) as eluent afforded 5,6-dihydro-4-hydroxy-6-(6-hydroxyhexyl)-3-methoxy-*N*-methylmorphinan (61 mg, 28%) as a colourless oil. R_f 0.28 ($CHCl_3$–MeOH 9 : 1); ν_{max}(neat)/cm^{-1} 3516, 3312 (OH), 1607 (ArC=C), 1278 ($ArOCH_3$); δ_H 1.28–1.37 (4H, m, CH_2), 1.44 (2H, m, CH_2), 1.50–1.59 (4H, m, H-8_{ax} and H-8_{eq}), 1.68 (1H, dt, J 12.2 and J 4.9, CH_2), 1.85–1.92 (3H, m, CH_2, H-14), 1.97–2.12 (3H, m, CH_2, H-7_{ax} and H-7_{eq}), 2.09 (1H, td, J_{gem} 12.2 and $J_{16ax,15eq}$ 3.4, H-16_{ax}), 2.17 (1H, s, OH), 2.41 (3H, s, NCH_3), 2.54 (1H, dd, J_{gem} 12.2 and $J_{16eq,15}$ 2.9, H-16_{eq}), 2.69 (1H, dd, J_{gem} 18.1 and $J_{10\alpha,9}$ 5.9, H-10α), 2.94–2.97 (1H, m, H-9), 2.95 (1H, d, J_{gem} 18.1, H-10β), 3.63 [1H, t, J 6.8, $(CH)_4CH_2OH$], 3.83 (3H, s, OCH_3), 5.95 (1H, br s, OH), 6.28 (1H, s, H-5), 6.58 (1H, d, $J_{1,2}$ 8.3, H-1), 6.65 (1H, d, $J_{2,1}$ 8.3, H-2); δ_C 23.9 (C-10), 24.3 (C-8), 25.5, 27.5, 28.6 and 28.7 (CH_2), 32.8 (C-15), 37.0 (C-19), 37.2 (C-13), 37.3 (C-7), 42.45 (NCH_3), 43.6 (C-14), 48.2 (C-16), 56.0 (OCH_3), 58.1 (C-9), 63.0 (CH_2OH), 108.2 (C-2), 118.3 (C-1), 124.2 (C-6), 127.75 (C-11), 129.4 (C-5), 135.5 (C-12), 144.2 (C-3), 144.9 (C-4) [Found (*m/z* FAB): 386.2682. $C_{24}H_{36}NO_3$ (M^+ + 1) requires 386.2695].

6-(Hexylidene)-7,8-dihydro-6-deoxycodeine

To a cooled, stirred suspension of hexyltriphenylphosphonium bromide (1.72 g, 4.02 mmol) in THF (20 cm^3) was added potassium *tert*-butoxide (0.45 g, 4.01 mmol) in one portion. After 1 h, dihydrocodeinone (1.0 g, 3.34 mmol) was added to the deep orange ylide solution. The mixture was stirred for 1 h at 20 °C before being heated at reflux for 5 h. After cooling, the solvent was removed and the residue redissolved in chloroform and then washed with water (3 × 10 cm^3). The organic phase was dried and chloroform removed under reduced pressure. Purification by column chromatography using $CHCl_3$–MeOH (94 : 6) as eluent afforded 6-(hexylidene)-7,8-dihydro-6-deoxycodeine as a colourless oil (775 mg, 63%) in a 6 : 8 : 1 ratio of inseparable *E* : *Z* isomers.

