Title: PROCESS FOR THE PRODUCTION OF (+)-MORPHINE

Abstract: The invention relates to a process for the production of (+)-morphine from (-)-sinomenine comprising contacting (-)-sinomenine with H2/Pd/C under conditions effective for converting sinomenine to 7(S)(+)-dihydrosinomenine or 7(R)(+)-dihydrosinomenine or a mixture thereof; contacting the resulting 7(S)(+)-dihydrosinomenine or 7(R)(+)-dihydrosinomenine or a mixture thereof with polyphosphoric acid or Eaton's reagent under conditions effective for converting 7(S)(+)-dihydrosinomenine or 7(R)(+)-dihydrosinomenine or a mixture thereof to (-)-dihydrocodeine; contacting the resulting (+)-dihydrocodeine either with (MeO)3SiCl followed by TsOH followed by NBA/MsOH under conditions effective for converting (+)-dihydrocodeine to (+)-1,7-dibromodihydrocodeine dimethylketal; contacting the resulting (+)-1,7-dibromodihydrocodeine dimethylketal with t-butoxide followed by acid conditions effective for converting (+)-1,7-dibromodihydrocodeine dimethylketal to (+)-1-bromocodeinone; contacting the resulting (+)-1-bromocodeinone with LiAlH4 followed by BBr3 under conditions effective for converting (+)-1-bromocodeinone to (+)-morphine; or with o-iodoxybenzoic acid (IBX) and 4-methoxyphenyl-N-oxide under conditions effective for converting (+)-dihydrocodeine to (+)-codeinone; contacting the resulting (+)-codeinone with sodium borohydride followed by BBr3 under conditions effective for converting (+)-codeinone to (+)-morphine; and in either case recovering the resulting (+)-morphine as product. The invention also relates to novel compounds produced during the process.
DESCRIPTION

PROCESS FOR THE PRODUCTION OF (+)-MORPHINE

The present invention relates to a process for the production of (+)-morphine from (-)-sinomenine, to the production of the novel intermediate compounds, and to certain intermediate steps in such a process.

The function of naturally occurring, (-)-morphine in pain relief is well known. However, recently the properties of its synthetic stereoisomer (+)-morphine have been considered. Stringer et al, in Neuroscience Letters 295 (2000) 21-24, report that (+)-morphine, but not (-)-morphine, has low micro-molar affinity for the site of the N-methyl-D-aspartate (NMDA) receptor in the rat forebrain and suggest the clinical potential for racemic (+)(-)morphine or a non-racemic mixture of (+)(-)morphine in the treatment of neuropathic pain.

Although the clinical potential of (+)-morphine has been postulated, further studies in this area are hindered by the limited commercial availability of (+)-morphine, a problem highlighted in DDT Vol. 6, No. 14 July 2001 in a review article which goes on to suggest (at p746) alternative approaches to achieving NMDA receptor antagonist activity.

The conversion of (-)-sinomenine to (+)-morphine has been reported by Iijima et al in J. Org. Chem., Vol. 43, No. 7, 1978, p1462, with reference to earlier work by

It is an object of the present invention to provide an improved synthetic route from (-)-sinomenine to (+)-morphine and to provide novel intermediate compounds that may be useful for production of a medicament for use in the treatment or prophylaxis of pain.

In accordance with the present invention there is provided a process for the production of (+)-morphine (formula 6) from (-)-sinomenine (formula 1) comprising at least two reaction steps and at least one intermediate product, comprising (+)-1,7-dibromodihydrocodeinone dimethylketal (formula 4) or (+)-codeinone (formula 7).

The chemical formulae 1 to 8 referred to herein are specified in the reaction schemes below.

In one process according to the invention, at least three reaction steps and at least two intermediate products are provided, one of the at least two intermediate products comprising 7(S)-(+)dihydrosinomenine (formula 2) or 7(R)-(+)dihydrosinomenine or a mixture of both isoforms.
In another process according to the invention, at least four reaction steps and at least three intermediate products are provided, one of the at least three intermediate products comprising (+)-dihydrocodeinone (formula 3).

