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Racemization of (*S*)-(+)-10,11-dimethoxyaporphine and (*S*)-(+)-aporphine: efficient preparations of (*R*)-(−)-apomorphine and (*R*)-(−)-aporphine via a recycle process of resolution

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Abstract—Efficient preparations of (*R*)-(−)-apomorphine (*R*)-**1** and (*R*)-(−)-aporphine (*R*)-**2** based on a recycle process of resolution are described. In this recycle process of resolution, (*RS*)-(±)-10,11-dimethoxyaporphine **3** as the precursor of **1**, and (*RS*)-(±)-aporphine **2** were successfully resolved into both enantiomers with (+)-dibenzoyltartaric acid (DBTA). The desired (*R*)-**3** and (*R*)-**2** were obtained and then, respectively, transformed to compound (*R*)-**1**, the hydrochloride salt of (*R*)-**1**, diacetate compound **4** and the hydrochloride salt of (*R*)-**2**; while the undesired (*S*)-**3** and (*S*)-**2** were racemized to obtain a racemate, which was suitable for further resolution. A method for the racemization of the undesired (*S*)-**3** and (*S*)-**2** was extensively studied, in order to obtain high-yielding racemization conditions. A plausible mechanism for the racemization of (*S*)-**3** and (*S*)-**2** was also proposed.

1. Introduction

The importance of chiral compounds is widely recognized. In general, there are two typical ways to obtain chiral compounds. One is asymmetric synthesis, while the other is chiral resolution. Despite the revolutionary advances in asymmetric synthesis over the last few decades, resolution as a 'low-tech' method is still the most important approach to chiral compounds especially in large scale preparations or industrial syntheses, as it is often the most economical and convenient method. However, only a maximum theoretical yield of 50% can be achieved during resolution, discarding of the other half (i.e., the unwanted isomer) is economically and environmentally unacceptable. For this reason, some strategies such as recycling resolution (recycle process of resolution),[1–9] dynamic kinetic resolution (DKR),[10–12] etc.[13,14] have recently been developed and can usually be used to overcome this disadvantage. These strategies seem attractive, because the undesired isomer can be recycled, meaning a theoretical yield of 100% can still be obtained. For the strategy of recycling resolution (recycle process of resolution), the resolution is performed first to separate two isomers, and then racemization of the unwanted isomer is carried in a separate step. The resolution and racemization can thus be repeated for multiple cycles in order to obtain an as high as possible yield of the desired isomer, the whole procedure is quite simple and easy to operate. Herein, we report our preparations of (*R*)-(−)-apomorphine (*R*)-**1** and its analogue (*R*)-(−)-aporphine (*R*)-**2** via a recycle process of resolution.

(*R*)-(−)-Apomorphine and its non-oxygenated analogue (*R*)-(−)-aporphine are of pharmaceutical value,[15–22] and therefore have attracted much interest from synthetic chemists. Although the total syntheses of (*RS*)-(±)-apomorphine (*RS*)-**1** and (*RS*)-(±)-aporphine (*RS*)-**2** have been well documented,[23–31] preparations of (*R*)-(−)-apomorphine and (*R*)-(−)-aporphine are rare.[32–37] Recently we have become interested in developing an effective method to obtain enough quantity of (*R*)-(−)-apomorphine and (*R*)-(−)-aporphine in order to test their physiological roles, so a strategy based on recycling resolution was chosen to be used for this purpose.

2. Results and discussion

It is obviously not reasonable to directly resolve (*RS*)-**1** considering the fact that apomorphine is unstable and

