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An efficient synthesis of the opioid analgesic (*R*)-phenampromide via an aziridinium ion

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ABSTRACT

A simple and efficient synthesis of the opioid analgesic agent (*R*)-phenampromide with high enantiopurity (>99% ee) via the formation of an aziridinium ion as a key step using commercially available starting material is described.

1. Introduction

There has been an increasing demand for producing and marketing single enantiomer drug substances rather than racemates, which may contain both the active and inactive enantiomers in an equimolar ratio.[1] Due to the potentially large differences in biological activities of the two enantiomers of a particular drug substance, there is a need for producing enantiomerically pure new drugs and to enantioenrich old ones so that they display high enantiomeric purity.[2] Phenampromide **1** is an opioid analgesic, which is considered to be structurally similar to isomethadone.[3] Phenampromide belongs to the ampromide family of drugs, which also include propiram and diampromide (Fig. 1). According to the literature, (*R*)-phenampromide has greater analgesic potency than its (*S*)-enantiomer.[4] Studies also revealed that based on the structure of phenampromide, U50,488, a highly selective kappa opioid agonist was discovered.[5] Few reports are currently available for the synthesis of the (*R*)-enantiomer of phenampromide, which mainly involve resolution processes.[3,4]

Wright et al.[3] synthesized (*R*)-**1** starting from 2-bromopropionyl bromide, which upon treatment with piperidine followed by subsequent transformations yielded *rac*-phenampromide **1** (Scheme 1). Finally, *rac*-phenampromide was resolved using L-malic acid. Portoghese[4] reported another synthesis of (*R*)-**1** starting with 2-chloropropionic acid. This method involved the resolution of an intermediate using quinine followed by number of steps to accomplish the synthesis (Scheme 1). These methods suffer from certain drawbacks, such as low overall yields, the use of expensive reagents and chemicals, protection and deprotection steps. Hence a method, which could provide easy access to optically active phenampromide and its analogues would be highly desirable.

Epoxides are considered to be a versatile functional group that are used for the industrial production of several important compounds and in the synthesis of many intermediates.[6] Investigations in our laboratory have demonstrated the potential utility of these epoxides for the synthesis of many optically active pharmaceuticals.[7,8] Herein we report a concise and simple synthesis of (*R*)-phenampromide (*R*)-**1** starting from commercially available (*R*)-epichlorohydrin, thereby devising a new approach that would enable the synthesis of other ampromide families of drugs with high enantiomeric purity.

2. Results and discussion

The retrosynthetic analysis of (*R*)-**1** is depicted in Scheme 2. In Route 1, we envisaged that the optically active aziridine (*R*)-**5** would serve as a key intermediate for the synthesis, which could be transformed into the final product via aziridine ring opening and amide formation. The key intermediate (*R*)-**5** can be obtained from (*R*)-epichlorohydrin (*R*)-**2** via epoxide opening and reduction protocols. Alternatively, this chiral precursor (*R*)-**2** could be utilized for Route 2 via intermediate (*R*)-**9**. Our synthesis commenced with commercially available (*R*)-epichlorohydrin, which on treatment with aniline in methanol under reflux condition followed by $LiAlH_4$ reduction furnished the amino alcohol derivative (*S*)-**4** (Scheme 3). Compound (*S*)-**4** underwent a Mitsunobu reaction (Table 1, entry 1–4) to afford the optically active aziridine (*R*)-**5**,

