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# Hydrogenolysis of the cyclopropyl group into an isopropyl group in the presence of a platinum catalyst and hydrobromic acid

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ABSTRACT

Reduction of cyclopropylmethylamines proceeded under mild reaction conditions in the presence of platinum (IV) oxide catalyst and hydrobromic acid at rt, providing isobutylamines and no linear butylamines. The ring cleavage reaction was widely applicable to cyclopropane rings in various compounds such as *N*-cyclopropylalkyl, *O*-cyclopropylalkyl, and *C*-cyclopropylalkyl derivatives. Although unactivated cyclopropane rings were also cleaved, the cyclobutane ring was tolerated under the same reaction conditions.



## 1. Introduction

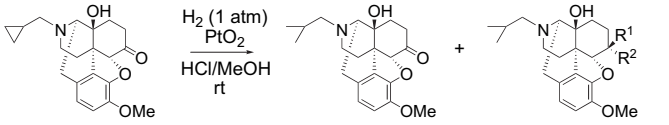
The smallest carbocycle, the cyclopropane ring, is so highly strained that hydrogenolysis of cyclopropane ring can proceed in the presence of a transition metal catalyst, such as nickel, rhodium, palladium, iridium, and platinum, etc.[1] Catalytic hydrogenolysis of cyclopropane rings is applied in the total synthesis of natural products[2] or drug candidate research.[3,4] However, hydrogenolysis of unactivated cyclopropane rings generally requires harsh reaction conditions such as high pressure and/or high temperature, while cyclopropane rings activated by some conjugated substituent, such as an aromatic ring, acyl group, or vinyl group react more easily.[1a] We have recently reported that hydrogenolysis of the *N*-cyclopropylmethyl group in naltrexone methyl ether **1a** in the presence of platinum (IV) oxide and hydrobromic acid proceeded under mild reaction conditions ($H_2$ (1 atm), rt).[5] Although the cyclopropane ring in **1a** was not activated by any conjugated substituents, the cyclopropane ring was easily cleaved. Our hydrogenolysis conditions were widely applicable to various cyclopropane rings including unactivated ones. Herein, we describe the scope of the catalytic hydrogenolysis of cyclopropane rings under our reduction conditions.

## 2. Results and discussion

### 2.1. Hydrogenolysis of *N*-cyclopropylmethyl group in morphinan derivatives

Treatment of naltrexone methyl ether **1a** in the presence of platinum (IV) oxide and hydrochloric acid under hydrogen (1 atm) gave *N*-isobutyl derivative **2a** along with compounds **3a** and **4a** (Table 1). Although hydrochloric acid effectively facilitated the ring cleavage of the cyclopropyl group, the reduction of the keto group

**Table 1**
Hydrogenolysis of naltrexone methyl ether **1a** with various amounts of platinum (IV) oxide




**1a** → **2a** + **3a**: $R^1$=H, $R^2$=OH; **4a**: $R^1$=OH, $R^2$=H

| Entry | $PtO_2$ (equiv) | Reaction Time | Yield (%) | | | |
|---|---|---|---|---|---|---|
| | | | **2a** | **3a** | **4a** | Recovery of **1a** |
| 1 | 0.1 | 5 days | 32 | 11 | 12 | 46 |
| 2 | 0.3 | 37 h | 52 | 14 | ND[a] | 12 |
| 3 | 0.8 | 20 h | 48 | 13 | 20 | ND[a] |

[a] Not detected.

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occurred concomitantly. To achieve chemoselective opening of the cyclopropane ring, we attempted the reduction of compound **1a** in the presence of various amounts of platinum (IV) oxide. When 0.1 equiv of the catalyst was used, the reaction rate was very slow and a large amount of the starting material **1a** was recovered (Table 1, entry 1). While a three-fold increase in the amount of the catalyst to 0.3 equiv accelerated the reaction rate (entry 2), a further increase to 0.8 equiv of the catalyst decreased the chemoselectivity (entry 3). Therefore, we chose to use 0.3 equiv of the catalyst for further investigations. Our efforts to substitute palladium on carbon as a catalyst instead of platinum (IV) oxide resulted in the recovery of the compound **1a**.

We next examined the effect of various acids using 0.3 equiv of platinum (IV) oxide (Table 2). In the presence of acetic acid or trifluoroacetic acid (TFA), the reduction proceeded nonselectively (Table 2, entries 3 and 4). Perchloric acid rather improved the chemoselectivity of the reduction in comparison to acetic acid or TFA, but the yield of objective compound **2a** was low (entry 7). On the other hand, (±)-camphorsulfonic acid (CSA) or hydroiodic acid mainly resulted in recovery of starting material **1a** (entries 5 and 11). In the case of methanesulfonic acid, complex mixture products were obtained and no objective product **2a** was detected (entry 6). In the absence of acid, reduction of the keto group only proceeded and cleavage of the cyclopropane ring was not observed (entry 12). Among the investigated acids, hydrobromic acid gave compound **2a** predominantly (entries 8 and 9), with the concentration of hydrobromic acid having hardly any influence on the chemoselectivity. In contrast, variations in the concentration of hydrochloric acid had a notable effect on chemoselectivity (entries 1 and 2), suggesting that an optimal acid would be hydrobromic acid. The reaction at 50 °C in the presence of hydrobromic acid gave the objective product **2a** in 54% yield along with 40% recovery of the compound **1a** (entry 10). These results suggest that the acidity[6] would play an important role in both facilitation of the ring opening reaction and the chemoselectivity. Although among the examined acids hydroiodic acid is the strongest acid,[6] the reaction with hydroiodic acid never proceeded (entry 11). Hydroiodic acid itself and/or small amount of iodine included in the acid might function as a catalyst poison.[7] As expected, cleavage of the cyclopropane ring occurred at the less hindered bond to afford the *N*-isobutyl derivative **2a**, and no detection of the linear butyl derivative. Additionally, a strong acid may promote intramolecular hemiacetal formation in compound **1a** to afford hemiacetal **7** (Fig. 1),[8] resulting in the protection of the ketone moiety from reduction.

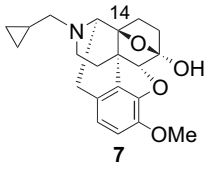
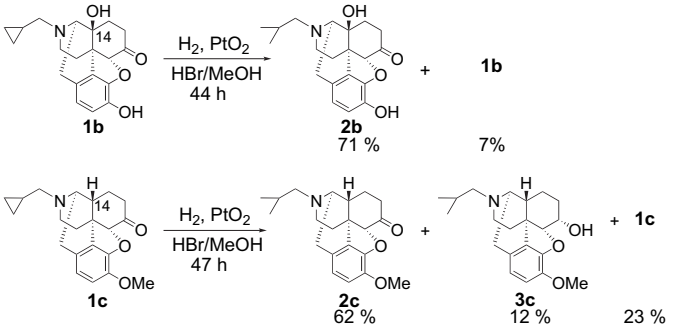


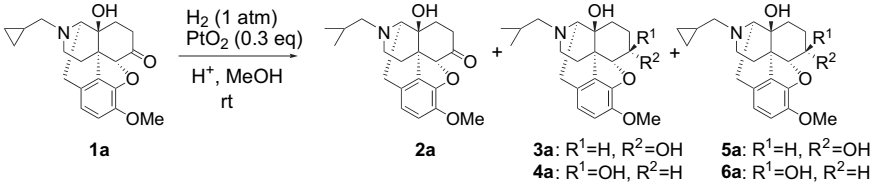

**Figure 1.** Structure of hemiacetal **7**.

To confirm the participation of the 14-hydroxyl group in formation of the hemiacetal, we attempted the reduction of naltrexone (**1b**), having a 14-hydroxyl group, and *N*-cyclopropylmethylnorhydrocodone (**1c**),[9] lacking the 14-hydroxyl group. Under the same conditions, the reactions afforded the corresponding products **2b** (71%) and **2c** (62%) and **3c** (12%) (Scheme 1). These results support the idea that intramolecular hemiacetal formation would participate in protecting the ketone moiety from reduction.