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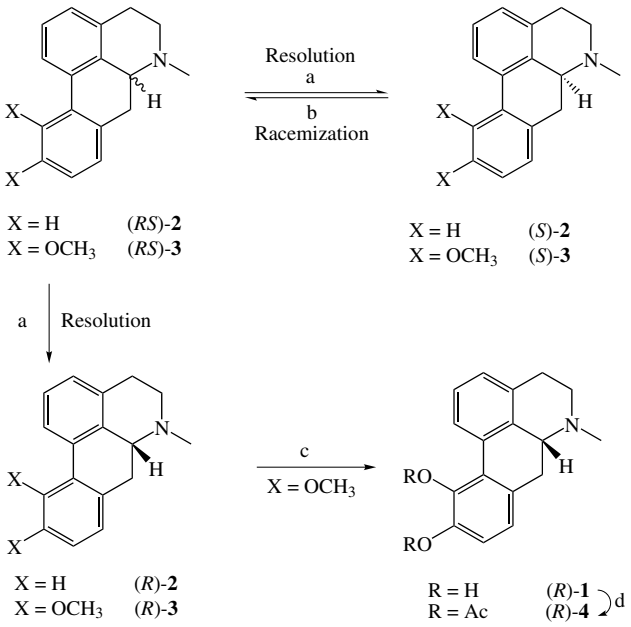
rapidly turns dark green on exposure to light and air, the better way is to resolve the stable (*RS*)-(±)-10,11-dimethoxyaporphine (*RS*)-**3** first to gain (*R*)-(−)-10,11-dimethoxyaporphine (*R*)-**3**, and then transform it into (*R*)-**1** after ether cleavage (Scheme 1, X = OCH_3). Compound (*RS*)-**2** is very stable, and can therefore be directly resolved into (*R*)-**2** and (*S*)-**2** (Scheme 1, X = H).



Scheme 1. Reagents and conditions: (a) 1 equiv (+)-DBTA in EtOAc: *i*-PrOH (3:2); (b) 2–3 equiv KOH in DMSO at 120 °C for 2 h; (c) reflux in HBr–AcOH (6 h); (d) large excess of pyridine and Ac_2O at rt.

We found that the total syntheses reported by Neumeyer et al.[28] starting from the Reissert's compound were much more convenient than others. As a result Neumeyer et al.'s procedure[28] was followed in our laboratory in order to obtain (*RS*)-**2** and (*RS*)-**3**.

With racemic compounds (*RS*)-**2** and (*RS*)-**3** in hand, we attempted to resolve them with natural (+)-tartaric acid to obtain (*R*)-**2** and (*R*)-**3** according to Saari et al.'s report,[38] but unfortunately the salts of **2** and **3** with (+)-tartaric acid precipitated very slowly in several solvents tried, and the yields were low. We then turned our attention to several other chiral acids for resolving (*RS*)-**2** and (*RS*)-**3**. The chiral acids we examined included (−)-malic acid, (−)-acetyl malic acid, (+)-10-camphorsulfonic acid, (+)-diacetyl tartaric acid, (+)-di-*p*-toluoyl tartaric acid, and (+)-dibenzoyl tartaric acid. Finally, we found that both (*RS*)-**2** and (*RS*)-**3** can be efficiently resolved with (+)-dibenzoyl tartaric acid (DBTA). The salts of **2** and **3** with (+)-DBTA precipitated quite fast in the mixed solvent of ethyl acetate and isopropanol. By adjusting the ratio of ethyl acetate and isopropanol to 3:2, the highest yields (43% for **2** and 42% for **3**, respectively) of resolution could be reached. There is another advantage when using (+)-DBTA as a resolving agent, it can be recovered from aqueous solution by extraction with ethyl acetate after neutralization with hydrochloric acid. (*RS*)-**2** can also be resolved with (+)-di-*p*-toluoyl tartaric acid as has been reported by Cannon et al.,[37] (+)-DBTA is cheaper and gave a better yield here.

