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On the formation of a side product with hexahydroaporphine-like structure in the Grewe cyclization of dextromethorphan

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Abstract Factors leading to the formation of a hexahydroaporphine-like cyclizing side product were studied systematically for the first time and the ratio of this side product was controlled effectively. To understand better the electronic effect of substrates on the formation of side products, different 1-benzyloctahydroisoquinolines with substituted groups on nitrogen or benzene ring were compared. A plausible mechanism of cyclizing reaction was proposed, and key intermediates as well as transition states were analyzed using DFT calculations.

Keywords Grewe cyclization · Dextromethorphan · Hexahydroaporphine-like side product · DFT calculation

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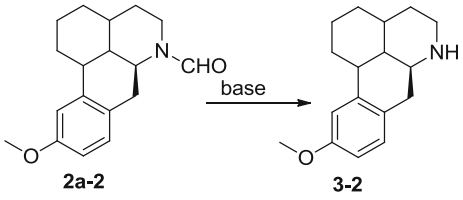
Introduction

Dextromethorphan [(+)-3-methoxy-17-methy-(9α,13α,14α)-morphinan, DXM], a non-narcotic morphinan derivative, has been widely used as an antitussive for almost 50 years and has recently attracted considerable attention because of its anticonvulsant and neuroprotective properties [1–5]. Its application in medicine ranges from pain relief to psychological applications. Dextromethorphan as an oral drug is available as lozenges, capsules, tablets, and cough syrups, in a variety of prescription medications and over-the-counter cough and cold remedies.

The key reaction in the preparation of DXM is Grewe cyclization. Grewe [6–8] achieved the first cyclization transformation, as postulated by Robinson [9–13] and Schopf [14–17], of 1-benzylisoquinoline derivatives into compounds with a ring system of morphine alkaloids with 65 % yield [6]. Subsequently, Schinider [18], Koelsch [19], Ochiai [20, 21], Sasamoto [22], Meyers [23], and Tian [24] chose *N*-methyl-1-benzylisoquinoline derivatives as precursors to react with phosphoric acid, hydrochloric acid, or hydrobromic acid at higher temperatures (130–160 °C or reflux in phosphoric acid), where the corresponding *N*-methylmorphinan or 3-hydroxy-*N*-methylmorphinan was obtained as the major product, along with several side products. Since the discovery by Leimgruber et al. [25] that *N*-formyl derivatives of octahydroisoquinoline in concentrated phosphoric acid cyclizes to classical morphinans almost 400 times faster than *N*-methyl derivatives, another route with *N*-formyl-1-benzylisoquinoline derivatives as precursors in the cyclization reactions to afford the corresponding morphinans in higher yields has been employed [26–33].

Fadnavis and co-workers offered an improved cyclization procedure to achieve *N*-formylated morphinan in higher purity using solid acid (>98 % purity by HPLC) [34]. However, when we repeated the experiment described in this literature, significant amounts (4 %) of unidentified side product was discovered by HPLC analysis. To elucidate the structure of this side product, the side product was deformylated, and the deformylated side product was isolated by preparative HPLC, NMR spectroscopy and LC–MS of the deformylated side product showed that this side product was (6a,S)-10-methoxy-2,3,3a,3a',4,5,6,6a,7,11b-decahydro-1*H*-dibenzo[*de*,*g*]-quinolone, **3–2** (Scheme 1; see also Supporting Information). This compound, formed as a side product in the cyclization of 1-benzyloctahydroisoquinolines, was first proven to possess the apomorphine-like structure by Hoffmann degradation [35]. It was later isolated in the form of hydrobromide or *d*-tartrate by Sawa et al. and proven from the degradation products to have the hexahydroaporphine structure [36].



Scheme 1 Deformylation of the hexahydroaporphine-like side product

Two mechanistic pathways have been outlined for the formation of this hexahydroaporphine-like side product: one by olefinic isomerization in the Grewe cyclization reaction, [25] the other through a Wagner-Meerwein type rearrangement [37–41]. To reduce the amount of side product, we investigate various cyclization conditions and discuss the electronic effect of 1-benzyloctahydroisoquinolines with substituents on the nitrogen or the benzene ring on the cyclizing reaction and side product formation, respectively. It is necessary to pointed out that apart from the hexahydroaporphine side product discussed in this paper, another potential side product may be demethylated product [34]. A possible mechanism of the cyclization reaction is also presented.

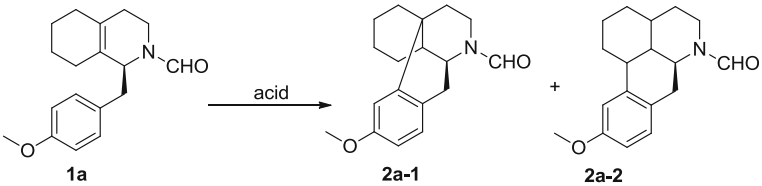
Results and discussion

Based on previous reports, [25] (+)-1-(*p*-methoxybenzyl)-2-formyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (**1a**) was chosen as the precursor to react with a variety of Brønsted acids in order to find the optimal cyclization reagent (Table 1). The initial experiment was carried out at 10 °C in CF_3SO_3H and the reaction was completed quickly with the side product in significant amounts (18 % yield) detected by HPLC analysis (Table 1, entry 1). When the reaction was performed in typical sulfonic acids (H_2SO_4, CH_3SO_3H, Eaton's reagent [42]), it took longer time to complete, but was accompanied by a relatively smaller amount of the side product (Table 1, entries 2–4). When phosphoric acids were employed as cyclization reagent (Table 1, entries 6–7), we observed a higher purity of *N*-formylated product (**2a-1**), especially for the reaction in anhydrous phosphoric acid providing the side product (**2a-2**) in less than 4 %. However, carboxylic acids, solid acids, and hydrogen acids failed to induce the cyclizing reaction (Table 1, entries 5, 8–14).

Further variations of the reaction conditions (temperature, concentration, and amounts of phosphoric acid) revealed that 60 °C was suitable for this reaction (Table 2, entries 1–4); 93 % phosphoric acid (5:1 V/W) was the best in terms of price and side product ratio (Table 2, entries 5–11). Interestingly, in toluene, the reaction proceeded smoothly, but when EtOH, THF, DMF, or DCM was employed, respectively, cyclization was distinctly inhibited rather than promoted (Table 2, entries 12–16). Moreover, the addition of Lewis acid was less effective (Table 2, entries 17–22). Thus, the optimized reaction conditions for Grewe cyclization of **1a** involved a 93 % concentration of phosphoric acid (5:1 V/W) in air at 60 °C and without additional organic solvent or Lewis acid.

After optimizing the reaction conditions, we investigated the dependence of the precursor on the cyclization reaction by employing a variety of 1-benzyloctahydroisoquinolines with substituents on the nitrogen and the benzene ring of the substrate, respectively (Table 3). Remarkably, (+)-1-(*p*-methoxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroiso-quinoline hardly converted to the corresponding morphinan under optimized reaction conditions, which could be attributed to high electron density at the nitrogen (Table 3, entry 2). As electron-withdrawing groups drastically reduce the basicity of the nitrogen atom, [26, 27] we speculated that *N*-acyl or *N*-sulfonyl 1-benzyloctahydroisoquinolines with electron-rich substituents

Table 1 Screening of Brønsted acids in Grewe cyclization



Entry	Brønsted acids	Time (h)	Conversion of **1a** (%)	Purity		Ratio (**2a-1/2a-2**)
				2a-1 (%)	**2a-2** (%)	
1[a]	CF_3SO_3H	1 min	100	54.2	17.7	75.4/24.6
2[a]	H_2SO_4	24	82	70.5	5.0	93.4/6.6
3	CH_3SO_3H	6	100	84.3	11.6	87.9/12.1
4	Eaton's reagent	4	100	83.0	10.9	88.4/11.6
5[b]	TsOH	48	4	3.2	0.3	91.4/8.6
6	PPA	17	100	89.9	6.3	93.5/6.5
7	H_3PO_4 (100 %)	32	100	91.7	3.6	96.2/3.8
8[b]	$CH_3PO_3H_2$	32	<2	Trace	N.D[c]	–
9[b]	H_3PO_3	32	12	7.0	0.5	93.3/6.7
10	CF_3COOH	48	<2	Trace	N.D	–
11	HCOOH	48	<2	N.D	N.D	–
12	CH_3COOH	48	<2	N.D	N.D	–
13	HCl (37 %)	48	52	15.4	1.1	93.3/6.7
14[d]	HBr solution (33 %)	24	100	Trace	Trace	–

Unless otherwise specified, the reaction was carried out in the presence of **1a** (1.0 g), Brønsted acids (5.0 mL) at 60 °C. Conversion, purity and ratio were based on HPLC analysis

[a] Reaction temperature was 10 °C

[b] Solid acid was dissolved in acetic acid

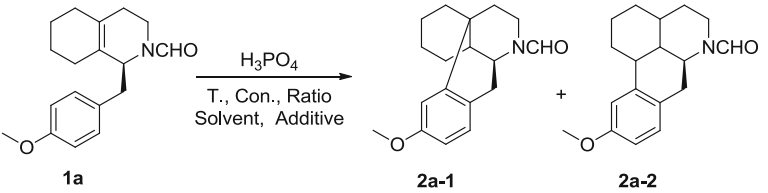
[c] N.D. = not detected

[d] Hydrogen bromide was dissolved in acetic acid and (+)-*N*-formyl-1-(*p*-hydroxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline was the major product

might increase the yield (Table 3, entries 3–9). Interestingly, a variation of substituents such as acetyl, propionyl, ethoxycarbonyl, and trifluoroacetyl groups on the nitrogen did not affect the ratio of the side product (Table 3, entries 3–6). Unexpectedly, (+)-*N*-trichloroacetyl-1-(*p*-methoxybenzyl)octahydroisoquinoline produced the corresponding cyclization product (**2g**) in considerably lower isolated yield even though the amount of side product was very little. For the structures with sulfonyl groups on the nitrogen, the reaction proceeded well (Table 3, entries 8–9). The best overall performance was obtained with the trifluoromethylsulfonyl substituent, which gave **2i** in 87 % yield with the lowest amount of side product.

