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Combined biological and chemical catalysis in the preparation of oxycodone

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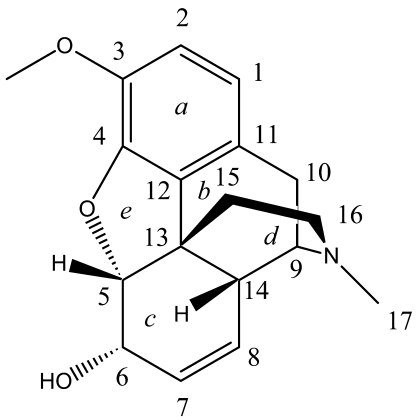
Abstract—The opioid oxycodone was produced from codeine, using a combination of chemical and biological catalysis. The use of novel functionalized ionic liquids permitted this reaction to be performed in a single solvent.

1. Introduction

The opioid oxycodone (14β-hydroxydihydrocodeinone, **1**) is finding increasing application in clinical medicine as both an analgesic and antitussive agent,[1,2] as well as being an intermediate synthon in the preparation of narcotic antagonists such as naloxone (**2**) and naltrexone (**3**).[3] Current methods for the production of oxycodone proceed from thebaine (**4**), an opium alkaloid of comparatively low abundance. These preparations additionally suffer from the use of harsh reaction conditions, hazardous reagents and the need for extensive chromatography to purify the final product.[4] Preparations from more readily available feedstocks, such as morphine (**5**) and codeine (**6**), are available[5,6] but suffer from poor yields and the need to isolate sensitive intermediates. The use of biocatalysis as a clean and efficient alternative for the production of specific opioids from morphine and codeine has been extensively investigated; enzymes isolated from a strain of *Pseudomonas putida* have been previously shown to be capable of performing a number of chemical transformations upon the morphinan nucleus.[7]

In particular, the $NADP^+$-dependent morphine dehydrogenase (MDH) from this organism is known to oxidize the hydroxyl group in the 6-position of both morphine and codeine, leading to the α,β-unsaturated ketones morphinone (**7**) and codeinone (**8**), respectively.[8] Additional enzymes have been observed to elicit catalytic hydrogenation of the 7,8-double bond (see Scheme 1), N-demethylation and other processes.[9,10]



Scheme 1. The structure and labelling of the morphinan nucleus in (−)-codeine.

Despite these advances, the fundamental step in the conversion of **6** to **1**-namely the hydroxylation of the 14-position—has proven difficult to accomplish either chemically or biocatalytically. The direct allylic hydroxylation of codeine is nowadays generally considered impossible;[11] the few published methods proceed through preliminary oxidation to **8** followed by hydroxylation of the dienol tautomer (**9**), in an analogous manner to the commercial hydroxylation of thebaine.[12] These processes are in turn hampered by the reactivity and sensitivity of this intermediate, leading to poor yields and the formation of copious by-products. Enzyme catalysed 14-hydroxylation of codeinone has likewise been reported[13] and appears to proceed through a similar mechanism;[14] again, however, yields are poor and the aqueous environment leads to the decomposition of much of the substrate. Additionally, in both of the above cases, hydroxylation at the 14-position of **8** leads to 14β-hydroxycodeinone (**10**). A further hydrogenation step is then required to give **1**. Consequently, a method was sought

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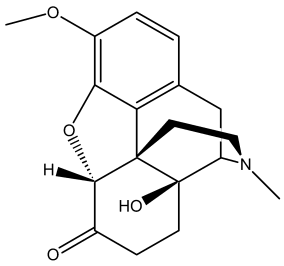

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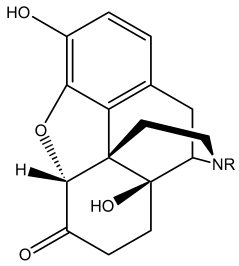
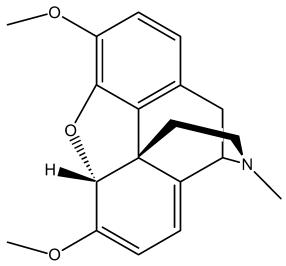


2 (R = allyl)
3 (R = cyclopropylmethyl)



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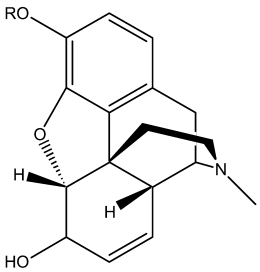
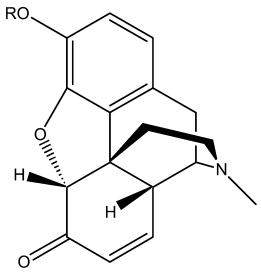
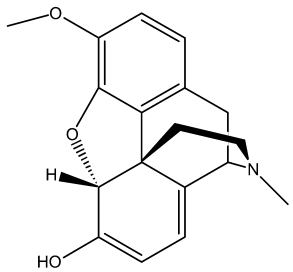


5 (R = H)
6 (R = methyl)



7 (R = H)
8 (R = methyl)



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whereby the codeinone sourced from the MDH-catalysed oxidation of codeine may be directly converted to oxycodone.

