Asymmetric-catalysed preparation and stereochemistry of *(R,R)-,(S,R)*-(6-fluoro-2-chromanyl)-1,2-ethanediol

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(*R,R*)-,(*S,R*)-1-(6-fluoro-2-chromanyl)-1,2-ethanediol **1a**/**1b** were prepared by hydrolytic kinetic resolution (HKR) of terminal racemic epoxides using (*R,R*)-SalenCo(OAc) as a catalyst. Their configurations were established by comparison with two authentic samples by HPLC.

Keywords: resolution, configuration, HPLC

1-(6-Fluoro-2-chromanyl)-1,2-ethanediol **1** exists as four stereoisomers (*R,R-/S,S-; S,R-/R,S-*). All of them are important intermediates for the synthesis of bis[2-(6-fluoro-2-chromanyl)-2-hydroxyethyl]amine, a new *β*-adrenergic blocking agent.[1] In order to develop a synthetic method for this pharmaceutical on the large-scale, a simple process for the preparation of optical active pure **1** is required. In our initial synthetic research we have developed a new method for preparation of the diastereoisomer (*R,R*)-**1a** by the hydrolytic kinetic resolution (HKR) of terminal epoxide (*R,R*-**2a**/*S,S*-**2b**) using (*R,R*)-SalenCo(OAc) as a catalyst. We have also synthesised 1,2-diol (*S,R*)-**1b** in the same way from terminal epoxides (*R,S*-**3a**/*S,R*-**3b**) (as shown in Scheme 1). We now report the asymmetric-catalysed preparation and the stereochemical proofs of the configurations of (*R,R*)-**1a** and (*S,R*)-**1b** established by the high-performance liquid chromatography (HPLC).

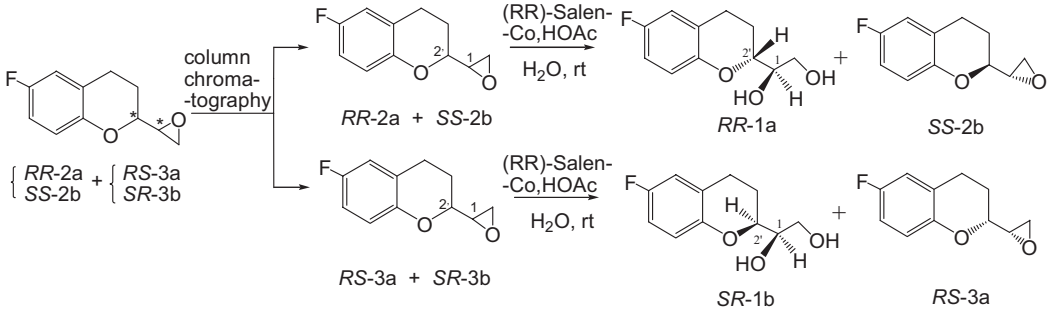
Results and discussion

One facile approach had been reported for the synthesis of optical active pure **1**.[2] The diastereoisomeric (*R,R*)-**1** and (*S,R*)-**1** were synthesised from allyl alcohol by Sharpless asymmetric epoxidation (SAE) (shown in Scheme 2). However, recently E.N. Jacobsen and coworkers have explored an attractive process for the preparation of chiral building blocks by hydrolytic kinetic resolution (HKR) of terminal epoxides.[3] HKR, with SalenCo(OAc) being used as a recyclable chiral catalyst and water as the only reagent, affords highly valuable terminal epoxides and 1,2-diols in high yields with high enantiomeric purity.

Our experiments commenced from (6-fluoro-2-chromanyl)oxirane which has two chiral centres and exists as four stereoisomers (*R,R*-**2a**/*S,S*-**2b**; *R,S*-**3a**/*S,R*-**3b**). The two pairs epoxides of (*R,R*-**2a**/*S,S*-**2b**) and (*R,S*-**3a**/*S,R*-**3b**) are diastereoisomers and could be separated easily on silica gel, presumably due to the small distance between the stereoisomeric chiral centres of chromane–oxirane. Using the reported hydrolytic kinetic resolution (HKR) of terminal epoxides of E.N. Jacobsen and coworkers, the racemic epoxides (*R,R*-**2a**/*S,S*-**2b**) and (*R,S*-**3a**/*S,R*-**3b**) were catalytically resolved by (*R,R*)-Salen Co(OAc) at room temperature in water. Thus, racemic epoxides (*R,R*-**2a**/*S,S*-**2b**) provided an optically active 1,2-diol **1a** and an optically active epoxide **2b**; the racemic epoxides (*R,S*-**3a**/*S,R*-**3b**) formed an optically active 1,2-diol **1b** and an optically active epoxide **3a**.