(*E*)-6-(Hexylidene)-7,8-dihydro-6-deoxycodeine

R_f 0.60 ($CHCl_3$–MeOH 9 : 1); ν_{max}(neat)/cm^{-1} 1634 (C=C), 1606

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(ArC=C), 1276 ($ArOCH_3$); δ_H 0.89 [3H, t, J 6.8, =CH-$(CH_2)_4CH_3$], 0.91–0.99 (1H, m, CH_2), 1.32–1.41 (6H, CH_2, H-8_{ax} and H-8_{eq}), 1.45–1.52 (1H, m, CH_2), 1.74 (1H, dq, J_{gem} 12.2, $J_{15eq,16eq}$ 3.4, H-15_{eq}), 1.88 (1H, td, J_{gem} 12.2 and $J_{15ax,16eq}$ 4.9, H-15_{ax}), 2.02–2.08 (2H, m, CH_2), 2.16 (1H, ddd, $J_{14,8ax}$ 12.2, $J_{14,8aq}$ 5.4 and $J_{14,9}$ 2.9, H-14), 2.20–2.35 (2H, overlapping resonances, CH_2), 2.33 (1H, dd, J_{gem} 18.6 and $J_{10,9}$ 5.9, H-10α), 2.25 (1H, td, J 12.2 and J 3.9, CH_2), 2.40 (3H, s, N–CH_3), 2.50 (1H, dd, J_{gem} 12.2, $J_{16eq,15eq}$ 3.4, H-16_{eq}), 2.98 (1H, d, J_{gem} 18.6, H-10β), 3.07 (1H, dd, $J_{9,10\alpha}$ 5.9, $J_{9,14}$ 2.9, H-9), 3.84 (3H, s, O–CH_3), 5.19 (1H, s, H-5), 5.31 [1H, t, J 7.3, $CH(CH_2)_4CH_3$], 6.58 (1H, d, $J_{1,2}$ 7.8, H-1), 6.69 (1H, d, $J_{2,1}$ 7.8, H-2); δ_C 14.0 [$CH(CH_2)_4CH_3$], 19.2 (C-10), 22.6 (C-8), 24.4, 28.6, 29.7, 31.45, 31.6 (5 × CH_2), 36.4 (C-15), 41.4 (C-14), 42.9 (N–CH_3), 43.6 (C-13), 47.0 (C-16), 56.3 (OCH_3), 59.8 (C-9), 89.4 (C-5), 113.2 (C-2), 118.3 (C-1), 127.2 (C-11), 129.8 (C-12), 132.2 [=$CH(CH_2)_4CH_3$], 133.6 (C-6), 142.3 (C-3), 145.4 (C-4) [Found (*m*/*z* FAB): 368.2591. $C_{24}H_{34}NO_2$ (M^+ + 1) requires 368.2590].

(*Z*)-6-(Hexylidene)-7,8-dihydro-6-deoxycodeine
δ_H(selected peaks) 4.87 (1H, s, H-5), 5.73 [1H, t, J 7.3, CH-$(CH_2)_4CH_3$]; δ_C 13.9 [$CH(CH_2)_4CH_3$], 20.0 (C-10), 22.4 (C-8), 24.7, 25.5, 26.7, 29.1, 31.0 (5 × CH_2), 35.7 (C-15), 41.2 (C-14), 42.9 (NCH_3), 44.1 (C-13), 47.5 (C-16), 56.7 (OCH_3), 59.7 (C-9), 91.2 (C-5), 113.6 (C-2), 118.5 (C-1), 125.9 [=$CH(CH_2)_4CH_3$], 127.1 (C-11), 130.8 (C-13), 134.6 (C-6), 142.8 (C-3), 145.4 (C-4).

Diimide reduction of 6-(hexylidene)-7,8-dihydro-6-deoxycodeine
To a cooled stirred mixture of 6-(hexylidene)-7,8-dihydro-6-deoxycodeine (585 mg, 1.59 mmol), hydrazine hydrate (1 cm^3, 32 mmol) in 95% ethanol (4.5 cm^3) was added hydrogen peroxide [27.5% (2 cm^3, 16 mmol)] dropwise. The mixture was then stirred for 16 h at 30–40 °C before a further 1 cm^3 of hydrazine hydrate (32 mmol) and 2 cm^3 of hydrogen peroxide (16 mmol) were added. After 7 h, the mixture was cooled to ambient temperature and the solvent removed under reduced pressure. The residue was purified by column chromatography using $CHCl_3$–MeOH (95:5) as eluent affording **31** as a colourless oil (300 mg, 51%).