While 43% of the desired (*R*)-**3** was obtained from the resolution of the (*RS*)-**3** with (+)-DBTA, 40% of undesired (*S*)-**3** was also obtained. Since (*S*)-(−)-apomorphine (*S*)-**1** does not possess significant biological activity, compound (*S*)-**3** as a precursor of (*S*)-**1** could be discarded. We attempted to find a method to convert this unwanted compound (*S*)-**3** into the useful (*R*)-**3**. This conversion was achieved by transforming (*S*)-**3** into (*RS*)-**3** and then into (*R*)-**3**. Compound (*S*)-**3** was thus recycled just by repeating this racemization and resolution procedure. Herein, the racemization of (*S*)-**3** was extensively studied, and many conditions were tried, which are summarized in Table 1. As can be seen in Table 1, (*S*)-**3** can be efficiently racemized into (*RS*)-**3** with a strong base such as potassium hydroxide, sodium methoxide, sodium ethoxide, and potassium *tert*-butoxide in DMSO at a temperature higher than 120 °C (Table 1, entries 1, 2, 4, 8, 10, and 12). It is difficult to understand why sodium hydroxide was not a suitable base for the racemization, when 10 equiv of sodium hydroxide was used, only a slight amount of racemization occurred even when heating at 140 °C for 2 h (entry 6). The solvent effect is dramatic here, DMSO is the only favorable solvent. Other solvents such as DMF, methanol, ethanol, etc. could not be used here. Temperature had a notable impact on the racemization, the temperature should not be kept below 120 °C (entries 3, 9, and 11).

We also attempted the racemization of (*S*)-**2** in order to convert the unwanted (*S*)-**2** into the useful (*R*)-**2**. We found that the racemization of (*S*)-**2** could also be carried out (entries 16–18). The favorable solvent was DMSO, with the temperature kept at 120–140 °C. Suitable bases were potassium hydroxide, sodium ethoxide, and potassium ethoxide. Surprisingly, the strong base sodium hydroxide also failed here to racemize (*S*)-**2** into (*RS*)-**2** (entry 15) as it did for (*S*)-**3** (entry 6), which implies something we have not yet known for a possible mechanism of racemization.

It should be pointed out that there is no need to always use enantiomerically pure (*S*)-**3** and (*S*)-**2** for the racemization experiment, the optically enriched compounds from the mother liquid of the resolution can also be directly used for the method, (*R*)-**3** and (*R*)-**2** can also be racemized into (*RS*)-**3** and (*RS*)-**2** under the same conditions.

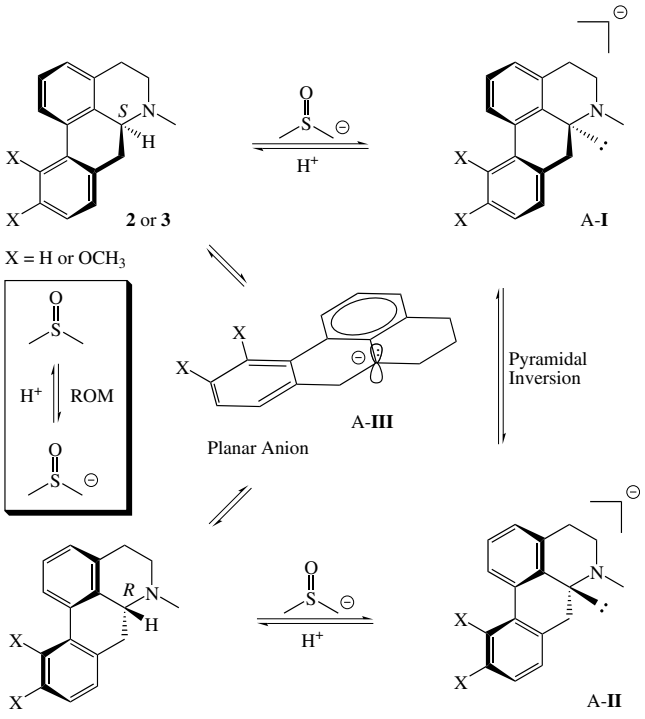
Davis et al. reported an example of racemization of (*R*)-**3** in 1980,[39] when they wanted to prepare (*S*)-(+)-apomorphine from (*R*)-(−)-apomorphine. Davis et al.'s method of racemization included two steps: palladium-catalyzed dehydrogenation and reduction of an enamine with sodium cyanoborohydride. Obviously, our method outlined herein is more inexpensive and more convenient than Davis et al.'s report.