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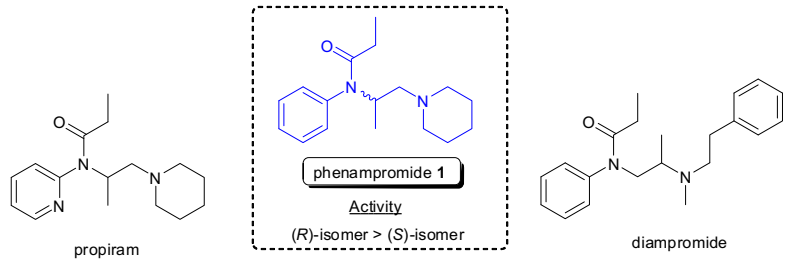
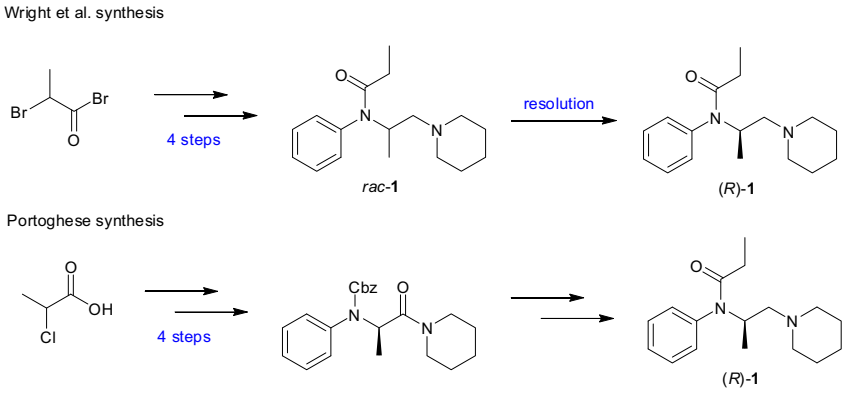
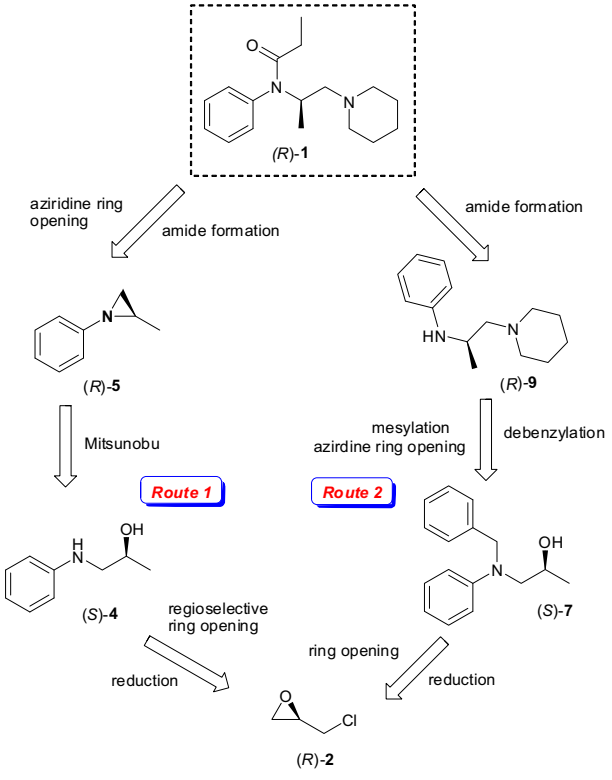


Figure 1. Examples of few opioid analgesic from ampromide family.



Scheme 1. Reported approaches for the synthesis of (*R*)-**1**.



Scheme 2. Retrosynthetic analysis of (*R*)-phenampromide.

but all our attempts failed to produce the required key intermediate. Additionally, we tried to mesylate the (*S*)-**4** derivative in order to convert it into the desired aziridine, but it also failed to proceed (Table 1, entry 5). Thus, we turned our attention towards Route 2.

The ring opening of (*R*)-**2** was carried out using *N*-benzylaniline followed by $LiAlH_4$ reduction to afford (*S*)-**7** in good yield (Scheme 4). Mesylation of compound (*S*)-**7** went smoothly to provide the crude mesylate (*S*)-**8** which upon treatment with Et_3N and piperidine in refluxing toluene furnished (*R*)-**9** via ring opening of the aziridinium ion. It should be noted that the ring opening of aziridinium ion could be performed using different amines, which may facilitate a diverse range of phenampromide analogues. N-debenzylation of compound (*R*)-**9** using catalytic $Pd(OH)_2$ under H_2 pressure, followed by treatment with propionyl chloride in the presence of a base afforded the target compound (*R*)-phenampromide (*R*)-**1** with high enantiopurity (ee >99%).