In addition, structures with different substituent groups on the aromatic ring were investigated (Table 3, entries 1, 10–14). In general, the reactivity of the substrates

Table 2 Screening of other conditions in Grewe cyclization



1a **2a-1** **2a-2**

Entry	Acid	Additive	Sol-vent	Conversion of **1a** (%)	Purity		Ratio (**2a-1/2a-2**)
					2a-1 (%)	**2a-2** (%)	
1[a]	H_3PO_4 (100 %)	–	–	90	83.6	2.7	96.8/3.2
2	H_3PO_4 (100 %)	–	–	100	91.7	3.6	96.2/3.8
3[b]	H_3PO_4 (100 %)	–	–	100	91.3	4.6	95.2/4.8
4[c]	H_3PO_4 (100 %)	–	–	100	87.3	5.2	94.4/5.6
5	H_3PO_4 (85 %)	–	–	65	60.1	2.1	96.6/3.4
6	H_3PO_4 (90 %)	–	–	87	80.2	1.9	97.7/2.3
7	H_3PO_4 (93 %)	–	–	100	90.3	2.3	97.6/2.4
8	H_3PO_4 (95 %)	–	–	100	89.6	2.5	97.2/2.8
9	H_3PO_4 (93 %): **1a** = 9:1	–	–	100	92.3	2.4	97.5/2.5
10	H_3PO_4 (93 %): **1a** = 7:1	–	–	100	91.5	2.4	97.4/2.6
11	H_3PO_4 (93 %): **1a** = 3:1	–	–	98	86.5	2.7	97.0/3.0
12[d]	H_3PO_4 (93 %)	–	EtOH	<1	N.D[f]	N.D	–
13	H_3PO_4 (93 %)	–	THF	<1	N.D	N.D	–
14	H_3PO_4 (93 %)	–	DMF	<1	N.D	N.D	–
15	H_3PO_4 (93 %)	–	DCM	52	49.0	0.9	98.2/1.8
16	H_3PO_4 (93 %)	–	Toluene	100	89.4	2.3	97.5/2.5
17[e]	H_3PO_4 (93 %)	$Cu(OAc)_2{\cdot}H_2O$	–	100	88.4	2.6	97.1/2.9
18	H_3PO_4 (93 %)	$Ni(OAc)_2{\cdot}4H_2O$	–	100	87.6	2.6	97.3/2.9
19	H_3PO_4 (93 %)	$Co(OAc)_2{\cdot}4H_2O$	–	100	87.4	2.6	97.1/2.9
20	H_3PO_4 (93 %)	$Zn_3(PO_4)_2$	–	100	88.4	2.6	97.1/2.9
21	H_3PO_4 (93 %)	$FePO_4$	–	100	87.3	2.6	97.1/2.9
22	H_3PO_4 (93 %)	$AlPO_4$	–	100	89.1	2.7	97.1/2.9

The reaction was carried out in the presence of **1a** (1.0 g) and corresponding concentration phosphoric acids (5.0 mL) at 60 °C for 32 h. Conversion, purity, and ratio were based on HPLC analysis

[a] The reaction was carried out at 50 °C

[b] 70 °C

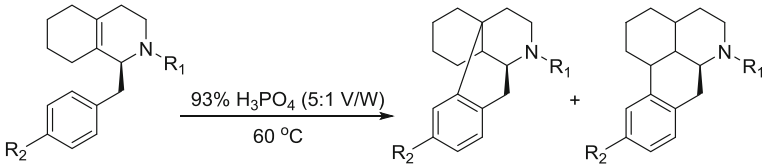
[c] 80 °C, respectively

[d] The reaction was carried out in the presence of **1a** (0.5 g), H_3PO_4 (93 %, 2.5 mL), and solvent (2.5 mL) at 60 °C for 32 h

[e] The reaction was carried out in the presence of **1a** (0.5 g), H_3PO_4 (93 %, 2.5 mL), and Lewis acid (5 mol %) at 60 °C for 32 h

[f] N.D. = not detected

Table 3 Acid-catalyzed cyclization of *N*-acyl-1-benzyloctahydroisoquinolines



1 **2-1** **2-2**

Entry	R_1	R_2	Time (h)	Product **2a**-**2m**	Yield[a] (%)	Ratio (**2-1/2-2**)
1	CHO	OCH_3	32	**2a**	90	97.6/2.5
2	CH_3	OCH_3	32	**2b**	N.D[b]	–
3	CH_3CO	OCH_3	12	**2c**	85	98.6/1.4
4	CH_3CH_2CO	OCH_3	12	**2d**	84	98.6/1.4
5	EtOCO	OCH_3	12	**2e**	86	98.4/1.6
6	CF_3CO	OCH_3	8	**2f**	93	98.4/1.6
7	CCl_3CO	OCH_3	72	**2g**	55	99.6/0.4
8	CH_3SO_2	OCH_3	4	**2h**	70	98.7/1.3
9	CF_3SO_2	OCH_3	120	**2i**	87	>99.9/0.1
10	CHO	OH	12	**2j**	87	96.9/3.0
11	CHO	OCH_2CH_3	32	**2k**	89	97.9/2.1
12	CHO	$OCH_2CH_2CH_3$	32	**2l**	91	98.3/1.7
13	CHO	CH_3	24	**2m**	89	98.9/1.1
14	CHO	Cl	96	**2n**	57	93.6/6.4

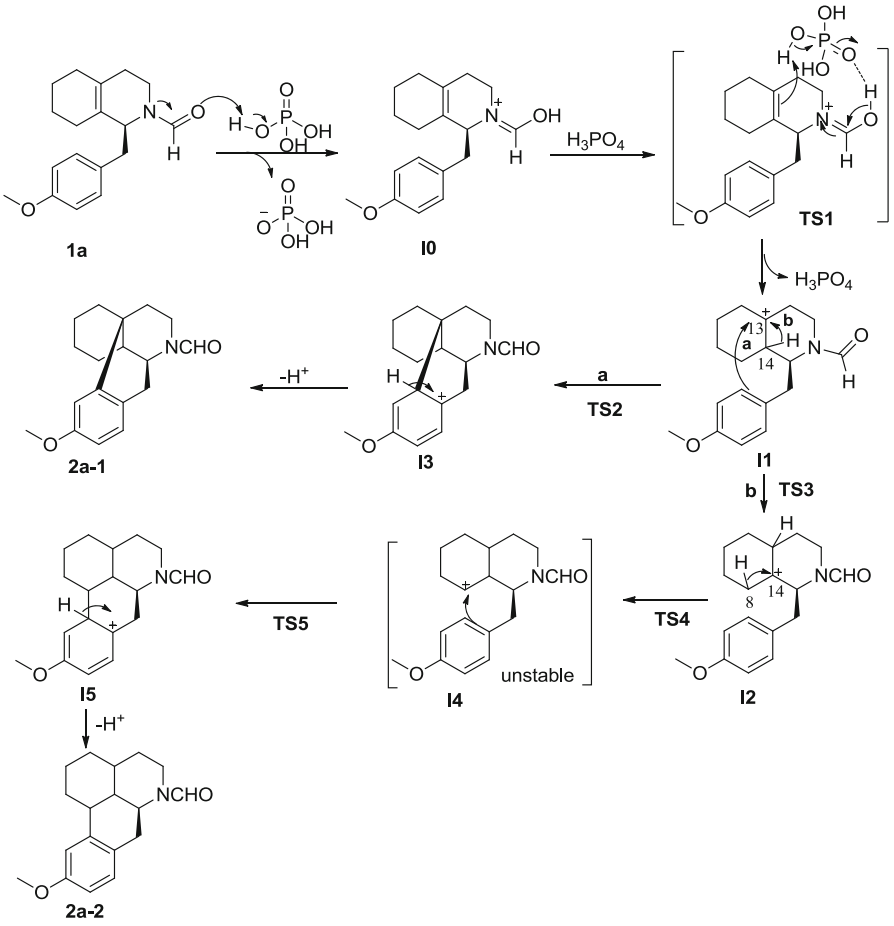
Reaction was carried out in the presence of **1** (1.0 g), H_3PO_4 (93 %, 5.0 mL) at 60 °C. Ratio was based on HPLC analysis

[a] Isolated yield

[b] N.D. = not detected

with an electron-donating group (e.g. OH, OMe, OEt, $OCH_2CH_2CH_3$, Me) on the benzene ring was higher than that with an electron-withdrawing group (e.g. Cl), and morphinan with chlorine on the para-position resulted in 6.4 % cyclization side product while the product with methyl substituent was associated with only of 1.1 % undesired side product based on HPLC analysis.

