Efficient Preparation of *(R)*-2-chloromandelic Acid Via a Recycle Process of Resolution

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ABSTRACT Efficient preparation of *(R)*-2-chloromandelic acid *(R)*-**1** based on a recycle process of resolution is described. In the process, the desired *(R)*-**1** was obtained by coordination-mediated resolution with *D*-O,O'-di-(p-toluoyl)-tartaric acid in the presence of Ca^{2+}. Meanwhile, the undesired *(S)*-**1** could be racemized in the presence of sodium hydroxide and the product was suitable for further resolution. A carbanion mechanism for the racemization of *(S)*-**1** is proposed. *Chirality 00:000–000, 2015.* © 2015 Wiley Periodicals, Inc.

KEY WORDS: 2-chloromandelic acid; *D*-O,O'-di-(p-toluoyl)-tartaric acid; coordinative resolution; Dutch resolution; racemization

Enantiopure (*R*)-2-chloromandelic acid *(R)*-**1** is the key chiral intermediate for the industrial synthesis of clopidogrel, an antiplatelets aggregation agent that can decrease the risk of cardiovascular disease in patients with acute coronary syndromes.[1,2] The preparation of *(R)*-**1** has been investigated by the following general methods: 1) asymmetric synthesis via metal catalyst[3–5] or biocatalyst;[6,7] 2) racemic resolution by chromatography;[8] 3) enzymatic resolution;[9–15] and 4) diastereomeric salt resolution.[16–20]In methods (1–3), *(R)*-**1** can be obtained in high optical purity. However, these methods are used mainly in the laboratory because of the high price of efficient chiral catalysts and the limitation of equipment. Therefore, resolution of racemates via diastereomeric intermediates is the most frequently used method for the production of chiral compounds, especially in large-scale preparation or industrial synthesis.

Four kinds of resolving agents were used to resolve *rac*-**1**: N-benzyl-α-phenylethanamine,[16,17] alanine,[18] 1-aryl-2-amino-1,3-propane-diol,[19] and aryloxypropylamine.[20] These resolutions can be achieved via diastereomeric salts, which are always composed of the acid **1** and amine resolving agents. However, almost all amine resolving agents are toxic or expensive. The Mravik group applied optically active O,O'-dibenzoyltartaric acid (DBTA), which is usually used for the resolution of amines, as a new resolving reagent for racemic carboxylic acid derivatives.[21–23] Compared with chiral amines, optically pure DBTA, the derivative of tartaric acid **2**, is a relatively cheap and nontoxic reagent. Therefore, this method is promising for the resolution of racemic acids.

In the aforementioned methods, the maximum theoretical yield was only 50% during resolution and discarding the other half (the unwanted isomer) is uneconomical. For this reason, it is highly desirable to exploit the unwanted isomer by means of racemization and a theoretical yield of 100% can be obtained.[24] Thus, it is necessary to design an efficient process such that *(S)*-**1** can be racemized into *rac*-**1**.

The exceptional behavior of DBTA prompted us to use some tartaric acid derivatives in the resolution of **1**. In our previous work, **1** could be successfully resolved via molecular complex formation with calcium hydrogen DBTA.[25] It is a pity that the resolving efficiency was medium. In order to improve resolving efficiency and realize a recycle process of resolution, we explored the resolution with tartaric acid derivatives and the racemization of *(S)*-**1**. The resolution and racemization could thus be repeated for multiple cycles in order to obtain a yield of *(R)*-**1** as high as possible. Herein, the optimal results are presented on the resolution of *rac*-**1** with tartaric acid derivatives. Moreover, the method and a plausible mechanism for the racemization of the undesired *(S)*-**1** were extensively studied.

MATERIALS AND METHODS

General

Racemic 2-chloromandelic acid was obtained from Guangde Keyuan Chemical Company (China). The resolving agents *D*-DBTA **3**, D-O,O'-di-(p-toluoyl)-tartaric acid (D-DTTA **4**) and D-O,O'-di-(p-methoxybenzoyl)-tartaric acid (D-DMTA **5**) were obtained from Chengdu Likai Chiral Company (China) or made in our laboratory.[26] All solvents were purified by standard procedures. All chemicals were analytically pure. The ^{1}H NMR spectra were taken on a Bruker (400 MHz) spectrometer. Chemical shifts of ^{1}H NMR are expressed in ppm with the residual signal of DMSO as an internal standard (δ = 2.5 ppm). Melting points were obtained on a digital melting point apparatus and reported uncorrected. IR spectra were measured on a Nicolet MX-1 spectrometer by the KBr method at room temperature. Optical rotations of chiral compounds were measured on Perkin-Elmer (Boston, MA) 341 automatic polarimeter at room temperature. Mass spectra were obtained using a Bruker (Billerica, MA) AmaZon SL mass spectrometer. The enantiomeric excess (*ee*) value of 2-chloromandelic acid was determined by HPLC analyses using an Agilent-1100 instrument equipped with Daicel Chiralpak AS-H column (4.6 × 250 mm).