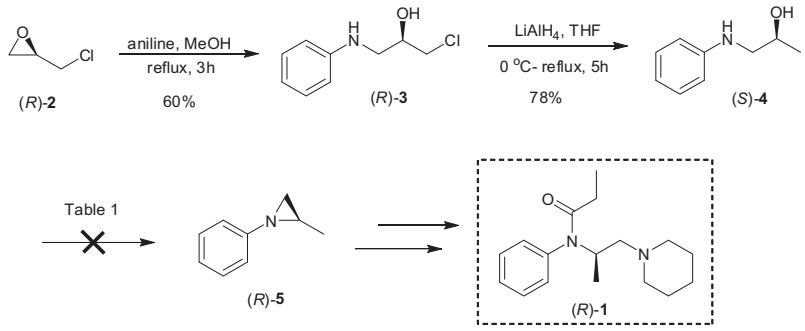
3. Conclusion

In conclusion, we have reported an efficient new route for the synthesis of (*R*)-phenampromide (*R*)-**1** via aziridinium ring formation as the key step using simple commercially available starting materials. The final product has been obtained with high enantiopurity (ee >99%). We envisage that this simple protocol may find application in the synthesis of other ampromides with high enantiomeric purity.

4. Experimental

4.1. General

Solvents were purified and dried by standard procedures prior to use. IR spectra were obtained from Perkin–Elmer Spectrum one spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AC-200 NMR spectrometer. Spectra were obtained in $CDCl_3$. Monitoring of reactions was carried out using TLC plates Merck Silica Gel 60 F254 and visualization with UV light (254 and 365 nm), I_2 and anisaldehyde in ethanol as development reagents. Optical rotations were measured with a JASCO P 1020



Scheme 3. Attempted synthesis for (*R*)-**1**.

Table 1
Attempted conditions for the synthesis of (*R*)-**5**

Entry	Conditions	Result
1.	DIAD, Bu_3P, toluene, reflux, 4 h	N.R.
2.	DIAD, Bu_3P, THF, reflux, 4 h	N.R.
3.	DIAD, PPh_3, toluene, rt, 12 h	N.R.
4.	DIAD, PPh_3, toluene, reflux, 6 h	Trace
5.	MsCl, DCM, 0 °C–rt,12 h	N.R.

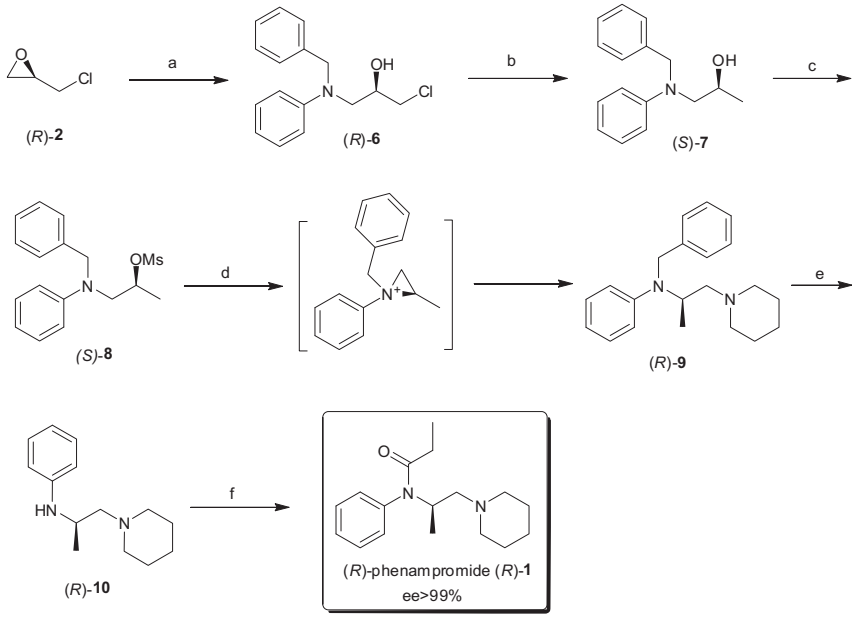
digital polarimeter. Mass spectra were recorded at ionization energy 70 eV on API Q Star Pulsar spectrometer using electrospray ionization. Enantiomeric excess was determined by chiral HPLC.