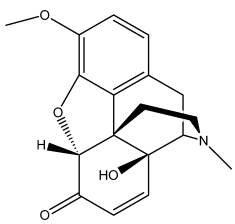
2. Results and discussion

2.1. Conversion of codeine to oxycodone

In order to achieve this conversion, the 14-hydroxyl group must be introduced with concomitant saturation of the 7,8-double bond. Hydration of this bond in codeinone proceeds in the classical manner of conjugate addition to yield 8-hydroxydihydrocodeinone (**11**).[15] Of interest in this respect was the observation that, in aqueous solution, codeinone exists in a state of dynamic equilibrium with its β,γ-unsaturated isomer, neopinone (**12**), proceeding via the dienol tautomer **9** (Scheme 2).[16] Direct Markovnikov addition of water across the double bond of this isomer, in contrast to that of codeinone, leads directly to **1**.

In the absence of any known hydratase capable of performing this hydration biocatalytically, a series of chemical reagents known to elicit Markovnikov hydration of substituted alkenes were therefore applied to equilibrated mixtures of codeinone and neopinone, with generally poor results. The majority of these reagents either failed to hydrate at all or resulted in the predominant formation of unwanted by-products such as **11**. In several cases, the entire morphinan skeleton suffered rearrangement or lysis. Nevertheless, a small number of reagents were observed to elicit the formation of oxycodone. In particular, the use of bis(acetylacetonato)cobalt (II) to catalyse the reaction of the alkene moiety with molecular oxygen and phenylsilane (as reported by Isayama and Mukaiyama[17]) not only resulted in the high yielding conversion of **12** to **1**, but did so without any effect upon **8**. This was interpreted to be a result of the deactivation of the codeinone double bond towards electrophilic addition (and thus silylperoxide formation), due to its α,β-conjugation with the carbonyl group on carbon 6; furthermore, the absence of any 7-hydroxydihydrocodeinone argued for the inability of this system to elicit conjugate hydride reduction (with subsequent α oxidation) even in the presence of dioxygen, which might otherwise be expected.[18] Steric constraints inhibiting α-attack ensured the correct orientation of the introduced hydroxyl group, whilst the tertiary nature of the substituted carbon atom rendered impossible the lysis of the silylperoxide to ketonic products. When the reaction was performed in tetrahydrofuran, an equilibrium mixture of 74:26% codeinone/neopinone was thus converted to an effectively isoproportional mixture of codeinone and oxycodone (Scheme 3). The efficacy of a cobalt-based catalyst was particularly interesting in view of Coop and Rice's observation of 14-hydroxylation of the codeinone/neopinone system using cobalt (III) acetate.[12]

In view of its observed inactivity towards codeinone, this catalytic process was examined in protic solvents. Since THF did not permit the enolization of either **8** or **12**, it was



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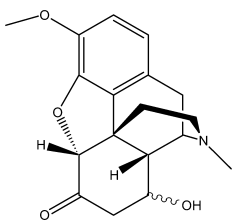

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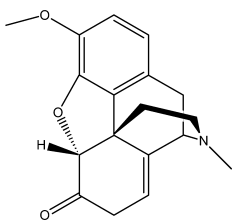

