SYNTHETIC STUDIES ON COLCHICINE : REACTION OF HOMOMORPHINANDIENONES#

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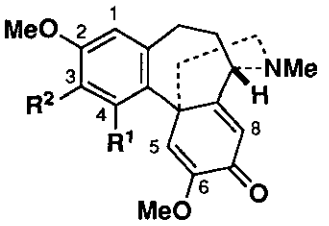
Abstract --- For the purpose of synthetic approaches toward colchicine (**2**) from *O*-methylandrocymbine (**1a**), reaction of homomorphinandienones (**1a,b**) was carried out. Oxidation of **1a,b** with 35% aqueous hydrogen peroxide gave a separable diastereomeric mixture of *N*-oxides (**5,6**). Polonovski reaction of the *N*-oxides (**5**) with acetic anhydride in CH_2Cl_2 afforded *N*-demethyl-*N*-acetamide (**7a**), whereas that of **5** and **6** with acetic anhydride in the presence of triethylamine gave enamines (**8a,b**) together with *N*-demethyl-*N*-acetamides (**7a,b**). Furthermore, reaction of enamines (**8a,b**) with *N*-bromosuccinimide in dimethoxyethane-H_2O or methanol produced α-bromo amides (**9a,b**).

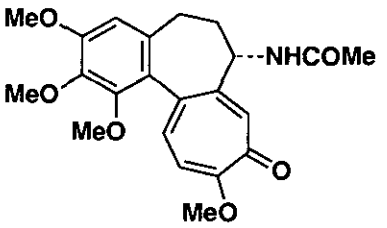
O-Methylandrocymbine (**1a**),[1] one of homomorphinandienone alkaloids isolated from *Colchicum* species, has been considered to be the biosynthetic key precursor of colchicine (**2**)[2,3] ; hydroxylation of **1a** generates the alcohol (**3**), which suffers ring expansion of cyclohexa-2,5-dienone moiety through cyclopropanation to lead to demecolcine (**4**). Although many reports[4-6] on synthesis of **1a** have appeared, few attempts to convert **1a** to colchicine (**2**) have been made.

Dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday.

Therefore, our interest was focused on transformation of homomorphinandienone (**1**) to 6-7-7 ring fused system, which is a basic skeleton of colchicine (**2**). In this paper, we describe Polonovski reaction of homomorphinandienone *N*-oxides (**5**,**6**) and reaction of the corresponding enamines (**8a**,**b**) with *N*-bromosuccinimide (NBS).



1a,b



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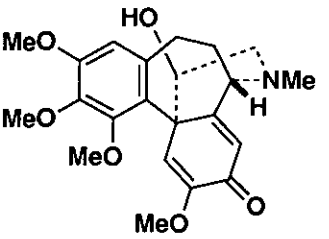
a : R^1=R^2=OMe **b** : R^1=R^2=H



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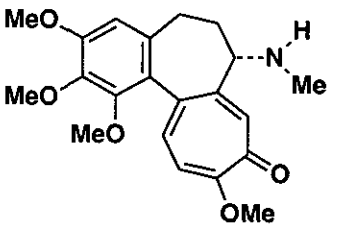

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(Scheme 1)