**Scheme 1.** Hydrogenolysis of *N*-cyclopropylmethyl morphinan derivatives **1b** and **1c**.

**Table 2**
Hydrogenolysis of naltrexone methyl ether **1a** catalyzed by platinum (IV) oxide in the presence of various acids




| Entry | Acid[a] | Reaction Time (h) | Yield (%) | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | **2a** | **3a** | **4a** | **5a** | **6a** | Recovery of **1a** |
| 1 | 1 M HCl | 20 | 62 | 27 | 11 | ND[e] | ND[e] | ND[e] |
| 2 | 37% HCl | 37 | 52 | 12 | ND[e] | ND[e] | ND[e] | 12 |
| 3 | AcOH | 48 | 4 | 6 | ND[e] | 70 | 12 | 8 |
| 4 | TFA[c] | 24 | 18 | 24 | 12 | 4 | 14 | 15 |
| 5 | (±)-CSA[d] | 37 | 14 | ND[e] | ND[e] | ND[e] | ND[e] | 36 |
| 6 | $MeSO_3H$ | 34 | ND[e] | 9 | 18 | ND[e] | 18 | 2 |
| 7 | 70% $HClO_4$[c] | 14 | 20 | 33 | 47 | ND[e] | ND[e] | ND[e] |
| 8 | 1 M HBr | 37 | 61 | ND[e] | ND[e] | ND[e] | ND[e] | ND[e] |
| 9 | 48% HBr | 37 | 76 | 2 | ND[e] | ND[e] | ND[e] | ND[e] |
| 10[b] | 48% HBr | 36 | 54 | ND[e] | ND[e] | ND[e] | ND[e] | 40 |
| 11 | 57% HI | 39 | ND[e] | ND[e] | ND[e] | ND[e] | ND[e] | 100 |
| 12 | None | 56 | ND[e] | ND[e] | ND[e] | 77 | 7 | ND[e] |

[a] A ratio of acid to MeOH is 1:1.2.
[b] The reaction was carried out at 50 °C.
[c] Only acid was used as a solvent.
[d] 1 equiv of (±)-CSA was used.
[e] Not detected.

### 2.2. Hydrogenolysis of the *N*-cyclopropylalkyl group

We next attempted hydrogenolysis of general cyclopropylalkylamines. In the first attempt using cyclopropylmethylamine **8** (Fig. 2), not only cleavage of the cyclopropane ring but also reduction of the naphthyl group proceeded. Therefore, compounds **9** having the dimethoxyphenyl group were used to prevent the reduction of the aromatic ring (Table 3). After 12 h of reaction, cyclopropylmethylamine **9a** was converted to isobutylamine **10a** in 59% yield with recovery of **9a** (19%) (Table 3, entry 1), while prolongation of the reaction time to 24 h increased the yield of isobutylamine **10a** (entry 2).

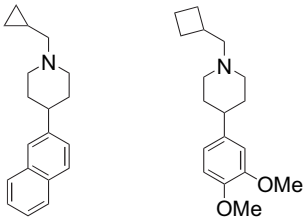
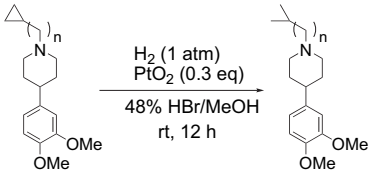



**Figure 2.** Structures of cyclopropylmethylamine **8** and cyclobutylmethylamine **11**.

**Table 3**
Hydrogenolysis of *N*-cyclopropylalkylamines **9**




| Entry | 9 | *n* | Product | Yield (%) |
|---|---|---|---|---|
| 1 | **a** | 1 | **10a** | 59[a] |
| 2[b] | **a** | 1 | **10a** | 65 |
| 3 | **b** | 2 | **10b** | 94 |
| 4 | **c** | 3 | **10c** | 76 |

[a] Cyclopropylmethylamine **9a** was also recovered in 19% yield.
[b] The reaction was carried out for 24 h.

We first hypothesized that the σ-electrons between the nitrogen and the carbon of the cyclopropylmethyl group would be donated to the protonated nitrogen, a process that is facilitated by the extreme stability of the cyclopropylcarbinyl cation[10,11] which may promote the activation of the cyclopropane ring (Fig. 3). Therefore, we presumed that this hydrogenolysis of the cyclopropane ring would be applicable to only the cyclopropylmethylamines. However, the reduction of both cyclopropylethylamine **9b** and cyclopropylpropylamine **9c** gave the respective branched alkylamines **10b** and **10c** in good to excellent yield (Table 3, entries 3 and 4) and no linear alkylamines were detected in all cases. These unexpected results may suggest the direct activation of the cyclopropane ring by hydrobromic acid. The attempted ring cleavage of cyclobutylmethylamine **11** (Fig. 2) resulted in recovery of **11**.

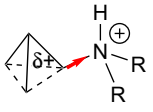
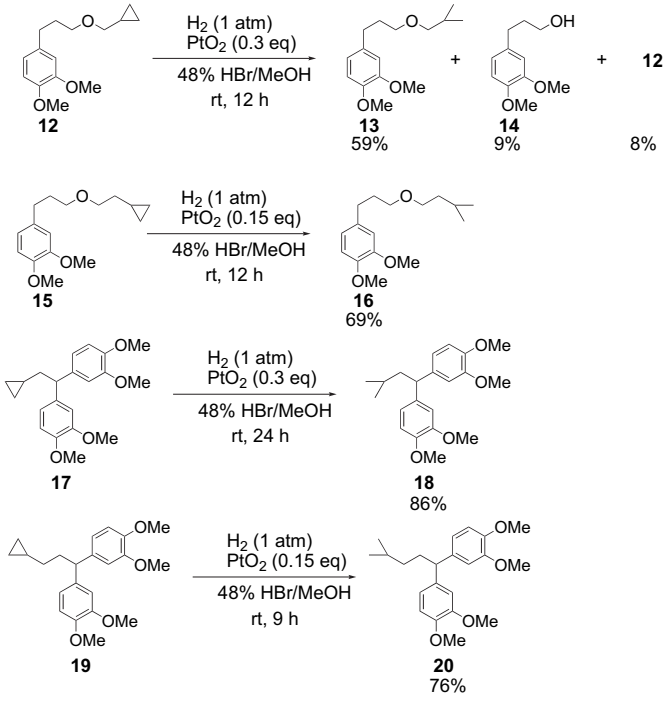



**Figure 3.** Diagram of the activated cyclopropane ring. The σ-electrons between the nitrogen and carbon in the cyclopropylmethyl group may be released to the protonated nitrogen (red arrow) because of the extremely stable cyclopropylcarbinyl cation.

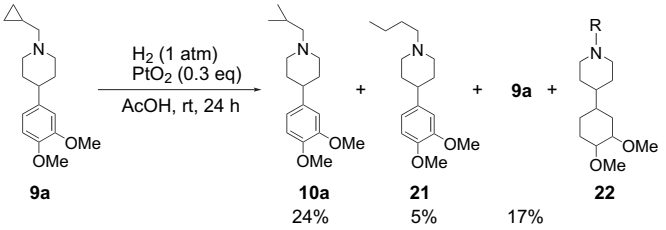
### 2.3. Hydrogenolysis of the *O*- or *C*-cyclopropylalkyl group

To investigate the scope of this reaction, cleavage of the cyclopropane ring in *O*-cyclopropylalkyl and *C*-cyclopropylalkyl derivatives **12**, **15**, and **17**, **19** was attempted to afford the corresponding ring opening products **13**, **16**, and **18**, **20** in moderate to good yields, respectively (Scheme 2). Neither linear *O*-alkyl nor *C*-alkyl derivatives were detected. In the case of *O*-cyclopropylmethyl derivative **12**, alcohol **14** was obtained as a by-product.[12] Why alcohol **14** was obtained is not clear, but the stability of the cyclopropylcarbinyl cation[13] may affect the preparation of alcohol **14**. The examples in Scheme 2 indicate that the reaction conditions would be widely applicable to various compounds possessing a cyclopropane ring.




**Scheme 2.** Hydrogenolysis of *O*-cyclopropylalkyl and *C*-cyclopropylalkyl derivatives **12**, **15**, **17**, and **19**.

Although hydrogenolysis of the cyclopropane ring has been frequently carried out using platinum (IV) oxide in the presence of acetic acid,[2–4] these reaction conditions in the presence of acetic acid were not optimal in our investigation using naltrexone methyl ether **1a** (Table 2). Therefore, we repeated the attempted hydrogenolysis of cyclopropane ring in cyclopropylmethylamine **9a** in the presence of acetic acid instead of hydrobromic acid (Scheme 3). The reduction of cyclopropylmethylamine **9a** gave isobutylamine **10a** (24%) along with linear butylamine **21** (5%) and starting material **9a** (17%). Moreover, reduction of the benzene ring was also observed.[14] This outcome indicates that the hydrogenolysis reaction conditions




**Scheme 3.** Hydrogenolysis of cyclopropylmethylamine **9a** in the presence of acetic acid instead of hydrobromic acid. The yield of **22** was not determined. For details, see the Experimental section and Ref. 14.

in the presence of hydrobromic acid were more chemo- and regioselective. Of the reported methods for this transformation, the reaction protocol that we present in this study for cleavage of the cyclopropane ring appears to be the optimal conditions.