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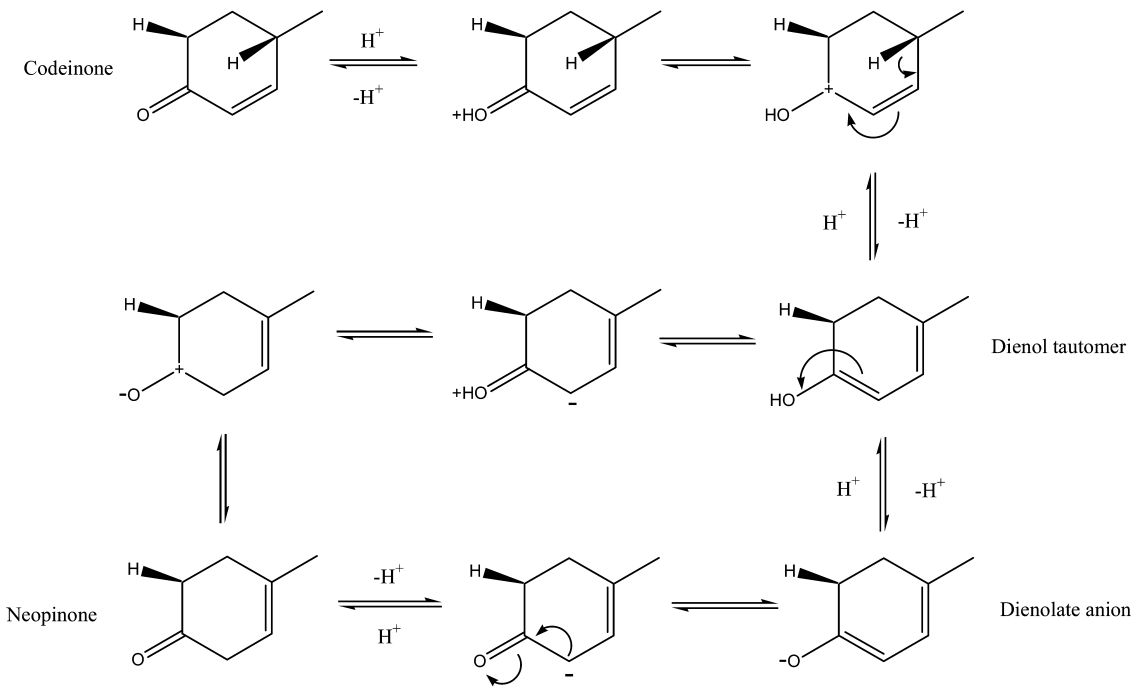


Scheme 2. Protic dienolization of the c-ring in the codeinone–neopinone isomerization.

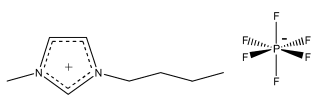
impossible to convert any of the considerable codeinone in the isolated equilibrium mixtures to neopinone and thence to oxycodone. If this enolization was permitted to occur through a protic medium, then the total morphinan content of the reaction should become available to the catalyst; as **12** was removed by conversion to **1**, so the perturbation of the equilibrium would result in further conversion of **8** to **12**. In practice, the limitations imposed by the pK_a of standard solvents severely hampered this; the enolization rate in primary alcohols was too slow to significantly enhance the yield on a reasonable timescale, whereas stronger acids gave rise to protonation of the amine group and a significant degree of decomposition. Addition of a small quantity of water to the THF solution was more successful in promoting equilibration and did not significantly affect the hydration reaction. Since the hydration was irreversible, this procedure ultimately resulted in the conversion of codeinone to oxycodone in 68% yield.

The preparation of oxycodone was thus achieved from codeine in a two-stage process, using a combination of enzymatic and chemical catalysis. The need to extract the codeinone/neopinone mixture from the aqueous biocatalytic reaction prior to the hydration step remained nonetheless a considerable disadvantage; being necessitated by the occurrence of side-reactions and the poor activity of the cobalt catalyst in aqueous solution, together with its destructive effect upon the biological components. The insolubility of phenylsilane in water and the ready availability of hydroxide led to the gradual accumulation of undesirable alternative products, notably **11**. Consequently, a means was sought whereby the enzymatic oxidation, codeinone/neopinone isomerization and hydration may be performed in a concomitant fashion.

2.2. Ionic liquids as solvents for combined catalysis

The absence of a suitable solvent in which to perform this type of combined bio/chemical catalytic process in 'one pot' has long been a major impediment to the industrial application of biocatalysis. Conventional organic solvents are incapable of functioning as satisfactory solvents for most enzymes[19] and, unless anhydrous, generally elicit denaturation. Water is an equally poor solvent for many organic substrates. Ionic liquids have recently elicited much interest as solvents for both chemical and biological catalysis,[20,21] but have not previously been shown to permit the combination of these two methods in a single reaction vessel. However, by utilizing ionic liquids incorporating specific functional groups, it has proven possible to perform both enzyme-catalysed and transition metal-catalysed reactions upon a common substrate in a single solvent.