Resolution of Rac-2-Chloromandelic Acid Rac-1

2-Chloromandelic acid (466 mg, 2.5 mmol) and water (14 mL) were added to a warm solution of *D*-DTTA **4** (772 mg, 2.0 mmol) and CaO (112 mg, 2.0 mmol) in isopropanol (14 mL). The mixture was heated to reflux for 1 h, then cooled to room temperature and stirred for another 3 h. 544 mg (69.3% yield and 99% *ee*) of the salt of *(R)*-**1**·Ca·**4** was obtained as colorless crystals after recrystallizing three times in mixed solvents (^{i}PrOH: H_2O = 2:1). mp: 179°C (dec.); IR (KBr): ν = 3422, 2973, 1705, 1612, 1577, 1273, 1179, 1128, 1048 and 750 cm^{-1}; ^{1}H NMR

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(400 MHz, DMSO-d_6, δ): 7.83-7.85 (m, 4H), 7.30-7.44 (m, 4H+4H), 5.63 (s, 2H), 5.10 (s, 1H), 2.36 (s, 6H) ppm.; MS (ESI, m/z): $[M + H]^+$ 611.1; found, 610.9.

The complex *(R)*-**1**·Ca·**4** was suspended in 10% hydrochloric acid (10 mL) and toluene (5 mL). The mixture was warmed to 80°C for a short period with vigorous stirring, and then cooled to room temperature. The precipitate (DTTA) was filtered. The toluene layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic phases were combined, dried over anhydrous sodium sulfate, and concentrated in vacuum. 10 mL of warm toluene was added to the residue and then the undissolved DTTA was filtered off. The filtrate was concentrated to yield 140 mg (60%) of *(R)*-2-chloromandelic acid with 99% *ee*; mp: 116–117°C, $[\alpha]_D^{20} = -124$ (c = 1 in H_2O); the *(R)*-**1** reported in Aldrich (Milwaukee, WI) Chemistry: $[\alpha]_D^{23} = -126$ (c = 3 in H_2O). ^{1}H NMR (400 MHz, DMSO-d_6, δ): 7.30-7.52 (m, 4H), 5.34 (s, 1H) ppm. The enantiomeric purity of *(R)*-**1** was determined by HPLC analyses using an Agilent-1100 (Palo Alto, CA) instrument with hexane/isopropanol (90/10) and 0.05% trifluoroacetic acid as eluent under detection wavelength of 222 nm. The flow rate was 1.0 mL/min. Retention time: *(R)*-**1** 17.3 min, *(S)*-**1** 19.4 min.

Racemization of (S)-2-Chloromandelic Acid (S)-1

A typical racemization process in Table 2 is described as follows. The optically enriched compound *(S)*-2-chloromandelic acid was obtained from the mother liquid in the above resolution. A solution of *(S)*-2-chloromandelic acid (100 mg, 0.54 mmol, 67% *ee*) in DMSO (5 mL) and H_2O (0.1 mL) was stirred in a round-bottom flask. Powdered sodium hydroxide (64 mg, 1.6 mmol) was added and stirred at 160 °C for 2 h. The mixture was diluted with 10% hydrochloric acid. The aqueous solution (pH <2) was extracted with ethyl acetate (3 × 10 mL). The combined extracts were washed successively with water (10 mL) and brine (10 mL). The collected organic layers were dried over $MgSO_4$, filtered, and concentrated. The product (82 mg, 82% yield) was obtained as a white solid.

