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Calcium(II)-mediated resolution of methyl *o*-chloromandelate with chiral *O*,*O*′-dibenzoyltartaric acid in preparative scale

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Abstract: We report here the coordination-mediated resolution of methyl *o*-chloromandelate, which is a key intermediate for clopidogrel, in preparative scale. The reaction of CaO, optically pure (2*R*, 3*R*)-*O*,*O*′-dibenzoyltartaric acid, and methyl *o*-chloromandelate in ethanol solution afforded a mixed-ligands calcium(II) complex that was further purified by stirring of the crystals in hot methanol. Methyl (*R*)-*o*-chloromandelate was obtained in good enantiomeric excess value (>99.5%) and yield (71%) by treatment of the complex with acid. At the same time, (2*R*, 3*R*)-*O*,*O*′-dibenzoyltartaric acid was recovered in 72% yield. In addition, methyl (*S*)-*o*-chloromandelate was obtained in good enantiomeric excess value (>99.5%) and yield (73%) by recovery from the mother liquor and resolution with the same procedure for methyl (*R*)-*o*-chloromandelate, except that (2*S*, 3*S*)-*O*,*O*′-dibenzoyltartaric acid was used as the resolving reagent.

Keywords: calcium(II); coordination; methyl (*R*)-*o*-chloromandelate; methyl (*S*)-*o*-chloromandelate; *O*,*O*′-dibenzoyltartaric acid; resolution.

Introduction

Chiral drugs play more and more important roles in our everyday life (Lin et al., 2011). There are three ways to obtain the enantiomerically enriched substances: natural chiral compounds or their derivatives, optical resolution of racemates, and asymmetric synthesis. Although many asymmetric catalytic reactions were developed in recent years, optical resolution is more widely used in the pharmaceutical industry (Lorenz and Seidel-Morgenstern, 2014).

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Methyl (*R*)-*o*-chloromandelate, a key intermediate for clopidogrel (Bousquet and Musolino, 1999), can be prepared using the following three methods. The first one is the esterification of the corresponding (*R*)-carboxylic acid, which can be resolved by some traditional resolution methods (Hyoda and Nawata, 2001; Noda et al., 2001; Peng et al., 2012; Yin et al., 2010; Hu et al., 2012; Wang et al., 2012; Chen and Yang, 2014). The second one is the direct asymmetric catalysis, in which methyl *o*-chlorobenzoylformate or α-diazo-(2-chlorophenyl)acetate can be transformed to methyl (*R*)-*o*-chloromandelate by some chiral metal catalysts (Zhu et al., 2008, 2010; Yin et al., 2009). The last one is biotransformation, in which *o*-chlorobenzoylformate can be transformed to methyl (*R*)-*o*-chloromandelate with some enzymes (Ema et al., 2007, 2008; Uhm et al., 2007; Jeong et al., 2010; Ma et al., 2012; Ni et al., 2012; Shen et al., 2012; Xu et al., 2014). However, these methods were studied mainly in the laboratory because of the high costs.

The optically pure derivatives of tartaric acid can be used in the coordination-mediated resolution of chiral acids, alcohols, esters, and P-heterocycles (Mravik et al., 1996, 1997, 1998; Xu et al., 2005; Ujj et al., 2010, 2015; Bagi et al., 2014, 2016a,b). The reaction of the corresponding salt, resolution reagent, and racemate can afford a mixed-ligands complex, in which the resolution reagent and one of the enantiomers coordinate to the metal ion. The single enantiomer can be obtained by treatment of the complex with acid. Because they are a series of relatively cheap and nontoxic resolution agents, this method is a promising one in the pharmaceutical industry.

Herein, we report the coordination-mediated resolution of methyl *o*-chloromandelate with chiral *O*,*O*′-dibenzoyltartaric acid (DBTA) and CaO in preparative scale.