Dialkylimidazolium-based ionic liquids such as 1-*n*-butyl-3-methylimidazolium hexafluorophosphate (BMIm PF_6, **13**) have been used in biocatalysis in both single- and two-phase systems.[22] The enzymes used in the pure ionic liquids have been primarily rugged lyases and lipases,[23] which have also shown activity in molecular organic solvents. In the two-phase systems, water-immiscible ionic liquids have been effectively used as substrate reservoirs, with the actual catalytic processes taking place in the aqueous phase.[24] Cofactor-dependent enzyme biocatalysis has not previously been observed in pure ionic liquids.



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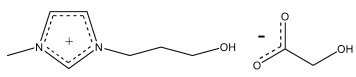
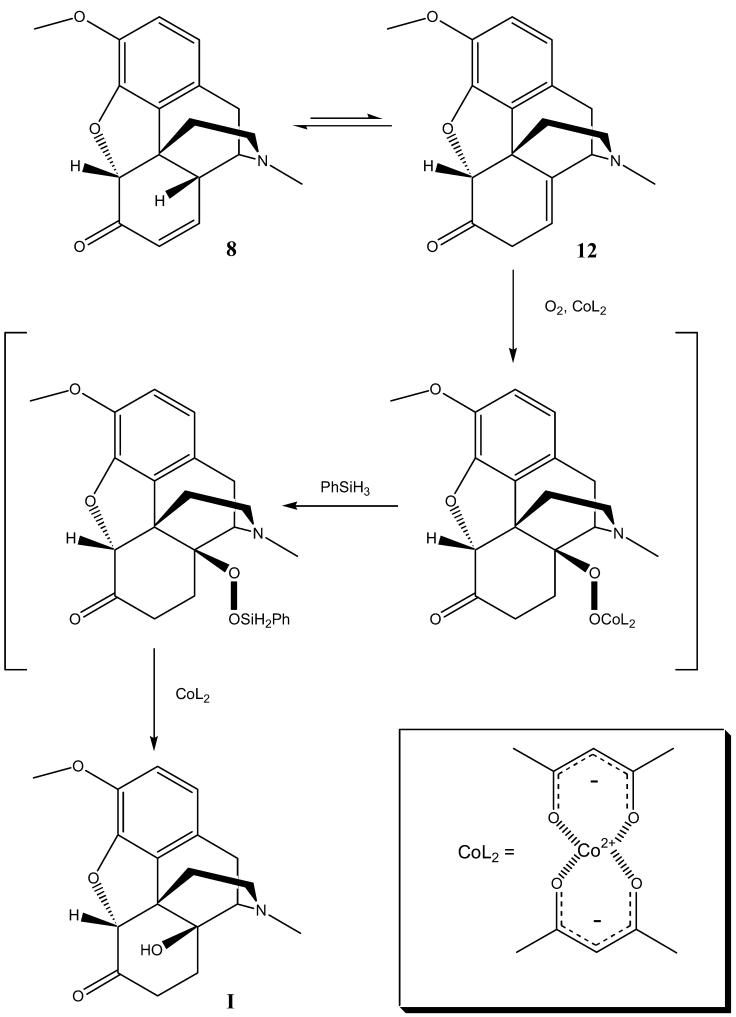


14

This is unsurprising in view of the hydrophobic nature of



Scheme 3. Conversion of codeinone (**8**) to oxycodone (**1**), by Markovnikov hydration of neopinone (**12**).[17] *Conditions* used: 200 mM alkaloid (64 mM **12**) in 5 mL THF, 0.64 alkaloid equiv. (2 equiv. **12**) $PhSiH_3$, 6.3 total alkaloid wt% $Co(acac)_2$, O_2 atmosphere. Yield: 92% from **12**, 29% overall.

solvents such as **13**, which exhibit poor hydrogen bond donor/acceptor properties and whose interaction with highly polar, hydrophilic enzyme surfaces is consequently very limited. By incorporating hydrogen bonding functional moieties into this type of ionic liquid structure, it has proven possible to elicit dissolution of enzymes and their cofactors, thus permitting homogeneous biocatalysis to occur.[25] The most dramatic improvements in enzyme dissolution and activity for the MDH system were observed when hydroxylated ionic liquids were used as reaction solvents. Initial experiments were performed using the glycolate salt of the simple hydroxylated **13** analogue 1-(3-hydroxypropyl)-3-methylimidazolium (3-HOPMIm glycolate, **14**). This solvent proved to be capable of simultaneously dissolving the substrate, enzyme and cofactor. Dissolution of the biological molecules in the ionic liquids was hampered by slow diffusion resulting from their relatively high viscosity. It was consequently elicited by vortexing followed by centrifugation, with the supernatant solutions being micro-filtered to remove any suspended matter. Dissolution was confirmed by means of infra-red spectroscopy, based on the characteristic shifts of the protein amide absorbances in ionic solution.[25] The activities demonstrated by the enzyme under these conditions was manifestly greater than that shown by suspensions (or extremely small concentration solutions) of the enzyme in anhydrous molecular organic solvents or in **13**, suggesting homogeneous catalysis with little denaturation.