6β-Hexyl-7,8-dihydro-6-deoxycodeine 31
R_f 0.60 ($CHCl_3$–MeOH 9:1); ν_{max}(neat)/cm^{-1} 1632, 1607 (ArC=C), 1276 ($ArOCH_3$); δ_H 0.87 (3H, t, J 6.4, C_5H_{10}–CH_3), 0.88–0.96 (2H, m, CH_2), 1.21–1.39 (10H, br s, H-6 and CH_2), 1.46–1.54 (1H, m, CH_2), 1.66 (1H, br d, J_{gem} 12.2, H-15_{eq}), 1.62–1.76 (2H, m, CH), 1.77 (1H, td, J_{gem} 12.2 and $J_{15ax,16eq}$ 4.9, H-15_{ax}), 2.12–2.17 (1H, m, H-14), 2.16 (1H, td, J_{gem} 12.2, $J_{16ax,15}$ 3.4, H-16_{ax}), 2.35 (1H, dd, J_{gem} 18.6 and $J_{10\alpha,9}$ 5.4, H-10α), 2.39 (3H, s, NCH_3), 2.50 (1H, dd, J_{gem} 12.2, $J_{16eq,15}$ 3.9, H-16_{eq}), 2.99 (1H, d, J_{gem} 18.1, H-10β), 3.05 (1H, br s, H-9), 3.87 (3H, s, OCH_3), 4.15 (1H, d, $J_{5,6}$ 7.8, H-5), 6.59 (1H, d, $J_{1,2}$ 7.8, H-1), 6.69 (1H, d, $J_{2,1}$ 8.3, H-2); δ_C 13.9 (C_5H_{10}–CH_3), 20.0 (C-10), 22.5, 25.0, 26.5, 27.6, 29.3, 31.65, 34.1 and 35.6 (8 × CH_2), 35.6 (C-15), 39.95 (C-6), 42.4 (C-13), 42.7 (NCH_3), 43.35 (C-14), 47.4 (C-16), 56.55 (O–CH_3), 59.6 (C-9), 95.4 (C-5), 113.7 (C-2), 118.2 (C-1), 126.8 (C-11), 130.7 (C-12), 132.2 (C-3), 144.3 (C-4) [Found (*m*/*z* FAB): 370.2724. $C_{24}H_{36}NO_2$ (M^+ + 1) requires 370.2746].

6-(2-Dimethylaminoethylidene)-7,8-dihydro-6-deoxycodeine
To a cooled, stirred suspension of (2-dimethylaminoethyl)-triphenylphosphine bromide (4.15 g, 10.02 mmol) in THF (35 cm^3) was added potassium *tert*-butoxide (1.12 g, 9.98 mmol) in one portion. After 1 h, dihydrocodeinone (1.50 g, 5.01 mmol) was added to the pale yellow solution. The mixture was stirred for 1 h at 20 °C before being heated at reflux for 6 h. After cooling, the solvent was removed and the residue redissolved in chloroform and then washed with water (3 × 6 cm^3). The organic phase was dried and the chloroform removed. Purification of the residue by column chromatography using $CHCl_3$–MeOH–NH_3 (90:10:1) as eluent afforded 6-(2-dimethylaminoethylidene)-7,8-dihydro-6-deoxycodeine as a colourless oil (1.40 g, 58%) containing an 8:1 ratio of inseparable *E*:*Z* isomers.