On the basis of reported work [34, 38–42] and the current experiments, a plausible mechanism is proposed with model substrate **1a** as outlined in Scheme 2. As the aldehyde group on the nitrogen is essential for the reaction, and N-methylated substrate won't react with any of the acid, the initial protonation site is probably at the aldehyde oxygen. First, the reaction of N-formyl benzylisoquinoline (**1a**) is initiated by addition of the phosphoric acid to generate the highly reactive quaternary ammonium intermediate **I0**. Intermediate **I0** reacts further with phosphoric acid to give the carbocation intermediate **I1**, which may follow two pathways. In pathway **a**, the desired product **2a-1** is formed directly by nucleophilic attack from the aromatic ring. In pathway **b**, carbocation **I2** is produced



Scheme 2 A plausible cyclization mechanism induced by phosphoric acid

by ortho-hydrogen migration. Subsequent to the hydride transfer step, the resulting intermediate **I2** undergoes [1–8] –H migration once again forming an unstable carbocation (**I4**), and the aromatic ring is attacking the carbocation affording side product **2a-2**.

However, it was difficult to capture the cyclization intermediates experimentally. To confirm our hypothesis further, DFT calculations were performed to explore the energies of the key intermediates and transition states of both reaction pathways (Scheme 2 and Figs. 1, 2). According to our calculations, in pathway **b**, the rate limiting step is the conversion from **I2** to **I5**, the energy barrier for the conversion from **I2** to **I5** is 21.0 kcal/mol, while the energy barrier for the conversion from **I1** to **I3** (rate limiting step in pathway **a**) is only 5.0 kcal/mol. These results suggest that pathway **a** is kinetically more favorable than pathway **b**. Therefore, under low temperature conditions, the rate determining step for byproduct formation (from I2 to I4) should not be easily passed, and the side product formation effectively

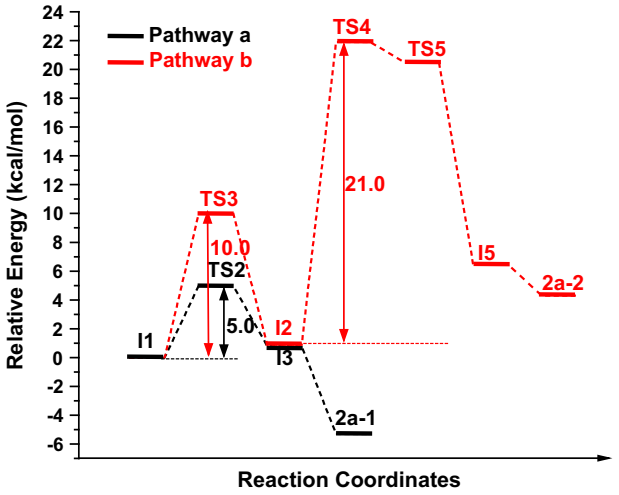


Fig. 1 Comparison of relative free energies for the product **2a-1** and side product **2a-2**

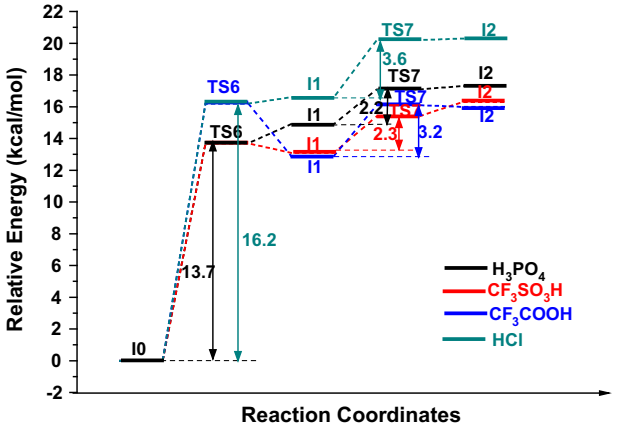


Fig. 2 Reaction barrier profiles for different acids

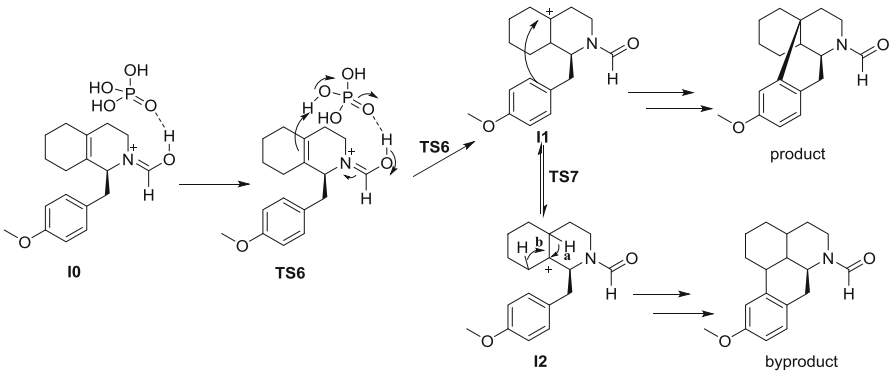
controlled. This is consistent with our experimental data (Table 2, entries 1–4). In addition, we also compared the energies of the final products of both pathways. As expected, the energy of the main product **2a-1** is much lower than that of the side product **2a-2** (−5.3 vs. +4.3 kcal/mol).

Motivated by our computational results, experiments at lower temperature (40 °C) was employed in order to further reduce the amount of the side product, and the solid acid Amberyst 15 was used as the catalyst in order to increase the reaction performance at low temperature according to Fadnavis et al. [34] (Table 4). After optimization of the phosphoric acid concentration, we obtained the best reaction conditions by using phosphoric acid (98 %) as the cyclization acid, reactant ratio of

Table 4 Grewe cyclization reaction conducted at 40 °C

Entry	Proton acid	Additive	Time (h)	Conversion of **1a** (%)	Purity		Ratio (**2a-1/2a–2**)
					2a-1 (%)	**2a-2** (%)	
1	H_3PO_4 (93 %)	Amberyst 15 (50 %)	70	88	84.6	1.4	98.4/1.6
2	H_3PO_4 (98 %)	Amberyst 15 (50 %)	34	100	95.0	1.9	98.0/2.0
3	H_3PO_4 (100 %)	Amberyst 15 (50 %)	34	100	94.1	2.3	97.6/2.4

Reaction was carried out in the presence of **1a** (1.0 g), H_3PO_4 (5.0 mL), Amberlyst 15 (50 %) at 40 °C. Conversion, purity, and ratio were based on HPLC analysis



Scheme 3 Two pathways of the product and side product

5:1 (V/W), an addition of Amberlyst 15 (50 %), and performed the reaction in air at 40 °C for 34 h. This resulted in a cyclization product of 95 % purity concomitantly with 2.0 % of the side product.

To understand why H_3PO_4 is better than the other acids in terms of catalytic efficiency, DFT calculations were also employed to evaluate the reaction barriers of the proton transfer steps of different acids. In our calculations, acids first protonate the keto oxygen (**I0**). Different acids then function as proton shuttles to mediate the proton transfer from the hydroxyl to the olefin carbon (Scheme 3, Table 5). We found that the reaction barriers for H_3PO_4 and CF_3SO_3H were lower than those of CF_3COOH and HCl (13.7 vs 16.2 kcal/mol; Table 5), which is consistent with our experimental data listed in Table 1. After proton transfer, 1,2-hydride shift can occur to give **I2**, which is the precursor of the side product. In principle, a higher reaction barrier of this step should give lower side product ratio. We found that the reaction barrier in presence of H_3PO_4 (17.1 kcal/mol) is higher than those using CF_3COOH (16.1 kcal/mol) or CF_3SO_3H (15.4 kcal/mol), implying that H_3PO_4 should give lower side product ratio. For HCl, although the barrier of the 1,2-hydride shift step is high, the barrier for the proton transfer is also high, which leads to low conversion rate (Table 5). Overall, the calculations are fully consistent with our experimental findings.