RESULTS AND DISCUSSION

Resolution of 2-Chloromandelic Acid

DBTA has been successfully used in calcium salt formation for the resolution of *rac*-**1**, via diastereomeric salt formations.[25] In this method, the best resolution efficiency could reach 58.2% in the mixture of water and isopropanol (Table 1, entry 2). Tartaric acid and its diaryl carboxylate derivatives D-DBTA **3**, D-DTTA **4**, and D-DMTA **5** are widely used and nontoxic at chiral resolution agents (Fig. 1). To improve the resolution efficiency of **1**, tartaric acid derivatives (**3**, **4**, and **5**) were explored with diastereomeric calcium salts. In this study, we first explored a mixed group of D-DBTA, D-DTTA, and D-DMTA as resolving agents. The mixture of resolving agents was added to the solution of equimolar amounts of *rac*-**1** and CaO in ^{i}PrOH-H_2O, and the precipitate was analyzed by HPLC and ^{1}H NMR, which showed that DTTA was the major component in the diastereomeric salt. *(R)*-**1** was obtained at 48.5% efficiency and 54.7% *ee* (Table 1, entry 1). Dutch resolution is the use of structurally related resolving agents.[27] In the resolution of *rac*-**1**, the resolving efficiency of the Dutch resolution was not as good as that of D-DBTA or D-DTTA individually (Table 1, entries 1, 2, and 4), and D-DTTA was the best resolving agent. *(R)*-**1** was obtained at 62.2% efficiency and 54.4% *ee* in complex formation (Table 1, entry 4). Thus, an effective resolving agent, DTTA, could be successfully selected by "Dutch resolution."

TABLE 1. Resolution of *rac*-1 by tartaric acid derivatives (D-DBTA 3, D-DTTA 4 and D-DMTA 5) and CaO

Entry	**1**: CaO : **3** : **4** : **5**[a]	*ee* (%)[b]	Yield (%)[c]	Eff.(%)[d]
1	3:3:1:1:1	54.7	88.6 (1:3:2)[e]	48.5
2	1:1:1:0:0	53.8	108.2	58.2
3	1:1:0:0:1	47.1	95.8	45.1
4	1:1:0:1:0	54.4	114.4	62.2
5	0.9:1:0:1:0	52.3	114.6	59.9
6	0.8:1:0:1:0	65.6	101.8	66.8
7	0.7:1:0:1:0	60.7	89.2	54.1
8	0.6:1:0:1:0	61.6	76.4	47.1

[a]The initial molar ratio of *rac*-**1**, CaO, **3**, **4**, and **5**.
[b]In all experiments, *(R)*-**1** was obtained and the enantiomeric purity was determined by HPLC.
[c]The yield of the diastereomeric salt based on half the initial complex.
[d]Resolving efficiency, defined as a product of the yield of the diastereomeric salt and the *ee* of the liberated **1**.
[e]The molar ratio of **3**, **4**, and **5** in the precipitated salt was determined by ^{1}H NMR.

In order to improve the efficiency of the resolution, several kinds of solvents, such as methanol, ethanol, isopropanol, water, acetone, and acetonitrile were surveyed and their mixtures were examined. The mixed solvent of isopropanol and water was found to be an excellent solvent system. We initially utilized tartaric acid derivatives as chiral host reagent to resolve 2-chloromandelic acid and found the standard molar ratio of racemic guest and resolving agent was 1:1. But the efficient molar ratio of tartaric acid derivative neutral calcium salt and racemic compound may be another ratio.[21,22] Thus, different ratios were studied and the ratio of 0.8:1 was found to be the best in the resolving efficiency (Table 1, entry 6). Unfortunately, it was difficult to obtain the qualified single crystal of less soluble salts for X-ray crystallographic analysis. The structures of the resolution intermediates were characterized with ^{1}H NMR and mass spectra. In the experiments, ^{1}H NMR demonstrated that the ratio of **4** and **1** in the less-soluble salt is close to 1:1. Mass spectra analysis suggested that the resulting complex was formulated as *(R)*-**1**·Ca·**4**. After third being recrystallized from the mixed solvents (^{i}PrOH: H_2O = 2:1), the calcium complex of *(R)*-**1**·Ca·**4** was suitably acidified to give *(R)*-**1** by extraction with 99% *ee*. Thus, utilizing **4** as a resolving agent, optical pure *(R)*-**1** was prepared with 99% *ee* in 60% yield.

Racemization of (S)-2-Chloromandelic Acid

While 60% of *(R)*-**1** was obtained from the resolution of the *rac*-**1** with *D*-DTTA and Ca^{2+}, undesired *(S)*-**1** remains as waste. Compound *(S)*-**1**, which is a precursor of inactive clopidogrel enantiomer, could be discarded. We attempted to find a method to convert this unwanted compound (*S*)-**1** into the useful *(R)*-**1**. The conversion could be achieved by transforming *(S)*-**1** into *rac*-**1** and then into *(R)*-**1**. Compound *(S)*-**1** was thus recycled just by repeating the racemization and resolution procedure. Herein, the racemization of *(S)*-**1** was extensively studied and many conditions were tried, which are summarized in Table 2.