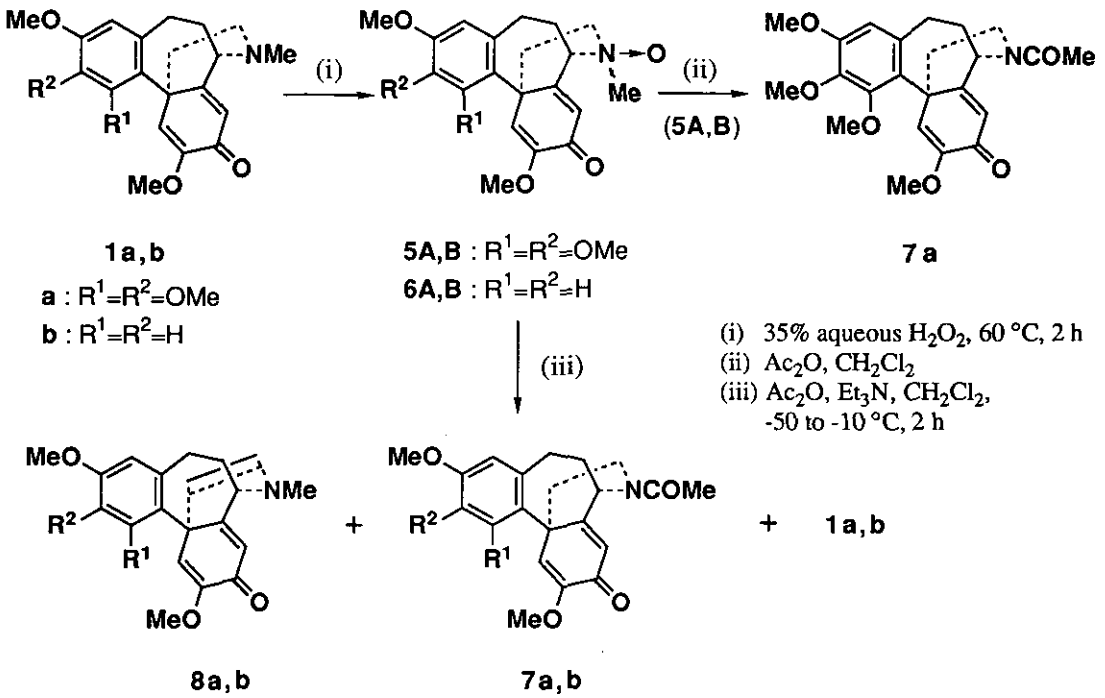
Result and Discussion

Polonovski Reaction of Homomorphinandienone *N*-Oxides (5a,b) : Reaction of amine *N*-oxide with acetic anhydride (Ac_2O) has been well known to give secondary amine or the corresponding *N*-acetamide (Polonovski reaction).[7,8] On the other hand, reaction with Ac_2O in the presence of base affords the corresponding enamine.[8,9] Therefore, Polonovski and modified Polonovski reactions seem to be one of versatile methods for synthesis of various substituted piperidine systems.[8,9] Thus, we expected that this reaction might be applicable to functionalization of piperidine ring in homomorphinandienones (**1**).

The *N*-oxide of *O*-methylandrocymbine (**1a**) was prepared as follows. A mixture of **1a** and 35% aqueous hydrogen peroxide (H_2O_2) was heated at 60 °C for 2 h. The reaction mixture was purified by preparative thin layer chromatography (tlc) to afford two diastereomeric *N*-oxides (**5A** and **5B**) in 18.1 and 36.9% yields, respectively (polarity, **5A**<**5B**). The structures of *N*-oxides were confirmed by down-field shift of signals for the *N*-methyl groups (**5A** : δ 3.32 and **5B** : δ 3.29) in nuclear magnetic resonance (nmr), although the relative stereochemistry of two diastereomers was uncertain. The similar reaction of **1b** furnished, after purification by preparative tlc, two diastereomers of the *N*-oxides (**6A** and **6B**) in 14.9 and 48.3% yields, respectively (polarity, **6A**<**6B**) (Scheme 2). The *N*-oxides were somewhat unstable on standing at ambient temperature. Therefore, oxidized products were subjected to Polonovski reaction without further purification.

A diastereomeric mixture of the *N*-oxides (**5**) obtained from **1a** was allowed to react with Ac_2O at 60 °C to afford the *N*-demethyl-*N*-acetamide (**7a**) in 19.8% yield. Therefore, we tried to prepare enamines from the *N*-oxides (**5** and **6**).

Stütz and Stadler[10] have reported that treatment of amine *N*-oxide with Ac_2O in the presence of triethylamine (Et_3N) produces enamine predominantly. As a model experiment, a diastereomeric mixture of the *N*-oxides (**6**) was conducted with Ac_2O-Et_3N in CH_2Cl_2 at -50 to -10 °C for 2 h. The reaction mixture was purified by basic alumina column chromatography to give the enamine (**8b**), *N*-demethyl-*N*-acetamide (**7b**), and homomorphinandienone (**1b**) in 31.7, 5.9, and 9.5% yields, respectively. The structure of the enamine (**8b**) was determined by the nmr spectrum showing signals due to olefinic proton as each one proton doublet (J=7 Hz) at δ 4.18 and 6.19. Similarly, a diastereomeric mixture of the *N*-oxides (**5**) derived from *O*-methylandrocymbine (**1a**) gave the enamine (**8a**), *N*-demethyl-*N*-acetamide (**7a**) and *O*-methylandrocymbine (**1a**) in 31.7, 5.0, and 8.3% yields, respectively (Scheme 2). When the reaction was carried out in acetonitrile (MeCN) as a solvent, similar results were also obtained. As being less stable at room temperature, the enamines (**8a**,**b**) were immediately employed to the further reaction.



1a,b
a : R^1=R^2=OMe
b : R^1=R^2=H

5A,B : R^1=R^2=OMe
6A,B : R^1=R^2=H

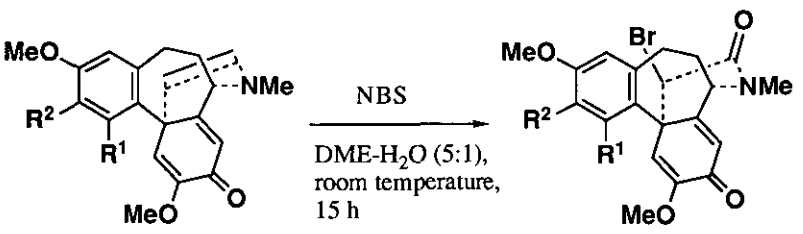
7a

(i) 35% aqueous H_2O_2, 60 °C, 2 h
(ii) Ac_2O, CH_2Cl_2
(iii) Ac_2O, Et_3N, CH_2Cl_2, -50 to -10 °C, 2 h

8a,b **7a,b**

(Scheme 2)

Reaction of Enamines (8a,b) : With the desired enamines in our hand, reaction of enamines was carried out. At first, introduction of dihydroxy or diacetoxy groups to vicinal position of the double bond in enamine moiety was examined.[11] However, these attempts were unfruitful. In contrast to these findings, reaction of **8b** with NBS in a mixture of dimethoxyethane (DME) and H_2O[16] at room temperature gave the α-bromo amide (**9b**) in 49.9% yield. Similarly, the enamine (**8a**) gave the α-bromo amide (**9a**) in 38.9% yield.

