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An Improved Process for the Preparation of (+)-3-Methoxy-*N*-formylmorphinan

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ABSTRACT: Two major steps, *N*-formylation of (−)-octabase and cyclization of the *N*-formylated product, involved in synthesis of (+)-3-methoxy-*N*-formylmorphinan, a key intermediate for production of dextromethorphan (DXM), have been improved to achieve higher yields in shorter time with fewer effluents. Methods of analysis of chemical and enantiomeric purities of the intermediates by HPLC and strategies for easy recovery and recycle of the reagents have been devised.

INTRODUCTION

(+)-3-Methoxy-*N*-methylmorphinan (dextromethorphan) **1** is used as the main ingredient of cough syrups.[1] It is produced from enantiomerically pure (−)-1-(4-methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline **2** (octabase) which is obtained by resolution of the racemic mixture with (−)-mandelic acid.[2]The amine group is protected by formylation to obtain **3** which is then cyclized to obtain (+)-3-methoxy-*N*-formylmorphinan **4**. Removal of formyl group by hydrolysis and subsequent *N*-methylation of **5** produces the required dextromethorphan **1** (Scheme 1).[3]

The overall process involves corrosive reagents such as sulphuric acid, KOH, sodium methoxide, etc. and long reaction hours. The aim of present work was to improve upon the existing techniques, reduce the amounts of acids and alkalis, and recover the reagents (wherever possible) to reduce the pollutants and operating costs. In addition, it was necessary to establish HPLC analytical procedures to determine the chemical as well as enantiomeric purities of the various intermediates since we were unable to find appropriate procedures in literature.

RESULTS AND DISCUSSION

Formylation of (−)-Octabase 2. A number of methods for formylation of amines exist in literature. General formylation methodologies typically employ mixed anhydrides including acetic/formic acid anhydride,[4] formic acid/ethyl dimethylaminopropylcarbodiimide (EDAC),[5] formic acid/DCC[6] and formylpivaloyl anhydride.[7]Formylation with formates such as 2,2,2-trifluoroethyl formate,[8] pentafluorophenylformate,[9] cyanomethylformate,[10] and ammonium formate[11] have also been reported. In addition, chloral,[12] formic acid/Lewis acids,[13] PEG-400,[14] KF-alumina,[15] and solid-supported reagents[16] have also been used in *N*-formylation reactions. However, the simplest possible reagent for *N*-formylation is the formate ester.

In the synthesis of DXM **1** the (−)-octabase **2** is usually obtained as a crystalline (−)-mandelate salt after resolution of racemic octabase with (−)-mandelic acid. For the *N*-formylation reaction, the mandelate salt is treated with alkali, and the free amine is isolated by extraction with an organic solvent such as toluene. According to a U.S. Patent,[3] the octabase is heated with freshly distilled methyl formate at 65−70 °C for 24 h under nitrogen atmosphere to obtain the *N*-formylated product **3** in 92% yield. In a similar fashion, analogous compounds have been formylated[17] by refluxing the amine solution in dry DMF with ethyl formate for 60 h under argon atmosphere. After workup the formylated product **3** is obtained in 95% yield. Use of a combination of methyl formate and sodium methoxide has been described during the preparation of (+)-1-(*m*-methoxybenzyl)-*N*-formyl-1,2,3,4,5,6,7,8-octahydroisoquinoline. A similar approach has been used by Sheldon and co-workers for formylation of imines.[19] The octabase has also been formylated by using chloral in chloroform.[18]

We have repeated the procedures described in refs 3 and 17−19 and found that the conversion of the octabase was >90% (as analyzed by HPLC, but the purity of the dark-brown *N*-formylated product was less than 80% with several unidentified impurities. From a mechanistic point of view, the formylation of an amine can be catalyzed by a base such as sodium methoxide or an acid. Since the mandelate salt of the resolved octabase already contains mandelic acid, we decided to use the salt itself in the formylation step. Thus, the mandelate salt was directly refluxed with ethyl formate (1:10 w/v) for 48 h. Initially, the mandelate salt was insoluble, but the reaction mixture became clear as the reaction proceeded to completion. In this process, ethyl formate acts both as the reagent and the solvent. After cooling, the mandelic acid was extracted with sodium carbonate solution. The *N*-formylated product was obtained from the ethyl formate layer in quantitative yield (>98% purity by HPLC). Unreacted ethyl formate was recovered by distillation, and mandelic acid was recovered after acidification of the carbonate extract, again in near quantitative yield. This improved procedure avoids the step involving treatment of mandelate salt with alkali and solvent extraction of octabase with the added advantage of vastly improved product purity.