## 3. Conclusion

We found that reduction of cyclopropylmethylamines proceeded under mild reaction conditions in the presence of platinum (IV) oxide catalyst and hydrobromic acid at rt to provide isobutylamines without the production of linear butylamines. The ring cleavage reaction was widely applicable to cyclopropane rings in various compounds such as *N*-cyclopropylalkyl, *O*-cyclopropylalkyl, and *C*-cyclopropylalkyl derivatives. Unactivated cyclopropane rings were readily cleaved, and the cyclobutane ring was tolerated under the same reaction conditions. Hydrogenolysis of cyclopropane rings has been frequently carried out using platinum (IV) oxide in the presence of acetic acid, but our attempted reduction of cyclopropylmethylamine in the presence of acetic acid instead of hydrobromic acid gave isobutylamine along with linear butylamine. Moreover, reduction of the benzene ring occurred concomitantly. Our reaction protocol for the chemo- and regioselective cleavage of various cyclopropane rings, including unactivated rings, appears to be one of the best conditions among all the methods reported to date.

## 4. Experimental section

### 4.1. General

Melting points were measured on a Yazawa BY–10 melting point apparatus. Infrared (IR) spectra were measured on a JASCO FT/IR–460Plus. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian Mercury–300 (300 MHz) spectrometer. Chemical shifts were reported as $\delta$ values (ppm) related to tetramethylsilane (TMS). Mass spectra (MS) were measured on a JMS–AX505HA or JMS–700 M Station instruments by applying a fast atom bombardment (FAB), electron ionization (EI), or electron splay ionization (ESI) method. The progress of the reaction was determined on Merck Silica Gel Art. 5715. Column chromatographies were carried out using Kanto Silica Gel 60 N or Fuji Silysia DM2035 (The surface of the silica gel was modified by amino group). Preparative TLCs were performed using Merck Silica Gel Art. 5744 or Fuji Silysia NH TLC plate.

### 4.2. General procedure of catalytic hydrogenolysis

To the solution of compound **9a** (51 mg, 0.19 mmol) in 48% HBr (0.33 mL) and MeOH (0.4 mL) was added $PtO_2$ (15 mg, 0.054 mmol) and stirred at rt for 24 h under $H_2$. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. To the obtained residue was added 2 M NaOH solution and extracted with AcOEt. The combined organic layers were washed with brine and dried over anhydrous $Na_2SO_4$. After removing the solvent under reduced pressure, the residue was purified by preparative TLC ($CHCl_3$/MeOH=15/1) to give compound **10a** (33 mg, 65%) as a colorless oil.

### 4.3. 4,5α-Epoxy-14β-hydroxy-17-isobutyl-3-methoxymorphinan-6-one (2a)

A colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.87 (d, *J*=6.7 Hz, 3H), 0.88 (d, *J*=6.7 Hz, 3H), 1.44–1.63 (m, 2H), 1.65–1.80 (m, 1H), 1.80 (ddd, *J*=2.9, 4.9, 13.4 Hz, 1H), 2.02–2.40 (m, 5H), 2.42–2.60 (m, 2H), 2.84 (d, *J*=5.9 Hz, 1H), 2.94 (dt, *J*=5.1, 14.4 Hz, 1H), 3.04 (d, *J*=18.5 Hz, 1H), 3.83 (s, 3H), 4.60 (s, 1H), 5.13 (br s, 1H), 6.56 (d, *J*=8.2 Hz, 1H), 6.63 (d, *J*=8.2 Hz, 1H). IR (neat, $cm^{-1}$): 3380, 3017, 2955, 2833, 1729, 1504, 1440, 1282, 1257. HRMS (ESI): $[M+Na]^+$ Calcd for $C_{21}H_{27}NNaO_4$: 380.1838. Found: 380.1820.

### 4.4. 4,5α-Epoxy-17-isobutyl-3-methoxymorphinan-6α,14β-diol (3a)

A colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.91 (d, *J*=6.5 Hz, 3H), 0.92 (d, *J*=6.3 Hz, 3H), 1.10–1.26 (m, 1H), 1.40–1.86 (m, 5H), 2.10–2.31 (m, 4H), 2.44–2.52 (m, 1H), 2.63 (dd, *J*=6.3, 18.5 Hz, 1H), 2.82 (d, *J*=6.3 Hz, 1H), 3.10 (d, *J*=18.5 Hz, 1H), 3.86 (s, 3H), 4.13–4.24 (m, 1H), 4.64 (d, *J*=4.7 Hz, 1H), 5.02 (br s, 1H), 6.60 (d, *J*=8.2 Hz, 1H), 6.72 (d, *J*=8.2 Hz, 1H). (A proton of OH group was not observed.) IR (neat, $cm^{-1}$): 3397, 2953, 2833, 1634, 1606, 1504, 1453, 1381, 1336, 1282. HRMS (ESI): $[M+Na]^+$ Calcd for $C_{21}H_{29}NNaO_4$: 382.1994. Found: 382.2002.

### 4.5. 4,5α-Epoxy-17-isobutyl-3-methoxymorphinan-6β,14β-diol (4a)

A colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.90 (d, *J*=6.4 Hz, 3H), 0.91 (d, *J*=6.4 Hz, 3H), 1.29–1.40 (m, 1H), 1.44–1.84 (m, 4H), 1.86–2.01 (m, 1H), 2.05–2.32 (m, 4H), 2.42–2.50 (m, 1H), 2.62 (dd, *J*=5.9, 18.6 Hz, 1H), 2.83 (d, *J*=5.9 Hz, 1H), 3.08 (d, *J*=18.3 Hz, 1H), 3.54–3.63 (m, 1H), 3.86 (s, 3H), 4.48 (d, *J*=5.6 Hz, 1H), 6.61 (d, *J*=8.2 Hz, 1H), 6.71 (d, *J*=8.2 Hz, 1H) (Two protons of OH groups were not observed.) IR (neat, $cm^{-1}$): 3492, 2963, 2923, 2822, 1637, 1510, 1439, 1286. HRMS (ESI): $[M+Na]^+$ Calcd for $C_{21}H_{29}NNaO_4$: 382.1994. Found: 382.1989.

### 4.6. 17-Cyclopropylmethyl-4,5α-epoxy-3-methoxymorphinan-6α,14β-diol (5a)

A colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.07–0.17 (m, 2H), 0.47–0.59 (m, 2H), 0.77–0.92 (m, 1H), 1.10–1.27 (m, 1H), 1.41–1.71 (m, 3H), 1.73–1.86 (m, 1H), 2.15–2.30 (m, 3H), 2.33 (dd, *J*=6.3, 12.8 Hz, 1H), 2.36 (dd, *J*=6.5, 12.7 Hz, 1H), 2.58–2.70 (m, 1H), 2.60 (dd, *J*=6.6, 18.6 Hz, 1H), 3.04 (d, *J*=18.6 Hz, 1H), 3.08 (d, *J*=6.6 Hz, 1H), 3.86 (s, 3H), 4.14–4.27 (m, 1H), 4.65 (d, *J*=4.5 Hz, 1H), 5.02 (br s, 1H), 6.59 (d, *J*=8.2 Hz, 1H), 6.72 (d, *J*=8.2 Hz, 1H). IR (neat, $cm^{-1}$): 3397, 2938, 1504, 1452, 1281. HRMS (ESI): $[M+Na]^+$ Calcd for $C_{21}H_{27}NNaO_4$: 380.1838. Found: 380.1847.

### 4.7. 17-Cyclopropylmethyl-4,5α-epoxy-3-methoxymorphinan-6β,14β-diol (6a)

A colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.07–0.17 (m, 2H), 0.47–0.59 (m, 2H), 0.76–0.91 (m, 1H), 1.30–1.43 (m, 1H), 1.45–1.70 (m, 3H), 1.87–2.02 (m, 1H), 2.07–2.30 (m, 2H), 2.36 (d, *J*=6.5 Hz, 2H), 2.59–2.69(m, 1H), 2.61 (dd, *J*=5.9, 18.5 Hz, 1H), 2.94 (br s, 1H), 3.04 (d, *J*=18.6 Hz, 1H), 3.10 (d, *J*=5.9 Hz, 1H), 3.54–3.66 (m, 1H), 3.86 (s, 3H), 4.49 (d, *J*=5.6 Hz, 1H), 5.17 (br s, 1H), 6.61 (d, *J*=8.2 Hz, 1H), 6.71 (d, *J*=8.2 Hz, 1H). IR (neat, $cm^{-1}$): 3392, 2934, 1502, 1439, 1280, 1257. HRMS (ESI): $[M+H]^+$ Calcd for $C_{21}H_{28}NO_4$: 358.2018. Found: 358.2004.