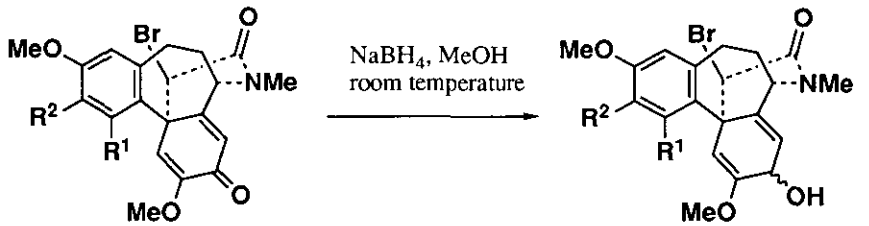


8a,b **9a,b**

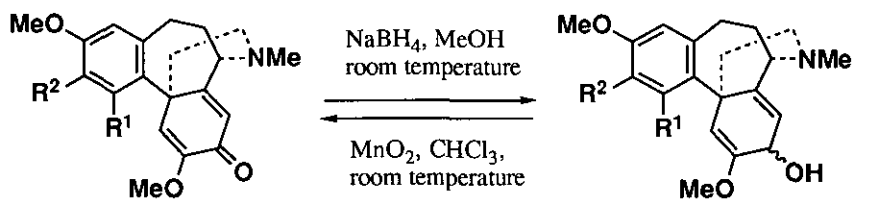
a : R^1=R^2=OMe **b** : R^1=R^2=H

(Scheme 3)

The nmr spectra of **9a,b** showed signals for the *N*-methyl groups (δ 2.87 for **9a** ; δ 2.85 for **9b**) in more down-field region than those (δ 2.37[6] for **1a** ; δ 2.35[17] for **1b**) of homomorphinandienones (**1a,b**), respectively. The infrared (ir) spectra showed an absorption at 1670 cm^{-1}, which was assigned to an amide-carbonyl group by the following evidence. Reduction of **9a** and **9b** with $NaBH_4$ in methanol (MeOH) gave the dienols (**10a** and **10b**), ir spectra of which showed an absorption at the same frequency (1670 cm^{-1}). Furthermore, 1,2-reduction of the dienones (**9a,b**) with $NaBH_4$ was supported by the observation that $NaBH_4$ reduction of homomorphinandienones (**1a,b**) produced the dienols (**11a,b**) reversible to the parent dienones by oxidation with manganese(IV) oxide (MnO_2).



9a,b **10a,b**



(**11a**)

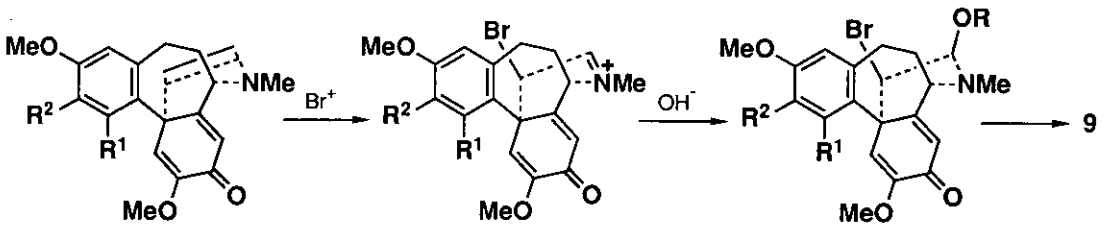
1a,b **11a,b**

a : R^1=R^2=OMe **b** : R^1=R^2=H

(Scheme 4)

Formation of the α-bromo amides (**9a,b**) was deduced as follows ; the enamines (**8a,b**) were attacked at their β-position by bromo cation to produce the iminium ion (**12**), which reacted with hydroxide anion to give the corresponding bromohydrin (**13**), and finally **13** underwent auto-oxidation or oxidation with NBS to afford the amides (**9a,b**). To avoid the oxidation of bromohydrin to α-bromo amide, therefore, reaction of **8a** with NBS in MeOH or in a mixture of DME-MeOH was

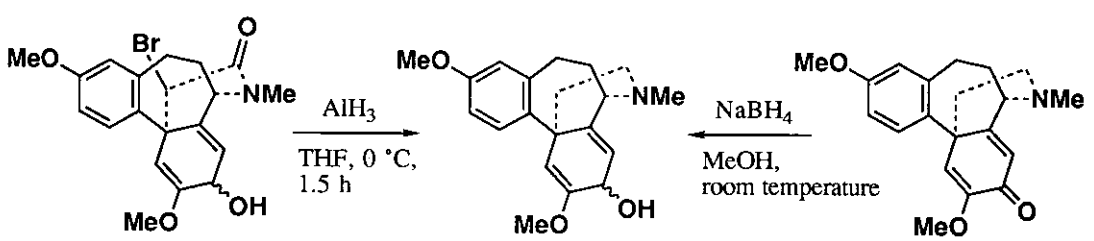
carried out. However, the α-bromo amide (**9a**) was also formed in moderate yield without formation of the desired α-methoxy-β-bromoamine (**14**).