Results and discussion

Preparation of Ca(*L*-HL_0)$_2$((*R*)-1)$_2$

The resolving agent Ca(*L*-HL_0)$_2$ was prepared by the reaction of a solution of *L*-DBTA (*L*-H_2L_0) and CaO in hot

ethanol for approximately 2 h (Mravik et al., 1996). Then, racemic methyl *o*-chloromandelate (*Rac*-**1**) in ethanol was added. After stirring for about 30 min at 80°C, a white precipitate formed, and the suspension was stirred for an additional 5 hours at the same temperature (Figure 1). The white precipitate was collected by filtration and characterized as Ca(*L*-HL_0)$_2$((*R*)-1)$_2$ by elemental and ICP analyses. The coordinative complex was further purified by stirring of the crystals in hot methanol. The complete dissolution of the crystals was not necessary because the procedure was sufficient enough to obtain the diastereomerically pure complex (Ujj et al., 2015). In the complex, there are two *L*-HL_0^- ions and two methyl (*R*)-*o*-chloromandelate molecules that coordinate to a calcium(II) ion. The reason is that calcium(II) has a large coordinating capacity for oxygen-containing ligands (Mravik et al., 1996; Ujj et al., 2010, 2015; Bagi et al., 2014, 2016a,b).

Decomposition of the complex

The (*R*)-(−)-form of methyl *o*-chloromandelate was obtained in good enantiomer selectivity [>99.5% enantiomeric excess (ee)] and yield (71%) by treatment of the complex with 2 mol/L hydrogen chloride. At the same time, *L*-DBTA was recovered in 72% yield. The results show that the reaction can be performed very well in kilograms grade. Therefore, this method is promising for the preparation of methyl (*R*)-*o*-chloromandelate and clopidogrel in the pharmaceutical industry.

Recovery and resolution of methyl (*S*)-*o*-chloromandelate from the mother liquor

Although methyl (*S*)-*o*-chloromandelate ((*S*)-**1**) cannot be used in the synthesis of clopidogrel, it is still a potential chiral reagent. Therefore, the crude methyl (*S*)-*o*-chloromandelate was recovered by treatment of the mother liquor, which was obtained from the preparation of Ca(*L*-HL_0)$_2$((*R*)-1)$_2$, and resolved by the same procedure for methyl (*R*)-*o*-chloromandelate, except that *D*-DBTA was used as the resolving reagent. Optically active methyl (*S*)-*o*-chloromandelate was obtained in good enantiomer selectivity (>99.5% ee) and yield (73%).

Conclusions

We have described a successful example of coordination-mediated resolution of methyl *o*-chloromandelate in preparative scale using chiral *O*,*O*′-dibenzoyltartaric acid