A plausible mechanism of the racemization is now proposed. As described in Scheme 2, the proton at the stereogenic center of (*S*)-**3** or (*S*)-**2** is weakly acidic, it could be removed by a strong base affording a pyramidal carbanion

Table 1. Racemization of (*S*)-(+)-**3** and (*S*)-(+)-**2**

Entry	Compound	Base (equiv)	Solvent	Temperature (°C)	Time (h)	PR[a] (%)	Yield[b] (%)
1	(*S*)-**3**	KOH (5)	DMSO	120	2	100	94
2	(*S*)-**3**	KOH (2)	DMSO	120	2	100	95
3	(*S*)-**3**	KOH (2)	DMSO	100	2	65	97
4	(*S*)-**3**	KOH (0.5)	DMSO	140	5	100	80
5	(*S*)-**3**	KOH (10)	DMF	120	4	10	78
6	(*S*)-**3**	NaOH (10)	DMSO	140	2	6	85
7	(*S*)-**3**	NaOH (10)	DMF	120	4	3	84
8	(*S*)-**3**	EtONa (2)	DMSO	120	2	100	89
9	(*S*)-**3**	EtONa (10)	EtOH	80[c]	10	24	96
10	(*S*)-**3**	MeONa (2)	DMSO	120	2	100	88
11	(*S*)-**3**	MeONa (10)	MeOH	70[c]	12	15	92
12	(*S*)-**3**	*t*-BuOK (2)	DMSO	120	2	100	90
13	(*S*)-**3**	*t*-BuOK (2)	DMF	120	5	25	90
14	(*S*)-**2**	LiOH (5)	DMSO	140	2	0	95
15	(*S*)-**2**	NaOH (5)	DMSO	140	2	5	92
16	(*S*)-**2**	KOH (3)	DMSO	120	2	100	96
17	(*S*)-**2**	EtONa (3)	DMSO	120	2	100	89
18	(*S*)-**2**	EtOK (3)	DMSO	120	2	100	88

[a] Percentage of racemization.
[b] Isolated yield of compound **3** or **2**.
[c] Refluxing.



Scheme 2.

A-**I** in which an unshared electron pair occupies a downward sp^3 hybrid orbital,[40,41] and the configuration of the stereogenic center is retained. Carbanion A-**I** will automatically change into the other pyramidal carbanion A-**II** via a *Waldern* type inversion[42] upon heating, an unshared electron pair will occupy an upward sp^3 hybrid orbital in A-**II**, and the configuration of the stereogenic center will be inverted. The above pathway should be reversible, which means that both (*S*)-**3** (or **2**) and (*R*)-**3** (or **2**) can be racemized into (*RS*)-**3** (or **2**). It is notable that a rapid *Waldern* type inversion between A-**I** and A-**II** needs relatively high energy to overcome the interconversion barrier, because torsional strain of both pyramidal carbanions plays a significant role. This is why a complete racemization of (*S*)-**3** (or **2**) needs a temperature higher than 120 °C as shown in Table 1. We also propose that potassium hydroxide first reacts with DMSO to form a more reactive anion species (potassium methylsulfinyl methide)[43–46] which then reacts with **3** (or **2**) to form the intermediate anion A-**I**, thus the dramatic solvent effect can be understood.

Another mechanism for the racemization of (*S*)-**3** or (*S*)-**2** is also possible. The removal of the proton at the stereogenic center of (*S*)-**3** or (*S*)-**2** by a strong base affords a planar carbanion (A-**III**)[47] in which an unshared electron pair occupies a conjugate p orbital leading to delocalization of the electron pair and thus stabilizing the carbanion. Protonation of the planar carbanion (A-**III**) would definitely produce a racemic compound [(*RS*)-**3** or (*RS*)-**2**] due to equal probabilities of access of the proton on both faces of the plane.

Actually, the shape (planar or pyramidal) of a carbanion probably depends upon the counterion. For example, a potassium cation tends to furnish a planar benzylic carbanion (A-**III**), while a lithium cation tends to furnish a pyramidal carbanion (A-**I** or A-**II**).[47] Whenever a pyramidal or planar carbanion was involved in the mechanism, racemization would consequently occur. A carefully designed experiment would support our proposed mechanism, when the mixture of (*S*)-**2** and 2 equiv of potassium hydroxide was stirred for 2 h at 120 °C in the deuterated solvent (DMSO-d_6), ^{1}H NMR analysis of the isolated product showed that a deuterium atom was incorporated at the stereogenic center of (*RS*)-**2**, which means that a carbanion formed during the racemization.