In still another process according to the invention (in which (+)-1,7-dibromodihydrocodeinone dimethylketal is an intermediate product), at least five reaction steps and at least four intermediate products are provided, one of the at least four intermediate products comprising (+)-1-bromocodeinone (formula 5).

In one preferred process according to the invention, (-)-sinomenine is converted to (+)-morphine according to the following reaction scheme (A):
The preferred reagent for reaction scheme A, step 1 is H₂/Pd/C.

Preferred reagents for reaction scheme A, step 2 include polyphosphoric acid and Eatons reagent.

Preferred reagents for reaction scheme A, step 3 include (MeO)₂CH followed by TsOH or camphorsulphonic acid followed by NBA/MeOH or N-bromosuccinimide (NBS).

Preferred reagents for reaction scheme A, step 4 include tBuOK followed by H⁺.

Preferred reagents for reaction scheme A, step 5 include LiAlH₄ followed by BBr₃, BCl₃ or trimethylsilyl iodide (TMS-I).

One preferred process according to the invention provides a synthesis of (+)-morphine comprising:

a) contacting (-)-sinomenine with H₂/Pd/C under conditions effective for converting (-)-sinomenine to 7(S)-(+) dihydrosinomenine or 7(R)-(+) dihydrosinomenine;

b) contacting the resulting 7(S)-(+) dihydrosinomenine or 7(R)-(+) dihydrosinomenine or mixture thereof with polyphosphoric acid or Eatons reagent
under conditions effective for converting 7(S)-(+)dihydrosinomenine or 7(R)-(+)
dihydrosinomenine to (+)-dihydrocodeinone;

c) contacting the resulting (+)-dihydrocodeinone with (MeO)$_3$CH followed by TsOH
followed by NBA/MeOH under conditions effective for converting (+)-
dihydrocodeinone to (+)-1,7-dibromodihydrocodeinone dimethylketal;

d) contacting the resulting (+)-1,7-dibromodihydrocodeinone dimethylketal with $t$-
butoxide followed by acid under conditions effective for converting (+)-1,7-
dibromodihydrocodeinone dimethylketal to (+)-1-bromocodeinone;

e) contacting the resulting (+)-1-bromocodeinone with LiAlH$_4$ followed by BBr$_3$
under conditions effective for converting (+)-1-bromocodeinone to (+)-morphine;
and

f) recovering the resulting (+)-morphine as product.

g) further processing the (+)-morphine into a medicament.

The invention further provides a process for the synthesis of 1,7-
dibromodihydrocodeinone dimethylketal from (-)-sinomenine by steps a) to c)
indicated above.

Also provided in accordance with the invention is a process for the synthesis of
(+)-morphine from (+)-1,7-dibromodihydrocodeinone dimethylketal by steps d) to
f) indicated above.
In a further process according to the invention (in which (+)-codeinone is an intermediate product) there are provided at least three reaction steps providing at least two intermediate products, one of the at least two intermediate products comprising (+)-codeine.

Accordingly, the process of the invention may comprise at least three reaction steps providing at least two intermediate products, one of the at least two intermediate products being selected from 7(S)/(R)-(+)–dihydrosinomenine, (+)-dihydrocodeinone and (+)-codeine.

Another preferred process in accordance with the invention comprises at least four reaction steps providing at least three intermediate products, two of the at least three intermediate products being selected from 7(S)/(R)-(+)–dihydrosinomenine, (+)-dihydrocodeinone and (+)-codeine.

The process of the invention may comprise at least five reaction steps providing at least four intermediate products, three of the at least four intermediate products being 7(S)/(R)-(+)–dihydrosinomenine, (+)-dihydrocodeinone and (+)-codeine.