(*E*)-6-(2-Dimethylaminoethylidene)-7,8-dihydro-6-deoxycodeine
R_f 0.26 ($CHCl_3$–MeOH–NH_3 90:10:1); ν_{max}(neat)/cm^{-1} 1635 (C=C), 1606 (ArC=C), 1276 ($ArOCH_3$); δ_H 0.95 (1H, m, J_{gem} 12.2 and $J_{8,7}$ 4.9, H-8_{ax}), 1.51 (1H, m, J_{gem} 12.2 and $J_{8,7}$ 3.9, H-8_{eq}), 1.73 (1H, m, J_{gem} 12.2, H-15_{eq}), 1.89 (1H, td, J_{gem} 12.2 and $J_{15ax,16eq}$ 4.9, H-15_{ax}), 2.10–2.24 (3H, m, H-7_{ax}, H-7_{eq} and H-14), 2.23 (1H, td, J_{gem} 12.2, $J_{16ax,15}$ 3.9, H-16_{ax}), 2.25 [6H, s, $CHCH_2N(CH_3)_2$], 2.34 (1H, dd, J_{gem} 18.6 and $J_{10\alpha,9}$ 5.4, H-10α), 2.40 (3H, 3, NCH_3), 2.52 (1H, dd, J_{gem} 12.2, $J_{16eq,15}$ 3.9, H-16_{eq}), 2.99 (1H, d, J_{gem} 18.6, H-10β), 3.08 (1H, dd, $J_{9,10\alpha}$ 5.4 and $J_{9,14}$ 2.9, H-9), 3.26 [2H, t, J 6.83, $CHCH_2(CH_2)_2$], 3.85 (3H, s, O–CH_3), 5.16 (1H, s, H-5), 5.38 [1H, t, J 6.8, $CHCH_2N(CH_3)_2$], 6.60 (1H, d, $J_{1,2}$ 8.3, H-1), 6.70 (1H, d, $J_{2,1}$ 8.3, H-2); δ_C 19.9 (C-10), 24.6 (C-8), 32.1 (C-7), 36.2 (C-15), 41.9 (C-14), 42.9 (NCH_3), 43.9 (C-13), 45.4 [$N(CH_3)_2$], 47.1 (C-16), 56.4 (OCH_3), 57.4 [$CHCH_2N(CH_3)_2$], 59.7 (C-9), 89.25 (C-5), 113.4 (C-2), 118.6 (C-1), 127.2 (C-11), 129.05 [$CHCH_2N(CH_3)_2$], 129.7 (C-12), 136.2 (C-6), 142.5 (C-3), 145.0 (C-4) [Found (*m*/*z* FAB): 355.2378. $C_{22}H_{31}N_2O_2$ (M^+ + 1) requires 355.2386].

(*Z*)-6-(2-Dimethylaminoethylidene)-7,8-dihydro-6-deoxycodeine
δ_H(selected peaks) 4.89 (1H, s, H-5), 5.88 [1H, t, J 6.83, =$CHCH_2N(CH_3)_2$]; δ_C(selected peaks) 90.7 (C-5), 122.2 [=$CHCH_2N(CH_3)_2$].

Diimide reduction of 6-(2-dimethylaminoethylidene)-7,8-dihydro-6-deoxycodeine
To a cooled stirred mixture of 6-(2-dimethylaminoethylidene)-7,8-dihydro-6-deoxycodeine (1.71 g, 4.82 mmol) and hydrazine hydrate (3.0 cm^3, 96 mmol) in 95% ethanol (8 cm^3) was added to 27.5% aqueous hydrogen peroxide (6 cm^3, 48 mmol) dropwise over 30 min. The mixture was then stirred for 3 h at 30–40 °C before a further 3.0 cm^3 of hydrazine hydrate (96.4 mmol) and 6 cm^3 of hydrogen peroxide (48 mmol) were added. The mixture was then stirred for a further 20 h at 30–40 °C. The mixture was then cooled, concentrated to half its original volume and then extracted with chloroform (4 × 15 cm^3). The organic phase was dried, and the solvent removed to give a gum which was purified by column chromatography using as eluent $CHCl_3$–MeOH–NH_3 (90:10:2) and then $CHCl_3$–MeOH–NH_3 (95:5:2) to afford **32** (260 mg, 15%) and **33** (141 mg, 8%) as colourless oils.