8 **12** **13** : R=H
14 : R=Me

(Scheme 5)

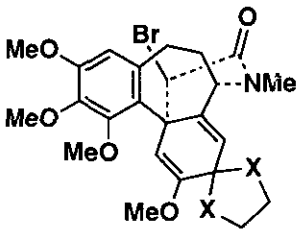
In order to introduce the oxygenated functional group to piperidine system, several reactions of the α-bromo amide were investigated. Yoon and Brown[18] have reported that haloamide was selectively reduced to haloamine by aluminum hydride (AlH_3) in tetrahydrofuran (THF). Thus, the dienol (**10b**) was treated with AlH_3[18] in THF at 0 °C for 1.5 h. However, the debrominated amine (**11b**) was formed exclusively. The structure of **11b** was confirmed by comparison of its nmr and ir spectra with those of the authentic sample obtained by $NaBH_4$ reduction of homomorphinandienone (**1b**). Alternatively, reaction of the α-bromo amide (**10a**) with aqueous potassium hydroxide (KOH) in THF at room temperature did not take place, whereas base treatment in MeOH under heating gave inseparable products.



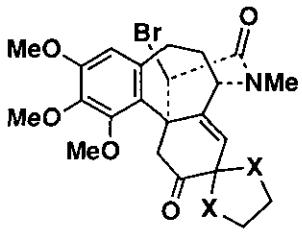
10b **11b** **1b**

(Scheme 6)

Reaction of *O*-Methylandrocymbine (1a) with 1,2-Ethanedithiol : Next, we planed the direct ring expansion of cyclohexa-2,5-dienone moiety of the α-bromo amides (**9a**,**b**). The protection of a dienone-carbonyl group of **9a**,**b** would lead to enol ether (**15**) or the ketone (**16**). Acid treatment of the enol ether or base treatment of the ketone would generate **17** by the cyclopropanation, which should be a key step for construction of tropolone skeleton.



15 X=O, S



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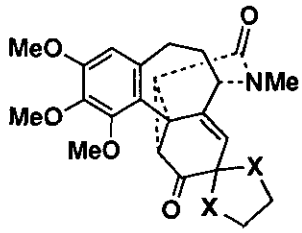

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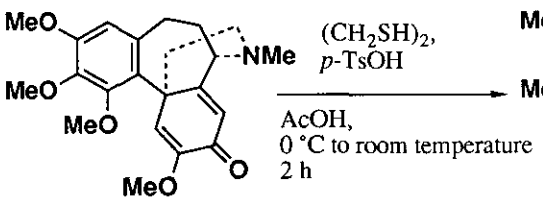
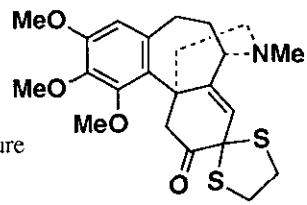
(Scheme 7)

With this in mind, as a model experiment we examined ketalization of **1a**. However, ketalization of **1a** with 1,3-dioxolane in benzene containing *p*-toluenesulfonic acid (*p*-TsOH) did not take place. In contrast, thioketalization of **1a** with 1,2-ethanedithiol[19] in AcOH containing *p*-TsOH gave the α-keto thioketal (**18**) in 45% yield, whereas that in CH_2Cl_2 containing etherial boron trifluoride (BF_3•OEt_2) afforded an inseparable mixture. The α-keto thioketal might be formed through the acid hydrolysis of the enol ether (**19**).



1a



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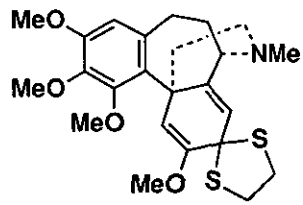

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(Scheme 8)

Transformation of the homomorphinandienones (**1**) into the enamines (**8**) was achieved effectively by modified Polonovski reaction in the presence of Et_3N, and the enamines (**8**) could be converted into the α–bromo amides (**9**). However, the ring expansion of dienone moiety of **9** through cyclopropanation have remained still.

ACKNOWLEDGEMENT

The authors are indebted to Miss N. Sawabe and Mrs. F. Hasegawa of this Faculty for ^{1}H-nmr and ms spectral measurements, and to Sankyo Co., Ltd. for elemental analyses.

EXPERIMENTAL

General : Melting points were measured on a Yanako micro melting point apparatus (hot-plate model) and are uncorrected. Ir spectra were taken with a Hitachi model 260 spectrophotometer in $CHCl_3$ solution, unless otherwise noted. ^{1}H-Nmr spectra were recorded on a JEOL model FX-100 spectrometer in $CDCl_3$ solution as δ values (ppm) relative to tetramethylsilane. CH_2Cl_2 and MeCN as reaction solvents were distilled from CaH_2 prior to use. Preparative tlc was performed on 20 × 20 cm plates coated with 0.5 mm thickness of Merck Kieselgel 60 containing F-254 indicator. Column chromatography was carried out on silica gel (Wakogel C-200), unless otherwise noted.