In one preferred process according to the invention, (-)-sinomenine is converted to (+)-morphine according to the following reaction scheme (B):
The preferred reagent for reaction scheme B, step 1 is $\text{H}_2/\text{Pd/C}$.

Preferred reagents for reaction scheme B, step 2 include polyphosphoric acid and Eatons reagent.

Preferred reagents for reaction scheme B, step 3 include o-iodoxybenzoic acid and 4-methoxypyridine-N-oxide.

Preferred reagents for reaction scheme B, step 4 include sodium borohydride.

Preferred reagents for reaction scheme B, step 5 include BBr$_3$, BCl$_3$ or trimethylsilyl iodide (TMS-I).

One preferred process according to the invention provides a synthesis of (+)-morphine comprising:

a) contacting (-)-sinomenine with H$_2$/Pd/C under conditions effective for converting (-)-sinomenine to 7(S)-(+)-dihydrosinomenine or 7(R)-(+)dihydrosinomenine;

b) contacting the resulting 7(S)-(+)dihydrosinomenine or 7(R)-(+)dihydrosinomenine or mixture thereof with polyphosphoric acid or Eatons reagent under conditions effective for converting 7(S)-(+)dihydrosinomenine or 7(R)-(+)dihydrosinomenine to (+)-dihydrocodeineone;
c) contacting the resulting (+)-dihydrocodeinone with o-iodoxybenzoic acid and 4-methoxypyridine-N-oxide under conditions effective for converting (+)-dihydrocodeinone to (+)-codeinone;
d) contacting the resulting (+)-codeinone with sodium borohydride under conditions effective for converting (+)-codeinone (+)-codeine;
e) contacting the resulting (+)-codeine with BBr₃ under conditions effective for converting (+)-codeine to (+)-morphine;
f) recovering the resulting (+)-morphine as product; and
g) further processing the (+)-morphine into a medicament.

The invention further provides a process for the synthesis of (+)-codeinone from (-)-sinomenine by steps a) to c) indicated above.

Also provided in accordance with the invention is a process for the synthesis of (+)-morphine from (+)-codeinone by steps d) to f) indicated above.
The invention also provides for the (+)-morphine produced by steps a) to f) to be further processed into a medicament. It will be apparent that the medicament may be prepared in a number of formats, such as oral, trans-dermal and suppository for example, to allow for different methods of administration and the medicament may also be prepared in a certain manner in order to confer desirable pharmacokinetic or bioavailability properties. The medicament may be used in the treatment or prevention of pain.

Also provided in accordance with the present invention are pharmaceutically active salts of (+)-morphine, including (+)-morphine tartrate. The invention further provides the use of (+)-morphine tartrate, or of other pharmaceutically active salts of (+)-morphine in the treatment or prophylaxis of pain.

The invention also provides a process for converting (+)-dihydrocodeinone to (+)-codeinone comprising contacting (+)-dihydrocodeinone with a reagent effective for converting (+)-dihydrocodeinone to (+)-codeinone under conditions effective for said conversion. The effective reagent preferably comprises o-iodoxybenzoic acid (IBX) or a similar material in combination with 4-methoxypyridine-N-oxide or a similar material.

The process of the invention will now be more particularly described with reference to the following Examples.
Example 1

A synthesis of (+)-morphine was conducted in accordance with the invention, using the following process steps.

Step 1 – Preparation of a mixture of 7(R)- and 7(S)-(+)–dihydrosinomenine

(-)-Sinomenine-HCl (25 g) was dissolved in methanol (750 ml). 10% Pd/C (0.5 g) was then added. The mixture was then hydrogenated (1 atm, balloon) with stirring overnight (20 h). Thin layer chromatography (4:1 CHCl₃:MeOH) showed the reaction to be complete. The solution was then filtered through Celite and evaporated to dryness to obtain a mixture of 7(R)- and 7(S)-(+)–dihydrosinomenine (23.1 g). Two further reactions on the same scale produced 24.5 g of product.