4.1.1. (*R*)-1-(Benzyl(phenyl)amino)-3-chloropropan-2-ol (*R*)-6

To a stirred solution of (*R*)-epichlorohydrin (*R*)-**2** (0.98 g, 10.6 mmol) and methanol (8 ml) at room temperature was added *N*-benzyl aniline (1.94 g, 10.6 mmol) dissolved in methanol (10 ml) for 5 min. The reaction mixture was then refluxed for 24 h. After completion of the reaction methanol was evaporated under reduced pressure and the crude product was purified by column chromatography (silica gel, petroleum ether/ethyl acetate, 85:15) so as to afford (*R*)-**6** as an oil (1.9 g, 65%); $[\alpha]_D^{25} = -10.8$ (*c* 1.06, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 3.47–3.71 (m, 4H), 4.13–4.22 (m, 1H), 4.64 (s, 2H), 6.73–6.84 (m, 3H), 7.17–7.35 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 148.2 (C), 137.8 (C), 129.3 (CH, 2 carbons), 128.6 (CH, 2 carbons), 127.0 (CH), 126.8 (CH), 117.9 (CH), 113.4 (CH), 69.0 (CH), 55.7 (CH_2), 54.8 (CH_2), 47.7 (CH_2); MS: *m*/*z* 275 $[M+H]^+$.

4.1.2. (*S*)-1-(Benzyl(phenyl)amino)propan-2-ol (*S*)-7

A solution of (*R*)-**6** (1.4 g, 5.0 mmol) in dry THF (15 mL) was added dropwise to a suspension of $LiAlH_4$ (0.2 g, 5.7 mmol) in dry THF (15 mL) at 0 °C. After being stirred at room temperature for 30 min, the mixture was refluxed for 6 h. After completion of the reaction, the mixture was allowed to cool to 0 °C and aq KOH (5 mL) was added slowly followed by the addition of ethyl acetate (25 mL). The residue was filtered over Celite and the filtrate was washed with water, brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified over column chromatography (silica gel, petroleum ether/EtOAc, 80:20) to afford (*S*)-**7** as an oil (1.13 g, 94%); $[\alpha]_D^{25} = +8.3$ (*c* 1.02, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.16 (d, *J* = 6.5 Hz, 3H), 3.20–3.43 (m, 2H), 3.99–4.13 (m, 1H), 4.57 (s, 2H), 6.65–6.76 (m, 3H), 7.09–7.27 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 156.3 (C), 140.0 (C), 129.2 (CH, 3 carbons), 128.6 (CH, 3 carbons), 126.9 (CH), 126.7 (CH), 113.4 (CH), 113.2 (CH), 65.5 (CH), 59.6 (CH_2), 55.3 (CH_2), 20.2 (CH_3); MS: *m*/*z* 242 $[M+H]^+$.



Scheme 4. *Reagents and conditions*: (a) *N*-benzylaniline, MeOH, reflux, 24 h, 65%; (b) $LiAlH_4$, THF (dry), 0 °C to reflux, 6 h, 94%; (c) MsCl, Et_3N, DCM, 0 °C, 2 h; (d) piperidine, Et_3N, toluene, reflux, 8 h, 30% (two steps); (e) $Pd(OH)_2$, H_2 (60 psi), MeOH, 6 h, 91%; (f) propionyl chloride, K_2CO_3, toluene, 0 °C to rt, 4 h, 69%.

4.1.3. (*R*)-*N*-Benzyl-*N*-(1-(piperidin-1-yl)propan-2-yl)aniline (*R*)-9

To a pre-cooled (0 °C) solution of alcohol (*S*)-**7** (1.1 g, 4.5 mmol) in dry DCM (50 mL) was added triethylamine (1.9 mL, 13.6 mmol) followed by the slow dropwise addition of methanesulfonyl chloride (0.4 mL, 5.9 mmol). The reaction mixture was stirred at 10 °C for 2 h before quenching with water, more DCM was added and extracted with water, washed with brine and evaporated under reduced pressure. The crude product (*S*)-**8** was used for the next step without purification.