Finally, by refluxing with an excess of hydrobromic acid instead of hydroiodic acid in acetic acid, the dimethyl ether bonds of (*R*)-**3** were cleaved to furnish the title compound (*R*)-**1** in a good yield. Free apomorphine is quite unstable, hence it was transformed into the crystalline apomorphine hydrochloride (*R*)-**1**-HCl which can be stored in a refrigerator for more than 6 months. It can also be transformed into the stable compound (*R*)-(−)-10,11-diacetoxyaporphine **4** which is converted in vivo to free apomorphine. This diester derivative of (*R*)-(−)-apomorphine serves as a prodrug of apomorphine and exhibits an extended half-life.[48]

3. Conclusion

In conclusion, a recycling resolution method for the preparations of (*R*)-(−)-apomorphine and (*R*)-(−)-aporphine has been described. Racemization of (*S*)-(+)-10,11-dimethoxyaporphine and (*S*)-(+)-apomorphine was extensively studied, and the best conditions found. A possible mechanism for the racemization has also been proposed.

4. Experimental

4.1. General methods

Melting points are uncorrected. ^{1}H NMR spectra were acquired on a Bruker AM-500 instrument. Chemical shifts were given on the delta scale as parts per million (ppm) with tetramethylsilane (TMS) as the internal standard. IR spectra were recorded on Nicolet Magna IR-550. Mass spectra were recorded on HP5989A. Column chromatography was performed on silica gel. Optical rotations of chiral compounds were measured on WZZ-1S automatic polarimeter at room temperature. All solvents were purified by standard procedures. All chemicals were analytically pure. Racemic compounds (*RS*)-**2** and (*RS*)-**3** were prepared according to a known procedure.[28] (+)-Dibenzoyl tartaric acid (DBTA) was obtained from Aldrich company or made in our laboratory.[49]

4.2. Resolution of (*RS*)-10,11-dimethoxyaporphine (*RS*)-3

A solution of (+)-dibenzoyl tartaric acid (4.61 g, 12.86 mmol) in ethyl acetate (45 ml) was transferred into a three-necked flask with a magnetic stirrer bar. Then a solution of racemic 10,11-dimethoxyaporphine (3.80 g, 12.86 mmol) in ethyl acetate (15 ml) was added dropwise within 5 min at room temperature, and white crystals formed in 15 min. The mixture was heated at reflux, after which isopropanol (40 ml) was added, and the mixture turned clear. Refluxing was continued for 1 h, and then the mixture was allowed to cool to room temperature and then to 0 °C in an ice bath, causing white needles to precipitate. Filtration separated the white needles from the mother liquid which was used to recover (*S*)-(+)-10,11-dimethoxyaporphine at the later stage. The white needles (4.20 g) were recrystallized in the mixed solvent of ethyl acetate (35 ml) and isopropanol (25 ml) to produce (*R*)-(−)-10,11-dimethoxyaporphinium (+)-dibenzoyl tartrate (3.55 g) with a specific rotation value of $[\alpha]_D^{20} = +10.1$ (*c* 1, methanol). The salt was dissolved in water (20 ml), the pH of the aqueous solution was then adjusted to 9 by addition of potassium carbonate, and the aqueous solution was extracted twice with ethyl acetate (25 ml × 2). Combined extracts were dried over anhydrous sodium sulfate, and then evaporated to dryness to afford (*R*)-(−)-10,11-dimethoxyaporphine (1.60 g, 5.42 mmol) in 42% yield, $[\alpha]_D^{20} = -172.3$ (*c* 1.4, methanol).