### 4.8. 4,5α-Epoxy-3,14β-dihydroxy-17-isobutylmorphinan-6-one (2b)

A white crystal. Mp: 187–190 °C. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.93 (d, *J*=6.6 Hz, 3H), 0.95 (d, *J*=6.7 Hz, 3H), 1.52–1.70 (m, 2H), 1.71–1.84 (m, 1H), 1.87 (ddd, *J*=3.1, 4.9, 13.4 Hz, 1H), 2.11–2.25 (m, 2H), 2.26–2.64 (m, 6H), 2.91 (d, *J*=5.9 Hz, 1H), 3.03 (dt, *J*=5.1, 14.5 Hz, 1H), 3.09 (d, *J*=18.5 Hz, 1H), 4.70 (s, 1H), 6.59 (d, *J*=8.1 Hz, 1H), 6.71 (d, *J*=8.2 Hz, 1H). (A proton of OH group was not observed.) IR (KBr, $cm^{-1}$): 3198, 2957, 1721, 1620, 1462, 1243. HRMS (ESI): $[M+Na]^+$ Calcd for $C_{20}H_{25}NNaO_4$: 366.1681. Found: 366.1675.

### 4.9. 4,5α-Epoxy-17-isobutyl-3-methoxymorphinan-6-one (2c)

A colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.84 (d, $J$=6.3 Hz, 3H), 0.85 (d, $J$=6.4 Hz, 3H), 1.09–1.25 (m, 1H), 1.58–1.80 (m, 3H), 1.96 (dt, $J$=4.6, 11.9 Hz, 1H), 2.02–2.38 (m, 6H), 2.44–2.56 (m, 2H), 2.87 (d, $J$=18.3 Hz, 1H), 3.08 (dd, $J$=2.8, 5.3 Hz, 1H), 3.83 (s, 3H), 4.56 (s, 1H), 6.55 (d, $J$=8.1 Hz, 1H), 6.62 (d, $J$=8.2 Hz, 1H). IR (neat, $cm^{-1}$): 2950, 1728, 1503, 1439, 1274, 1258. HRMS (ESI): $[M+Na]^+$ Calcd for $C_{21}H_{27}NNaO_3$: 364.1889. Found: 364.1888.

### 4.10. 4,5α-Epoxy-17-isobutyl-3-methoxymorphinan-6α-ol (3c)

A colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.90 (d, $J$=6.6 Hz, 3H), 0.91 (d, $J$=6.6 Hz, 3H), 1.00–1.18 (m, 1H), 1.36–1.59 (m, 3H), 1.60–1.79 (m, 2H), 1.87 (dt, $J$=4.2, 12.0 Hz, 1H), 2.07 (br s, 1H), 2.14–2.30 (m, 4H), 2.30–2.45 (m, 1H), 2.52 (dd, $J$=3.7, 11.6 Hz, 1H), 2.91 (d, $J$=18.3 Hz, 1H), 3.06 (br d, $J$=2.7 Hz, 1H), 3.87 (s, 3H), 3.96–4.07 (m, 1H), 4.59 (d, $J$=5.1 Hz, 1H), 6.61 (d, $J$=7.8 Hz, 1H), 6.71 (d, $J$=8.4 Hz, 1H). IR (neat, $cm^{-1}$): 3427, 2948, 1636, 1503, 1450, 1278. HRMS (ESI): $[M+Na]^+$ Calcd for $C_{21}H_{29}NNaO_3$: 366.2045. Found: 366.2042.

### 4.11. 1-Isobutyl-4-(3,4-dimethoxyphenyl)piperidine (10a)

A colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.92 (d, $J$=6.6 Hz, 6H), 1.71–2.05 (m, 7H), 2.11 (d, $J$=7.2 Hz, 2H), 2.35–2.51 (m, 1H), 2.98 (br d, $J$=11.7 Hz, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 6.74–6.84 (m, 3H). IR (neat, $cm^{-1}$): 2950, 2869, 2833, 2802, 2773, 1606, 1590, 1516, 1465, 1417, 1380, 1338, 1260, 1158, 1142, 1118, 1095, 1031, 1004, 804. HRMS (EI): $[M]^+$ Calcd for $C_{17}H_{27}NO_2$: 277.2042. Found: 277.2051.

### 4.12. 1-Isopentyl-4-(3,4-dimethoxyphenyl)piperidine (10b)

A colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.92 (d, $J$=6.6 Hz, 6H), 1.38–1.69 (m, 3H), 1.73–1.95 (m, 4H), 1.97–2.18 (m, 2H), 2.28–2.58 (m, 3H), 3.11 (br d, $J$=11.1 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 6.73–6.85 (m, 3H). IR (neat, $cm^{-1}$): 2996, 2932, 2869, 2803, 2766, 1590, 1517, 1465, 1260, 1233, 1142, 1029. HRMS (EI): $[M]^+$ Calcd for $C_{18}H_{29}NO_2$: 291.2198. Found: 291.2205.

### 4.13. 4-(3,4-Dimethoxyphenyl)-1-(4-methylpentyl) piperidine (10c)

A colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.89 (d, $J$=6.6 Hz, 6H), 1.12–1.37 (m, 2H), 1.45–1.66 (m, 3H), 1.68–1.89 (m, 4H), 2.01 (dt, $J$=3.9, 11.1 Hz, 2H), 2.26–2.52 (m, 3H), 3.06 (br d, $J$=11.7 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 6.73–6.84 (m, 3H). IR (neat, $cm^{-1}$): 2934, 2869, 2801, 2763, 1590, 1517, 1466, 1417, 1374, 1261, 1142, 1031. HRMS (EI): $[M]^+$ Calcd for $C_{19}H_{31}NO_2$: 305.2355. Found: 305.2352.

### 4.14. 4-(3-Isobutoxypropyl)-1,2-dimethoxybenzene (13)

A colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.92 (d, $J$=6.9 Hz, 6H), 1.79–1.95 (m, 3H), 2.60–2.69 (m, 2H), 3.17 (d, $J$=6.6 Hz, 2H), 3.41 (t, $J$=6.5 Hz, 2H), 3.86 (s, 3H), 3.87 (s, 3H), 6.69–6.82 (m, 3H). IR (neat, $cm^{-1}$): 2952, 2854, 1516, 1466, 1261, 1237, 1156, 1141, 1114, 1032. HRMS (FAB): $[M]^+$ Calcd for $C_{15}H_{24}O_3$: 252.1725. Found: 252.1725.

### 4.15. 3-(3,4-Dimethoxyphenyl)propan-1-ol (14)

A colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.81–1.93 (m, 2H), 2.65 (t, $J$=7.7 Hz, 2H), 3.67 (t, $J$=6.5 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 6.68–6.82 (m, 3H) (A proton of OH group was not observed.) IR (neat, $cm^{-1}$): 3388, 2937, 1516, 1465, 1260, 1236, 1154, 1141, 1028. HRMS (FAB): $[M]^+$ Calcd for $C_{11}H_{16}O_3$: 196.1099. Found: 196.1103.

### 4.16. 4-(3-Isopentyloxypropyl)-1,2-dimethoxybenzene (16)

A colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.91 (d, $J$=6.6 Hz, 6H), 1.48 (q, $J$=6.9 Hz, 2H), 1.61–1.79 (m, 1H), 1.80–1.93 (m, 2H), 2.64 (t, $J$=7.7 Hz, 2H), 3.41 (t, $J$=6.3 Hz, 2H), 3.43 (t, $J$=6.9 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H) 6.67–6.83 (m, 3H). IR (neat, $cm^{-1}$): 2952, 2867, 1516, 1465, 1262, 1237, 1156, 1141, 1112, 1032. HRMS (FAB): $[M]^+$ Calcd for $C_{16}H_{26}O_3$: 266.1882. Found: 266.1877.

### 4.17. 4,4′-(3-Methylbutane-1,1-diyl)bis(1,2-dimethoxybenzene) (18)

A colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.92 (d, $J$=6.6 Hz, 6H), 1.38–1.55 (m, 1H), 1.85 (t, $J$=7.5 Hz, 2H), 3.71–3.95 (m, 1H), 3.83 (s, 6H), 3.84 (s, 6H), 6.73 (br s, 2H), 6.75–6.83 (m, 4H). IR (neat, $cm^{-1}$): 3000, 2953, 2867, 2834, 1604, 1590, 1514, 1464, 1415, 1260, 1144, 1029, 759. HRMS (EI): $[M]^+$ Calcd for $C_{21}H_{28}O_4$: 344.1988. Found: 344.2001.

### 4.18. 4,4′-(4-Methylpentane-1,1-diyl)bis(1,2-dimethoxybenzene) (20)

The reaction was carried out using 10-fold amount of MeOH compared to the general procedure because compound **19** did not dissolve in the general procedure solvent. A colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.87 (d, $J$=6.6 Hz, 6H), 1.10–1.21 (m, 2H), 1.47–1.67 (m, 1H), 1.89–2.40 (m, 2H), 3.68–3.80 (m, 1H), 3.84 (s, 6H), 3.85 (s, 6H), 6.69–6.83 (m, 6H). IR (neat, $cm^{-1}$): 2952, 1590, 1514, 1464, 1415, 1257, 1144, 1030. HRMS (FAB): $[M]^+$ Calcd for $C_{22}H_{30}O_4$: 358.2144. Found: 358.2142.