6β-(2-Dimethylaminoethyl)-7,8-dihydro-6-deoxycodeine 32
R_f 0.33 ($CHCl_3$–MeOH–NH_3 90:10:2); ν_{max}(neat)/cm^{-1} 1634, 1608 (ArC=C), 1276 ($ArOCH_3$); δ_H 0.92 (1H, t, J 12.2, H-7_{ax}), 0.92 (1H, t, J 12.2, H-8_{ax}), 1.27–1.36 (1H, m, H-6), 1.37–1.46 [1H, m, $CH_2CH_2N(CH_3)_2$], 1.46–1.51 (1H, m, H-8_{eq}), 1.64–1.68 (2H, m, H-7_{eq} and H-15_{eq}), 1.77 (1H, td, J_{gem} 12.2 and $J_{15ax,16eq}$ 4.9, H-15_{ax}), 1.88–1.96 [1H, m, $CH_2CH_2N(CH_3)_2$], 2.11–2.17 (1H, m, H-14), 2.16 (1H, td, J_{gem} 12.2, $J_{16ax,15}$ 4.4, H-16_{ax}), 2.20 [6H, s, $CH_2CH_2N(CH_3)_2$], 2.26 [1H, td, J_{gem} 11.7 and J 4.4, $CH_2CH_2N(CH_3)_2$], 2.34 (1H, dd, J_{gem} 18.1 and $J_{10\alpha,9}$ 5.4, H-10α), 2.35–2.42 [1H, m, $CH_2CH_2N(CH_3)_2$], 2.39 (3H s, NCH_3), 2.49 (1H, dd, J_{gem} 12.2, $J_{16eq,15}$ 3.9, H-16_{eq}), 2.99 (1H, d, J_{gem} 18.1, H-10β), 3.04 (1H, dd, $J_{9,10\alpha}$ 4.9 and $J_{9,14}$ 2.9, H-9), 3.87 (3H, s, OCH_3), 4.16 (1H, d, $J_{5,6}$ 8.3, H-5), 6.59 (1H, d, $J_{1,2}$ 8.3, H-1), 6.69 (1H, d, $J_{2,1}$ 8.3, H-2); δ_C 20.0 (C-10), 24.9 (C-8), 27.7 (C-7), 32.7 [$CH_2N(CH_3)_2$], 35.65 (C-15), 38.2 (C-6), 42.6 (C-13), 42.8 (NCH_3), 43.4 (C-14), 45.3 [2 × $N(CH_3)_2$], 47.5 (C-16), 56.7 (OCH_3), 57.1 [$CH_2CH_2N(CH_3)_2$], 59.6 (C-9), 95.4 (C-5), 113.9 (C-2), 118.4 (C-1), 127.05 (C-11), 130.7 (C-12), 143.35 (C-3), 144.3 (C-4) [Found (*m*/*z* FAB): 357.2535. $C_{22}H_{33}N_2O_2$ (M^+ + 1) requires 357.2542].

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6β-(2-Dimethylaminoethyl)-7,8-dihydro-6-deoxycodeine-N^{20}-oxide 33