General Procedure for Preparation of Homomorphinandienone *N*-Oxides (**5** and **6**) : A mixture of homomorphinandienone (**1**) and 35% aqueous H_2O_2 was heated with stirring at 60 °C (bath temperature) for 2 h. To a stirred, ice-cooled reaction mixture was added a small portion of 10% Pd-C. After the evolution of gas ceased, the mixture was diluted with CH_2Cl_2 and stirred for additional 30 min. The CH_2Cl_2 solution was dried over anhydrous K_2CO_3 and filtrated. The filtrate was condensed *in vacuo* to give an oily residue, which was separated by preparative tlc (developing solvent ; $CHCl_3$: MeOH = 10 : 1, v / v). In the further reaction, the *N*-oxides (**5**,**6**) were used without separation of isomers.

O-Methylandrocymbine *N*-Oxides (**5A** and **5B**) : From reaction of *O*-methylandrocymbine[6] (**1a**) (32.3 mg, 0.084 mmol) and 35% aqueous H_2O_2 (0.3 ml), **5A** (6.1 mg, 18.1%) and **5B** (12.4 mg, 36.9%) were obtained as each oil (polarity : **5A**<**5B**).

5A : ^{1}H-Nmr δ : 3.32 (3H, s, NMe), 3.65, 3.80, 3.83, 4.04 (12H, each s, 4×OMe), 6.33 (1H, s, C_5-H), 6.40 (1H, s, C_8-H), 6.79 (1H, s, C_1-H) ; ir : 1680, 1640, 1620 cm^{-1} ; ms *m/z* : 401 (M^+).
5B : ^{1}H-Nmr δ : 3.29 (3H, s, NMe), 3.64 (3H, s, OMe), 3.81 (6H, s, 2×OMe), 4.04 (3H, s, OMe), 6.28 (1H, s, C_5-H), 6.44 (1H, s, C_8-H), 6.76 (1H, s, C_1-H) ; ir : 1670, 1640, 1620 cm^{-1} ; ms *m/z* : 401 (M^+).
2,6-Dimethoxyhomomorphinandienone *N*-Oxides (**6A** and **6B**) : From reaction of 2,6-dimethoxyhomomorphinandienone[17] (**1b**) (30.6 mg, 0.095 mmol) and 35% aqueous H_2O_2 (0.3 ml), **6A** (4.8 mg, 14.9%) and **6B** (15.5 mg, 48.3%) were obtained as each oil (polarity : **6A**<**6B**).
6A : ^{1}H-Nmr δ : 3.42 (3H, s, NMe), 3.66, 3.78 (6H, each s, 2×OMe), 6.10 (1H, s, C_5-H), 6.50 (1H, s, C_8-H), 6.54 (1H, d, *J*=4 Hz, C_1-H), 6.84 (1H, dd, *J*=4, 12 Hz, C_3-H), 7.34 (1H, d, *J*=12 Hz, C_4-H) ; ir : 1670, 1640, 1620 cm^{-1} ; ms *m/z* : 341 (M^+).
6B : ^{1}H-Nmr δ : 3.24 (3H, s, NMe), 3.64, 3.78 (6H, each s, 2×OMe), 6.06 (1H, s, C_5-H), 6.48 (1H, s, C_8-H), 6.50 (1H, d, *J*=4 Hz, C_1-H), 6.83 (1H, dd, *J*=4, 12 Hz, C_3-H), 7.40 (1H, d, *J*=12 Hz, C_4-H) ; ir : 1670, 1640, 1620 cm^{-1} ; ms *m/z* : 341 (M^+).

Polonovski Reaction of *N*-Oxides (**5**) with Ac_2O : *A mixture of N-oxides* (**5**) *obtained from O-*methylandrocymbine (**1a**) (50 mg, 0.13 mmol) and Ac_2O (0.5 ml, 0.53 mmol) was heated with *stirring at 60 °C for 2 h. H_2O was added to an ice-cooled reaction mixture.* After being stirred for 1 h under cooling, the mixture was neutralized with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. *The $CHCl_3$ extract was washed with brine and dried over anhydrous K_2CO_3.* After removal of the solvent, the residue was purified by preparative tlc (developing solvent ; $CHCl_3$: MeOH=30 : 1, v / v) to afford *N*-demethyl-*N*-acetyl-*O*-methylandrocymbine (**7a**) (10.3 mg, 19.8%) as brown crystals, mp 228-230 °C (MeOH). ^{1}H-Nmr δ : 2.10, 2.20 [3H, each s, NCOMe (2:1)], 3.70, 3.83 (6H, each s, 2×OMe), 4.07, 4.10 [3H, each s, OMe, (1:2)], 5.51, 5.63 (1H, each dd, *J*=4, 12 Hz, methine proton), 6.35 (1H, s, C_5-H), 6.31, 6.37 [1H, each s, C_8-H, (1:2)], 6.73, 6.79 [1H, each s, C_1-H, (2:1)] ; ir (KBr) : 1660, 1630 cm^{-1} ; high resolution ms *m/z* : calcd for $C_{23}H_{27}NO_6$: 413.1836 ; found : 413.1823 ; ms *m/z* : 413 (M^+).