Step 2(i) – Preparation of (+)-dihydrocodeinone from a mixture of 7(R) and 7(S)-(+)–dihydrosinomenine

Polyphosphoric acid (300 g) was added to a mixture of 7(R) and 7(S)-(+)–dihydrosinomenine (15 g) obtained from step 1. The mixture was heated to 70°C and stirred for 1.25 h. After cooling to room temperature the mixture was poured into a stirred solution of 30% NH₃ (200 ml), CHCl₃ (200 ml) and ice, the addition was slow in order to avoid overheating. Occasionally, more ice was added to
control the temperature and finally NH₃ solution was added to make the solution basic (ca pH 8). The solution was then saturated with NaCl and extracted with CHCl₃ (3 x 200 ml). The combined extracts were then dried (Na₂SO₄), filtered and evaporated to dryness to provide (+)-dihydrocodeinone (7.5 g) as a beige solid.

Step 2(ii) – Alternative preparation of (+)-dihydrocodeinone from a mixture of 7 (R) and 7(S)-(+) -dihydrosinomenine

In an alternative method for Step 2, polyphosphoric acid was replaced with Eatons reagent (7% phosphorus pentoxide in methanesulphonic acid). The reaction was complete after 10 min at 70°C, affording the product in near quantitative yield as beige solid.

Step 3a – Preparation of (+)-dihydrocodeinone dimethylketal from (+)-dihydrocodeinone

(Method derived from that described in J Med Chem, 1976, vol 19, No 10, p1174). (+)-Dihydrocodeinone (4.5 g) from step 2 was heated with trimethylorthoformate (TMO) (7.4 ml) in methanol (80 ml) to effect solution. Conc. H₂SO₄ (1.4 ml) was added and the mixture heated to reflux (70°C). After 6h a small amount of starting material remained and the mixture was left to stir overnight at room temperature (17 h). Further portions of TMO (2.5 ml) and
H₂SO₄ (0.3 ml) were added and the solution heated to reflux again for 2h, after which TLC showed only a trace of the starting material. The cooled mixture was poured into 0.5M Na₂CO₃ solution (100 ml) and extracted with CHCl₃ (100 ml). The separated organic phase was washed with brine, dried (Na₂SO₄) and evaporated to yield (+)-dihydrocodeinone dimethylketal (5.1g).

Step 3b – Preparation of Δ⁶-dihydrothebaine from (+)-dihydrocodeinone dimethylketal

(Method derived from that described in J Med Chem, 1976, vol 19, No 10, p174). A solution of p-toluenesulphonic acid (2.45 g) in dry CHCl₃ (100 ml) was added to the (+)-dihydrocodeinone dimethylketal (4.1 g) in dry CHCl₃ (100 ml) and the solution then heated at 120°C for 15 min, collecting a distillate of ca 100 ml. The reaction mixture was cooled to 0°C and poured into cold 0.5M Na₂CO₃ (100 ml). The layers were separated and the aqueous phase washed with CHCl₃ (100 ml). The combined organic phases were then washed with brine, dried (Na₂SO₄) and evaporated to give Δ⁶-dihydrothebaine (3.5 g) as an oil which solidified on standing.

Step 3c – Preparation of (+)-1,7-dibromodihydrocodeinone dimethylketal

Δ⁶-Dihydrothebaine (2.1 g) from step 3b was dissolved in CHCl₃ (200 ml) and cooled to -5°C. HBr-H₂O (1.13 ml of a 6.7 mmol solution) was added and the
mixture stirred for 2 min. Saturated NaBr solution (150 ml) was added (at 0°C) and the mixture shaken. The layers were separated and the aqueous phase was washed with CHCl₃ (50 ml). The combined organic phases were dried (Na₂SO₄) and evaporated. The residue was then dissolved in methanol (80 ml), cooled (to 0°C) and treated dropwise with a cooled solution (0°C) of NBA (0.92 g) in MeOH (60 ml) over 30 min. The slightly orange solution was evaporated and dissolved by shaking with CHCl₃ (150 ml) and 2M aqueous NaOH (30 ml). After separation, the aqueous phase was extracted with CHCl₃ (30 ml) and the combined organic phases washed with water (100 ml) and brine (100 ml) then dried (Na₂SO₄) and evaporated to give crude (+)-1,7-dibromohydrocodeinone dimethylketal (2.5 g).