The mother liquid from the above resolution was concentrated to dryness, and dissolved in water (50 ml). The aqueous solution was made alkaline (pH = 9) by the addition of potassium carbonate, and extracted twice with ethyl acetate (25 ml × 2). The combined extracts were evaporated to dryness to give a residue. Ethanol (20 ml) and concentrated hydrochloric acid (1 ml, 12 mmol) were then added. The solution was heated at reflux for 1 h, and then evaporated to dryness under a vacuum to give a viscous oil which was recrystallized in acetone to yield white crystals of (*S*)-(+)-10,11-dimethoxyaporphine hydrochloride. The white crystals were dissolved in water (20 ml) to form a clear aqueous solution which was made alkaline (pH = 9) with potassium carbonate and twice extracted with ethyl acetate (20 ml × 2). The combined extracts were washed with brine (10 ml) and dried over anhydrous sodium sulfate. Removal of the solvent afford (*S*)-(+)-10,11-dimethoxyaporphine (1.53 g, 5.18 mmol) in 40% yield, $[\alpha]_D^{20} = +172.1$ (*c* 1.5, methanol).

4.3. Typical procedure for the racemization of (*S*)-(+)-10,11-dimethoxyaporphine (*S*)-3

A solution of (*S*)-(+)-10,11-dimethoxyaporphine (2.00 g, 6.77 mmol) in DMSO (20 ml) was transferred into a round bottom flask with a stirrer bar under N_2. Powdered potassium hydroxide (0.76 g, 13.55 mmol) was added, and then the mixture was heated to around 120 °C. Stirring was continued at 120 °C for 2 h. After the mixture was cooled to room temperature, it was diluted with water (80 ml). The diluted aqueous solution was extracted twice with toluene (40 ml × 2), the combined extracts were washed successively with water (30 ml) and brine (10 ml). After drying with anhydrous sodium sulfate, the solvent was removed by a rotavapor. The residue was chromatographed through a short column of silica gel to give racemic 10,11-dimethoxyaporphine (1.90 g, 6.43 mmol) in 95% yield. ^{1}H NMR showed that the product here was identical to the sample from the total synthesis and thus can be used for further resolution.

4.4. Preparation of (*R*)-(−)-apomorphine hydrochloride 1–HCl

(*R*)-(−)-10,11-Dimethoxyaporphine (1.21 g, 4.10 mmol) was dissolved in acetic acid (20 ml), an aqueous solution of HBr (20 ml, 48% w/v) was added. The mixture was heated at reflux for 6 h while stirring under N_2. Then the reaction solution was concentrated to dryness under vacuum, the residue was dissolved in water (20 ml). The aqueous solution was made alkaline (pH = 8) with $NaHCO_3$, and extracted twice with ethyl acetate (20 ml × 2). The

combined extracts were washed with brine (10 ml) and dried over anhydrous sodium sulfate. Removal of the solvent gave a bluish oily residue, which was immediately dissolved in ethanol (20 ml). Concentrated hydrochloric acid (0.7 ml, 8.4 mmol) and activated carbon (0.5 g) were added, and the solution heated at reflux for 1 h under N_2. The solution was filtered to remove activated carbon and evaporated to dryness under vacuum. Dry acetone (15 ml) was added, and the mixture stirred vigorously for half an hour, then left to stand overnight in a refrigerator. The off-white solid was collected by filtration and washed with ethyl acetate. (*R*)-(−)-Apomorphine hydrochloride (1.01 g, 3.32 mmol) was thus obtained in 81% yield, $[\alpha]_D^{20} = -48.1$ (*c* 1.0, water) {lit.[50] $[\alpha]_D^{25} = -48.0$ (*c* 1.2, water)}. ^{1}H NMR (CD_3OD): δ 8.43 (d, $J = 7.9$ Hz, 1H), 7.36 (t, $J = 7.8$ Hz, 1H), 7.16 (d, $J = 7.6$ Hz, 1H), 6.74 (d, $J = 8.0$ Hz, 1H), 6.70 (d, $J = 8.0$ Hz, 1H), 4.26 (d, $J = 12.1$ Hz, 1H), 3.79 (dd, $J = 5.2$, 11.8 Hz, 1H), 3.49 (dt, $J = 3.5$, 12.8 Hz, 1H), 3.32–3.43 (m, 2H), 3.19 (s, 3H), 3.10 (dd, $J = 3.4$, 17.5 Hz, 1H), 2.77 (t, $J = 13.7$ Hz, 1H). MS(EI) *m*/*z* (% relative intensity) 267 (M^+, 63), 266(100), 248(11), 224(22), 206(8), 178(5), 152(6), 131(14).