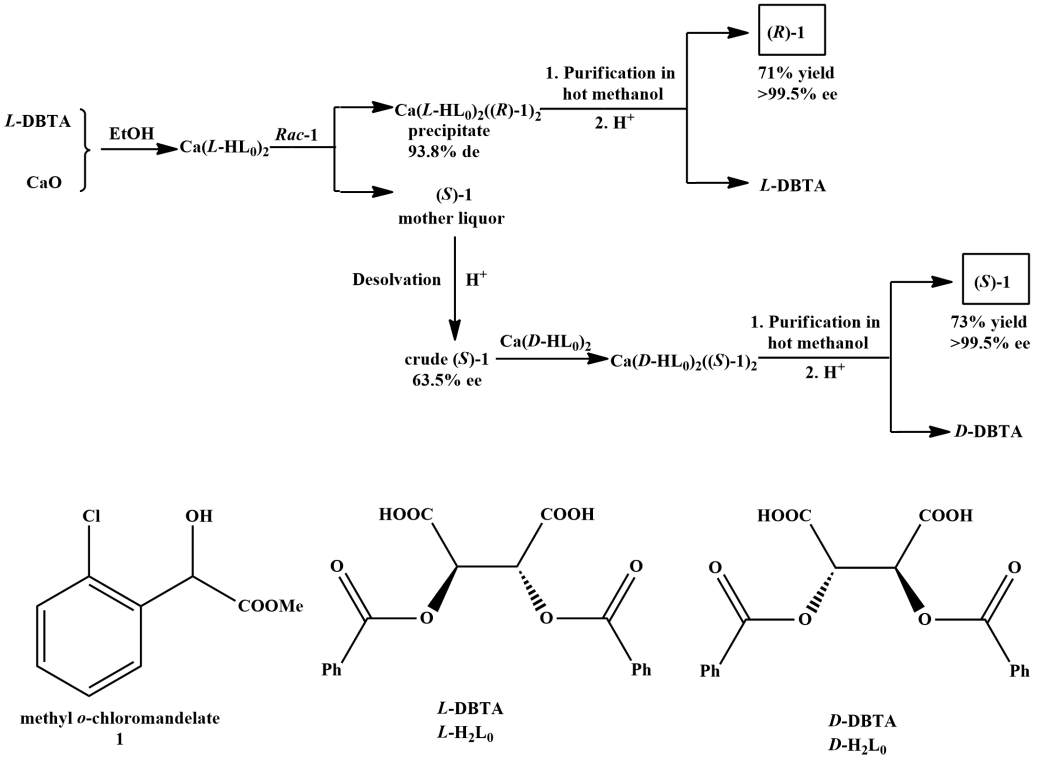

Figure 1: Coordination-mediated resolution of methyl *o*-chloromandelate with chiral *O*,*O*′-dibenzoyltartaric acid.

and CaO as resolving reagents. Methyl (*R*)-*o*-chloromandelate can be obtained in high enantiomeric excess value (>99.5%) and yield (71%). Moreover, methyl (*S*)-*o*-chloromandelate in the mother liquor can also be resolved in high enantiomeric excess value (>99.5%) and yield (73%) by the same way after recovery.

Experimental

Material and reagents

All the other reagents were purchased from commercial sources and were used without purification.

Physical measurements

Optical rotations were measured on a Perkin-Elmer 341 polarimeter (Perkin-Elmer, Waltham, MA, USA). IR spectra were recorded on a SHIMADZU IRTracer-100 spectrophotometer (Shimadzu (China), Shanghai, China) over the range 4000–400 cm^{-1} using KBr pellets. ^1H NMR spectra were measured on a Bruker (600 MHz) spectrometer (Bruker, Germany). The elemental (C, H, N) analyses of the powdered samples were performed on a Perkin-Elmer model 240C automatic instrument. The concentration of Ca^{2+} in the complex was determined using an IRIS Advantage (Thermo-Fisher Scientific, Carlsbad, CA, USA) ICP spectrophotometer after heating to 400°C and treatment with acid. The enantiomeric excess value of methyl *o*-chloromandelate was determined by HPLC analyses using an Shimadzu LC20AT instrument (Shimadzu (China), Shanghai, China) equipped with Daicel Chiralpak AD-H column (4.6×250 mm) [hexane/2-propanol (95:5); flow rate, 1.0 mL/min; detection wavelength, 254 nm; retention time, 14.1 min for (*S*)-form, 15.4 min for (*R*)-form].

Resolution of methyl *o*-chloromandelate

Preparation of Ca(*L*-HL_0)$_2$((*R*)-1)$_2$: CaO (77 g, 1.375 mol) was added to a solution of *L*-DBTA · H_2O (1036 g, 2.75 mol) in 1700 mL of ethanol at 80°C. After stirring for approximately 2 h, CaO was dissolved and the mixture became clear. Racemic methyl *o*-chloromandelate (1000 g, 5 mol) in 500 mL of ethanol was added. After stirring for about 30 min at 80°C, a white precipitate formed, and the mixture was stirred for an additional 5 h at the same temperature. The crystals were filtered off and washed with ethanol to give 1185 g of Ca(*L*-HL_0)$_2$((*R*)-1)$_2$. Yield: 82% (based on the half of racemic methyl *o*-chloromandelate). Anal. ($C_{54}H_{44}O_{22}Cl_2Ca$) C, H, Ca: calcd., 56.11%, 3.84%, 3.47%; found, 56.18%, 3.89%, 3.5%. IR absorption bands (cm^{-1}): 3360 (s), 3068 (w), 2950 (w), 1732 (s), 1688 (s), 1665 (s), 1452 (m), 1277 (w), 1128 (w), 1097 (w), 1030 (w), 764 (w), 706 (m). De: 93.8% (the diastereomeric excess of the complex was determined by the enantiomeric excess of methyl *o*-chloromandelate described below). ^1H NMR (600 MHz, DMSO-d6), δ: 7.97–7.98 (m, 4H, Ar-H), 7.64–7.76 (m, 2H, Ar-H), 7.51–7.54 (m, 5H, Ar-H), 7.44–7.45 (m, 1H, Ar-H), 7.35–7.38 (m, 2H, Ar-H), 6.35 (brs, 1H, OH), 5.72 (s, 2H, CH), 5.44 (s, 1H, CH), 3.63 (s, 3H, CH_3) ppm.