R_f 0.13 ($CHCl_3$–MeOH–NH_3 90 : 10 : 2); ν_{max}(neat)/cm^{-1} 1634, 1610 (ArC=C), 1276 ($ArOCH_3$); δ_H 0.93 (1H, dd, J_{gem} 12.2, $J_{8ax,7eq}$ 2.3, H-8_{ax}), 1.09 (1H, m, J_{gem} 12.2, J 1.5, H-7_{ax}), 1.28–1.38 (1H, m, H-6), 1.51–1.57 (1H, m, H-8_{eq}), 1.64–1.69 (2H, m, H-7_{eq} and H-15_{eq}), 1.79 (1H, td, J_{gem} 12.2 and $J_{15ax,16eq}$ 4.9, H-15_{ax}), 2.07 [2H, m, $CH_2CH_2N(CH_3)_2$], 2.12–2.22 (1H, m, H-14), 2.15 (1H, td, J_{gem} 12.2, $J_{16ax,15eq}$ 4.4, H-16_{ax}), 2.35 (1H, dd, J_{gem} 18.6 and $J_{10\alpha,9}$ 5.3, H-10α), 2.39 (3H, s, NCH_3), 2.51 (1H, dd, J_{gem} 12.2, $J_{16eq,15eq}$ 3.9, H-16_{eq}), 3.01 (1H, d, J_{gem} 18.6, H-10β), 3.07 (1H, m, H-9), 3.19 [3H, s, $CH_2CH_2N(CH_3)_2$], 3.22 [3H, s, $CH_2CH_2N(CH_3)_2$], 2.29–2.40 [1H, m, $CH_2N(CH_3)_2$], 3.42–3.52 [1H, m, $CH_2CH_2N(CH_3)_2$], 3.85 (3H, s, OCH_3), 4.23 (1H, d, $J_{5,6}$ 8.3, H-5), 6.64 (1H, d, $J_{1,2}$ 8.3, H-1), 6.71 (1H, d, $J_{2,1}$ 8.3, H-2); δ_C 20.0 (C-10), 24.9 (C-8), 28.5 (C-7), 29.4 [CH_2-$CH_2N(CH_3)_2$], 35.6 (C-15), 38.50 (C-6), 42.9 (NCH_3), 42.9 (C-13), 43.2 (C-14), 47.4 (C-16), 56.4 (OCH_3), 58.1 [CH_2-$CH_2N(CH_3)_2$], 59.35 [$CH_2CH_2N(CH_3)_2$], 59.5 (C-9), 69.6 [$CH_2CH_2N(CH_3)_2$], 95.0 (C-5), 113.3 (C-2), 119.0 (C-1), 127.05 (C-11), 130.3 (C-12), 143.4 (C-3), 143.8 (C-4) [Found (*m*/*z* FAB): 373.2489. $C_{22}H_{33}N_2O_2$ (M^+ + 1) requires 373.2489].

Attempted Wittig reaction between dihydrocodeinone and cyclohexyltriphenylphosphonium bromide

To a stirred suspension of cyclohexyltriphenylphosphonium bromide (2.16 g, 5.08 mmol) in THF (50 cm^3), maintained at 20 °C, was added potassium *tert*-butoxide (0.56 g, 4.99 mmol) in one portion. After 1 h, dihydrocodeinone (1.00 g, 3.34 mmol) was added to the deep red-coloured solution. The mixture was stirred for a further 90 min at 20 °C and then heated under reflux for 18 h. The solvent was then removed and the residue redissolved in DCM and washed three times with water. The organic phase was dried and the solvent removed to give a semi-solid. Purification of the residue by column chromatography using $CHCl_3$–MeOH–NH_3 (90 : 10 : 1) as eluent afforded 690 mg (35%) of the 'dimer' **37**.

Codiene 'dimer' 37

R_f 0.20 ($CHCl_3$–MeOH–NH_3 90 : 10 : 1); *m*/*z* (FAB) 599.2 (M^+ + 1, 100%); ν_{max}(Nujol)/cm^{-1} 3333 (OH), 1631; δ_H 0.32–0.51 (1H, m), 0.84–1.14 (4H, m), 1.22–1.34 (1H, m), 1.57–1.67 (1H, m), 1.88–2.15 (5H, m), 2.27 (1H, td, J_{gem} 12.1 and J 3.5, H-16_{ax}), 2.36 (3H, s, NCH_3), 2.37 (3H, s, NCH_3), 2.35–2.73 (6H, m), 2.83 (2H, br s), 2.99 (1H, d, J_{gem} 18.7, H-10β), 3.18 (1H, m, $J_{9,14}$ 3.5), 3.81 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 5.01 (1H, s, H-5), 5.95 (1H, s, OH), 6.59 (1H, d, $J_{1,2}$ 8.2, H-1), 6.60 (1H, d, $J_{1,2}$ 8.1, H-1), 6.65 (1H, d, $J_{2,1}$ 8.4, H-2), 6.71 (1H, d, $J_{2,1}$ 8.2, H-2), the signal for O*H* was not detected; δ_C 19.7 (C-10), 20.3, 21.5 (C-8, C-8′), 24.3 (C-10), 27.25 (C-7), 30.2 (C-14), 31.2, 34.7 (C-15, C-15′), 38.89 (C-14), 40.3 (C-13), 42.45, 43.01 (NCH_3, NCH_3), 43.3 (C-13′), 46.45, 46.6 (C-16, C-16′), 55.9, 57.1 (OCH_3, O–CH_3), 57.6, 59.4 (C-9, C-9′), 82.95 (C-6), 85.4 (C-5), 88.3 (C-5′), 108.45 (C-2), 114.5 (C-2′), 115.4 (C-7′), 119.0, 119.1 (C-1, C-1′), 125.5, 126.9 (C-11, C-11′), 129.7, 131.2 (C-12, C-12′), 142.7, 143.3 (C-3, C-3′), 144.9 (C-6′), 145.0, 149.4 (C-4, C-4′) [Found (*m*/*z* FAB): 599.3104. $C_{36}H_{43}N_2O_6$ (M^+ + 1) requires 599.3121].