To a stirred solution of (*S*)-**8** in dry toluene was added triethylamine (0.6 mL, 4.9 mmol) followed by the addition of piperidine (0.8 mL, 8.1 mmol). The reaction mixture was refluxed for 8 h and the solvent was evaporated in vacuo. Next, DCM (25 mL) was added and the organic layer was washed with water (2 × 15 mL), brine, dried over Na_2SO_4 and evaporated under reduced pressure. The crude oil obtained was purified over column chromatography (silica gel, petroleum ether/EtOAc, 80:20) so as to afford (*R*)-**9** as an oil (0.4 g, 30%); $[\alpha]_D^{25}$ = +26.5 (*c* 1.25, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.25 (d, *J* = 6.5 Hz, 3H), 1.39–1.58 (m, 6H), 2.23–2.54 (m, 6H), 4.20–4.30 (m, 1H), 4.42 (s, 2H), 6.61–6.73 (m, 3H), 7.10–7.34 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 149.2 (C), 140.4 (C), 128.9 (CH, 2carbons), 128.2 (CH, 2carbons), 126.4 (CH, 2carbons), 126.3 (CH), 116.3 (CH), 113.4 (CH, 2 carbons), 62.6 (CH_2), 55.2 (CH_2, 2carbons), 50.9 (CH), 48.8 (CH_2), 26.0 (CH_2, 2carbons), 24.3 (CH_2), 16.6 (CH_3); MS: *m*/*z* 331 $[M+Na]^+$.

4.1.4. (*R*)-*N*-(1-(Piperidin-1-yl)propan-2-yl)aniline (*R*)-10

To a solution of (*R*)-**9** (0.2 g, 0.6 mmol) in methanol (10 mL) was added palladium hydroxide (0.02 g, 10–20 wt %) and the reaction mixture was stirred under hydrogen (60 psi) for 6 h. After completion of the reaction (indicated by TLC), the catalyst was filtered over a plug of celite bed and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, petroleum ether/acetone, 80:20) so as to afford (*R*)-**10** as a colorless oil (0.12 g, 91%); $[\alpha]_D^{25}$ = −22.3 (*c* 1.28, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.20 (d, *J* = 6.0 Hz, 3H), 1.47–1.59 (m, 6H), 2.23–2.47 (m, 6H), 3.38–3.54 (m, 1H), 6.64–6.73 (m, 3H), 7.13–7.21 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 148.5 (C), 129.1 (CH, 2carbons), 117.1 (CH), 113.6 (CH, 2carbons), 64.5 (CH_2), 54.5 (CH_2, 2carbons), 45.6 (CH), 26.0 (CH_2, 2carbons), 24.3 (CH_2), 19.8 (CH_3); MS: *m*/*z* 219 $[M+H]^+$.

4.1.5. (*R*)-*N*-Phenyl-*N*-(1-(piperidin-1-yl)propan-2-yl) propionamide (*R*)-1

To a solution of compound (*R*)-**10** (0.1 g, 0.45 mmol) in dry toluene (2 ml) was added K_2CO_3 (0.13 g, 0.9 mmol). The reaction mixture was cooled to 0 °C and propionyl chloride (0.045 ml, 0.5 mmol) was added slowly and stirred at 10 °C for 4 h. After completion of the reaction, the solid was filtered and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, petroleum ether/acetone, 95:5) to afford (*R*)-**1** as a colorless oil (0.08 g, 69%); $[\alpha]_D^{25}$ = −28.4 (*c* 1.05, $CHCl_3$) {lit.[3] $[\alpha]_D^{25}$ = −16.3 (*c* 2, H_2O)}; ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.00–1.04 (m, 6H), 1.40–1.43 (m, 2H), 1.52–1.59 (m, 4H), 1.89–1.97 (m, 3H), 2.12–2.24 (m, 3H), 2.49–2.50 (m, 2H), 5.16–5.18 (m, 1H), 7.08–7.09 (m, 1H), 7.38–7.41 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 173.7 (CO), 138.8 (C), 130.6 (CH, 2carbons), 128.9 (CH), 128.0 (CH, 2carbons), 62.2 (CH_2), 54.5 (CH_2, 2carbons), 46.5 (CH), 28.4 (CH_2), 26.2 (CH_2, 2carbons), 24.5 (CH_2), 17.4 (CH_3), 9.7 (CH_3); MS: *m*/*z* 297 $[M+Na]^+$; ee >99% [Chiralcel OD-H (250 × 4.6 mm) column; eluent: *n*-hexane/ethanol (96:4); flow rate 0.5 mL/min; detector: 254 nm] [(*R*)-isomer t_R = 9.675 min, (*S*)-isomer t_R = 10.600 min].

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A. Supplementary data

Supplementary data (copies of ^{1}H NMR, ^{13}C NMR of all the compounds & chiral HPLC chromatograph of the final compound) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2017.06.001.

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