Cyclization of *N*-Formyl Octabase 3 to (+)-3-Methoxy-*N*-formylmorphinan, 4. Acid-catalyzed cyclization of (+)-1-(*p*-methoxybenzyl)-2-formyl-1,2,3,4,5,6,7,8-octahydroisoquinoline **3** (*N*-formyl octabase) is the key step in the preparation of 3-methoxy-*N*-methyl morphinans. A U.S. Patent[3] describes the

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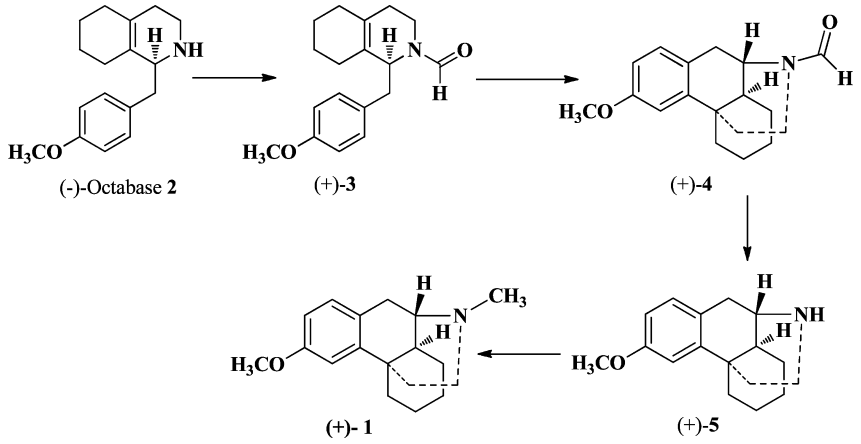
Scheme 1. Synthesis of dextromethorphan (DXM)



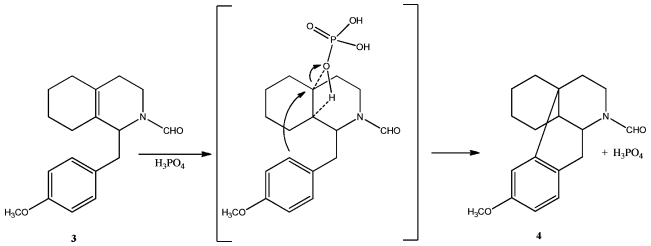
necessity of protecting the amine groups with an electron-withdrawing group before cyclization. For example, when the octabase was directly converted to its *N*-methyl derivative, 1-(*p*-methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline, and cyclized by treatment with a mixture of phosphoric acid and hydrochloric acid, 3-hydroxy-*N*-methyl morphinan was obtained as the major product (67−69%) along with several other side products. When the amino group was protected with an electron-withdrawing group such as acetyl or formyl, the required cyclized product **4** was obtained with 90% yield. This reaction was carried out in 99% phosphoric acid or polyphosphoric acid, or a mixture of 99% phosphoric acid and sulphuric acid at 70−80 °C for 20 h. The crude cyclized product was purified by distillation at 206−210 °C at 0.25 mm. In another report,[20] *N*-acetylated octabase was cyclized in anhydrous methane sulfonic acid at room temperature. The reaction was complete after 144 h.

Since the *N*-formyl group is easily removed by alkali hydrolysis in better yields and shorter times compared to the corresponding *N*-acetyl group, protection with formyl group is preferred. We have repeated the cyclization reactions described in the patents. We have observed that reactions in commercially available 85−88% phosphoric acid solution lead to formation of *O*-demethylation product in significant amounts (5−7%) along with some unidentified coloured impurities, and it is indeed necessary to use >99% phosphoric acid. To achieve this, water content of commercial phosphoric acid was reduced to 6−7% by azeotropic distillation with toluene, and large quantities of phosphorus pentoxide (12−13 g/100 g) were added. This was hazardous as well as an expensive affair. In addition, the reaction took 3 days to complete as against the 20 h claimed in the patent. The product was highly coloured, and recycle of phosphoric acid was impossible due to the presence of several impurities. Clearly, the cyclization process needed vast improvements.