Dehydration of 37

To a solution of **37** (281 mg, 0.47 mmol) in dichloromethane (3 cm^3) was added 2 M HCl (2 cm^3) and the mixture was stored overnight at room temperature. The pH of the mixture was then adjusted to 9 by the addition of aqueous K_2CO_3 and extracted three times with DCM. The combined organic phases were dried and evaporated to afford a brown oil. Purification of this oil by column chromatography using $CHCl_3$–CH_3OH–NH_3 (90 : 10 : 1) as eluent afforded 135 mg (50%) of the furan **35** as a pale brown solid, R_f 0.48 ($CHCl_3$–MeOH–NH_3 90 : 10 : 1); ν_{max}(neat)/cm^{-1} 3507 (OH), 1632 (C=C), 1605 (ArC=C), 1579 (C–N); δ_H 1.62–1.76 (2H, m, H-8_{ax}, H-8_{eq}), 1.82–2.01 (5H, m, H-8, H-14, 3 × H-15), 2.38 (3H, s, NCH_3), 2.43 (3H, s, N–CH_3), 2.12–2.58 (10H, m, 2 × H-7, H-8′, H-10α, H-14, H-15, 4 × H-16), 2.71 (1H, dd, J_{gem} 18.0 and J 5.1, H-10α), 2.93 (1H, m, J 3.5, H-9), 3.01 (1H, d, J_{gem} 18.3, H-10β), 3.07 (1H, d, J_{gem} 18.3, H-10β), 3.20 (1H, dd, $J_{9,10\alpha}$ 5.7, $J_{9,14}$ 2.8, H-9), 3.82 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 5.53 (1H, s, H-5), 6.62 (1H, d, J 8.4, H-1), 6.66 (1H, d, J 8.4, H-1), 6.69 (1H, d, J 8.4, H-2), 6.73 (1H, d, J 8.2, H-2), 7.46 (1H, br s, OH); δ_C 20.2 (C-7), 20.25 (C-10), 21.2 (C-8), 24.0 (C-10′), 24.0 (C-8′), 33.4, 35.54 (C-15, C-15′), 37.2 (C-13), 41.4 (C-14), 42.4, 42.9 (N–CH_3, N–CH_3), 44.3 (C-14′), 44.5 (C-13′), 46.4, 46.8 (C-16, C-16′), 55.7, 56.3 (O–CH_3, O–CH_3′), 57.0, 59.4 (C-9, C-9′), 84.5 (C-5), 109.5 (C-2), 113.4 (C-2′), 118.4, 118.5, 118.7 (C-1, C-1′, C-7), 123.0, 124.6, (C-11, C-11′), 126.95, 128.5 (C-12, C-12′), 128.7 (C-5), 143.1, 144.5, 144.7, 145.25, 146.5 (C-3, C-3′, C-4, C-6, C-6′), 154.45 (C-4) [Found (*m*/*z* FAB): 581.3022. $C_6H_{41}N_2O_5$ (M^+ + 1) requires 581.3015].