### 4.19. Hydrogenolysis of cyclopropylmethylamine 9a in the presence of AcOH

To the solution of cyclopropylmethylamine **9a** (50 mg, 0.18 mmol) in AcOH (0.7 mL) was added $PtO_2$ (16 mg) and stirred at rt under $H_2$. After removing catalyst by filtration, the filtrate was poured into 2 M NaOH solution and extracted with AcOEt. The combined organic layers were washed with brine and dried over anhydrous $Na_2SO_4$ followed by removing the solvent under reduced pressure to give crude product (49 mg). The residue was purified by preparative TLC ($CHCl_3$/MeOH/$NH_4OH$=50/1/0.1) to give isobutylamine **10a** (12.1 mg, 24%) and linear butylamine **21** (2.3 mg, 5%) along with recovery of **9a** (8.3 mg, 17%).

*4.19.1. 1-Butyl-4-(3,4-dimethoxyphenyl)piperidine (**21**).* A colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.93 (t, $J$=7.4 Hz, 3H), 1.22–1.41 (m, 2H), 1.46–1.59 (m, 2H), 1.75–1.87 (m, 4H), 1.94–2.10 (m, 2H), 2.32–2.52 (m, 3H), 3.07 (br d, $J$=11.4 Hz, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 6.72–6.86 (m, 3H). IR (neat, $cm^{-1}$): 2932, 2871, 2802, 2764, 1590, 1517, 1465, 1417, 1375, 1261, 1232, 1141, 1031. HRMS (ESI): $[M+H]^+$ Calcd for $C_{17}H_{28}NO_2$: 278.2120. Found: 278.2123.

### 4.20. Preparation of 1-(cyclopropylmethyl)-4-(3,4-dimethoxyphenyl)piperidine (9a)

*4.20.1. 1-Benzyl-4-(3,4-dimethoxyphenyl)-1,2,3,6-tetrahydropyridine (**23**).* Under Ar, to the solution of 4-bromoveratrole (0.1 mL, 0.7 mmol) in THF (0.7 mL) was added 1.63 M solution of *n*-BuLi in hexane (0.43 mL, 0.7 mmol) dropwise at −78 °C. After 1 h, to the mixture was added the solution of 1-benzyl-4-piperidone (0.12 mL, 0.6 mmol) in THF (0.6 mL) and stirred at the same temperature for 1 h, then stirred at rt for 2.5 h. The reaction mixture was poured into saturated $NaHCO_3$ solution and extracted with AcOEt. The combined organic layers were washed with distillated water and brine, and dried over anhydrous $Na_2SO_4$ followed by removing the solvent

under reduced pressure. The resulting residue was roughly purified by silica gel column chromatography ($CHCl_3$/MeOH=50/1–30/1) to give an oily yellow material (143 mg). The obtained material (143 mg) was dissolved in 85% phosphoric acid (5 mL) and stirred at 80 °C for 2 h. The reaction mixture was poured into 7 M ammonia and extracted with $CHCl_3$. The combined organic layers were washed with distillated water and dried over anhydrous $Na_2SO_4$ followed by removing the solvent under reduced pressure. The residue was purified by silica gel column chromatography (NH silica gel, hexane/AcOEt=50/1–30/1) to give the title compound **23** (81 mg, 41%) as a white powder. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.43–2.52 (m, 2H), 2.60–2.71 (m, 2H), 3.07–3.14 (m, 2H), 3.57 (s, 2H), 3.79 (s, 3H), 3.81 (s, 3H), 5.88–5.93 (m, 1H), 6.72–6.76 (m, 1H), 6.83–6.88 (m, 2H), 7.16–7.34 (m, 5H). IR (KBr, $cm^{-1}$): 1517, 1249, 1142, 1028. HRMS (ESI): $[M+H]^+$ Calcd for $C_{20}H_{24}NO_2$: 310.1807. Found: 310.1793.

*4.20.2. 1-Benzyl-4-(3,4-dimethoxyphenyl)piperidine (**24**).* To the solution of compound **23** (81 mg, 0.3 mmol) in MeOH (0.5 mL) and 10% HCl–MeOH (0.5 mL) was added 10% Pd/C (12 mg) and stirred at rt for 24 h under $H_2$. The catalyst was removed by filtration and the resulting filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (NH silica gel, hexane/AcOEt=3/1) to give the title compound **24** (48 mg, 58%) as a white amorphous solid. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.73–1.86 (m, 4H), 2.00–2.14 (m, 2H), 2.38–2.52 (m, 1H), 3.02 (br d, $J$=11.7 Hz, 2H), 3.56 (s, 2H), 3.85 (s, 3H), 3.87 (s, 3H), 6.74–6.84 (m, 3H), 7.22–7.40 (m, 5H). IR (KBr, $cm^{-1}$): 2931, 2754, 1519, 1451, 1255, 1231, 1137, 1028. HRMS (EI): $[M]^+$ Calcd for $C_{20}H_{25}NO_2$: 311.1885. Found: 311.1895.

*4.20.3. 2,2,2-Trichloroethyl 4-(3,4-dimethoxyphenyl)piperidine-1-carboxylate (**25**).* To the solution of compound **24** (662 mg, 2.1 mmol) in 1,1,2,2-tetrachloroethane (2 mL) were added $K_2CO_3$ (588 mg, 4.3 mmol) and 2,2,2-trichloroethyl chloroformate (0.6 mL, 4.4 mmol), and refluxed for 23 h under Ar. The reaction mixture was poured into 2 M HCl solution and extracted with $CHCl_3$. The combined organic layers were washed with distillated water and dried over anhydrous $Na_2SO_4$ followed by removing the solvent under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$) to give the title compound **25** (805 mg, 94%) as a yellow oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.66 (dq, $J$=4.1, 12.8 Hz, 2H), 1.88 (br d, $J$=12.9 Hz, 2H), 2.66 (tt, $J$=3.6, 12.0 Hz, 1H), 2.80–3.10 (m, 2H), 3.85 (s, 3H), 3.87 (s, 3H), 4.35 (br d, $J$=13.2 Hz, 2H), 4.78 (d, $J$=2.7 Hz, 2H), 6.70–6.86 (m, 3H). IR (neat, $cm^{-1}$): 2938, 1715, 1517, 1440, 1254, 1215. HRMS (ESI): $[M+Na]^+$ Calcd for $C_{16}H_{20}Cl_3NNaO_4$: 418.0356. Found: 418.0357.

*4.20.4. Cyclopropyl(4-(3,4-dimethoxyphenyl)piperidin-1-yl)methanone (**26**).* To the solution of compound **25** (951 mg, 2.4 mmol) in AcOH (9 mL) was added Zn powder (6.1 g, 92.6 mmol) and stirred at rt for 11 h under Ar. The Zn powder was removed by filtration and the resulting filtrate was poured into ammonia solution, and then extracted with $CHCl_3$/*i*-PrOH=2/1. The combined organic layers were washed with distillated water and brine, and dried over anhydrous $Na_2SO_4$ followed by removing the solvent under reduced pressure to give the crude product (530 mg) as a white powder. To the solution of the crude product (530 mg) in $CH_2Cl_2$ (5 mL) were added $Et_3N$ (1 mL, 7.2 mmol) and cyclopropanecarbonyl chloride (0.6 mL, 12 mmol) at 0 °C and stirred at rt for 17 h under Ar. The reaction mixture was poured into saturated $NaHCO_3$ solution and extracted with $CHCl_3$. The combined organic layers were washed with distillated water and dried over anhydrous $Na_2SO_4$ followed by removing the solvent under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=100/0–1/2) to give the title compound **26** (658 mg, 95%) as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.76 (br d, $J$=7.8 Hz, 2H), 0.99 (br s, 2H), 1.50–2.02 (m, 5H), 2.52–2.78 (m, 2H), 3.18 (br t, $J$=12.3 Hz, 1H), 3.85 (s, 3H), 3.87 (s, 3H), 4.34 (br d, $J$=12.6 Hz, 1H), 4.76 (br d, $J$=12.3 Hz, 1H), 6.64–6.86 (m, 3H). IR (neat, $cm^{-1}$): 3005, 2935, 2849, 1633, 1517, 1451, 1254, 1213. HRMS (FAB): $[M+H]^+$ Calcd for $C_{17}H_{24}NO_3$: 290.1756. Found: 290.1750.