General Procedure for Polonovski Reaction of *N*-Oxides (**5** and **6**) with Ac_2O in the Presence of Et_3N : A solution of *N*-oxides in CH_2Cl_2 or MeCN was stirred at -50 °C (bath temperature) for 10

min under argon atmosphere. Ac_2O was added slowly to this solution and the mixture was stirred at the same temperature for 5 min, to which was added Et_3N dropwise. After being stirred for 5 min, the mixture was warm up to -20 ~ -10 °C and stirring was continued at the same temperature for 2 h. The reaction mixture was basified by saturated aqueous $NaHCO_3$ and warm up to room temperature. Then the product was taken up in CH_2Cl_2. The CH_2Cl_2 extract was washed with H_2O and dried over anhydrous Na_2SO_4. Removal of CH_2Cl_2 *in vacuo* gave an oily residue, which was purified by basic alumina (ICN Alumina B, Akt. I) column chromatography (eluent : CH_2Cl_2).

(i) **5** (38.7 mg, 0.097 mmol), Ac_2O (0.10 ml, 1.06 mmol), Et_3N (0.69 ml, 4.95 mmol), and CH_2Cl_2 (0.7 ml) were used ; column chromatography (3 g) of a crude product (24.8 mg) gave 12,13-dehydro-*O*-methylandrocymbine (**8a**) (12.2 mg, 31.7%), **7a** (2.0 mg, 5.0%), and **1a** (3.1 mg, 8.3%) (polarity : **8a**<**7a**<**1a**). **8a** : oil ; ^{1}H-nmr δ : 2.73 (3H, s, NMe), 3.65, 3.80, 3.83, 3.96 (12H, each s, 4×OMe), 5.00, 6.92 (2H, each d, *J*=7 Hz, enamine-H), 6.16, 6.23, (2H, each s, 2×dienone-H), 6.78 (1H, s, C_1-H) ; ir : 1660, 1640, 1610 cm^{-1} ; high resolution ms *m/z* : calcd for $C_{22}H_{25}NO_5$: 383.1759 ; found : 383.1745 ; ms *m/z* : 383 (M^+).

(ii) **6** (41.0 mg, 0.127 mmol), Ac_2O (0.11 ml, 1.16 mmol), Et_3N (0.80 ml, 5.74 mmol), and CH_2Cl_2 (1.1 ml) were used ; column chromatography (3 g) of a crude product (33.1 mg) produced 12,13-dehydro-2,6-dimethoxyhomomorphinandienone (**8b**) (11.5 mg, 31.7%), **7b** (2.5 mg, 5.9%), and **1b** (3.7 mg, 9.5%), respectively (polarity : **8b**<**7b**<**1b**). **8b** : oil ; ^{1}H-nmr δ : 2.86 (3H, s, NMe), 3.74, 3.80 (6H, each s, 2×OMe), 4.18, 6.19 (2H, each d, *J*=7 Hz, enamine-H), 6.05. 6.16 (2H, each s, 2×dienone-H), 6.56~6.65 (2H, m, arom-H), 7.18 (1H, d, *J*=12 Hz, C_1-H) ; ir : 1660, 1640, 1610 cm^{-1} ; high resolution ms *m/z* : calcd for $C_{20}H_{21}NO_3$: 323.1497 ; found : 323.1515 ; ms *m/z* : 323 (M^+).

(iii) **5** (25.2 mg, 0.063 mmol), Ac_2O (0.06 ml, 3.23 mmol), Et_3N (0.45 ml, 3.23 mmol), and MeCN (0.51 ml) were used ; column chromatography (2 g) of an oily residue (19.2 mg) gave enamine (**8a**) (7.9 mg, 32.7%), **7a** (1.9 mg, 7.3%), and **1a** (2.5 mg, 10.3%), respectively.

General Procedure for Reaction of Enamines (**8a** and **8b**) with NBS : To an ice-cooled, stirred solution of enamine (**8**) in a mixture of DME and H_2O (5 : 1) was added NBS in one portion. The mixture was stirred at room temperature overnight. After addition of H_2O, the reaction mixture was

extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and condensed *in vacuo*. The oily residue obtained was purified by recrystallization or column chromatography.

(i) **8a** (26.4 mg, 0.069 mmol), NBS (18.32 mg, 0.103 mmol), and DME-H_2O (5 ml) were used ; a crude product (28.9 mg) was crystallized from EtOAc to afford 13-bromo-2,3,4,6-tetramethoxy-12-oxohomomorphinandienone (**9a**) (12.8 mg, 38.9%), mp 188-190 °C. ^{1}H-Nmr δ : 2.87 (3H, s, NMe), 3.69 (3H, s, OMe), 3.81 (6H, s, OMe), 4.16 (3H, s, OMe), 5.68 (1H, s, C_{13}-H), 6.32, 6.36 (2H, each s, 2×dienone-H), 6.46 (2H, each s, C_1-H) ; ir : 1670, 1650, 1630 cm^{-1} ; high resolution ms *m/z* : calcd for $C_{22}H_{24}NO_6Br$: 477.0785 ; found : 477.0770 ; ms *m/z* : 477 (M^+), 479 (M^++2).