From a mechanistic point of view, the cyclization process possibly involves formation of phosphate ester (Scheme 2) as suggested by Klerk.[21]

This implies that the presence of a protic acid would help in accelerating the reaction. Although the patent[3] describes the use of a mixture of sulphuric and phosphoric acids, it is not clear whether the reaction was faster in the mixture than in pure phosphoric acid since all reactions were carried out uniformly for 18−20 h. In addition, handling of concentrated sulphuric acid and subsequent neutralization is a hazardous and polluting

Scheme 2. Possible mechanism of cyclization catalyzed by phosphoric acid



affair. It was interesting to try to use a solid acid catalyst instead of sulphuric acid in combination with phosphoric acid. Since it is rather difficult to recover and recycle phosphoric acid which also acts as a reaction medium, it was also interesting to try to use an organic solvent which can be recovered by distillation and minimize the amount of phosphoric acid that can be used. With these two goals in mind we have performed the cyclization reaction in toluene and diethyl carbonate using a combination of commercially available 85% phosphoric acid and solid acid catalysts such as Amberlyst 15 H^+ ion-exchange resin and phosphotungstic acid (Table 1).

In toluene, phosphotungstic acid supported on Amberlyst 15 H^+ ion-exchange resin did not catalyze the cyclization reaction. The reaction did proceed in diethyl carbonate, but product purity was unacceptable. It appeared that phosphoric acid is indeed necessary for cyclization. The reaction in 85% phosphoric acid alone took 72 h for completion (entry 3), and the product was contaminated with 5% of *O*-demethylation product (+)-3-hydroxy-*N*-formylmorphinan along with 10% of other unidentified impurities. When the reaction was carried out in >99% phosphoric acid, the product quality was acceptable, but the reaction period was long (72 h, entry 4). In comparison, in the presence of Amberlyst 15 resin, the reaction in 85% phosphoric acid was complete in 10 h (entry 5). Additionally, the reduced reaction period decreased the formation of side products such as demethylation of the methoxy group, to a considerable extent, and cyclized product with high purity (>98%) and high yields (>98%) were obtained. Considering this aspect, the reaction conditions in entry 5 were considered as most suitable for performing a bench-scale reaction where the methodologies for product isolation and recycle of reagents had to be properly developed.

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Table 1. Cyclization of (+)-*N*-formyl octabase 3[a]

S. no	catalyst	solvent	temp (°C)	reaction period (h)	conversion (%)	purity (%)
1	phosphotungstic acid (20%) supported on Amberlyst 15	toluene	110	18	nil	–
2	phosphotungstic acid (20%) supported on Amberlyst 15	diethylcarbonate	120	18	20	50
3	85% phosphoric acid (40 mL) + **3** (10 g)	no solvent	80	72	>98	85
4	93% phosphoric acid (40 g) + P_2O_5 (5 g)+ **3** (5 g)	no solvent	55	72	>98	>98
5	Amberlyst 15 (5g) + 85% phosphoric acid (40 mL) + **3** (10 g)	no solvent	80	10	>98	>98

[a]Reaction conditions: entries 1 and 2: 500 mg **3** in 10 mL solvent, catalyst 1 g. Conversion and purities are based on HPLC analysis.

A bench-scale reaction was carried out at 100 g scale, and the product was recovered in near quantitative yield. The enantiomeric purity (ee 96%) was determined as *N*-phenylacetyl derivative after removal of *N*-formyl protection. Compared to the processes reported in the literature, the present modifications have reduced the reaction period from 3 days to 10 h, dispensed with the necessity of using 99% phosphoric acid, and improved product purity to a considerable extent. The overall process is more environmentally friendly as well as cost-effective.

EXPERIMENTAL SECTION

General. IR spectra were recorded on a Perkin Elmer RX-1 FT-IR system. ^{1}H NMR (300 MHz) spectra were recorded on Bruker Avance-300 MHz spectrometer. Optical rotations were measured with Horiba-SEPA-300 digital polarimeter. Mass measurements were performed on Q STAR mass spectrometer (Applied Biosystems, U.S.A.). HPLC analysis was carried out on Shimadzu HPLC unit equipped with PDA detector. All other reagents and solvents used were of analytical grade obtained from Hi Media and Qualigens, India. Amberlyst 15 was obtained from Fluka. The resin was washed with water and then with methanol and finally dried in oven at 50 °C overnight before use. The racemic octabase and resolved mandelate salt of (−)-octabase were a generous gift from M/s Alekhya Drugs Pvt Ltd., Hyderabad, India.