Step 4a – Preparation of (+)-1-bromocodeinone dimethylketal

Crude (+)-1,7-dibromohydrocodeinone dimethylketal from step 3b (2.5 g) was dissolved in DMSO (50 ml) together with potassium tert-butoxide (1.32 g) and the mixture stirred overnight at room temperature. A further portion of potassium tert-butoxide (0.33 g) was added and the mixture then heated at 60°C for 6 h. After cooling, toluene (150 ml) and water (150 ml) were added, the layers separated and the aqueous further extracted with toluene (50 ml). The combined organics were washed with water (100 ml) and brine (100 ml) then dried (Na₂SO₄) and evaporated to give crude (+)-1-bromocodeinone dimethylketal (1.85 g).
Step 4b – Preparation of (+)-1-bromocodeinone

The bromoketal product from step 4a (1.85 g) was dissolved in dilute aqueous HCl and heated at 70°C for 30 min. On cooling to 0°C the solution was neutralised to pH 7 with 2M NaOH (0°C) and then extracted with CHCl₃ (100 ml and 50 ml). The combined organic phases were washed with brine and dried (Na₂SO₄). Evaporation afforded an off-white solid (1.15 g). The aqueous phase was basified (pH 10) and further extracted with CHCl₃ to afford more product (0.6 g). The two product samples were combined and flash chromatography afforded (+)-1-bromocodeinone (0.42 g) and (+)-1-bromodihydrocodeinone as an unwanted by-product.

Step 5a – Preparation of (+)-codeine

(Method derived from White et al, Tetrahedron, 1983, 39, 2393, which describes the preparation of (-)-codeine). (+)-1-Bromocodeinone (400 mg) from step 4b was taken in THF (20 ml) and LiAlH₄ (0.2 g) was added. The mixture was heated under reflux for 14h. After cooling, 1:1 THF:H₂O (10 ml) was added, followed by saturated aqueous sodium potassium tartrate (5 ml). The mixture was extracted with CH₂Cl₂ (100 ml + 50 ml) and the combined organic phases were washed with water (100 ml) and dried (MgSO₄). Flash chromatography of the residue afforded (+)-codeine (240 mg) as a white solid.
Step 5b(i) – Conversion of (+)-codeine to (+)-morphine

(+)-Codeine (120 mg) from step 5a was dissolved in dry CHCl₃ (2.5 ml) and the resulting solution treated under N₂ at 20°C with BBr₃ solution (2.4 ml of a 1.0 M solution in CH₂Cl₂), which was added over two minutes. Stirring was continued for 15 min and the mixture was then poured into a mixture of ice (10 g) and NH₄OH (30% NH₃). Crystalline material formed initially but after 30 min at 0°C, the material dissolved. The aqueous mixture was transferred to a separating funnel (rinsing with 10 ml CHCl₃, 10 ml H₂O and 2.5 ml NH₄OH), saturated with NaCl and extracted with 3:1 CHCl₃:EtOH (2 x 25 ml). The combined organic phases were dried (MgSO₄) and evaporated to give (+)-morphine (130 mg).