(ii) **8b** (15.3 mg, 0.047 mmol), NBS (13.0 mg, 0.073 mmol), and DME-H_2O (3 ml) were used ; column chromatography (1 g) of a crude product (16.9 mg) with EtOAc-hexane (1 : 1, v / v) gave 13-bromo-2,6-dimethoxy-12-oxohomomorphinandienone (**9b**) (9.5 mg, 49.9%) as an oil ; ^{1}H-nmr δ : 2.85 (3H, s, NMe), 3.68, 3.77 (6H, each s, 2×OMe), 5.04 (1H, s, C_{13}-H), 5.78, 6.52 (2H, each s, 2×dienone-H), 6.56 (1H, d, *J*=4 Hz, C_1-H), 6.80 (1H, dd, *J*=4, 8 Hz, C_3-H), 7.36 (1H, d, *J*=8 Hz, C_4-H) ; ir : 1670, 1650, 1630 cm^{-1} ; high resolution ms *m/z* : calcd for $C_{20}H_{20}NO_4Br$: 417.0574 ; found : 417.0568 ; ms *m/z* : 417 (M^+), 419 (M^++2).

Reaction of Enamines (**8a**) with NBS in the Presence of MeOH : (i) A solution of NBS (21.9 mg, 0.123 mmol) in a mixture of MeOH (1 ml) and DME (2 ml) was added dropwise to a stirred, ice-cooled solution of **8a** (30.2 mg, 0.079 mmol) in DME (4 ml). Work-up of the reaction mixture as usual (extraction with CH_2Cl_2) gave an oily residue (40.5 mg), which was purified by column chromatography (4 g) with EtOAc-hexane (1 : 1 ~ 2 : 1, v / v) to afford the α-bromo amide (**9a**) (16.0 mg, 42.4%).

(ii) A mixture of **8a** (33.9 mg, 0.089 mmol) and NBS (24.6 mg, 0.138 mmol) in MeOH (3 ml) was stirred at room temperature for 14 h. The work-up similar to that described above gave an oil (33.5 mg), whose column chromatography (1 g) with EtOAc-hexane (2 : 1, v / v) afforded the α-bromo amide (**9a**) (20.8 mg, 49.2%).

Reduction of α-Bromo Amides (**9a**,**b**) with $NaBH_4$: To a stirred, ice-water cooled solution of α-bromo amide (**9**) in MeOH was added $NaBH_4$ in one portion, and the whole was stirred at room temperature. Concentrated aqueous NH_4OH was added to the reaction mixture and the product was taken up in $CHCl_3$. The $CHCl_3$ extract was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The oily residue was subjected to column chromatography.

(i) **9a** (17.8 mg, 0.037 mmol), $NaBH_4$ (7 mg, 0.019 mmol), and MeOH (1 ml) were used ; column chromatography (1 g) of a crude product (15.3 mg) with EtOAc-hexane (1 : 1, v / v) and EtOAc afforded 13-bromo-2,3,4,6-tetramethoxy-12-oxohomomorphinandien-7-ol (**10a**) (7.6 mg, 42.6%) as an oil ; ^{1}H-nmr δ : 2.84 (3H, s, NMe), 3.64, 3.79, 3.80, 4.06 (12H, each s, 4×OMe), 4.18-4.32, 4.56-4.78 [1H, each m, C_7-H (3:2)], 5.25, 5.28 [1H, each s, C_{13}-H (3:2)], 5.59 (1H, s, C_5-H), 5.98 (1H, d, *J*=4 Hz, C_8-H), 6.27 (1H, s, C_1-H); ir : 3600-3400, 1670, 1660 cm^{-1} ; ms *m/z* : 479 (M^+), 481 (M^++2).

(ii) **9b** (10.8 mg, 0.026 mmol), $NaBH_4$ (11.4 mg, 0.301mmol), and MeOH (1 ml) were used ; 13-bromo-2,6-dimethoxy-12-oxohomomorphinandien-7-ol (**10b**) (12.1 mg, quantitative) was obtained as an oil, whose analytical tlc showed a single spot. 60 MHz-^{1}H-Nmr δ : 2.80 (3H, s, NMe), 3.58, 3.70 (6H, each s, 2×OMe), 4.40-4.80 (1H, m, C_7-H), 4.70 (1H, s, C_{13}-H), 4.90 (1H, s, C_5-H), 6.03 (1H, d *J*=2.5 Hz, C_8-H), 6.63-6.93 (2H, m, C_3- and C_4-H) ; ir : 3600-3300, 1670, 1660, 1615 cm^{-1} ; ms *m/z* : 419 (M^+), 421 (M^++2).

Reduction of Homomorphinandienones (**1a**,**b**) with $NaBH_4$: To a stirred, ice-water cooled solution of homomorphinandienone (**1**) in MeOH was added $NaBH_4$ in one portion, and the mixture was stirred at room temperature. Concentrated aqueous NH_4OH was added to the reaction mixture and the product was taken up in $CHCl_3$. The $CHCl_3$ extract was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The oily residue was subjected to column chromatography.