Reaction of (isopropyl)triphenylphosphonium iodide with dihydrocodeinone

To a cooled, suspension of (isopropyl)triphenylphosphonium iodide (1.4 g, 3.34 mmol) in THF (20 cm^3) was added potassium *tert*-butoxide (0.37 g, 3.34 mmol) in one portion. After 1 h, dihydrocodeinone (0.5 g, 1.67 mmol) was added to the deep orange-coloured solution. A colour change to yellow was immediately observed and the mixture was stirred for a further hour at 20 °C before being heated under reflux for 13 h. After cooling, the solvent was removed and the residue redissolved in chloroform and then washed three times with water. The organic phase was dried and the chloroform removed. Purification by column chromatography using $CHCl_3$–MeOH (9 : 1) and then $CHCl_3$–MeOH–NH_3 (95 : 5 : 1) as eluent afforded 144 mg of unreacted dihydrocodeinone, 79 mg (8%) of the aldolisation product **38** and 32 mg (3%) of the furan **37**.

Aldolisation product 38

R_f 0.30 ($CHCl_3$–MeOH–NH_3 90 : 10 : 1); ν_{max}(neat)/cm^{-1} 3337 (OH), 1722 (C=O), 1636, 1609 (ArC=C), 1272 ($ArOCH_3$); δ_H 1.09–1.23 (3H, m, 3 × H-8), 1.45 (1H, br d, J_{gem} 13.7, H-7_{eq}), 1.54 (1H, m, J_{gem} 12.2, H-15_{eq}), 1.69 (1H, td, J_{gem} 12.2, H-7_{ax}), 1.78 (1H, m, J_{gem} 12.7, H-15_{eq}), 1.89 (1H, td, J_{gem} 12.2 and $J_{15,16}$ 4.9, H-15_{ax}), 2.06 (1H, td, J_{gem} 12.2 and J 4.9, H-15_{ax}), 2.13–2.29 (5H, m, H-8, H-10α, H-14, 2 × H-16_{eq}), 2.35 (1H, dd, J_{gem} 18.1 and $J_{10\alpha,9}$ 5.37, H-10α, 2.38 (3H, s, NCH_3), 2.40 (3H, s, NCH_3), 2.48 (1H, td, J_{gem} 12.2 and J 3.9, H-16_{ax}), 2.54 (1H, td, J_{gem} 12.2 and J 3.9, H-16_{ax}), 2.61 (1H, dt, J_{gem} 12.2 and J 2.9, H-14), 2.77 (1H, dd, J_{gem} 12.7 and J 2.9, H-7), 2.98 (1H, d, J_{gem} 18.1, H-10β), 3.00 (1H, d, J_{gem} 18.6, H-10β), 3.05 (1H, br s, H-9), 3.15 (1H, m, $J_{9,14}$ 2.4, H-9), 3.86 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 4.56 (1H, s, H-5), 4.68 (1H, s, H-5), 6.62 (2H, d, $J_{1,2}$ 8.3, 2 × H-1), 6.69 (1H, d, $J_{2,1}$ 8.3, H-2), 6.71 (1H, d, $J_{2,1}$ 8.3, H-2) the signal for O*H* was not detected; δ_C 19.7 (C-8), 20.1 and 20.15 (C-10), 26.7 (C-8), 29.8 (C-7), 35.4 and 37.0 (C-15), 42.6 (C-14), 42.7 and 42.9 (NCH_3), 42.95 (C-14), 43.0 (C-13), 46.85 and 47.2 (C-16, C-16′), 48.3 (C-13), 56.2, 56.9 (OCH_3, OCH_3′), 57.1 (C-7′), 59.0 and 59.7 (C-9, C-9′), 72.8 (C-6), 91.7 and 92.8 (C-5, C-5′), 112.6 and 114.8 (C-2, C-2′), 119.3 and 119.8 (C-1, C-1′), 126.35 and 126.35 (C-11, C-11′), 127.1 and 130.3 (C-12, C-12′), 141.4 and 142.8 (C-3, C-3′), 145.2 and 145.3 (C-4, C-4′), 208.3 (C-6) [Found (*m*/*z* FAB): 599.3152. $C_{36}H_{43}$-N_2O_6 (M^+ + 1) requires 599.3121].

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