*4.20.5. 1-(Cyclopropylmethyl)-4-(3,4-dimethoxyphenyl)piperidine (**9a**).* Under Ar, to the suspension of $LiAlH_4$ (3 g, 11 mmol) in THF (15 mL) was added the solution of compound **26** (528 mg, 1.8 mmol) in THF (5 mL) dropwise at 0 °C and stirred at rt for 2 h. To the reaction mixture was added saturated $Na_2SO_4$ solution dropwise at 0 °C for decomposition of the excess $LiAlH_4$ and then added anhydrous $Na_2SO_4$. The resulting insoluble materials were removed by filtration. After concentration of the filtrate, the residue was purified by silica gel column chromatography (NH silica gel, hexane/AcOEt=10/1–4/1) to give the title compound **9a** (311 mg, 62%) as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.09–0.17 (m, 2H), 0.49–0.58 (m, 2H), 0.85–1.00 (m, 1H), 1.83 (ddd, $J$=3.3, 6.0, 12.5 Hz, 4H), 1.98–2.15 (m, 2H), 2.30 (d, $J$=6.3 Hz, 2H), 2.36–2.54 (m, 1H), 3.21 (br d, $J$=11.7 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 6.74–6.84 (m, 3H). IR (neat, $cm^{-1}$): 2930, 2912, 1518, 1232, 1140, 1026. HRMS (ESI): $[M+H]^+$ Calcd for $C_{17}H_{26}NO_2$: 276.1962. Found: 276.1964.

## 4.21. Preparation of 1-(2-cyclopropylethyl)-4-(3,4-dimethoxyphenyl)piperidine (9b)

*4.21.1. 2-Cyclopropyl-1-(4-(3,4-dimethoxyphenyl)piperidin-1-yl)-ethanone (**27**).* To the solution of compound **25** (1.6 g, 4.1 mmol) in AcOH (35 mL) was added Zn powder (18 g, 275 mmol) and stirred at rt for 17 h under Ar. The Zn powder was removed by filtration and the resulting filtrate was poured into ammonia solution, and then extracted with $CHCl_3$/*i*-PrOH=2/1. The combined organic layers were washed with distillated water and brine, and dried over anhydrous $Na_2SO_4$ followed by removing the solvent under reduced pressure to give the crude product (802 mg) as a white powder. To the solution of the crude product (802 mg), $Et_3N$ (0.67 mL, 4.8 mmol), and EDCI hydrochloride (932 mg, 4.9 mmol) in $CH_2Cl_2$ (11 mL) was added cyclopropylacetic acid (531 mg, 5.3 mmol) at 0 °C and stirred at rt for 14 h. The reaction mixture was poured into 2M HCl and extracted with $CHCl_3$. The combined organic layers were washed with saturated $NaHCO_3$ solution and distillated water, and dried over anhydrous $Na_2SO_4$ followed by removing the solvent under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=100/0–1/2) to give the title compound **27** (745 mg, 60%) as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.11–0.28 (m, 2H), 0.48–0.66 (m, 2H), 0.99–1.14 (m, 1H), 1.48–1.70 (m, 2H), 1.88 (br d, $J$=12.9 Hz, 2H), 2.31 (d, $J$=6.9 Hz, 2H), 2.52–2.76 (m, 2H), 3.12 (br t, $J$=12.3 Hz, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 3.94 (br d, $J$=12.9 Hz, 1H), 4.81 (br d, $J$=12.9 Hz, 1H), 6.66–6.85 (m, 3H). IR (neat, $cm^{-1}$): 3001, 2935, 1637, 1517, 1450, 1256. HRMS (FAB): $[M+H]^+$ Calcd for $C_{18}H_{26}NO_3$: 304.1913. Found: 304.1908.

*4.21.2. 1-(2-Cyclopropylethyl)-4-(3,4-dimethoxyphenyl)piperidine (**9b**).* Compound **9b** was synthesized from compound **27** in 75% yield according to the synthetic method of compound **9a** from compound **26**. A colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.02–0.10 (m, 2H), 0.38–0.49 (m, 2H), 0.58–0.74 (m, 1H), 1.38–1.51 (m, 2H), 1.69–1.88 (m, 4H), 1.94–2.13 (m, 2H), 2.36–2.55 (m, 3H), 3.06 (br d, $J$=11.7 Hz, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 6.72–6.85 (m, 3H). IR (neat, $cm^{-1}$): 2932, 1517, 1464, 1261, 1232, 1142, 1030. HRMS (FAB): $[M+H]^+$ Calcd for $C_{18}H_{28}NO_2$: 290.2120. Found: 290.2120.

## 4.22. Preparation of 1-(3-cyclopropylpropyl)-4-(3,4-dimethoxyphenyl)piperidine (9c)

*4.22.1. 3-Cyclopropyl-1-(4-(3,4-dimethoxyphenyl)piperidin-1-yl)-propan-1-one (**28**).* To the solution of compound **25** (697 mg,

1.8 mmol) in AcOH (25 mL) was added Zn powder (7.4 g, 114 mmol) and stirred at rt for 25 h under Ar. The Zn powder was removed by filtration and the resulting filtrate was poured into ammonia solution, and then extracted with $CHCl_3$/*i*-PrOH=2/1. The combined organic layers were washed with distillated water and brine, and dried over anhydrous $Na_2SO_4$ followed by removing the solvent under reduced pressure to give the crude product (323 mg) as a white powder. To the solution of the 3-cyclopropylpropanoic acid (0.14 mL, 1.2 mmol), $Et_3N$ (0.23 mL, 1.7 mmol) in $CH_2Cl_2$ (11 mL) was added ethyl chloroformate (0.2 mL, 1.7 mmol) at 0 °C and stirred at the same temperature for 1 h. To the reaction mixture was added the solution of the obtained crude product (323 mg) in $CH_2Cl_2$ (6 mL) and stirred at rt for 19 h. The reaction mixture was poured into saturated $NaHCO_3$ solution and extracted with $CHCl_3$. The combined organic layers were washed with distillated water and dried over anhydrous $Na_2SO_4$, followed by removing the solvent under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=30/1–1/3) to give the title compound **28** (297 mg, 64%) as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.02–0.16 (m, 2H), 0.35–0.50 (m, 2H), 0.67–0.82 (m, 1H), 1.48–1.78 (m, 4H), 1.89 (br d, *J*=12.9 Hz, 2H), 2.48 (t, *J*=7.8 Hz, 2H), 2.54–2.77 (m, 2H), 2.80–3.21 (m, 1H), 3.86 (s, 3H), 3.87 (s, 3H), 3.92–4.12 (m, 1H), 4.60–4.93 (m, 1H), 6.68–6.85 (m, 3H). IR (neat, $cm^{-1}$): 2998, 2934, 2852, 1639, 1518, 1448, 1256, 1142, 1028. HRMS (ESI): $[M+Na]^+$ Calcd for $C_{19}H_{27}NNaO_2$: 340.1889. Found: 340.1898.

*4.22.2. 1-(3-Cyclopropylpropyl)-4-(3,4-dimethoxyphenyl)piperidine (**9c**).* Compound **9c** was synthesized from compound **28** in 80% yield according to the synthetic method of compound **9a** from compound **26**. A colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −0.70–0.09 (m, 2H), 0.31–0.48 (m, 2H), 0.59–0.74 (m, 1H), 1.16–1.28 (m, 2H), 1.56–1.86 (m, 6H), 1.94–2.08 (m, 2H), 2.30–2.70 (m, 3H), 3.05 (br d, *J*=11.4 Hz, 2H), 3.84 (s, 3H), 3.85 (s, 3H), 6.72–6.83 (m, 3H). IR (neat, $cm^{-1}$): 2932, 1517, 1261, 1233, 1142, 1031. HRMS (ESI): $[M+H]^+$ Calcd for $C_{19}H_{30}NO_2$: 304.2277. Found: 304.2277.

### 4.23. 1-(Cyclobutylmethyl)-4-(3,4-dimethoxyphenyl)-piperidine (11)

Compound **11** was synthesized from compound **25** in 49% yield according to the synthetic method of compound **9a**. A colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.63–2.01 (m, 8H), 2.03–2.20 (m, 4H), 2.37–2.55 (m, 3H), 2.56–2.73 (m, 1H), 3.03 (br d, *J*=11.4 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 6.72–6.86 (m, 3H). IR (neat, $cm^{-1}$): 2934, 1519, 1250, 1232, 1138, 1025. HRMS (ESI): $[M+H]^+$ Calcd for $C_{18}H_{28}NO_2$: 290.2120. Found: 290.2124.

### 4.24. Preparation of 4-(3-(cyclopropylmethoxy)propyl)-1,2-dimethoxybenzene (12)

*4.24.1. 3-(3,4-Dimethoxyphenyl)propan-1-ol (**14**).* Under Ar, to the solution of 3-(3,4-dimethoxyphenyl)propanoic acid (3.1 g, 14.5 mmol) in THF (2 mL) was added 1.07 M solution of $BH_3$–THF complex in THF (46 mL, 49 mmol) dropwise at 0 °C and stirred at 30 °C for 1.5 h. Aqueous THF (THF/$H_2O$=1/1, 60 mL) was carefully added to the reaction mixture at 0 °C, and then $K_2CO_3$ was added. After separation and extraction with $Et_2O$, the organic layers were combined and dried over anhydrous $Na_2SO_4$ followed by removing the solvent under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=1/2) to give the title compound **14** (2.7 g, 95%) as a colorless oil.