In the initial reports on the HKR reaction, substrates such as aryl, vinyl, alkynyl terminal epoxides and epihalohydrins were evaluated.[3,4,5] These epoxides have only one chiral centre in their 1,2-oxirane structures. Moreover, all the resolution products were reported to give relative enantiomeric pure 1,2-diols or epoxides with the (*R,R*)- or (*S,S*)-SalenCo(OAc) catalyst.[6,7] In our HKR reaction of terminal epoxides (*R,R*-**2a**/*S,S*-**2b**) and (*R,S*-**3a**/*S,R*-**3b**) with (*R,R*)-SalenCo(OAc), the reactions provided both two resolved optical active isomer 1,2-diols **1a**/**1b** and two optical active isomer epoxides **2b**/**3a**. Although there was high enantioselectivity under the standard condition of Jacobsen's HKR, the absolute configuration of the two related isomer 1,2-diols and the two isomer epoxides was not established. We thought that, logically, the (*R,R*)-salenCo(OAc) should recognise the (*R*)-C_1 chiral centre of (*R,R*)-**2a**/(*S,R*)-**3b** in the oxirane ring according to the mechanism of HKR.[8] Thus, (*R,R*)-**2a** should be recognised by (*R,R*)-salenCo(OAc) and would be resolved to give (*R,R*)-1,2-diol **1a**. Likewise with (*S,R)*-**3b** to give (*S,R)*-1,2-diol **1b.**

To make sure if we had indeed prepared stereoisomers (*R,R)*-**1a** and (*S,R)*-**1b**, we prepared (*R,R*)- and (*S,R*)-(6-fluoro-2-chromanyl)-1,2-ethanediol **1** again according to the reported method[2] (shown in Scheme 2). In the synthesis method, (*R,R*)-**1** and (*S,R*)-**1** were formed by the Sharpless asymmetric epoxidation (SAE), so the absolute configuration of the two chiral carbons in chromanyl-1,2-ethanediols (C_2' and C_1) was known. We therefore evaluated the performance on HPLC by comparing the resolved sample **1a** with the synthesised sample (*R,R*)-**1,** and **1b** with (*S,R*)-**1**. The column for HPLC had a polysaccharide-based chiral



Scheme 1 The resolution of (*R,R*)-**1a** and (*S,R*)-**1b** by the HKR reaction.

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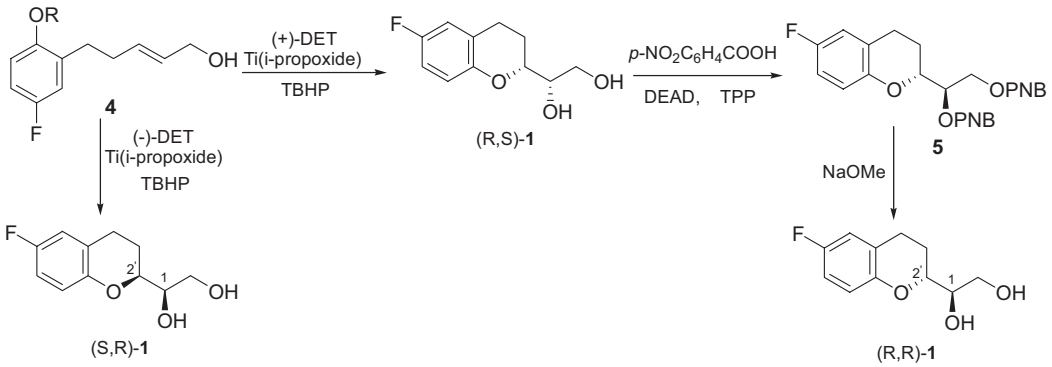

Scheme 2 The synthesis of (*R,R*)-**1** and (*S,R*)-**1** followed the reported method.

stationary phases[9] (see Experimental). The results showed that **1a** had the correct relative retention time (t_R) and strictly one peak of the same shape when the sample was mixed with (*R,R*)-**1**, as did **1b** and (*S,R*)-**1** (as shown in Fig. 1).