(i) **1a** (38.4 mg, 0.100 mmol), $NaBH_4$ (17 mg, 0.45 mmol), and MeOH (1 ml) were used ; column chromatography (0.8 g) of a crude product (35.0 mg) with $CHCl_3$-MeOH (30 : 1 ~ 10 : 1, v / v) afforded 2,3,4,6-tetramethoxyhomomorphinandien-7-ol (**11a**) (34.7 mg, 89.9%) as an oil ; ^{1}H-nmr δ : 2.38, 2.42 [3H, s, NMe (1:1.7)], 3.56, 3.79, 3.80, 3.96 (12H, each s, 4×OMe), 4.54, 4.61 (1H, each d, *J*=5 Hz and *J*=3 Hz, C_7-H (1:1.7)], 5.70, 5.74 [1H, each s, C_5-H, (1:1)], 5.74, 5.83 [1H, each

d, *J*=4 Hz, C_8-H (1.7:1)], 6.28 (1H, s, C_1-H); ir : 3600-3300, 1650 cm^{-1} ; high resolution ms *m/z* : calcd for $C_{22}H_{29}NO_5$: 387.2044 ; found : 387.2038 ; ms *m/z* : 387 (M^+).

(ii) **9b** (50.0 mg, 0.154 mmol), $NaBH_4$ (25.0 mg, 0.765 mmol), and MeOH (2.5 ml) were used ; column chromatography (1 g) of a crude product (75.2 mg) with $CHCl_3$-MeOH (30 : 1 ~ 10 : 1, v / v) afforded an oil, which was crystallized from Et_2O-hexane to give 2,6-dimethoxyhomomorphinandien-7-ol (**11b**) (38.6 mg, 76.7%), mp 158-160 °C. Analytical sample was obtained by recrystallization from Et_2O-hexane, mp 166-168 °C. Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37 ; H, 7.70 ; N, 4.28. Found : C, 73.45 ; H, 7.50 ; N, 4.27. ^{1}H-Nmr δ : 2.34, 2.38 [3H, s, NMe (3:2)], 3.56, 3.58 [3H, s, OMe, (3:2)], 3.76 (3H, s, OMe), 4.52-4.64 (1H, m, C_7-H), 5.02 (1H, d, *J*=4 Hz, C_5-H), 5.75, 5.85 (1H, each d, *J*=3 Hz and *J*=5 Hz, C_8-H (2:3)], 6.49 (1H, d, *J*=3 Hz, C_1-H), 6.74 (1H, dd, *J*=3, 10 Hz, C_3-H), 7.27 (1H, d, *J*=10 Hz, C_4-H) ; ir : 3590, 1660, 1610 cm^{-1} ; ms *m/z* : 327 (M^+).

Oxidation of Homomorphinandienol (**11a**) with MnO_2 : A suspension of the alcohol (**11a**) (24.2 mg, 0.0625 mmol) and active MnO_2 (48.9 mg, 0.562 mmol) in $CHCl_3$ (1 ml) was stirred at room temperature for 23 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give an oily residue (21.7 mg). Purification by column chromatography (1 g) with $CHCl_3$-MeOH (20 : 1, v / v) afforded *O*-methylandrocymbine (**1a**) (11.8 mg, 49.0%).

Reduction of 13-Bromohomomorphinandienol (**10b**) with Aluminum Hydride : To a stirred, ice cooled solution of the alcohol (**10b**) (12.1 mg) in THF (1 ml) was added slowly a 0.73M solution of AlH_3 [prepared from $LiAlH_4$ (3.20 g) and conc. H_2SO_4 (1.1 ml) in THF (60 ml)] in THF (0.1 ml). After stirring for 1 h under cooling, another THF solution of AlH_3 (0.1 ml) was added and the mixture was stirred for further 30 min. A mixture of THF and H_2O (1 ml, 1:1) and 0.83 mM aqueous NaOH solution (5 ml) was succesively added to the reaction mixture. The product was taken up in CH_2Cl_2. The CH_2Cl_2 extract was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, an oily residue (9.8 mg) was purified by preparative tlc (developing solvent ; $CHCl_3$: MeOH = 10:1) to afford the amine (**11b**) (5.8 mg, 49.6%), whose spectral data were identical with those of the dienol obtained by reduction of **1b** with $NaBH_4$.

Reaction of *O*-Methylandrocymbine (**1a**) with 1,2-Ethanedithiol in the Presence of *p*-TsOH : 1,2-Ethanedithiol (0.01 ml) and a catalytic amount of *p*-TsOH were added to a stirred, ice-cooled solution of *O*-methylandrocymbine (**1a**) (40.0 mg, 0.103 mmol) in AcOH (4 ml), and the whole was stirred at room temperature for 2 h. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 extract was successively washed with H_2O, 5% aqueous NaOH, and H_2O, and dried over anhydrous Na_2SO_4. Removal of CH_2Cl_2 under reduced pressure gave an oily residue (47.7 mg), which was subjected to column chromatography (4.77 g) with $CHCl_3$-MeOH (30 : 1, v / v) to afford 7,7-ethylenedithio-5,6-dihydro-2,3,4-trimethoxy-6-oxohomomorphinandiene (**18**) (21.0 mg, 45%), mp 135-138 °C (ether). ^{1}H-Nmr δ : 2.37 (3H, s, NMe), 3.05, 3.65 (1H, each d, *J*=12 Hz, C_5-H), 3.78, 3.95 (6H, each s, 2×OMe), 5.70 (1H, s, C_8-H), 6.23 (1H, s, C_1-H) ; ir : 1720 cm^{-1} ; high resolution ms *m/z* : calcd for $C_{23}H_{29}NO_4S_2$: 447.1536 ; found : 447.1542 ; ms *m/z* : 447 (M^+).

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