4.5. Preparation of diacetate of (*R*)-(−)-apomorphine 4

(*R*)-(−)-Apomorphine hydrochloride (0.91 g, 3.00 mmol), acetic anhydride (6 ml), and pyridine (1 ml) were mixed in a dry round bottom flask with a magnetic stirrer bar. When the mixture was stirred at room temperature for 3 h, the reaction was complete as monitored by TLC. The reaction mixture was then diluted with ethyl acetate (60 ml), and a solution of potassium carbonate (7.60 g, 0.055 mol) in water (60 ml) was added while stirring. The organic phase was separated, washed successively with water (20 ml) and brine (10 ml), and then dried over anhydrous sodium sulfate. Removal of the solvent gave a pale yellow crude oil which was chromatographed through a short column of silica gel to afford (*R*)-(−)-10,11-diacetoxyaporphine **4** (0.95 g, 2.71 mmol) in 90% yield, mp 127–128 °C (lit.[50] 127–128 °C), $[\alpha]_D^{20} = -137.1$ (*c* 0.3, methanol) and $[\alpha]_D^{20} = -89.0$ (*c* 0.5, 0.1 M HCl) {lit.[50] $[\alpha]_D^{24} = -88$ (*c* 1.12, 0.1 M HCl)}. ^{1}H NMR ($CDCl_3$): δ 7.75 (d, $J = 7.8$ Hz, 1H), 7.16–7.24 (m, 2H), 7.10 (d, $J = 7.7$ Hz, 1H), 7.07 (d, $J = 8.2$ Hz, 1H), 3.12–3.23 (m, 3H), 3.04 (dd, $J = 5.9$, 11.6 Hz, 1H), 2.75 (dd, $J = 3.1$, 16.3 Hz, 1H), 2.50–2.61 (m, 2H), 2.55 (s, 3H), 2.31 (s, 3H), 2.27 (s, 3H). MS(EI) *m*/*z* (% relative intensity) 351 (M^+, 77), 308(68), 266(100), 248(5), 224(10), 206(8), 165(5), 43(8).

4.6. Resolution of (*RS*)-aporphine (*RS*)-2

A solution of (+)-dibenzoyl tartaric acid (6.91 g, 19.29 mmol) in ethyl acetate (75 ml) was transferred into a three-necked flask, which was equipped with a condenser and a mechanical stirrer. Racemic aporphine (4.54 g, 19.29 mmol) was then quickly added at room temperature, which caused white crystals to form in 15 min. The mixture was then heated at reflux while stirring. After isopropanol (50 ml) was added, refluxing was continued for 1.5 h, causing the mixture to gradually became a clear solution. Refluxing was stopped, and the mixture allowed to cool slowly to room temperature. White needles precipitated, and the mixture was left to stand overnight. The crystals were separated from the mother liquid by suction. A white solid (5.70 g) was obtained and recrystallized in a mixed solvent of ethyl acetate (45 ml) and isopropanol (32 ml) to produce (*R*)-(−)-aporphinium (+)-dibenzoyl tartrate (5.00 g) with a specific rotation of $[\alpha]_D^{20} = +26.1$ (*c* 0.5, methanol). The salt was dissolved in water (30 ml), the pH of the aqueous solution adjusted to 10 by adding a powdered potassium carbonate. After double extraction of the aqueous solution with ethyl acetate (30 ml × 2), the extracts were combined and dried over anhydrous sodium sulfate. Removal of the solvent gave (*R*)-(−)-aporphine (1.96 g, 8.33 mmol) in 43% yield, $[\alpha]_D^{20} = -151.6$ (*c* 0.6, methanol). ^{1}H NMR ($CDCl_3$): δ 7.72 (d, $J = 7.7$ Hz, 1H), 7.57 (d, $J = 7.6$ Hz, 1H), 7.32(dd, $J = 7.1$, 7.3 Hz, 1H), 7.21–7.27 (m, 3H), 7.08 (d, $J = 7.5$ Hz, 1H), 3.15–3.26 (m, 3H), 3.08 (dd, $J = 5.8$, 11.4 Hz, 1H), 2.66–2.79 (m, 1H), 2.57 (s, 3H), 2.51–2.58 (m, 1H). MS(EI) *m*/*z* (% relative intensity) 235 (M^++1, 31), 234 (M^+, 100), 219(8), 203(3), 192(32), 178(3), 165(6), 44(6). IR(neat) 3050, 2900, 2750, 2700, 1475, 1440, 745, 700 cm^{-1}.