Step 5b(ii) – Alternative conversion of (+)-codeine to (+)-morphine

(+)-Codeine (70 mg) from step 5a was dissolved in CHCl₃ (1.5 ml) and the resulting solution treated under N₂ at room temperature with BBr₃ solution (0.94 ml of a 1.0 M solution in CH₂Cl₂), which was added over two minutes. Stirring was continued for 15 min and the mixture was then poured into a mixture of ice (8 g) and NH₄OH (2 ml) and stirred for 30 min. Crystalline material formed initially but after 30 min at 0°C, the material dissolved. The lower organic layer had the appearance of an emulsion and was separated. However, TLC revealed the presence only of impurities. The aqueous mixture was
extracted with 3:1 CHCl₃:EtOH (2 x 20 ml). The combined organic phases were
dried (MgSO₄) and evaporated to give (+)-morphine (60 mg).

The combined crude products from steps 5b(i) and 5b(ii) were dissolved in a
minimum volume of methanol and triturated with distilled water. After standing
for 15h (+)-morphine was afforded as an off-white solid.

**Example 2**

Step 1 – Preparation of 7(R)- and 7(S)-(+) -dihydrosinomenine

(-)-Sinomenine.HCl (100 g, 95% purity) was dissolved in water (1 L) and
10%Pd/C (2 g) was then added. The mixture was then hydrogenated (40°C,
1atm) with stirring overnight (24 h). The solution was then filtered through Celite,
the filtrate adjusted to pH 9 (4 N aqueous NaOH) and extracted with
dichloromethane (2 x 200ml). The aqueous layer was readjusted to pH 9,
extracted with dichloromethane (200ml) and the combined organics evaporated to
afford (+)-dihydrosinomenine (82.5 g, 99%).

Step 2 – Preparation of (+)-dihydrocodeinone from (+)-dihydrosinomenine

(+)-Dihydrosinomenine (10 g) was added to Eatons reagent (7% phosphorus
pentoxide in methanesulphonic acid, 50 ml). The mixture was heated to 70°C for
7 min and cooled to 0°C, then poured into a stirred solution of 30% aqueous NH₃
(100ml) and ice (200 g), keeping the addition slow to avoid overheating (less than 10°C). Occasionally, more ice was added to control the temperature. The solution was then extracted with dichloromethane (300 ml), the organic layer washed with brine, then dried (MgSO₄), filtered and evaporated. The residue was taken up in boiling acetone and filtered, and the filtrate evaporated to give (+)-dihydrocodeinone (7.7 g, 85%).

Step 3 (first alternative) – Conversion of (+)-dihydrocodeinone to (+)-codeinone

o-Iodoxybenzoic acid (IBX) (0.58 g) and 4-methoxypyridine-N-oxide (0.26 g) were added to DMSO (3.5 ml) and stirred under nitrogen at room temperature for 1 h, then (+)-dihydrocodeinone (0.52 g) in DMSO:DCM (1ml:1.5ml) added. After stirring overnight (16 h), 5% aqueous NaHCO₃ solution (10 ml) was added and the mixture extracted with chloroform (3 x 50 ml). The combined organics were flushed through a pad of Celite, washed with saturated aqueous NaHCO₃ solution, water and brine (50 ml each), dried (MgSO₄) and evaporated. Purification by flash chromatography (eluent CHCl₃:MeOH 10:1 + 0.5% TEA → 5:1 CHCl₃:MeOH + 0.5% TEA) afforded (+)-codeinone (54 mg, 10%).

Step 3 (second alternative) – Conversion of (+)-dihydrocodeinone to (+)-codeinone

o-Iodoxybenzoic acid (IBX) (0.58 g) and 4-methoxypyridine-N-oxide (0.26 g) were added to DMSO (3.5 ml) and stirred under nitrogen at room temperature in a
foil shielded flask for 1 h, then (+)-dihydrocodeinone (0.52 g) in DMSO:DCM (1ml:2.5ml) added. After stirring overnight (18 h), 5% aqueous NaHCO$_3$ solution (50 ml) was added and the mixture extracted with chloroform (3 x 50 ml). The combined organics were washed with water and brine (50 ml each), dried (MgSO$_4$) and evaporated. Purification by flash chromatography (eluent DCM:MeOH 20:1 + 0.5% TEA → 10:1 DCM:MeOH + 0.5% TEA) afforded (+)-codeinone (150 mg, 29%) and unreacted (+)-dihydrocodeinone (0.32 g, 62%). Conversion based on starting material consumed is 75%.