Table 5 Reaction barriers of TS1 and TS2 for different acids

Acid	I0	TS6	I1[a]	TS7	I2[a]
H_3PO_4	0.0	13.7	14.9	17.1	17.3[b]
CF_3SO_3H	0.0	13.7	13.1	15.4	16.3[b]
CF_3COOH	0.0	16.2	12.9	16.1	16.0
HCl	0.0	16.2	16.6	20.2	20.3[b]

Relative energy, in kcal/mol

[a] Intermediates in presence of the acid

[b] Free energies of I2 become higher than TS2 after adding the Gibbs corrections

Conclusions

In summary, we have provided the first systematic investigation of the leading factors to form the hexahydroaporphine-like cyclizing side product in Grewe cyclization. In this case, the ratio of the side product was controlled effectively (2.0 %) with the corresponding product (*N*-formyl-3-methoxymorphinan) in 95 % purity. Furthermore, it is suggested that the electronic effect of 1-benzyloctahydroisoquinolines with different substituent groups on the nitrogen and the benzene ring has great influence on the amount of cyclizing side product, among which *N*-trifluoromethylsulfonyl benzylisoquinoline generated the corresponding side product in the lowest ratio (<0.1 %). Finally, a novel cyclization mechanism is proposed based on the experimental results and DFT calculations, which supports and explains the rationalization of the observed cyclization reaction.

Experimental section

General

Unless otherwise noted, all the reactions were run under air in oven-dried parallel reaction tube and were heated on hot plates to an internal thermometer in Aplus PTC07B. All the solvents and reagents were purchased from the suppliers and used without additional purification. The ^{1}H NMR spectra were recorded at 400 MHz and the ^{13}C NMR spectra were recorded at 100/400 MHz in $CDCl_3$ or d_4-MeOH with TMS as internal standard. All shifts were given in ppm. All coupling constants (*J* values) were reported in Hertz (Hz). Column chromatography was performed on silica gel 200–300 mesh. Melting points were uncorrected and were obtained on a Laboratory Devices Mel-Temp II instrument.

HPLC analysis

Column Cadenza CD-18 (250 mm × 4.6 mm, 3 μm), Imtakt, Japan; Injection volume 1.0 μL. Detection wavelength and column temperature were 280 nm and 30 °C, respectively. At the start of analysis the mobile phase was consisted of 30 % acetonitrile −70 % water containing 0.1 % H_3PO_4. This was changed to 80 %

acetonitrile −20 % water containing 0.1 % H_3PO_4 in 45 min with total flow rate of 1.0 mL/min. Side product **3–2** was purified by America semipreparative high performance liquid chromatography (Gilson 281) and analyzed by Agela MP C18 (250 mm × 4.6 mm, 5.0 μm), Shimadzu LC-20AB.

Procedure for preparation of (6a,S)-10-methoxy-2,3,3a,3a[1],4,5,6,6a,7,11b-decahydro-1*H*-dibenzo[*de*,*g*]quinolone (3–2)

The crude product of Grewe Cyclization of **1a** 0.5 g was added to the methanol solution of NaOH (0.4 g NaOH in 10 mL MeOH), the mixture was refluxed for 5 h, solvent was evaporated under reduced pressure. The crude product was purified by semipreparative high performance liquid chromatography. ^{1}H NMR (400 MHz, d_4-MeOH) δ: 1.08–1.15 (m, 1H), 1.23–1.30 (m, 1H), 1.38–1.60 (m, 5H), 1.66–1.71 (m, 1H), 1.81–1.90 (m, 1H), 1.98 (d, J = 12.4 Hz, 1H), 2.46 (d, J = 12.4 Hz, 1H), 2.72–2.75 (m, 1H), 2.96–2.99 (m, 1H), 3.02–3.11 (m, 1H), 3.24–3.29 (m, 1H), 3.69 (s, 1H), 3.78 (s, 3H), 3.82 (m, 1H), 6.83 (dd, J = 2.0 Hz, 8.8 Hz, 1H), 6.88 (d, J = 2.0 Hz, 1H), 7.14 (d, J = 8.8 Hz, 1H); ^{13}C NMR (400 MHz, d_4-MeOH) δ: 20.3, 25.0, 28.2, 28.4, 29.6, 32.4, 36.3, 38.2, 41.0, 51.4, 54.3, 110.9, 112.0, 123.9, 130.2, 136.6, 158.9. LC–MS (ESI) calcd for $C_{17}H_{24}NO^+$([M + H]$^+$): 258.2, found: 258.2.

General procedure for preparation of (+)-*N*-formyl-1-(4-substituted) benzyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (1a, 1m-n)

(+)-Octabase-mandelate salt (15.0 g) was added to solution of 10 % sodium hydroxide (100 mL), and the mixture was stirred for 0.5 h. After that, the mixture was extracted with DCM (100 mL × 3), washed with brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated and concentrated to dryness to afford (+)-1-(4-substituted)benzyl-1,2,3,4,5,6,7,8- octahydroisoquinoline.

(+)-1-(4-substituted)benzyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (19.5 mmol) was added to a mixture of toluene (70 mL) and formic acid (29.25 mmol) in an oven-dried flask equipped with a stir bar and water segregator. The mixture was stirred at reflux until no water was separated. After cooling to room temperature, water (50 mL) was added to the mixture, and the organic phase was separated. The aqueous phase was extracted with toluene (50 mL × 2), and the combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The crude material was purified by column chromatography with cyclohexane: ethyl acetate (10:1–5:1) as eluent.

(+)-*N*-Formyl-1-(*p*-methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline (**1a**) Pale-yellow oil, yield: 95 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.66–1.69 (m, 4H), 1.81–1.93 (m, 4H), 2.08–2.26 (m, 2H), 2.60–2.67 (m, 0.6H), 2.80 (dd, J = 6.9 Hz, 14.1 Hz, 0.4H), 2.85–3.05 (m, 2 H), 3.30 (dd, J = 6.5 Hz, 13.2 Hz, 0.4H), 3.58 (d, J = 10.1 Hz, 0.6H), 3.76 (s, 3H), 4.37 (dd, J = 6.5 Hz, 13.2 Hz, 0.6H), 4.67 (bs, 0.4H), 6.78–6.83 (m, 2H), 6.97–7.06 (m, 2H), 7.38 (s, 0.6H), 7.92 (s, 0.4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.7, 22.8, 22.9, 27.6, 27.7, 29.7, 30.0, 30.1, 30.8, 33.3,

36.2, 37.4, 40.3, 53.2, 55.1, 60.7, 113.5, 114.0, 127.6, 127.8, 127.8, 128.8, 129.8, 129.9, 130.2, 130.4, 158.1, 158.3, 160.8, 161.0. HRMS (ESI) calcd for $C_{18}H_{24}NO_2^+$([M + H]$^+$): 286.1807, found: 286.1812.

(+)-*N*-Formyl-1-(*p*-methylbenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline (**1m**) Pale-yellow oil, yield: 92 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.64–1.93 (m, 8H), 2.06–2.21 (m, 2H), 2.28 (s, 3H), 2.64 (dd, J = 10.4 Hz, 13.6 Hz, 0.6H), 2.76 (dd, J = 7.2 Hz, 14.0 Hz, 0.4H), 2.85–3.06 (m, 2H), 3.28 (dd, J = 6.8 Hz, 13.2 Hz, 0.4H), 3.59 (d, J = 10.0 Hz, 0.6H), 4.36 (dd, J = 6.8 Hz, 13.2 Hz, 0.6H), 4.69 (bs, 0.4H), 6.94 (d, J = 8.0 Hz, 1.3H), 7.03 (s, 1.3H), 7.07 (d, J = 8.0 Hz, 1.4H), 7.35 (s, 0.6H), 7.89 (s, 0.4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.1, 22.7, 22.8, 22.9, 27.7, 29.7, 30.0, 30.1, 30.9, 33.3, 36.8, 38.0, 40.3, 53.2, 60.7, 127.8, 128.8, 128.9, 129.1, 129.4, 134.7, 134.9, 135.7, 136.2, 160.8, 161.0. HRMS (ESI) calcd for $C_{18}H_{24}NO^+$ ([M + H]$^+$): 270.1858, found: 270.1860.

(+)-*N*-Formyl-1-(*p*-chlorobenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline (**1n**) Pale-yellow oil, yield: 90 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.64–2.25 (m, 10H), 2.68 (dd, J = 10.4 Hz, 14.0 Hz, 0.6H), 2.80 (dd, J = 7.2 Hz, 14.0 Hz, 0.4H), 2.84–3.08 (m, 2H), 3.33 (dd, J = 7.2 Hz, 13.2 Hz, 0.4H), 3.60 (d, J = 10.4 Hz, 0.6H), 4.37 (dd, J = 7.2 Hz, 13.2 Hz, 0.6H), 4.70 (bs, 0.4H), 7.01 (d, J = 8.0 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 7.23 (dd, J = 8.0 Hz, 16.4 Hz, 2H), 7.41 (s, 0.6H), 7.91 (s, 0.4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.6, 22.7, 22.8, 27.6, 27.7, 29.6, 29.9, 30.1, 30.8, 33.4, 36.7, 37.7, 40.3, 53.0, 60.4, 127.5, 128.2, 128.8, 129.2, 130.6, 130.8, 132.1, 132.6, 136.4, 136.6, 160.8, 160.9. HRMS (ESI) calcd for $C_{17}H_{21}NOCl^+$ ([M + H]$^+$): 290.1312, found: 290.1303.