Supported Acid Catalysts Used in Table 1. Supported catalysts were prepared by stirring the support (1 g) with a methanolic solution of catalyst (10 mL). The mixture was stirred for 6 h at room temperature, followed by drying on a rotary evaporator. Finally, the catalyst was dried by heating at 140 °C under vacuum (2 mmHg pressure) for 3 h.

(+)-1-(*p*-Methoxybenzyl)-2-formyl-1,2,3,4,5,6,7,8-octahydroisoquinoline, (+)-3. (−)-Octabase-mandelate salt (409 g, 1 mol) was added to ethyl formate (5 L), and the mixture was refluxed for 48 h. The suspended mandelate salt slowly dissolved as the reaction proceeded towards completion. After completion of the reaction, the solution was cooled in ice, and cold saturated Na_2CO_3 solution (1 L) was added slowly with stirring. The layers were separated. Unreacted ethyl formate was recovered by distillation at atmospheric pressure (bp 54−55 °C), keeping the temperature of heating bath below 85 °C (3.94 L, 79%). It was necessary to retain some ethyl formate in the distillation flask since attempts to recover more ethyl formate by increasing the bath temperature resulted in darkening of product. The remaining ethyl formate was collected by distillation under reduced pressure (100 mmHg) with a liquid nitrogen trap (490 mL, 10%). *N*-formyl octabase was obtained as pale, honey-coloured oil (280 g, 99% yield). $[\alpha]^{25}_D$ + 16.4 (*c* 1, MeOH (e.e. 96% chiral HPLC of *N*-phenylacetyl derivative) lit[3] $[\alpha]^{25}_D$ + 23.4° (*c* 1, MeOH) for vacuum distilled product.

^{1}H NMR ($CDCl_3$, δ) 1.52−1.68 (m, 8H), 1.71−1.96 (m, 8H), 2.02−2.32 (m, 4H), 2.56−2.61 (m, 1H), 2.72−3.06 (m, 3H), 3.30 (dd, *J* = 6.56, 13.12 Hz, 1H), 3.52 (d, *J* = 10.22 Hz, 1H), 3.71−3.77 (m, 6H), 4.38 (dd, *J* = 6.7, 13.2 Hz, 1H), 4.7 (m, 1H), 6.78−6.89 (m, 4H), 6.98−7.10 (m, 4H), 7.42(s, 1H), 7.96 (s, 1H). IR (neat) 3006 cm^{-1}, 2930 cm^{-1}, 2835 cm^{-1}, 1655 cm^{-1} (CHO), 1511 cm^{-1}, 744 cm^{-1}; HRMS [ESI, $(M + H)^+$]: *m*/*z* calcd for $C_{18}H_{24}NO_2$: 286.1807; found: 286.1758.

The aqueous layer was acidified with 6 N HCl and extracted with ethyl acetate (3 ×1 L). The combined ethyl acetate layer was subjected to distillation at atmospheric pressure to recover ethyl acetate (bp 77−78 °C, 2.7 L, 90%). The remaining ethyl acetate was removed by distillation at reduced pressure with a liquid nitrogen trap (200 mL). (−)-Mandelic acid was obtained as a white crystalline solid (150 g, 99% yield).

(+)-3-Methoxy-*N*-formylmorphinan 4. The *N*-formyl octabase **3** (100 g) and commercially available 85% *o*-phosphoric acid (400 mL) were placed in a kettle reactor equipped with a mechanical stirrer and temperature controller. The reaction mixture was brought to 80 °C with stirring, and Amberlyst 15 ion-exchange resin (50 g) was added. The reactants were stirred at 150 rpm at 80 °C, and the conversion was followed by HPLC analysis. The reaction was complete in 10 h. The reaction mixture was then cooled to room temperature, ethyl acetate (400 mL) was added to the slurry, and the contents were stirred to obtain a free-flowing solution. The supernatant was decanted, and the resin was washed once with ethyl acetate (100 mL). The combined ethyl acetate layer was cooled in ice, water (500 mL) was added with stirring, and the layers were separated. The pale, honey-coloured organic layer was dried over calcium chloride, and the product was collected in quantitative yield (98 g, 98%) after distilling off the ethyl acetate layer. $[\alpha]^{25}_D$ + 120.3 (*c* 1, MeOH, (e.e. 96%, chiral HPLC of *N*-phenylacetyl derivative); lit[3] $[\alpha]^{25}_D$ +182 (*c* 1, MeOH) for vacuum distilled crystalline product (mp 106−109 °C).