This finding was especially interesting, since each isomer has its special chiral recognition capacity with the chiral stationary phase and the isomers could be clearly differentiated in this way.

Experimental

Reagents and apparatus

The mixture of "racemic epoxide" composing (*R,R*-**2a**/*S,S*-**2b**; *R,S*-**3a**/*S,R*-**3b**) was obtained from an authentic sample. The other solvents and reagents were of commercial quality from freshly opened containers. IR spectra were recorded on a Thermo Ncolet 670 spectrometer (KBr disk or liquid film), mass spectra on a TRIO 2000 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded at a 300 MHz and a 400 MHz of Varian Gemini instrument, respectively.

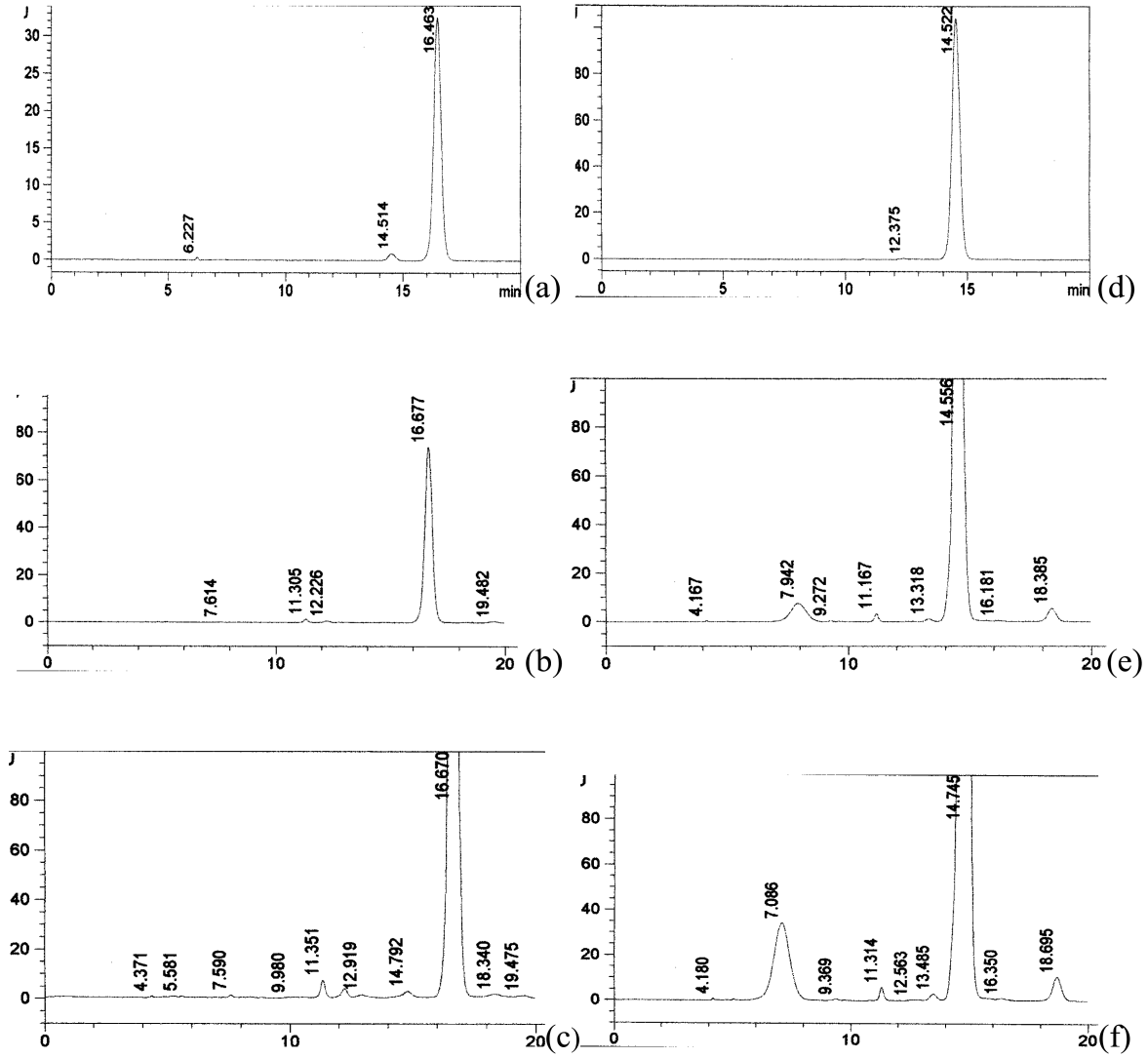

Fig. 1 The stereochemistry determination of *(R,R)*-**1a** and *(S,R)*-**1b** by HPLC.
(a) the resolved sample of (*R,R*)-**1a**; (b) the synthesised sample of (*R,R*)-**1**; (c) sample of (*R,R*)-**1a** plus sample of (*R,R*)-**1**; (d) the resolved sample of (*S,R*)-**1b**; (e) the synthesised sample of (*S,R*)-**1**; (f) sample of (*S,R*)-**1a** plus sample of (*S,R*)-**1**.

HPLC was carried out on a CUIRALDAK AD-H column, 250 × 4.6 (L × ID mm), 30 kg cm^{-2}, 1.0 ml min-1, rt, λ_{min} = 242 nm, *n*-hexane/*i*-prepared = 95/5.

*HKR reaction procedure of terminal epoxides (R,R-**2a**/S,S-**2b**) and (R,S-**3a**/S,R-**3b**)*

Racemic epoxide (*R,R*-**2a**/*S,S*-**2b**) and (*R,S*-**3a**/*S,R*-**3b**) was obtained respectively as an enantiomorphous mixture, which was isolated easily from the mixture of "racemic epoxide" composing (*R,R*-**2a**/*S,S*-**2b**; *R,S*-**3a**/*S,R*-**3b**) by flash column chromatography (1:2 of hexane/CH_2CH_2 as eluent).