(+)-N-Methyl-1-(p-methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline (**1b**) Formaldehyde (40 % dispersion in water, 1.76 g, 23.4 mmol) was added in a mixture solution of methanol (50 mL) and (+)-1-(4-methoxyl)benzyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (5.0 g, 19.5 mmol) in an oven-dried flask equipped with a stir bar. The solution was then heated to 40 °C and stirred for 1 h and allowed to cool to ambient temperature. After that, KBH_4 (0.63 g, 11.7 mmol) was added in batches and stirred for 1 h. The reaction was poured into H_2O (50 mL) and organic solvent was evaporated under reduced pressure. Then the resulting mixture was diluted with CH_2Cl_2, combined organic layers were washed with water, dried (Na_2SO_4), and concentrated to dryness. The crude material was purified by column chromatography (hexane/AcOEt/Et_3N = 10:1:0.01) to afford the desired product **1b**, yield 94 %. 1H NMR (400 MHz, $CDCl_3$) δ: 1.50–2.00 (m, 10H), 2.37 (s, 3H), 2.48–2.54 (m, 1H), 2.79 (t, J = 4.2 Hz, 2H), 2.88–2.95 (m, 2H), 3.77 (s, 3H), 6.80 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.8 Hz, 2H); 13C NMR (100 MHz, $CDCl_3$) δ: 23.0, 23.3, 28.1, 28.3, 30.2, 35.8, 43.0, 47.6, 54.9, 66.4, 113.3, 127.3, 129.3, 130.1, 133.0, 157.7. HRMS (ESI) calcd for $C_{18}H_{26}NO^+$([M + H]$^+$): 272.2014, found: 272.2020.

General procedure for preparation of (+)-*N*-Acyl-1-(4-methoxy)benzyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (1c-i)

The first step

(+)-Octabase-mandelate salt (15.0 g) was added to solution of 10 % sodium hydroxide (100 mL), and the mixture was stirred for 0.5 h. After that, the mixture was extracted with DCM (100 mL × 3), washed with brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated and concentrated to dryness to afford (+)-1-(4-methoxyl)benzyl-1,2,3,4,5,6,7,8-octahydroisoquinoline.

The second step

Et_3N (2.95 g, 29.25 mmol) was added in a mixture solution of DCM (50 mL) and (+)-1-(4-methoxyl)benzyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (5.0 g, 19.5 mmol) in an oven-dried flask equipped with a stir bar. Acyl chlorides or anhydrides (23.4 mmol) were then added dropwise and stirred at 0 °C or ambient temperature, until TLC indicated the total consumption of octahydroisoquinoline derivative. After the reaction was completed, approximately 50 mL water was added, and the organic phase was separated. The aqueous phase was extracted with DCM (50 mL × 2), and the combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness again. The crude material was purified by column chromatography with cyclohexane: ethyl acetate (15:1–5:1) as eluent.

(+)-*N*-Acetyl-1-(*p*-methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline (**1c**) Pale-yellow oil, yield: 94 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.25 (s, 1.5H), 1.35 (s, 1.5H), 1.63–1.70 (m, 4H), 1.78 (d, J = 16.0 Hz, 1H), 1.92 (d, J = 18.4 Hz, 3H), 2.04–2.26 (m, 2H), 2.69–2.81 (m, 1H), 2.84–3.04 (m, 2H), 3.46 (dd, J = 5.6 Hz, 13.2 Hz, 0.4 H), 3.78 (s, 3H), 3.82 (d, J = 10.0 Hz, 0.6H), 4.67 (dd, J = 5.6 Hz, 13.2 Hz, 0.6H), 4.89 (bs, 0.4H), 6.77–6.83 (m, 2H), 7.01–7.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.8, 21.6, 22.7, 22.8, 22.9, 27.8, 28.0, 29.7, 29.9, 30.0, 30.4, 34.1, 36.4, 37.2, 40.5, 54.2, 55.1, 55.2, 61.0, 113.4, 113.9, 127.8, 128.2, 129.0, 129.3, 130.3, 130.4, 130.5, 158.0, 158.4, 168.4, 169.3. HRMS (ESI) calcd for $C_{19}H_{26}NO_2^+$ ($[M + H]^+$): 300.1964, found: 300.1968.

(+)-*N*-Propionyl-1-(*p*-methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline (**1d**) Pale-yellow oil, yield: 93 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.68 (t, J = 7.6 Hz, 1.5H), 0.95 (t, J = 7.6 Hz, 1.5H), 1.53–2.17 (m, 12H), 2.60–2.71 (m, 1H), 2.77–2.95 (m, 2H), 3.41 (dd, J = 5.6 Hz, 13.2 Hz, 0.5H), 3.66 (s, 3H), 3.79 (d, J = 9.6 Hz, 0.5H), 4.59 (dd, J = 5.6 Hz, 13.2 Hz, 0.5H), 4.81 (bs, 0.5H), 6.67–6.73 (m, 2H), 6.91–6.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 8.3, 8.6, 21.7, 21.8, 21.9, 24.7, 25.7, 26.8, 27.1, 28.9, 29.0, 29.5, 33.3, 35.6, 36.2, 38.6, 53.1, 54.1, 54.2, 58.8, 112.3, 112.9, 126.6, 127.3, 128.2, 128.3, 129.4, 129.5, 129.6, 157.0, 157.3, 170.8, 171.6. HRMS (ESI) calcd for $C_{20}H_{28}NO_2^+$ ($[M + H]^+$): 314.2120, found: 314.2111.

(+)-*N*-Ethoxycarbonyl-1-(*p*-methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline (**1e**) Pale-yellow oil, yield: 89 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.94 (t, $J = 7.2$ Hz, 2H), 1.16 (t, $J = 7.2$ Hz, 1H), 1.57–1.72 (m, 5H), 1.88–2.15 (m, 5H), 2.63–3.01 (m, 3H), 3.64–3.68 (m, 0.6H), 3.74 (s, 3H), 3.78–3.82 (m, 1H), 4.01–4.04 (m, 0.8H), 4.12 (dd, $J = 6.0$ Hz, 13.2 Hz, 0.6H), 4.25 (d, $J = 7.2$ Hz, 0.6H), 4.47 (bs, 0.4H), 6.78 (d, $J = 8.0$ Hz, 2H), 7.01–7.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3, 14.7, 23.0, 27.9, 30.0, 30.1, 36.5, 36.9, 37.2, 37.6, 55.2, 56.5, 57.3, 60.7, 113.5, 128.1, 128.5, 128.9, 130.3, 130.7, 131.0, 155.2, 155.3, 158.0, 158.1. HRMS (ESI) calcd for $C_{20}H_{28}NO_3^+$ ($[M + H]^+$): 330.2069, found: 330.2064.

(+)-*N*-Trifluoroacetyl-1-(*p*-methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline (**1f**) Pale-yellow oil, yield: 92 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.60–1.92 (m, 8H), 2.14–2.21 (m, 2H), 2.82 (dd, $J = 7.6$ Hz, 14.0 Hz, 1H), 3.01–3.09 (m, 2H), 3.72 (dd, $J = 4.8$ Hz, 14.0 Hz, 1H), 3.77 (s, 3H), 4.78 (bs, 1H), 6.79 (d, $J = 8.8$ Hz, 2H), 7.04 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.6, 22.8, 27.6, 29.8, 30.6, 36.2, 39.7, 55.1, 56.1, 113.7, 127.8, 128.1, 129.1, 130.3, 155.0, 155.3, 158.4. HRMS (ESI) calcd for $C_{19}H_{22}NO_2F_3Na^+$ ($[M + Na]^+$): 376.1500, found: 376.1494.

(+)-*N*-Trichloroacetyl-1-(*p*-methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline (**1g**) Pale-yellow powder, yield: 86 %. m.p. 101–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.65–1.72 (m, 5H), 1.86–1.93 (m, 3H), 2.17–2.31 (m, 2H), 2.87 (dd, $J = 6.8$ Hz, 14.4 Hz, 1H), 2.94–3.02 (m, 1H), 3.09 (dd, $J = 5.2$ Hz, 14.4 Hz, 1H), 3.77 (s, 3H), 4.27 (dd, $J = 5.2$ Hz, 14.0 Hz, 1H), 4.79 (bs, 1H), 6.78 (d, $J = 8.4$ Hz, 2H), 7.09 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.7, 22.9, 27.8, 29.8, 30.0, 36.4, 42.2, 55.2, 57.9, 93.6, 113.6, 128.0, 128.0, 129.4, 130.6, 158.3, 158.8. HRMS (ESI) calcd for $C_{19}H_{22}NO_2Cl_3Na^+$ ($[M + Na]^+$): 424.0614, found: 424.0606.