^{1}H NMR ($CDCl_3$, δ) 1.02−1.72 (m, 24H), 2.35−2.48 (m, 2H), 2.61−2.69 (m,2H), 2.91−2.98 (m, 1H), 3.11−3.26 (m, 3H), 3.78−3.81 (m, 6H), 6.71−6.87 (m, 2H), 7.01−7.18 (m, 4H), 8.01 (s, 1H), 8.18 (s, 1H). IR (neat) 3006 cm−1, 2932 cm^{-1}, 2858 cm^{-1}, 1654 cm^{-1} (CHO), 743 cm^{-1}; HRMS [ESI, $(M + H)^+$]: *m*/*z* calcd for $C_{18}H_{24}NO_2$: 286.1807; found: 286.1742.

(+)-3-Hydroxy-*N*-formylmorphinan. Cyclization of octabase **2** was carried out as described above without addition of ion-exchange resin. The reaction was complete after 72 h. Formation of demethylated product (+)-3-hydroxy-*N*-formylmorphinan (5%) along with **4** (85%) was observed during HPLC analysis. The demethylated product obtained in the ethyl acetate layer was extracted with ice cold 4 N NaOH (2 × 25 mL). The combined alkali extracts were acidified with ice cold 4 N HCl, and the pale-brown emulsion obtained after acidification was extracted with ethyl acetate (2 × 25 mL).

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Evaporation of the solvent gave the demethylated product as a pale-yellow powder (5 g). Mp 128−130 °C; $[\alpha]^{25}_{D}$ +130.6 (*c* 1, MeOH).

^{1}H NMR ($CDCl_3$, δ) 1.07−1.83 (m, 18H), 2.29−2.69 (m, 4H), 2.93−3.30 (m, 3H), 3.66−3.71 (m, 1H), 4.12−4.19 (m, 1H), 4.61−4.64 (m, 1H), 5.3 (s, 1H), 6.24 (br s, 1H), 6.26 (br s, 1H), 6.67 (dd, *J* = 1, 2.5 Hz, 1H), 6.69 (dd, *J* = 1, 2.5 Hz, 1H), 6.80 (s, 1H), 6.81 (s, 1H), 6.94 (t, *J* = 8.5 Hz, 2H), 7.99 (s, 1H), 8.15 (s, 1H). HRMS [ESI, (M + H)$^+$]: *m*/*z* calcd for $C_{17}H_{22}NO_2$: 272.16451; found: 272.16509.

Recovery of the Resin and Phosphoric Acid. The recovered resin was washed with methanol, dried in the oven at 60 °C, and reused. The aqueous layer was heated to 90 °C and treated with activated charcoal (10 g) for 10 min and then filtered. Water was removed from the light-yellow phosphoric acid solution under reduced pressure on rotavapor at 90 °C. The recovered phosphoric acid could be recycled three times without developing impurities in the product. However, after the third recycle, phosphoric acid had to be discarded.

***N*-Phenylacetyl Octabase.** The octabase (*rac*- or enantiomerically pure, 1 g) was added to 4 N NaOH solution (10 mL). Phenylacetyl chloride (0.7 g) was added, and the contents were vigorously stirred for 10 min. The reaction mixture was extracted with ethyl acetate (2 × 5 mL). Evaporation of ethyl acetate gave the *N*-phenylacetyl derivative (1.45 g, 99%). The crude product was directly analyzed by chiral HPLC for determination of ee. A part of crude product was purified by column chromatography (R_f = 0.6, hexane/ethyl acetate, 3:2 v/v) for characterization. Mp 84−86 °C. $[\alpha]^{25}_{D}$ + 50.84 (*c* 1, MeOH) (ee 96%, chiral HPLC).