When provided with a stoichiometric equivalent of NADP, MDH was found to be active against codeine in **14** solution. The observed activity was, as expected, considerably diminished relative to that in water, but was far in excess of that observed in either **13** or conventional organic solvents, with an equilibrium concentration of 84:16 in favour of codeine being reached in 24 h. The codeinone thus produced was found to be considerably more stable in ionic solution than in aquo, such that decomposition of the accumulated product did not occur to any appreciable extent, even after several days at room temperature. Enolization was found to occur in **14**, but the equilibrium was found to lie more in favour of codeinone than was the case in water. The equilibration rate was much slower than in water, but reproducibly faster than that observed in ethanol. In view of this, the action of bis(acetylacetonato)-cobalt (II) upon the neopinone/codeinone mixture was investigated in **14**. Although the codeinone/neopinone could be extracted from ionic solution by conventional methods,

this was found to be destructive to both MDH and NADP; hence the enzyme was removed from solution by dialysis. The cobalt catalyst was then added directly to the equilibrated solution of the ketones in the ionic liquid, albeit at the risk of destroying the cofactor. The poor solubility of oxygen in ionic liquids necessitated the use of a continuous oxygen stream being bubbled through the solution. In this way, the catalytic process was found to take place smoothly, with practically all of the neopinone being converted to oxycodone within 12 h. It was found that the addition of the full equivalence of phenylsilane at the start of this reaction led to the reduction of a significant proportion of the codeinone to codeine, a phenomenon which was not observed in THF solution. This was controlled by the gradual addition of the hydride donor as the reaction progressed. The enolization rate of the ketones in **14** was unfortunately still too slow to result in the conversion of significant residual codeinone. However, the stability of this compound in ionic solution allowed for the re-establishment of equilibrium over time, after which the catalysis could be repeated. Hence it was found to be ultimately possible to convert up to 42% of the initial codeinone/neopinone mixture to oxycodone, albeit slowly. The addition of a small quantity of water was found to permit this equilibrium to establish more rapidly and with a more favourable bias towards neopinone, without exerting a major deleterious effect upon yield.

3. Conclusions

It has been shown that hydrophilic, functionalized ionic liquids can effectively act as solvents for both chemical and biological homogeneous catalysis. The specimen ionic liquid employed was found to be capable of dissolving both morphine dehydrogenase and its associated nicotinamide cofactor whilst permitting the retention of considerable catalytic activity against codeine. The same solvent was also found to permit both the codeinone/neopinone equilibration and the hydration of the neopinone double bond under bis(acetylacetonato)cobalt (II) catalysis. Consequently it has proven possible to convert codeine to oxycodone using a combination of biological and chemical catalysis in a common solvent. It is reasonable to expect that the application of a cofactor-recycling system within the biocatalytic system would enable this yield to be increased, rather than it being determined by the equilibrium position of the $NADP^+$/NADPH couple. This would also enable the exploitation of the much higher solubility of the alkaloid substrate in ionic liquids as opposed to water.

Although the sensitivity of the biological components to the chemical catalyst prevents this from being a true 'one pot' reaction, the solubility of substrate, enzyme, cofactor and chemical catalyst within the same solvent provides the potential for the development of continuous flow combined catalytic processes, whereby a solvent stream containing the substrate may be passed through a bioreactor, either using tethered enzymes or with subsequent dialysis and then on to further (biological or chemical) catalysts. In this way, the need to isolate and purify intermediate products such as codeinone is eliminated and the entire process may be operated as a continuous phase. We conclude that solvents of this type are ideal candidates for the development of combined biological/chemical catalytic processes and that they offer the potential to obviate several major current obstacles to the industrial practicality of biocatalysis.

4. Experimental

4.1. General procedures

Reagents were purchased from Sigma-Aldrich Co. Ltd, Gillingham, UK or Fisher Scientific UK Ltd, Loughborough, UK and were of the highest purity available. All reactions were performed in oven-dried glassware under an argon atmosphere unless otherwise stated. Tetrahydrofuran was twice distilled under argon. Ionic liquids were dried by freezing in liquid nitrogen and placing under high vacuum on an Edwards Modulyo freeze drier for 48 h, followed by heating to 80 °C under high vacuum for 18 h. Water content was determined using a KEM MKS-500 volumetric Karl Fischer titrator. Reactions were followed by TLC on Polygram SIL G/UV_{254} 0.20 mm silica coated plates, using an eluent of 84:14:2 chloroform/methanol: 0.880 ammonia solution. Column chromatography was performed using YMC-Gel 60A I-400/230 mesh silica.