(+)-*N*-Methylsulfonyl-1-(*p*-methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline (**1h**) Pale-yellow powder, yield: 83 %. m.p. 130–132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.61–1.72 (m, 5H), 1.92 (d, $J = 5.6$ Hz, 3H), 2.14 (d, $J = 16.8$ Hz, 1H), 2.25 (bs, 4H), 2.68 (dd, $J = 9.6$ Hz, 14.0 Hz, 1H), 2.98 (dd, $J = 4.0$ Hz, 14.4 Hz, 1H), 3.06–3.10 (m, 1H), 3.67 (dd, $J = 6.4$ Hz, 14.4 Hz, 1H), 3.76 (s, 3H), 4.11 (d, $J = 8.0$ Hz, 1H), 6.82 (d, $J = 8.4$ Hz, 2H), 7.11 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.7, 23.0, 28.0, 29.4, 30.1, 37.8, 38.5, 39.8, 55.2, 58.8, 113.7, 128.1, 128.8, 130.5, 130.8, 158.3. HRMS (ESI) calcd for $C_{18}H_{26}NO_3S^+$ ($[M + H]^+$): 336.1633, found: 336.1636.

(+)-*N*-Trifluoromethylsulfonyl-1-(*p*-methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline (**1i**) Pale-yellow powder, yield: 82 %. m.p. 65–67 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.61–1.73 (m, 5H), 1.82–1.98 (m, 3H), 2.10–2.21 (m, 2H), 2.90–2.99 (m, 3H), 3.72 (dd, $J = 7.2$ Hz, 14.4 Hz, 1H), 3.78 (s, 3H), 4.16 (bs, 1H), 6.83 (d, $J = 8.4$ Hz, 2H), 7.07 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.6, 22.8, 28.0, 30.0, 38.2, 40.4, 55.2, 59.9, 113.9, 128.3, 128.9, 130.6, 158.6. HRMS (ESI) calcd for $C_{18}H_{23}F_3NO_3S^+$($[M + H]^+$): 390.1351, found: 390.1345.

(+)-*N*-Formyl-1-(*p*-hydroxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline (**1j**)(+)-Octabase-mandelate salt (20.0 g) was added to solution of 10 % sodium hydroxide (150 mL), and the mixture was stirred for 0.5 h. After that, the mixture was extracted with DCM (150 mL × 3), washed with brine, and dried over anhydrous Na_2SO_4. The solvent was evaporated and concentrated to dryness to afford (+)-1-(4-methoxyl)benzyl-1,2,3,4,5,6,7,8-octahydroisoquinoline.

A mixture of (+)-1-(4-methoxyl)benzyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (10.0 g, 38.9 mmol) and 40 mL of 48 % hydrobromic acid was heated to reflux for 12 h. After cooling to room temperature, $NaHCO_3$ was added to reaction system until no bubble appeared. The mixture was then extracted with toluene (50 mL × 3), and the combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The crude material was added to a mixture of toluene (70 mL) and formic acid (3.45 g, 46.68 mmol) in an oven-dried flask equipped with a stir bar and water segregator. The mixture was stirred at reflux until no water was separated. After cooling to room temperature, water (50 mL) was added to the mixture with stirring and 10 % aq. NaOH (10 mL) was then added. The aqueous layer was separated, and the organic one was washed with water (50 mL × 2). The combined aqueous layers were added 2 M HCl until amounts of insoluble solid appeared, and the solid was filtered under reduced pressure to give the product as a yellow solid (**1j**). yield: 84 %, m.p. 178–180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.65–1.68 (m, 4H), 1.82–1.95 (m, 4H), 2.08–2.27 (m, 2H), 2.55–2.67 (m, 1H), 2.93–3.08 (m, 1.7H), 3.22–3.29 (m, 0.3H), 3.36–3.40 (m, 0.3H), 3.54 (d, J = 10.8 Hz, 0.7H), 4.41 (dd, J = 10.8 Hz, 13.2 Hz, 0.7H), 4.70 (d, J = 5.6 Hz, 0.3H), 6.68 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.0 Hz, 1.4H), 6.99 (d, J = 8.0 Hz, 0.6H), 7.32 (s, 0.7H), 7.84 (s, 0.3H), 8.14 (s, 0.3H), 8.71 (s, 0.7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.7, 22.8, 27.6, 29.7, 29.9, 30.0, 31.0, 33.7, 36.8, 37.5, 40.4, 53.8, 61.5, 115.3, 115.8, 127.3, 127.6, 128.2, 128.6, 130.3, 155.6, 156.1, 161.1, 161.8. HRMS (ESI) calcd for $C_{17}H_{22}NO_2^+$ ($[M + H]^+$): 272.1651, found: 272.1655.

General procedure for preparation of (+)-*N*-Formyl-1-(4-Alkoxy)benzyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (1k-l)

Sodium hydroxide (0.81 g, 20.3 mmol) was added to a solution mixture of DMF (50 mL) and (+)-*N*-formyl-1-(*p*-hydroxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline (5.0 g, 18.4 mmol) in an oven-dried flask equipped with a stir bar. The solution was stirred for 1 h at ambient temperature and alkyl chloride (20.3 mmol) was then added dropwise to the reaction mixture. After the starting material was completely consumed by TLC monitoring, the organic solvent was evaporated under reduced pressure. Then, the residual mixture was diluted with DCM (30 mL) and H_2O (30 mL), and the organic layer was seperated. The aqueous one was extracted with DCM (30 mL × 2), and combined organic layers were washed with water, dried (Na_2SO_4), and concentrated to dryness. The crude material was purified by column chromatography to afford corresponding product.

(+)-*N*-Formyl-1-(*p*-ethoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline (**1k**) Yield: 94 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30 (t, $J = 6.8$ Hz, 3H), 1.58–1.85 (m, 8H), 1.99–2.17 (m, 2H), 2.51–2.58 (m, 0.6H), 2.72 (dd, $J = 7.2$ Hz, 14.4 Hz, 0.4H), 2.77–2.96 (m, 2H), 3.21 (dd, $J = 5.6$ Hz, 13.2 Hz, 0.4H), 3.50 (d, $J = 10.0$ Hz, 0.6H), 3.90 (q, $J = 7.2$ Hz, 2H), 4.28 (dd, $J = 5.6$ Hz, 13.2 Hz, 0.6H), 4.59 (bs, 0.4H), 6.68–6.74 (m, 2H), 6.87–6.96 (m, 2H), 7.30 (s, 0.6H), 7.83 (s, 0.4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.8, 21.7, 21.8, 26.7, 28.9, 29.1, 29.8, 32.3, 35.2, 36.5, 39.4, 52.2, 59.8, 62.2, 62.3, 113.1, 113.6, 126.6, 126.7, 126.8, 127.8, 128.6, 128.8, 129.2, 129.4, 156.5, 156.8, 159.9, 160.1. HRMS (ESI) calcd for $C_{19}H_{26}NO_2^+$ ($[M + H]^+$): 300.1964, found: 300.1967.

(+)-*N*-Formyl-1-(*p*-propoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline (**1l**) Yield: 92 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.02 (t, $J = 7.6$ Hz, 3H), 1.64–1.93 (m, 10H), 2.06–2.26 (m, 2H), 2.62 (dd, $J = 10.4$ Hz, 14.0 Hz, 0.6H), 2.80 (dd, $J = 6.4$ Hz, 14.4 Hz, 0.4H), 2.85–3.04 (m, 2H), 2.90 (dd, $J = 6.4$ Hz, 13.2 Hz, 0.4H), 3.57 (d, $J = 10.0$ Hz, 0.6H), 3.87 (t, $J = 6.4$ Hz, 2H), 4.36 (dd, $J = 6.4$ Hz, 13.2 Hz, 0.6H), 4.67 (bs, 0.4H), 6.77–6.82 (m, 2H), 6.95–7.05 (m, 2H), 7.38 (s, 0.6H), 7.91 (s, 0.4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.5, 21.6, 21.7, 21.9, 26.7, 28.7, 29.0, 29.1, 29.8, 32.3, 35.2, 36.5, 39.4, 52.2, 59.8, 68.3, 68.4, 113.1, 113.6, 126.7, 126.8, 127.8, 128.7, 129.2, 129.4, 157.0, 159.8, 160.1. HRMS (ESI) calcd for $C_{20}H_{28}NO_2^+$ ($[M + H]^+$): 314.2120, found: 314.2127.

General procedure for Grewe cyclization reaction of (+)-*N*-acyl-1-(4-substituted)benzyl-1,2,3,4,5,6,7,8-octahydroisoquinoline

A mixture of phosphorus pentoxide (4.0 g) and phosphoric acid (10 mL) was stirred in an ice-water bath until a homogeneous solution was formed. A solution of (+)-*N*-acyl-1-(4-substituented)benzyl-1,2,3,4,5,6,7,8-octahydroisoquinoline **1** (1.0 g) in pre-prepared homogeneous phosphoric acid (5 mL) was added to a parallel reaction tube equipped with a magnetic stirrer, as well as temperature controller. The reaction mixture was stirred at 60 °C until starting material almost disappeared monitored by TLC. To quench the reaction, 5 mL ice-water was added to mixture system. Then resulting suspension was extracted with ethyl acetate (10 mL × 3), the combined organic phases were washed with brine, dried by Na_2SO_4, and concentrated to dryness. Column chromatography on silica gel eluted with a mixture of petroleum ether and EtOAc gave the almost corresponding product **2** and the ratio of product **2-1** and side product **2-2** was followed by HPLC analysis.