*4.24.2. 4-(3-(Cyclopropylmethoxy)propyl)-1,2-dimethoxybenzene (**12**).* Under Ar, to the suspension of *t*-BuOK (360 mg, 3.2 mmol) in DMF (2 mL) were added the solution of compound **14** (500 mg, 2.5 mmol) in DMF (2 mL) and (bromomethyl)cyclopropane (0.4 mL, 4.1 mmol), and stirred at rt for 7 h. The reaction mixture was poured into saturated $NH_4Cl$ solution and extracted with $CHCl_3$. The combined organic layers were washed with distillated water and dried over anhydrous $Na_2SO_4$ followed by removing the solvent under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=2/1) to give the title compound **12** (454 mg, 71%) as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.12–0.25 (m, 2H), 0.45–0.59 (m, 2H), 0.98–1.15 (m, 1H), 1.80–1.96 (m, 2H), 2.65 (t, *J*=7.8 Hz, 2H), 3.26 (d, *J*=6.9 Hz, 2H), 3.44 (t, *J*=6.6 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 6.69–6.82 (m, 3H). IR (neat, $cm^{-1}$): 3002, 2935, 2856, 1590, 1515, 1464, 1417, 1260, 1155, 1106, 1029, 763. HRMS (FAB): $[M]^+$ Calcd for $C_{15}H_{22}O_3$: 250.1569. Found: 250.1569.

### 4.25. 4-(3-(Cyclopropylmethoxy)propyl)-1,2-dimethoxybenzene (15)

To the solution of 2-cyclopropylethanol (213 mg, 2.5 mmol) and $Et_3N$ (0.65 mL, 4.7 mmol) in $CH_2Cl_2$ (3 mL) was added methanesulfonyl chloride (0.25 mL, 3.21 mmol) at 0 °C and stirred at the same temperature for 1 h. After removing the solvent under reduced pressure, crude 2-cyclopropylethy methanesulfonate was obtained as a white solid. Sodium hydride (60% in oil, 424 mg, 10 mmol) was washed with anhydrous hexane, and then suspended with DMF (3 mL). To the DMF suspension of NaH was added the solution of compound **14** (552 mg, 2.8 mmol) in DMF (3 mL) and stirred at rt for 40 min. To the obtained reaction mixture was added the suspension of crude 2-cyclopropylethy methanesulfonate in DMF (5 mL) at 0 °C and stirred at rt for 19 h. The reaction mixture was poured into saturated $NaHCO_3$ solution and extracted with $CHCl_3$. The combined organic layers were washed with distillated water and dried over anhydrous $Na_2SO_4$ followed by removing the solvent under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt/=5/1–4/1) to give the title compound **15** (375 mg, 57%) as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.02–0.1 (m, 2H), 0.34–0.53 (m, 2H), 0.67–0.83 (m, 1H), 1.48 (q, *J*=6.9 Hz, 2H), 1.78–1.94 (m, 2H), 2.64 (t, *J*=7.7 Hz, 2H), 3.43 (t, *J*=6.6 Hz, 2H), 3.49 (t, *J*=6.9 Hz, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 6.7–6.8 (m, 3H). IR (neat, $cm^{-1}$): 3435, 2933, 2857, 1516, 1465, 1261, 1237, 1156, 1115, 1031. HRMS (EI): $[M]^+$ Calcd for $C_{16}H_{24}O_3$: 264.1725. Found: 264.1719.

### 4.26. Preparation of 4,4′-(2-cyclopropylethane-1,1-diyl)bis(1,2-dimethoxybenzene) (17)

*4.26.1. Naphthalen-1-yl 2-cyclopropylacetate (**29**).* Under Ar, to the solution of 1-naphthol (1.6 g, 11.4 mmol) in $CH_2Cl_2$ (26 mL) were added $Et_3N$ (3.0 mL, 22.2 mmol), EDCI hydrochloride (2.1 g, 11.1 mmol), and cyclopropylacetic acid (0.5 mL, 7.0 mmol) at 0 °C and stirred at rt for 10 h. The reaction mixture was poured into 2 M HCl and extracted with $CH_2Cl_2$. The combined organic layers were washed with saturated $NaHCO_3$ solution and distillated water, and then dried over anhydrous $Na_2SO_4$ followed by removing the solvent under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=30/1–10/1) to give the title compound **29** (719 mg, 43%) as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.08–0.18 (m, 2H), 0.43–0.53 (m, 2H), 0.99–1.16 (m, 1H), 2.39 (d, *J*=7.2 Hz, 2H), 7.05 (dd, *J*=1.2, 7.5 Hz, 1H), 7.19–7.33 (m, 3H), 7.50 (d, *J*=8.1 Hz, 1H), 7.59–7.75 (m, 2H). IR (neat, $cm^{-1}$): 3064, 3006, 1767, 1599, 1509, 1462, 1389, 1317, 1256. HRMS (FAB): $[M+Na]^+$ Calcd for $C_{15}H_{14}O_2Na$: 249.0891. Found: 249.0886.

*4.26.2. 2-Cyclopropyl-1,1-bis(3,4-dimethoxyphenyl)ethanol (**30**).* Under Ar, to the solution of (3,4-dimethoxyphenyl)lithium

in THF (12 mL), which was prepared from 4-bromoveratrole (1.5 mL, 10.4 mmol) and 1.6 M solution of *n*-BuLi in hexane (6.3 mL, 10.1 mmol), was added the solution of compound **29** (1.04 g, 4.5 mmol) in THF (5 mL) dropwise at −78 °C, and stirred at the same temperature for 1 h and at rt for 21 h. The reaction mixture was poured into saturated $NaHCO_3$ solution and extracted with AcOEt. The combined organic layers were washed with distillated water and brine, and then dried over anhydrous $Na_2SO_4$ followed by removing the solvent under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=3/1) to give the title compound **30** (917 mg, 57%) as a colorless oil. $^1$H NMR (300 MHz, acetone-$d_6$) $\delta$ −0.02–0.07 (m, 2H), 0.27–0.37 (m, 2H), 0.68–0.83 (m, 1H), 2.21 (d, $J$=6.3 Hz, 2H), 2.84 (s, 1H), 3.75 (s, 6H), 3.77 (s, 6H), 6.84 (d, $J$=8.4 Hz, 2H), 6.99 (dd, $J$=2.1, 8.4 Hz, 2H), 7.15 (d, $J$=2.1 Hz, 2H). IR (neat, cm$^{-1}$): 3519, 3000, 2935, 2835, 1604, 1590, 1514, 1464, 1412, 1329, 1256, 1141, 1027, 763. HRMS (ESI): $[M+Na]^+$ Calcd for $C_{21}H_{26}NaO_5$: 381.1677. Found: 381.1678.

*4.26.3. 4,4′-(2-Cyclopropylethane-1,1-diyl)bis(1,2-dimethoxybenzene) (**17**).* To the solution of compound **30** (105 mg, 0.3 mmol) in MeOH (3 mL) was added 10% Pd/C (64 mg) and stirred at rt for 36 h under $H_2$. After removing the catalyst by filtration, the filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (hexane/AcOEt=2/1) to give the title compound **17** (86 mg, 86%) as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.02–0.11 (m, 2H), 0.35–0.44 (m, 2H), 0.53–0.68 (m, 1H), 1.88 (t, $J$=7.4 Hz, 2H), 3.83 (s, 6H), 3.84 (s, 6H), 3.93 (t, $J$=7.7 Hz, 1H), 6.70–6.84 (m, 6H). IR (neat, cm$^{-1}$): 2998, 2932, 2834, 1589, 1515, 1464, 1415, 1260, 1144, 1029. HRMS (FAB): $[M]^+$ Calcd for $C_{21}H_{26}O_4$: 342.1831. Found: 342.1832.

### 4.27. 4,4′-(3-Cyclopropylpropane-1,1-diyl)bis(1,2-dimethoxybenzene) (19)

*4.27.1. Naphthalen-1-yl 3-cyclopropylpropanoate (**31**).* To the solution of ethyl chloroformate (0.3 mL, 3.1 mmol) and $Et_3N$ (2 mL, 14.3 mmol) in $CH_2Cl_2$ (10 mL) was added 3-cyclopropylpropanoic acid (288 mg, 2.5 mmol) at 0 °C and stirred at the same temperature for 1 h. To the reaction mixture was added the solution of 1-naphthol (880 mg, 6.1 mmol) and stirred at rt for 15 h. The reaction mixture was poured into 1 M HCl solution and extracted with $CH_2Cl_2$. The combined organic layers were washed with distillated water and dried over anhydrous $Na_2SO_4$, followed by removing the solvent under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt=5/1) to give the title compound **31** (491 mg, 81%) as a colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.12–0.28 (m, 2H), 0.46–0.64 (m, 2H), 0.81–0.99 (m, 1H), 1.79 (q, $J$=7.5 Hz, 2H), 2.86 (t, $J$=7.5 Hz, 2H), 7.27 (dd, $J$=1.1, 7.4 Hz, 1H), 7.45–7.57 (m, 3H), 7.75 (d, $J$=8.4 Hz, 1H), 7.84–7.94 (m, 2H). IR (neat, cm$^{-1}$): 3068, 3001, 2925, 1760, 1509, 1390, 1358, 1258, 1224, 1115, 1014, 796, 770. HRMS (FAB): $[M+H]^+$ Calcd for $C_{16}H_{17}O_2$: 241.1229. Found: 241.1230.