^1H NMR spectra were recorded using a Jeol Lambda LA400 400 MHz spectrometer, at 23 °C in deuterated chloroform unless otherwise stated. Chemical shift values are given in ppm relative to a tetramethylsilane internal standard. Infrared spectra were taken on a Perkin–Elmer Spectrum One spectrophotometer, using KBr discs unless otherwise stated.

Codeine, codeinone, thebaine and oxycodone standards were supplied by Macfarlan Smith Limited. Neopinone was prepared from thebaine according to the method of Conroy.[26]

4.1.1. Synthesis of ionic liquids. BMIm PF_6 was prepared according to the method of Koel.[27] HOPMIm glycolate was prepared from 1-methylimidazole as follows.

20.53 g 1-Methylimidazole (redistilled, 250 mmol) and 3-chloro-1-propanol (1.1 equiv., 26.00 g) were placed in a 500 mL round-bottomed flask equipped with reflux condenser, magnetic stirrer and calcium chloride drying tube. The reaction mixture was heated to 80 °C for 48 h with continuous stirring, at the conclusion of which it was cooled to room temperature and washed three times with diethyl ether. The resultant 1-(3-hydroxypropyl)-3-methylimidazolium chloride (40.5 g) was dissolved in dry acetone and anhydrous potassium glycolate (1.05 equiv., 27.36 g) was added with stirring. Stirring was continued for a further 12 h, after which the reaction mixture was filtered to remove the precipitated potassium chloride. The acetone was removed in vacuo and the residue was diluted to 80% with dry acetonitrile. Following treatment with activated charcoal, the product was chromatographed on a 7 cm 60A silica column and the solvent was removed to yield 1-(3-hydroxypropyl)-3-methylimidazolium glycolate as a pale yellow liquid, yield 30.7 g (62%).[28]

^1H NMR [400 MHz, d_6-DMSO, δ (ppm)]: 1.92 (2H, q, 16,

β-CH_2), 2.0 (0.9H, br, $HOCH_2CO_2^-$), 3.40 (2H, t, 6, α-CH_2), 3.52 (2H, s, $CH_2CO_2^-$), 3.75 (1H, br, CH_2CH_2OH), 3.83 (3H, s, NCH_3), 4.21 (2H, t, 8, γ-CH_2), 7.65 (1H, d, 2, 4-*H*), 7.72 (1H, d, 2, 5-*H*), 9.13 (1H, s, 2-*H*).

FT-IR (Nujol mull, cm^{-1}): 1731, 1634, 1576, 3390, 1167, 871, 1061, 1088, 1228.

4.1.2. Codeine to codeinone in water using MDH. Codeine hydrochloride dihydrate (200 mg, 0.54 mmol) was dissolved in 10 mL argon-flushed p*H* 9.0, 50 mM dibasic potassium phosphate buffer containing 250 μL acetone (200 mg, 6.38 equiv.). 100 μg each of morphine dehydrogenase from *Pseudomonas putida* M10 and alcohol dehydrogenase from *Thermoanaerobium brockii* were added, together with 25 mg (0.06 equiv.) of β-nicotinamide adenine dinucleotide phosphate (NADP, sodium salt). The solution was stirred in the dark at 30 °C under an argon atmosphere. The reaction was followed by time-course sampling and analysis of the samples by thin layer chromatography and ^{1}H nuclear magnetic resonance spectroscopy. After 24 h the reaction mixture was adjusted to pH 11 with aqueous sodium hydrogen carbonate and extracted three times with 25 mL volumes of chloroform. The organic fractions were pooled and the solvent was removed in vacuo to yield 134 mg of crude crystalline residue, which was chromatographed on silica gel to yield codeine (72 mg) and a pure equilibrium (68:32) mixture of codeinone (**8**) and neopinone (**12**) (40 mg, 25%) as a pale brown crystalline material, which could not be further separated chromatographically and was analysed by ^{1}H NMR. If the reaction was left for 48 h, chromatography was hampered by the presence of decomposition products and the codeinone/neopinone yield was not increased.