(+)-3-Methoxy-17-formylmorphinan (**2a–1**) Pale-yellow oil, yield: 90 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.08–1.70 (m, 10H), 2.37 (d, $J = 9.6$ Hz, 1H), 2.42 (t, $J = 12.8$ Hz, 0.5H), 2.66 (t, $J = 17.6$ Hz, 1H), 2.95 (t, $J = 12.8$ Hz, 0.5H), 3.11–3.21 (m, 1H), 3.27 (dd, $J = 4.0$ Hz, 12.8 Hz, 0.5H), 3.69 (bs, 0.5 H), 3.79 (s, 3H), 4.17 (dd, $J = 4.0$ Hz, 12.8 Hz, 0.5H), 4.63 (bs, 0.5 H), 6.74 (d, $J = 8.4$ Hz, 1H), 6.84 (s, 1H), 7.02 (t, $J = 8.4$ Hz, 1H), 7.99 (s, 0.5H), 8.15 (s, 0.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.9, 26.2, 26.3, 30.8, 32.2, 34.9, 36.4, 36.5, 38.7, 38.8, 40.8,

41.1, 42.0, 43.7, 45.0, 46.3, 53.7, 55.2, 111.3, 111.4, 127.5, 128.0, 129.0, 129.1, 140.1, 158.6, 158.7, 160.6, 160.7. HRMS (ESI) calcd for $C_{18}H_{24}NO_2^+$([M + H]$^+$): 286.1807, found: 286.1812.

(+)-3-Methoxy-17-acetylmorphinan (**2c–1**) Pale-yellow oil, yield: 85 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.05–1.71 (m, 10H), 2.05 (s, 2H), 2.15 (s, 1H), 2.34 (d, J = 10.4 Hz, 1H), 2.59–2.70 (m, 1H), 2.91 (t, J = 13.2 Hz, 0.6H), 3.08–3.19 (m, 1H), 3.47 (d, J = 14.0 Hz, 0.6H), 3.78 (s, 3H), 3.91 (bs, 0.4H), 4.36 (d, J = 14.0 Hz, 0.4H), 4.85 (bs, 0.6H), 6.72 (d, J = 8.4 Hz, 1H), 6.83 (s, 1H), 7.01 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.9, 21.0, 25.2, 25.3, 25.7, 28.6, 30.0, 30.6, 34.6, 35.3, 36.6, 39.8, 40.1, 41.0, 42.7, 43.5, 45.9, 52.0, 54.1, 110.1, 110.3, 126.5, 127.4, 127.9, 128.0, 139.2, 157.4, 157.5, 167.7, 167.9. HRMS (ESI) calcd for $C_{19}H_{26}NO_2^+$ ([M + H]$^+$): 300.1964, found: 300.1968.

(+)-3-Methoxy-17-propionylmorphinan (**2d–1**) Pale-yellow oil, yield: 84 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.02–1.11 (m, 4H), 1.21–1.61 (m, 9H), 2.14–2.22 (m, 0.4H), 2.24–2.36 (m, 3H), 2.49–2.60 (m, 1H), 2.79 (td, J = 3.2 Hz, 13.2 Hz, 0.6 H), 3.00–3.09 (m, 1H), 3.43 (dd, J = 4.4 Hz, 13.6 Hz, 0.6H), 3.70 (s, 3H), 3.88 (bs, 0.4H), 4.30 (dd, J = 4.4 Hz, 13.6 Hz, 0.4H), 4.78 (bs, 0.6H), 6.64 (d, J = 8.4 Hz, 1H), 6.75 (d, J = 2.4 Hz, 1H), 6.92 (t, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3, 16.3, 16.4, 29.7, 61.6, 62.4, 62.5, 115.9, 116.0, 123.8, 127.2, 129.3, 131.7, 132.2, 134.5, 135.7, 135.8, 152.8, 156.1, 165.3. HRMS (ESI) calcd for $C_{20}H_{28}NO_2^+$ ([M + H]$^+$): 314.2120, found: 314.2111.

(+)-3-Methoxy-17-ethoxycarbonylmorphinan (**2e–1**) Pale-yellow oil, yield: 86 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.08 (t, J = 12.4 Hz, 1H), 1.22–1.36 (m, 7H), 1.48–1.67 (m, 5H), 2.36 (d, J = 10.8 Hz, 1H), 2.63–2.69 (m, 2H), 3.05–3.13 (m, 1H), 3.79 (s, 3H), 3.90 (d, J = 13.6 Hz, 0.5H), 4.09–4.17 (m, 2.5H), 4.25 (bs, 0.5H), 4.39 (bs, 0.5H), 6.71 (dd, J = 2.4 Hz, 8.4 Hz, 1H), 6.83 (d, J = 2.4 Hz, 1H), 7.00 (t, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.2, 14.7, 14.8, 22.1, 26.4, 31.3, 31.6, 36.6, 37.6, 38.2, 41.4, 41.7, 43.9, 44.0, 49.7, 50.0, 55.2, 61.1, 61.2, 111.0, 111.1, 111.3, 129.1, 140.5, 155.7, 158.4. HRMS (ESI) calcd for $C_{20}H_{28}NO_3^+$ ([M + H]$^+$): 330.2069, found: 330.2064

(+)-3-Methoxy-17-trifluoroacetylmorphinan (**2f–1**) Pale-yellow oil, yield: 93 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.05–1.14 (m, 1H), 1.26–1.76 (m, 9H), 2.39 (d, J = 10.4 Hz, 1H), 2.61–2.65 (m, 0.4H), 2.67–2.78 (m, 1H), 3.02 (td, J = 3.2 Hz, 13.6 Hz, 0.6H), 3.17–3.25 (m, 1H), 3.69 (d, J = 13.6 Hz, 0.6H), 3.80 (s, 3H), 4.10 (bs, 0.4H), 4.29 (dd, J = 4.8 Hz, 13.6 Hz, 0.4H), 4.78 (bs, 0.6H), 6.76 (dd, J = 2.4 Hz, 8.4 Hz, 1H), 6.85 (t, J = 2.4 Hz, 1H), 7.05 (t, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.8, 25.1, 25.2, 25.5, 29.5, 30.5, 35.0, 36.7, 39.8, 40.9, 42.6, 43.4, 48.4, 54.2, 110.4, 110.5, 126.0, 126.4, 128.1, 138.8, 157.7. HRMS (ESI) calcd for $C_{19}H_{22}NO_2F_3Na^+$ ([M + Na]$^+$): 376.1500, found: 376.1494.

(+)-3-Methoxy-17-trichloroacetylmorphinan (**2g–1**) Pale-yellow oil, yield: 55 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.95–1.03 (m, 1H), 1.16–1.60 (m, 9H), 2.30 (d, J = 9.6 Hz, 1H), 2.63 (d, J = 17.6 Hz, 1H), 2.80 (d, J = 17.6 Hz, 0.5H), 2.96 (t,

J = 13.6 Hz, 0.5H), 3.11 (dd, J = 6.4 Hz, 18.4 Hz, 1H), 3.71 (s, 3H), 4.19 (bs, 1H), 4.67 (d, J = 20.8 Hz, 1H), 6.67 (dd, J = 2.4 Hz, 8.4 Hz, 1H), 6.76 (d, J = 2.4 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.2, 20.0, 20.8, 21.7, 25.2, 25.3, 28.7, 30.6, 30.9, 35.0, 36.4, 38.2, 40.5, 41.8, 42.8, 50.4, 53.0, 54.2, 59.3, 92.7, 92.8, 110.3, 126.4, 126.5, 127.9, 128.0, 157.7, 170.1. HRMS (ESI) calcd for $C_{19}H_{22}NO_2Cl_3Na^+$ ($[M + Na]^+$): 424.0614, found: 424.0606.