The mother liquid from the above resolution was concentrated to dryness. Water (50 ml) was added, and the pH of the aqueous solution adjusted to 10 by adding powdered potassium carbonate. Two extractions of the alkaline aqueous solution with ethyl acetate (50 ml × 2) and evaporation of the solvent gave a residue which was dissolved in a mixed solvent of ethyl acetate (60 ml) and isopropanol (40 ml). (−)-Dibenzoyl tartaric acid (3.93 g, 10.97 mmol) was then added, and the mixture was heated at reflux for 2 h. The mixture was allowed to cool to room temperature and to stand overnight. A white solid (5.51 g) was obtained by suction and recrystallized in the mixed solvent of ethyl acetate (45 ml) and isopropanol (32 ml) to produce (*S*)-(+)-aporphinium (−)-dibenzoyl tartrate (4.8 g) with a specific rotation of $[\alpha]_D^{20} = -26.0$ (*c* 0.5, methanol). After the neutralization and extraction *per* the above procedure as described for (*R*)-(−)-aporphinium, (−)-dibenzoyl tartrate gave (*S*)-(+)-aporphine (1.91 g, 8.12 mmol) in 42% yield, $[\alpha]_D^{20} = +152.0$ (*c* 0.6, methanol).

4.7. Racemization of (*S*)-(+)-aporphine (*S*)-2

(*S*)-(+)-Aporphine (1.91 g, 8.12 mmol) was dissolved in DMSO (20 ml). Powdered potassium hydroxide (1.37 g, 24.41 mmol) was added, and then heated to around 120 °C. Stirring was continued at 120 °C under an atmosphere of N_2 for 2 h. After work-up *per* the procedure as described for (*S*)-(+)-10,11-dimethoxyaporphine, racemic aporphine (1.83 g, 7.78 mmol) was obtained in 96% yield. ^{1}H NMR showed that it was identical with the sample from the total synthesis and could thus be used for further resolution.

4.8. Preparation of (*R*)-(−)-aporphine hydrochloride 2–HCl

(*R*)-(−)-Aporphine (1.47 g, 6.25 mmol) was dissolved in ethanol (20 ml). Concentrated hydrochloric acid (1.0 ml, 12.0 mmol) was then added, and then the solution heated at reflux for 1 h under an atmosphere of N_2. Evaporation

of the solvent gave a pale yellow oily residue, which was triturated with ethyl acetate to give (*R*)-(−)-aporphine hydrochloride (1.49 g, 5.48 mmol) as a white solid in 88% yield, $[\alpha]_D^{20}$ − 106.6 (*c* 0.3, methanol) {lit.[37] $[\alpha]_D^{20} = -109.4$ (*c* 0.0019, methanol)}. ^{1}H NMR (CD_3OD): δ 7.82 (d, $J = 7.7$ Hz, 1H), 7.77 (d, $J = 7.8$ Hz, 1H), 7.37–7.45 (m, 3H), 7.30–7.35 (m, 1H), 7.25 (d, $J = 7.7$ Hz, 1H), 4.45–4.56 (m, 1H), 3.80–3.88 (m, 1H), 3.41–3.66 (m, 3H), 3.21 (s, 3H), 3.14 (dd, $J = 3.8$, 17.9 Hz, 1H), 3.03 (dd, $J = 13.9$, 14.0 Hz, 1H).

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