Step 4 – Conversion of (+)-codeinone to (+)-codeine

Sodium borohydride (13 mg, 0.34 mmol) was added to a solution of (+)-codeinone (50 mg, 0.17 mmol) in methanol (5 ml) and stirred at room temperature for 2 h. Water (10 ml) was added and the mixture extracted with chloroform (2 x 25 ml). The combined organics were dried (MgSO$_4$) and evaporated to afford (+)-codeine (41 mg, 81%).

Step 5 – Conversion of (+)-codeine to (+)-morphine

(+)-Codeine (0.95 g) was dissolved in CHCl$_3$ (dry, 9 ml) and the resulting solution added under N$_2$ at 20°C over two minutes to BBr$_3$ (1.83 ml) in CHCl$_3$ (50 ml). Stirring was continued for 15min and the mixture was then poured into a mixture of ice (28 g) and 28% aqueous NH$_3$ (7 ml). After 30min at 0°C no precipitate was observed and the sample evaporated to dryness. The residue was taken up in acetone : methanol (10:1, 15 ml), filtered and the filtrate evaporated to
give crude product which was purified by flash chromatography on silica gel (eluent CHCl₃:MeOH 4:1 → 3:1) affording (+)-morphine (0.56 g, 62%).

Example 3

Preparation of (+)-morphine tartrate:

A solution of (+)-morphine (75 mg) in water was treated with (+)-tartaric acid (20 mg) and the solution evaporated with gentle heating and crystallised, affording (+)-morphine tartrate as an off-white solid.
CLAIMS

1. A process for the production of (+)-morphine (formula 6) from (-)-sinomenine (formula 1) comprising at least two reaction steps and at least one intermediate product, the at least one intermediate product comprising (+)-1,7-dibromodihydrocodeinone dimethylketal (formula 4) or (+)-codeinone (formula 7).

2. A process according to claim 1 comprising at least three reaction steps providing at least two intermediate products, one of the at least two intermediate products comprising 7(S)-(+)—dihydrosinomenine or 7(R)-(+)—dihydrosinomenine or a mixture thereof.

3. A process according to claim 1 or claim 2 comprising at least three reaction steps providing at least two intermediate products, one of the at least two intermediate products comprising (+)-dihydrocodeinone.

4. A process according to any one of claims 1 to 3 comprising at least three reaction steps providing at least two intermediate products, one of the at least two intermediate products comprising (+)-1-bromocodeinone.

5. A process according to any one of claims 1 to 4 comprising at least three reaction steps providing at least two intermediate products, one of the at least two
intermediate products being selected from 7(S)/(R)-(+) dihydrosinomenine, (+)-dihydrocodeinone and (+)-1-bromocodeinone.

6 A process according to any one of claims 1 to 5 comprising at least four reaction steps providing at least three intermediate products, two of the at least three intermediate products being selected from 7(S)/(R)-(+) dihydrosinomenine, (+)-dihydrocodeinone and (+)-1-bromocodeinone.

7 A process according to any one of claims 1 to 6 comprising at least five reaction steps providing at least four intermediate products, three of the at least four intermediate products being 7(S)/(R)-(+) dihydrosinomenine, (+)-dihydrocodeinone and (+)-1-bromocodeinone.