(+)-3-Methoxy-17-methylsulfonylmorphinan (**2h–1**) Pale-yellow oil, yield: 70 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.93–1.03 (m, 1H), 1.17–1.47 (m, 6H), 1.57–1.65 (m, 2H), 1.72 (d, J = 12.8 Hz, 1H), 2.28 (d, J = 12.8 Hz, 1H), 2.64–2.75 (m, 2H), 2.81 (s, 3H), 3.04 (dd, J = 5.6 Hz, 18 Hz, 1H), 3.44 (dd, J = 4.0 Hz, 4.4 Hz, 1H), 3.71 (s, 3H), 3.98 (bs, 1H), 6.65 (dd, J = 2.4 Hz, 8.4 Hz, 1H), 6.74 (d, J = 2.4 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.0, 26.3, 26.4, 31.1, 36.4, 37.5, 39.4, 39.9, 41.6, 44.7, 51.9, 55.2, 111.3, 111.4, 127.8, 129.0, 140.0, 158.7. HRMS (ESI) calcd for $C_{18}H_{26}NO_3S^+$ ($[M + H]^+$): 336.1633, found: 336.1636

(+)-3-Methoxy-17-trifluoromethylsulfonylmorphinan (**2i–1**) Pale-yellow oil, yield: 87 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.26–1.84 (m, 10H), 2.38 (d, J = 12.4 Hz, 1H), 2.83–2.96 (m, 2H), 3.20 (dd, J = 6.0 Hz, 18.4 Hz, 1H), 3.68 (dd, J = 4.0 Hz, 13.6 Hz, 1H), 3.79 (s, 3H), 4.13 (bs, 1H), 6.76 (dd, J = 2.4 Hz, 8.4 Hz, 1H), 6.83 (d, J = 2.4 Hz, 1H), 7.06 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.8, 25.1, 25.3, 35.2, 36.2, 40.3, 40.5, 53.2, 54.2, 110.3, 110.7, 112.8, 117.4, 120.6, 126.0, 128.2, 129.6, 138.4, 157.9. HRMS (ESI) calcd for $C_{18}H_{23}F_3NO_3S^+$($[M + H]^+$): 390.1351, found: 390.1345.

(+)-3-Hydroxy-17-formylmorphinan (**2j–1**) Pale-yellow oil, yield: 87 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.08–1.14 (m, 1H), 1.26–1.33 (m, 3H), 1.40–1.69 (m, 6H), 2.33 (d, J = 10.0 Hz, 1H), 2.47 (td, J = 4.0 Hz, 13.2 Hz, 0.5H), 2.63 (t, J = 13.2 Hz, 1H), 2.97 (td, J = 3.6 Hz, 13.2 Hz, 0.5H), 3.09–3.20 (m, 1H), 3.26 (dd, J = 4.4 Hz, 13.2 Hz, 0.5H), 3.69 (s, 0.5H), 4.14 (dd, J = 4.4 Hz, 13.2 Hz, 0.5H), 4.63 (bs, 0.5H), 6.70 (d, J = 8.0 Hz, 1H), 6.82 (d, J = 2.0 Hz, 1H), 6.93 (t, J = 8.0 Hz, 1H), 7.99 (s, 0.5H), 8.15 (s, 0.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.9, 25.2, 25.3, 29.7, 31.2, 34.4, 35.3, 35.4, 37.5, 37.6, 39.7, 40.6, 40.9, 42.7, 43.9, 45.9, 52.5, 53.3, 111.2, 112.8, 112.9, 125.2, 125.8, 128.0, 128.1, 138.9, 154.6, 154.7, 160.0, 160.1. HRMS (ESI) calcd for $C_{17}H_{22}NO_2^+$ ($[M + H]^+$): 272.1651, found: 272.1655.

(+)-3-Ethoxy-17-formylmorphinan (**2k–1**) pale-yellow oil, yield: 89 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.08–1.13 (m, 1H), 1.26–1.70 (m, 12H), 2.37 (d, J = 10.0 Hz, 1H), 2.46 (td, J = 3.6 Hz, 13.2 Hz, 0.5H), 2.66 (t, J = 17.6 Hz, 1H), 2.95 (t, J = 13.2 Hz, 0.5H), 3.16 (td, J = 5.6 Hz, 17.6 Hz, 1H), 3.24 (dd, J = 4.4 Hz, 13.2 Hz, 0.5H), 3.69 (bs, 0.5H), 4.01 (q, J = 6.8 Hz, 2H), 4.15 (dd, J = 4.4 Hz, 13.2 Hz, 0.5H), 4.63 (bs, 0.5H), 6.72 (d, J = 8.4 Hz, 1H), 6.84 (s, 1H), 7.01 (t, J = 8.4 Hz, 1H), 7.99 (s, 0.5H), 8.15 (s, 0.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 20.9, 21.0, 25.2, 25.4, 29.8, 31.3, 34.0, 35.4, 35.5, 37.7, 37.8, 39.9, 40.2, 41.1, 42.7, 44.0, 45.4, 52.7, 62.3, 110.8, 111.0, 126.4, 127.0, 128.0, 128.1,

139.1, 157.0, 157.1, 159.6, 159.7. HRMS (ESI) calcd for $C_{19}H_{26}NO_2^+$ ([M + H]$^+$): 300.1964, found: 300.1967.

(+)-3-Propoxy-17-formylmorphinan (**2l–1**) Pale-yellow oil, yield: 91 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.97 (t, $J = 7.6$ Hz, 3H), 1.18–1.63 (m, 10 H), 1.70–1.78 (m, 2H), 2.30 (d, $J = 8.0$ Hz, 1H), 2.39 (td, $J = 4.0$ Hz, 12.8 Hz, 0.5H), 2.58 (t, $J = 17.6$ Hz, 1H), 2.88 (td, $J = 4.0$ Hz, 12.8 Hz, 0.5H), 3.08 (td, $J = 6.0$ Hz, 17.6 Hz, 1H), 3.19 (dd, $J = 4.0$ Hz, 12.8 Hz, 0.5H), 3.61 (t, $J = 4.4$ Hz, 0.5H), 3.82 (t, $J = 6.8$ Hz, 2H), 4.08 (dd, $J = 4.0$ Hz, 12.8 Hz, 0.5H), 4.55 (t, $J = 4.4$ Hz, 0.5H), 6.65 (dd, $J = 2.4$ Hz, 8.4 Hz, 1H), 6.76 (d, $J = 2.4$ Hz, 1H), 6.93 (t, $J = 8.4$ Hz, 1H), 7.91 (s, 0.5H), 8.07 (s, 0.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.6, 20.9, 21.7, 25.2, 25.3, 29.8, 31.2, 33.9, 35.4, 35.5, 37.7, 37.8, 39.8, 40.1, 41.0, 42.7, 44.0, 45.4, 52.7, 68.4, 110.8, 110.9, 111.0, 126.3, 126.8, 127.9, 128.0, 139.0, 157.1, 157.2, 159.6, 159.7. HRMS (ESI) calcd for $C_{20}H_{28}NO_2^+$ ([M + H]$^+$): 314.2120, found: 314.2127.

(+)-3-Methyl-17-formylmorphinan (**2m–1**) pale-yellow oil, yield: 89 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.97–1.02 (m, 1H), 1.20–1.61 (m, 9H), 2.22 (s, 3H), 2.32–2.38 (m, 1.5H), 2.58 (t, $J = 18.4$ Hz, 1H), 2.83 (t, $J = 13.2$ Hz, 0.5H), 3.03–3.18 (m, 1.5H), 3.60 (bs, 0.5H), 4.05 (d, $J = 9.2$ Hz, 0.5H), 4.53 (bs, 0.5H), 6.87 (d, $J = 1.2$ Hz, 2H), 7.00 (s, 1H), 7.89 (s, 0.5H), 8.05 (s, 0.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.4, 21.9, 21.9, 26.2, 26.3, 31.3, 32.7, 34.9, 36.3, 36.4, 38.4, 38.6, 41.0, 41.2, 42.2, 43.9, 45.2, 46.4, 53.8, 126.0, 126.9, 127.0, 128.0, 128.1, 132.4, 132.9, 136.2, 136.3, 138.5, 138.6, 160.6, 160.7. HRMS (ESI) calcd for $C_{18}H_{24}NO^+$ ([M + H]$^+$): 270.1858, found: 270.1860.

(+)-3-Chloro-17-formylmorphinan (**2n–1**) Pale-yellow oil, yield: 57 %. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.93–0.99 (m, 1H), 1.17–1.65 (m, 9H), 2.26–2.36 (m, 1.5H), 2.61 (t, $J = 20.8$ Hz, 1H), 2.78–2.83 (m, 0.5H), 3.09 (t, $J = 20.8$ Hz, 1H), 3.22 (dd, $J = 3.2$ Hz, 13.6 Hz, 0.5H), 3.64 (bs, 0.5H), 4.08 (dd, $J = 3.2$ Hz, 13.6 Hz, 0.5H), 4.56 (bs, 0.5H), 6.95–6.98 (m, 1H), 7.04 (d, $J = 8.0$ Hz, 1H), 7.19 (d, $J = 2.0$ Hz, 1H), 7.91 (s, 0.5H), 8.06 (s, 0.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.8, 25.0, 25.1, 25.2, 30.1, 31.5, 33.7, 35.2, 35.3, 37.7, 37.8, 39.6, 39.8, 40.8, 42.4, 43.7, 44.9, 52.2, 124.6, 124.7, 125.3, 125.4, 128.6, 128.7, 131.5, 131.6, 133.0, 133.6, 139.9, 140.0, 159.6. HRMS (ESI) calcd for $C_{17}H_{21}NOCl^+$ ([M + H]$^+$): 290.1312, found: 290.1303.

General procedure for computational modeling

Geometries of all the intermediates and transition states were optimized at the B3LYP/6-311 + G(d,p) level, followed by frequency calculations at the same level of theory to ensure these are stationary points and to extract Gibbs free energy corrections at 298 K. The Gaussian09 software was used for all DFT calculations.

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