^{1}H NMR [400 MHz, $CDCl_3$, δ (ppm)]: 1.81 (1H, m, codeinone 15α-*H*), 1.88 (0.47 H, m, neopinone 15α-*H*), 1.92 (0.45H, br, neopinone 15β-*H*), 2.03 (1H, t, 10, codeinone 15β-*H*), 2.27–2.34 (2.9H, dd+m, codeinone and neopinone 16-H_2), 2.42 (3H, s, codeinone N–CH_3), 2.48 (1.42H, s, neopinone N–CH_3), 2.57 (1H, d, 16, codeinone 10α-*H*), 2.77 (0.45H, d, 6, neopinone 10α-*H*), 3.07 (1H, d, 24, codeinone 10β-*H*), 3.16 (1H, s, codeinone 9-*H*), 3.27 (0.47H, d, 10, neopinone 10β-*H*), 3.33 (0.45H, br, neopinone 7α-*H*), 3.38 (1H, s, codeinone 14-*H*), 3.64 (0.47H, d, 6, neopinone 9-*H*), 3.81 (3H, s, codeinone 3-O–CH_3), 3.91 (1.4H, s, neopinone 3-O–CH_3), 3.95 (0.48H, d, 14, neopinone 7β-*H*), 4.67 (1H, s, codeinone 5-*H*), 5.00 (0.47H, s, neopinone 5-*H*), 5.50 (0.47H, d, 6, neopinone 8-*H*), 6.05 (1H, d, 14, codeinone 7-*H*), 6.58 (1H, d, 16, codeinone 2-*H*), 6.63–6.70 (2.94H, m, codeinone 1-*H* and 8-*H* and neopinone1-*H* and 2-*H*).[29]

FT-IR showed the characteristic carbonyl absorption bands at 1670 cm^{-1} (codeinone) and 1735 cm^{-1} (neopinone).

4.1.3. Codeine to codeinone in ionic liquid using MDH. Lyophilized MDH (100 μg) was dissolved in 10 mL dry (<100 ppm H_2O) 3-HOPMIm glycolate (**14**) with vortexing over 2 h. The resultant solution was centrifuged at 13,000 rpm for 5 min to remove suspended material and the supernatant was filtered through 0.2 μm Sartorius syringe filters. Dissolution of the protein was confirmed by Fourier transform infra-red spectroscopy. Anhydrous codeine free base (150 mg, 0.5 mmol) was added along with 380 mg (1 equiv.) NADP (sodium salt) and the solution was placed under argon. The reaction was shaken at 110 rpm, 30 °C with hourly sampling. Samples were taken by removing 500 μL of solution, diluting 20 times with water, adjusting to pH 10 with aqueous sodium carbonate and extracting three times with 5 mL volumes of diethyl ether. The organic fractions were pooled and the solvent was removed in vacuo. The residual solid was redissolved in $CDCl_3$ and analysed by ^{1}H NMR. This showed the progressive production of codeinone up to a yield of 16% after 24 h. A solution of MDH in the same solvent left to stand, in a desiccated environment, at room temperature for four weeks showed reduced activity, but nonetheless showed 10% conversion of codeine to codeinone when it was used under otherwise identical conditions to the above. When codeinone was allowed to stand in **14** solution for 24 h, NMR analysis gave a codeinone/neopinone ratio of 91:9 (see Table 1).

Attempts to repeat the above reaction in various molecular organic solvents and in **13** failed. FT-IR showed no significant protein dissolution after centrifugation and filtration. In both instances, unchanged codeine was recovered in practically quantitative yield, identical to standards. Codeinone was recovered in 98% yield after standing in dry **13** solution for 24 h. No neopinone was detected.

The addition of 5% water to the ionic liquid biotransformation did not significantly denature the enzyme. Rather, the repetition of the above procedure in 95:5 **14**/H_2O resulted in 26% conversion to an 85:15 mixture of codeinone/neopinone after 24 h. This was a significant improvement upon the corresponding two-phase reaction involving water and **13**, in which a maximum yield of 6% after 24 h was obtained.

4.1.4. Hydration of codeinone and neopinone. *(a) In THF*. An equilibrium mixture of codeinone (195 mg) and neopinone (92 mg) was dissolved in 5 mL dry tetrahydrofuran,

Table 1. Variation in catalytic yields with solvent

Solvent	Yield **8** from **6**, MDH (10 μg mL^{-1})	Equilibrium **8**:**12** ratio	Yield **1** from **12**, $Co(acac)_2$ (3.6 mg mL^{-1})
50 mM phosphate buffer, pH 9	37–44%	68:32%	Not performed due enolization and insolubility of **12**
Tetrahydrofuran, <100 ppm H_2O	<1%	100:0%	80–97%
BMIm PF_6 (**13**), <100 ppm H_2O	<1%	100:0%	75–88%
3-HOPMIm glycolate (**14**), <100 ppm H_2O	12–18%	91:9%	90–98%
3-HOPMIm glycolate (**14**), 5% H_2O	23–27%	85:15%	Not quantifiable due enolization.