^{1}H NMR ($CDCl_3$, δppm) 1.42−1.71(m, 8H), 1.73−1.92 (m, 8H), 2.01−2.29(m, 4H), 2.68−2.74 (m, 1H), 2.80−3.09 (m, 3H), 3.50−3.68 (m, 2H), 3.78 (s, 3H), 3.81 (s, 3H), 4.70 (dd, *J* = 6.56, 13.12 Hz, 1H), 4.98(m, 1H), 6.78 (*J* = 8.54 Hz, 2H), 6.9 (*J* = 8.54 Hz, 2H), 6.98−7.30 (m, 4H). IR (neat) 3000 cm^{-1}, 2927 cm^{-1}, 2832 cm^{-1}, 1629 cm^{-1} (C═O), 1511 cm^{-1}, 1244 cm^{-1}; HRMS ESI−MS: *m*/*z* [M + H]$^+$calcd for $C_{25}H_{30}NO_2$: 376.2276; found: 376.2267.

3-Methoxy-*N*-phenylacetylmorphinan. The *N*-formyl derivative **4** (enantiomerically pure or racemic) was deformylated to obtain **5** by refluxing the compound (1 g) in methanol (20 mL) and NaOH (2.5 N, 10 mL) overnight. Methanol was removed on rotavapor, and the crude amine was treated with phenylacetyl chloride in NaOH (as described above) to obtain the *N*-phenylacetyl derivative. The enantiomerically pure derivative was purified by column chromatography (R_f = 0.6, hexane/ethyl acetate, 3:2 v/v) for characterization. $[\alpha]^{25}_{D}$ + 120.64 (*c* 1, MeOH) (ee 96%, chiral HPLC).

^{1}H NMR ($CDCl_3$, δ) 1.18−1.68 (m, 24H), 2.28−2.46 (m, 4H), 2.78−3.10 (m, 4H), 3.48−3.70 (m, 4H), 3.88−3.94 (m, 6H), 6.66−7.47 (m, 16H). ESI−MS: *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{30}NO_2$: 376.2276; found: 376.2282.

HPLC Analysis. *N-Formyl octabase:* Column RP-8 (250 mm × 4.6 mm), Merck KGa, Germany. Injection volume 20 μL. Analysis was performed at room temperature using solvent gradient consisting of methanol and water containing 0.1% trifluoroacetic acid. At start of analysis the mobile phase consisted of 50% methanol−50% water. This was changed to 70% methanol−30% water in 10 min with total flow rate of 0.7 mL/min. The solvent gradient was changed from 70 to 80% methanol−20% water in 5 min and held at 80% methanol−20% water for 5 min. The solvent composition was brought back to 50% methanol−50% water in 5 min and maintained at same composition for 5 min more before the end of analysis. Detection wavelength, 220 nm. Retention times: (−)-mandelic acid, 10.19 min; (−)-octabase, 13.97 min; (+)-*N*-formyl octabase **3**, 21.56 min.

(+)-3-Methoxy-N-formylmorphinan and (+)-3-hydroxy-N-formylmorphinan: Column RP-8 (250 mm × 4.6 mm), Merck KGa, Germany. Mobile phase 70% MeOH−30% water containing 0.1% TFA; flow rate 0.7 mL/min; detection wavelength, 280 nm. Retention times: (+)-3-hydroxy-*N*-formylmorphinan, 6.9 min; (+)-3-methoxy-*N*-formylmorphinan **4**, 11.4 min; (+)-*N*-formyl octabase **3**, 12.74 min.

Determination of enantiomeric purity by chiral HPLC: Column Chiralcel-OD (250 mm × 5 mm), Daicel Chemical Industries, Japan. Mobile phase, 15% 2-propanol in hexane. Detection wavelength, 220 nm. Flow rate, 0.5 mL/min. Retention times: (+)-*N*-phenylacetyl octabase, 12.2 min; (−)-*N*-phenylacetyl octabase, 13.9 min. Flow rate 0.4 mL/min, retention times: (−)-3-methoxy-*N*-phenylacetylmorphinan, 18.0 min; (+)-3-methoxy-*N*-phenylacetylmorphinan, 19.7 min.

CONCLUSION

We have developed an efficient and environmentally friendly process for the synthesis of 3-methoxy-*N*-formylmorphinan, a key intermediate for production of DXM. The *N*-formylation of (−)-octabase can be done directly by refluxing with ethyl formate, and cyclization of the *N*-formylated product is efficiently catalyzed by Amberlyst 15 resin. Most of the reagents can be easily recovered and recycled.

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Notes

The authors declare no competing financial interest.

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