*4.27.2. 4,4′-(3-Cyclopropylpropane-1,1-diyl)bis(1,2-dimethoxybenzene) (**19**).* Compound **19** was synthesized from compound **31** in 47% yield according to the synthetic method of compound **17** from **29**. A colorless oil. $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ −0.09–0.01 (m, 2H), 0.30–0.48 (m, 2H), 0.60–0.76 (m, 1H), 1.10–1.22 (m, 2H), 2.02–2.18 (m, 2H), 3.77–3.87 (m, 1H), 3.83 (s, 12H), 6.71–6.83 (m, 6H). IR (neat, cm$^{-1}$): 2997, 2931, 2834, 1589, 1515, 1463, 1415, 1257, 1143, 1029. HRMS (ESI): $[M+Na]^+$ Calcd for $C_{22}H_{28}NaO_4$: 379.1885. Found: 379.1874.

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## References and notes

1. (a) Freifelder, M. *Practical Catalytic Hydrogenation*; Wiley & Sons: New York, NY, 1971; p 254–530; (b) Newham, J. *Chem. Rev.* **1962**, *63*, 123; (c) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165.
2. For recent examples: (a) Harmata, M.; Rashatasakhon, P. *Org. Lett.* **2000**, *2*, 2913; (b) Harrowven, D. C.; Lucas, M. C.; Howes, P. D. *Tetrahedron* **2001**, *57*, 9157; (c) Mehta, G.; Murthy, A. S. K.; Umarye, J. D. *Tetrahedron Lett.* **2002**, *43*, 8301; (d) Karimi, S.; Tavares, P. *J. Nat. Prod.* **2003**, *66*, 520; (e) Taber, D. F.; Frankowski, K. J. *J. Org. Chem.* **2005**, *70*, 6417; (f) Harmata, M.; Rashatasakhon, P.; Barnes, C. L. *Can. J. Chem.* **2006**, *84*, 1456; (g) Taber, D. F.; Tian, W. *J. Org. Chem.* **2008**, *73*, 7560.
3. For recent examples: (a) Robl, J. A.; Cimarusti, M. P.; Simpkins, L. M.; Brown, B.; Ryono, D. E.; Eileen Bird, J.; Asaad, M. M.; Schaeffer, T. R.; Trippodo, N. C. *J. Med. Chem.* **1996**, *39*, 494; (b) Hendrata, S.; Bennett, F.; Huang, Y.; Sannigrahi, M.; Pinto, P. A.; Chan, T.; Evans, C. A.; Osterman, R.; Buevich, A.; McPhail, A. T. *Tetrahedron Lett.* **2006**, *47*, 6469; (c) Irie, O.; Yokokawa, F.; Ehara, T.; Iwasaki, A.; Iwaki, Y.; Hitomi, Y.; Konishi, K.; Kishida, M.; Toyao, A.; Masuya, K.; Gunji, H.; Sakaki, J.; Iwasaki, G.; Hirao, H.; Kanazawa, T.; Tanabe, K.; Kosaka, T.; Hart, T. W.; Hallett, A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4642.
4. For recent other examples: (a) Kozhushkov, S. I.; Kostikov, R. R.; Molchanov, A. P.; Boese, R.; Benet-Buchholz, J.; Schreiner, P. R.; Rinderspacher, C.; Ghiviriga, I.; de Meijere, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 180; (b) de Meijere, A.; von Seebach, M.; Zöllner, S.; Kozhushkov, S. I.; Belov, V. N.; Boese, R.; Haumann, T.; Benet-Buchholz, J.; Yufit, D. S.; Howard, J. A. K. *Chem.—Eur. J.* **2001**, *7*, 4021; (c) Carrasco, H.; Foces-Foces, C.; Pérez, C.; Rodríguez, M. L.; Martín, J. D. *J. Am. Chem. Soc.* **2001**, *123*, 11970; (d) Föhlisch, B.; Bakr, D. A.; Fischer, P. *J. Org. Chem.* **2002**, *67*, 3682; (e) Anderson, J. E.; de Meijere, A.; Kozhushkov, S. I.; Lunazzi, L.; Mazzanti, A. *J. Am. Chem. Soc.* **2002**, *124*, 6706; (f) Kozhushkov, S. I.; Yufit, D. S.; Boese, R.; Bläser, D.; Schreiner, P. R.; de Meijere, A. *Eur. J. Org. Chem.* **2005**, 1409; (g) Li, W. Z.; Yang, Y. *Org. Lett.* **2005**, *7*, 3107; (h) Kuethe, J. T.; Zhao, D.; Humphrey, G. R.; Journet, M.; McKeown, A. E. *J. Org. Chem.* **2006**, *71*, 2192.
5. Fujii, H.; Osa, Y.; Ishihara, M.; Hanamura, S.; Nemoto, T.; Nakajima, M.; Hasebe, K.; Mochizuki, H.; Nagase, H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4978.
6. p*Ka* values: acetic acid: 4.76, trifluoroacetic acid: −0.6, methanesulfonic acid: −1.9, perchloric acid: −5.0, hydrochloric acid: −8, hydrobromic acid: −9, hydroiodic acid: −10 Miller, A. In *Writing Reaction Mechanisms in Organic Chemistry*; Academic Press: San Diego, 1992; pp 35–42.
7. Hydroiodic acid or iodine reportedly functioned as a rhodium or palladium catalyst poison, respectively; (a) Freedman, L. D.; Doak, G. O.; Petit, E. L. *J. Am. Chem. Soc.* **1955**, *77*, 4262; (b) Caddock, P. D.; Joyner, R. W.; Williams, B. P. *Catal. Lett.* **1989**, *2*, 27.
8. MaloneyHuss, K. E.; Portoghese, P. S. *J. Org. Chem.* **1990**, *55*, 2957.
9. (a) Gates, M.; Montzka, T. A. *J. Med. Chem.* **1964**, *7*, 127; (b) Osa, Y.; Ida, Y.; Yano, Y.; Furuhata, K.; Nagase, H. *Heterocycles* **2006**, *69*, 271.
10. (a) Gould, E. S. *Mechanism and Structure in Organic Chemistry*; Henry Holt: New York, NY, 1959; p 561–617; (b) Richey, H. G., Jr. In *Carbonium Ions*; Olah, G. A., Schleyer, P. R., Eds.; John Wiley & Sons: Canada, 1972; Vol. III, pp 1201–1294; (c) Olah, G. A.; Prakash Reddy, V.; Surya Prakash, G. K. *Chem. Rev.* **1992**, *92*, 69.
11. Nagase, H.; Yamamoto, N.; Nemoto, T.; Yoza, K.; Kamiya, K.; Hirono, S.; Momen, S.; Izumimoto, N.; Hasebe, K.; Mochizuki, H.; Fujii, H. *J. Org. Chem.* **2008**, *73*, 8093.
12. It is known that treatment of aryl cyclopropylmethyl ether with hydrochloric acid in methanol under reflux conditions resulted in cleavage of cyclopropylmethyl ether bond; (a) Wuts, P. G. M.; Greene, T. W. In *Greene's Protective Groups in Organic Synthesis*; John Wiley & Sons: New Jersey, 2007; p 390; (b) Nagata, W.; Okada, K.; Itazaki, H.; Uyeo, S. *Chem. Pharm. Bull.* **1975**, *23*, 2878.
13. Generally speaking, the cyclopropylmethyl tosylate is solvolyzed $10^6$ faster than isobutyl tosylate because the tosylate ion could be solvolitically eliminated from the cyclopropylmethyl tosylate to afford the very stable cyclopropylcarbinyl cation. In *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Lowry, T. H., Richardson, K. S., Eds.; Harper & Row: New York, NY, 1987; p 425–515.
14. The reduction of cyclopropylmethylamine **9a** (50 mg) gave 49 mg of crude product. $^1$H NMR spectra of crude product showed decrease in signals indicating cyclopropane ring, but value of integral stemmed from aromatic protons was smaller than the theoretical value. Aliphatic methoxy signal (around 3.4 ppm) and increase in value of integral derived from aliphatic protons (around 1–2 ppm) were also observed. Taken together, these observations strongly suggest that reduction of benzene ring would proceed concomitantly.