containing 18 mg bis(acetylacetonato)cobalt (II). Phenylsilane (70 mg, 2 neopinone equiv.) was added and the reaction was stirred under an oxygen atmosphere for 12 h, being monitored by TLC. At the conclusion of this period, the volatiles were removed in vacuo, the solid residue was resuspended in 15 mL chloroform and washed three times with 10 mL portions of dilute aqueous potassium carbonate. The organic fraction was dried over magnesium sulfate, filtered and chromatographed on silica gel to yield 90 mg (29% based on total ketone content, 92% based on neopinone alone) 14β-hydroxydihydrocodeinone (oxycodone, **1**).

^{1}H NMR [400 MHz, $CDCl_3$, δ (ppm)]: 1.55 (1H, m, 12, 15α-*H*), 1.63 (1H, d, 12, 8α-*H*), 1.83 (1H, d, 12, 8β-*H*), 2.15 (1H, t, 12, 15β-*H*), 2.26 (2H, m, 7α -*H*+16α-*H*), 2.37–2.41 (4H, s+m, 16α-*H*+N–CH_3), 2.42 (1H, m, 16β-*H*), 2.57 (1H, dd, 16, 10α-*H*), 2.83 (1H, d, 4, 9-*H*), 2.98 (1H, t, 12, 7β-*H*), 3.12 (1H, d, 16, 10β-*H*), 3.88 (3H, s, 3-O–CH_3), 4.64 (1H, s, 5-*H*), 5.05 (1H, br, O*H*), 6.61 (1H, d, 8, 2-*H*), 6.67 (1H, d, 8, 1-*H*).

FT-IR (KBr disc, cm^{-1}): 1722, 1501, 1446, 1260, 1036, 2936, 1346, 1165, 1145, 1018.

The balance of the material was almost entirely composed of codeinone; no neopinone could be detected in the codeinone fraction by NMR and no quantifiable amounts of 7- or 8-hydroxylated products were found.

When the above reaction was repeated with 200 mg pure neopinone, oxycodone (205 mg, 97%) was recovered as the sole product. When 200 mg pure codeinone was used, no oxycodone was detected and the balance of the starting material was recovered.

(b) In ionic liquid. An equilibrium mixture of codeinone and neopinone (as above) was dissolved in 5 mL dry 1-(3-hydroxypropyl)-3-methylimidazolium glycolate, containing 18 mg bis(acetylacetonato)cobalt (II). Phenylsilane (105 mg, 1 equiv., 120 μL) was added in 20 μL portions over 12 h, with vigorous stirring and under constant oxygen sparging. The reaction was monitored by TLC. At the conclusion of the reaction, the solution was diluted 10 times with water, basified with aqueous sodium carbonate and extracted five times with 10 mL portions of diethyl ether. The organic extracts were pooled, washed with brine, dried over magnesium sulfate and the solvent was removed in vacuo. The semi-solid residue was taken up in a small volume of terahydropyran and chromatographed on silica gel to yield **1** (96 mg, 98% from neopinone, 31% from codeinone/neopinone, 5% from codeine). The balance was composed primarily of unchanged codeinone, with smaller amounts of neopinone, codeine, neopine and an additional unknown compound which was not characterised. The isolated codeinone was redissolved in **14** and allowed to equilibrate for 72 h. The reaction was then repeated as above and the process was performed a third time with the recovered codeinone. After three runs, the total yield of oxycodone was 42% from codeinone/neopinone.

When the reaction was performed in an identical manner to (a) above, with simple substitution of 3-HOPMIm glycolate for THF, significant (up to 30%) reduction of codeinone and neopinone to (+/−)-codeine and (+/−)-neopine was observed. This was attributed to the poor solubility of oxygen in ionic liquids preventing sufficient silylperoxide formation and consequent reduction by the phenylsilane.

The repetition of reactions (a) and (b) above with the addition of 5% v/v water to the solution had a profound effect upon yields. As the enolisation of codeinone was facilitated, so a greater proportion of the total ketone content was found to undergo hydration, giving total yields of 68% (THF) and 55% (**14**) from the total ketone content.

Hence, if the entire reaction sequence were performed in 95:5 **14**/H_2O, **6** could be converted to **1** in 14% yield.

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