A three-neck round-bottom flask equipped with an overhead stirrer was charged with racemic epoxide (*R,R*-**2a**/*S,S*-**2b**) (0.51 g, 2.63 mmol), (*R,R*)-SalenCo(OAc) (0.0358 g, 0.053 mmol), H_2O (0.0259 g, 1.44 mmol). The mixture was stirred at room temperature for 24 h. Pentane (2 × 100 ml) was added, and the mixture was stirred vigorously for 5 min. The solution was separated from the solid residue by decantation. The residue was stirred with a 1:1 pentane/water mixture (2 × 100 ml) and filtered through glass wool. The layers were separated and the organic layer was washed with water (3 × 100 ml). The aqueous layer was then extracted with CH_2CH_2 (3 × 100 ml). All the CH_2CH_2 layers were combined and dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was recrystallised and afforded (*R,R*)-**1a** as white crystals (0.24 g, 42%). m.p. 104–105°C, $[\alpha]_D$ = + 98.30°(C = 0.053, MeOH) (we believe the C value has affected the $[\alpha]_D$ value), IR (KBr, cm^{-1}) *v*: 3275, 2958, 2902, 2847, 1629, 1589, 1496, 1434, 1221, 1091, 868, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.76–6.83 (m, 3H, Ar*H*), 4.07–4.12 (dddd, *J* = 10.6, 5.0, 2.6, 2.5, 1H, OC*H*CH_2), 3.81–3.89 (m, 3H, C*H*OH, CH_2OH), 2.82–2.92 (m, 2H, ArCH_2), 1.94–2.07 (m, 4H, CH*OH*, CH_2*OH*, OCHCH_2); ^{13}C NMR ($CDCl_3$, 400 MHz) δ: 117.6 (C_6H_5), 117.5 (C_6H_5), 115.5 (C_6H_5), 115.3 (C_6H_5), 114.1 (C_6H_5), 113.9 (C_6H_5), 76.8 (ArO*C*H) 73.6 (HO*C*HCH$_2$OH), 63.6 (HOCH*C*H$_2$OH), 24.6 (Ar*C*H$_2$), 23.55 (ArOCH*C*H$_2$); MS (EI, *m/z*,%): 213 (M^+ + H, 17), 212 (M^+, 91), 168 (25), 151 (100), 138 (25), 123 (24), 103 (27).