The complex was taken up in 1700 mL of methanol. The suspension was stirred at 60°C for 4 h and then cooled to room temperature. The crystals were filtered off, washed with methanol, and air-dried overnight at room temperature to give 1098 g of Ca(*L*-HL_0)$_2$((*R*)-1)$_2$. Yield: 76% (based on the half of racemic methyl *o*-chloromandelate). De: >99.5%.

Decomposition of the complex: The complex was suspended in 1000 mL of 2 mol/L hydrochloric acid and 1000 mL of toluene. The mixture was warmed to 60°C for 3 h with vigorous stirring, cooled to room temperature, and seeded with 2 g of *L*-DBTA · H_2O. The precipitate (*L*-DBTA · H_2O, 746 g) was filtered and washed with 500 mL of toluene. The toluene layer was separated, and the aqueous layer was extracted with toluene (3×100 mL). The organic phases were combined, washed with 0.5 mol/L $NaHCO_3$ solution (3×100 mL), and dried over sodium sulfate. The filtrate was concentrated to give optically active methyl (*R*)-*o*-chloromandelate (355 g). Yield: 71.0% (based on the half of racemic methyl *o*-chloromandelate). ee: >99.5%; $[\alpha]_D^{20} = -179.0$ (c=1.0, $CHCl_3$), {lit. (Ema et al., 2008) for the (*R*) isomer: $[\alpha]_D^{19}$: −178.3 (c=1.3, $CHCl_3$)}. ^1H NMR (600 MHz, $CDCl_3$), δ: 7.38–7.40 (m, 2H, Ar-H), 7.26–7.28 (m, 2H, Ar-H), 5.57 (s, 1H, CH), 3.76 (s, 3H, CH_3), 3.68 (brs, 1H, OH) ppm.

Recovery and resolution of methyl (*S*)-*o*-chloromandelate from the mother liquor: The mother liquor, which was obtained from the preparation of Ca(*L*-HL_0)$_2$((*R*)-1)$_2$, was concentrated by the evaporation of the solvent. The residue was suspended in 1000 mL of 1 mol/L hydrochloric acid and 1000 mL ethyl acetate. The mixture was warmed to 60°C for 2 h with vigorous stirring and then cooled to room temperature. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×100 mL). The organic phases were combined, washed with 0.5 mol/L $NaHCO_3$ solution (3×200 mL), and dried over sodium sulfate. The filtrate was concentrated to give crude methyl (*S*)-*o*-chloromandelate (565 g, 63.5% ee), which was resolved with *D*-DBTA · H_2O (1036 g) and CaO (77 g) in 2200 mL of ethanol by the same procedures described above for methyl (*R*)-*o*-chloromandelate. Optically active methyl (*S*)-*o*-chloromandelate (365 g) was obtained. Yield: 73.0% (based on the half of racemic methyl *o*-chloromandelate). ee: >99.5%; $[\alpha]_D^{20} = +179.1$ (c=1.0, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$), δ: 7.38–7.40 (m, 2H, Ar-H), 7.26–7.28 (m, 2H, Ar-H), 5.57 (s, 1H, CH), 3.76 (s, 3H, CH_3), 3.68 (brs, 1H, OH) ppm.

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