8 A process according to any one of claims 1 to 7 in which (-)-sinomenine is converted to (+)-morphine according to the following reaction scheme:
9 A process according to any one of claims 1 to 8 comprising contacting (-)-sinomenine with H₂/Pd/C under conditions effective for converting (-)-sinomenine to 7(S)-(+)‐dihydrosinomenine or 7(R)-(+)‐dihydrosinomenine or a mixture thereof; contacting the resulting 7(S)-(+)‐dihydrosinomenine or 7(R)-(+)‐dihydrosinomenine or a mixture thereof with polyphosphoric acid or Eatons reagent under conditions effective for converting 7(S)-(+)‐dihydrosinomenine or 7(R)-(+)‐dihydrosinomenine or a mixture thereof to (+)-dihydrocodeinone; contacting the resulting (+)-dihydrocodeinone with (MeO)₂CH followed by TsOH followed by NBA/MeOH under conditions effective for converting (+)-dihydrocodeinone to (+)-1,7-dibromodihydrocodeinone dimethylketal; contacting the resulting (+)-1,7-dibromodihydrocodeinone dimethylketal with t-butoxide followed by acid under conditions effective for converting (+)-1,7-dibromodihydrocodeinone dimethylketal to (+)-1-bromocodeinone; contacting the resulting (+)-1-bromocodeinone with LiAlH₄ followed by BB₃ under conditions effective for converting (+)-1-bromocodeinone to (+)-morphine; and recovering the resulting (+)-morphine as product.

10 A process according to any one of claims 1 to 3 comprising at least three reaction steps providing at least two intermediate products, one of the at least two intermediate products comprising (+)-codeine.
11 A process according to claim 10 comprising at least three reaction steps providing at least two intermediate products, one of the at least two intermediate products being selected from 7(S)/(R)-(+) - dihydrocodeinone and (+)- codeine.

12 A process according to claim 11 comprising at least four reaction steps providing at least three intermediate products, two of the at least three intermediate products being selected from 7(S)/(R)-(+) - dihydrocodeinone, (+)- dihydrocodeinone and (+)- codeine.

13 A process according to claim 12 comprising at least five reaction steps providing at least four intermediate products, three of the at least four intermediate products being 7(S)/(R)-(+) - dihydrocodeinone, (+)- dihydrocodeinone and (+)- codeine.

14 A process according to claim 13 in which (-)-sinomenine is converted to (+)-morphine according to the following reaction scheme:
15 A process according to claim 14 comprising contacting (-)-sinomenine with H₂/Pd/C under conditions effective for converting (-)-sinomenine to 7(S)-(±)-dihydrosinomenine or 7(R)-(±)-dihydrosinomenine or a mixture thereof; contacting the resulting 7(S)-(±)-dihydrosinomenine or 7(R)-(±)-dihydrosinomenine or a mixture thereof with polyphosphoric acid or Eaton's reagent under conditions effective for converting 7(S)-(±)-dihydrosinomenine or 7(R)-(±)-dihydrosinomenine or a mixture thereof to (+)-dihydrocodeinone; contacting the resulting (+)-dihydrocodeinone with o-iodoxybenzoic acid (IBX) and 4-methoxypyridine-N-oxide under conditions effective for converting (+)-dihydrocodeinone to (+)-codeinone; contacting the resulting (+)-codeinone with sodium borohydride followed by BBr₃ under conditions effective for converting (+)-codeinone to (+)-morphine; and recovering the resulting (+)-morphine as product.

16 A pharmaceutically active salt of (+)-morphine.

17 (+)-Morphine tartrate according to claim 16.

18 Use of (+)-morphine tartrate, or of other pharmaceutically active salts of (+)-morphine, in the treatment or prophylaxis of pain.
19 A process for converting (+)-dihydrocodeinone to (+)-codeinone comprising contacting (+)-dihydrocodeinone with a reagent effective for converting (+)-dihydrocodeinone to (+)-codeinone under conditions effective for said conversion.

20 A process according to claim 19 wherein the effective reagent comprises o-iodoxybenzoic acid (IBX) or a similar material in combination with 4-methoxypyridine-N-oxide or a similar material.