Racemic epoxide (*R,S*-**3a**/*S,R*-**3b**) was treated according to the above procedure and afforded (*S,R*)-**1b** (41%). m.p. 97–99°C, $[\alpha]_D$ = + 84.79°(C = 0.314, MeOH), e.e.% > 99%, ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 6.74–6.84 (m, 3H, Ar*H*), 4.03–4.06 (m, 1H, OC*H*CH_2), 3.89–3.93 (m, 3H, C*H*OH, CH_2OH), 2.79–2.94 (m, 2H, ArCH_2), 2.16 (s, 3H, *OH*, ArCH$_2$C*H*H, *OH*), 1.83–1.93(m, 1H, ArCH$_2$CH*H*); IR (KBr cm^{-1}) *v*: 3253, 3148, 2927, 2878, 1625, 1574, 1500, 1219, 1082, 808.

*Preparation procedure of the authentic samples of (R,R)-**1** and (S,R)-**1***

(*R,R*)- and (*S,R*)-(6-Fluoro-2-chromanyl)-1,2-ethanediol **1** were prepared according to the reported method.[2] (*R,R*)-**1**: m.p. 92–94°C, $[\alpha]_D$ = + 64°(C = 0.1, MeOH), e.e.% > 99.5%; ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 6.77–6.94 (m, 3H, Ar*H*), 4.08–4.11 (m, 1H, OC*H*CH_2), 3.81–3.90 (m, 3H, C*H*OH, CH_2OH), 2.87–2.92 (m, 2H, ArCH_2), 2.21 (m, 2H, *OH*, *OH*), 1.95–2.05 (m, 2H, ArCH$_2$CH_2); (*S,R*)-**1**: m.p. 87–89°C, $[\alpha]_D$ = + 70° (C = 0.1, MeOH), e.e.% > 99.5%; ^{1}H NMR ($CDCl_3$, 400 MHz), δ: 6.84–6.96 (m, 3H, Ar*H*), 4.15–4.18 (m, 1H, OC*H*CH_2), 3.89–4.05 (m, 3H, C*H*OH, CH_2OH), 2.94–3.00 (m, 2H, ArCH_2), 2.26–2.32 (m, 1H, *OH*), 1.98–2.03 (m, 2H, ArCH$_2$CH_2).

*Evaluation of (R,R)-**1a**, (S,R)-**1b**, (R,R)-**1** and (S,R)-**1** in HPLC*

Hexane/*i*-propanal (95:5 v/v) were mixed as eluent. The sample of 1,2-diol **1a** and the synthesised sample of 1,2-diol (*R,R*)-**1** were dissolved in eluent in two tubes separately. Sample **1a** was first injected onto a column in HPLC. The peak shape and the retention time (t_R) were recorded and investigated. There was a t_R of 16.463 min. Sample (*R,R*)-**1** was then injected onto the column and a t_R of 16.677 min was given. Third, the sample **1a** and (*R,R*)-**1** were mixed and injected onto the column. The mixture sample gave a t_R of 16.670 min and the peak shape of the mixture was the same as that of the individual samples.

The resolved sample **1b** and the synthesised sample (*S,R*)-**1** were tested according to the above procedure. **1b** gave a t_R of 14.522 min, (*S,R*)-**1** gave a t_R of 14.556 min. **1b** plus (*S,R*)-**1** gave a t_R of 14.745 min and a peak of the same shape as the individual compounds.

Conclusion

The terminal epoxides (*R,R*-**2a**/*S,S*-**2b**) and (*R,S*-**3a**/*S,R*-**3b**) had been asymmetric catalytically resolved by the HKR reaction using (*R,R*)-SalenCo(OAc) as catalyst. The resolved products of diastereoisomers **1a** and **1b** were evaluated with the chiral stationary phase on HPLC. It was found that **1a** and **1b** had strict stereochemistry relationships with the synthesised samples of (*R,R*)-**1** and (*S,R*)-**1** respectively. These relationships could be used as stereochemistry proofs to illustrate their configuration structure. We thus finally established the stereochemistry of 1,2-diols (*R,R*)-**1a** and (*S,R*)-**1b**.

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