Racemization of most carboxylic acids can be carried out with the coexistence of alkali and dimethyl sulfoxide.[28] Thus, the effects of the category and concentration of base, temperature, and reaction time on rate of racemization are discussed. As can be seen in Table 2, *(S)*-**1** can be efficiently racemized into *rac*-**1** with an inorganic base such as sodium hydroxide, potassium hydroxide, sodium carbonate at 160° C (Table 2, entries 2–4). However, an organic weak base is not a suitable base for racemization. Under the same condition, racemization almost never occurs with Et_3N. This means that strong alkalinity is favorable to racemization of **1**. It is

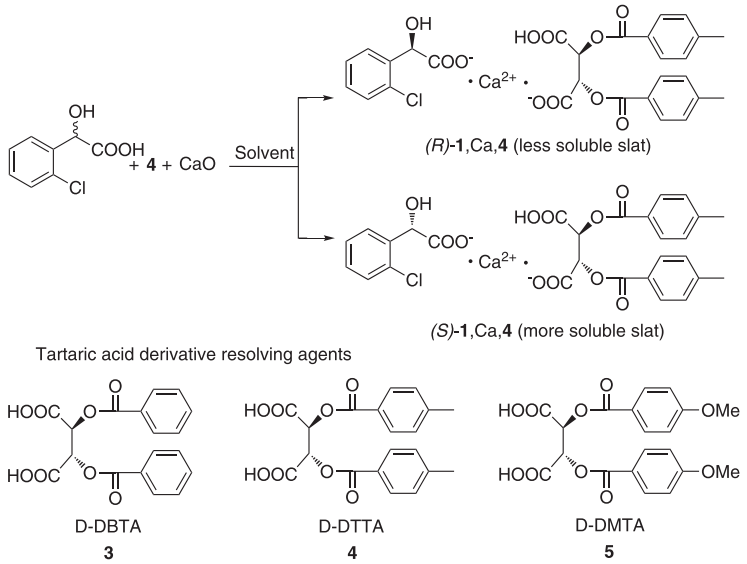

Fig. 1. The resolution of racemic 2-chloromandelic acid (*rac*-**1**).

TABLE 2. Racemization of *(S)*-1[a]

Entry	Base (equiv[b])	Solvent	Temperature[c] (°C)	Time (h)	PR[d] (%)
1	Et_3N (5)	Glycerin	160	5	0
2	Na_2CO_3 (5)	Glycerin	160	5	95
3	KOH (5)	Glycerin	160	5	100
4	NaOH (5)	Glycerin	160	5	100
5	NaOH (4)	Glycerin	160	5	97
6	NaOH (3)	Glycerin	160	5	94
7	NaOH (2)	Glycerin	160	5	43
8	NaOH (1)	Glycerin	160	5	9
9	NaOH (5)	H_2O	105[e]	5	0
10	NaOH (5)	EtOH	80[e]	5	15
11	NaOH (3)	Glycerin	130	1	3
12	NaOH (3)	Glycerin	130	2	71
13	NaOH (3)	Glycerin	160	1	36
14	NaOH (3)	Glycerin	180	1	96
15	NaOH (3)	DMF	160	3	35
16	NaOH (3)	DMSO	160	3	93
17	NaOH (2)	DMSO	160	1	67
18	NaOH (2)	DMSO	160	2	90
19	NaOH (2)	DMSO	160	3	92
20	NaOH (2)	DMSO	130	1	49
21	NaOH (2)	DMSO	130	2	62
22	NaOH (2)	DMSO	130	3	69
23	NaOH (2)	DMSO	130	4	74
24	NaOH (2)	DMSO	130	5	78
25	NaOH (1)	DMSO	160	3	5
26	NaOH (3)	DMSO+H_2O (2%)	160	2	100
27	NaOH (3)	DMSO+H_2O (20%)	160	3	72

[a]The initial enantiomeric purity of *(S)*-**1** is 67% *ee*.
[b]The molar ratio of base and *(S)*-**1**.
[c]Temperature of the oil bath.
[d]Percentage of racemization $(1-[\alpha]_{\text{product}} / [\alpha]_{\text{starting material}})$.
[e]Refluxing.

shown that the high temperature is another important factor in racemization (Table 2, entries 11, 13, and 14). With the increase of alkali concentration and heating time, the rate of racemization was significantly raised. It is notable that more than an equal amount of base was required in the racemization (Table 2, entries 8 and 25).

The solvent effect was dramatic. DMSO was the favorable solvent. Other high boiling solvents such as DMF, glycerin could be used too. But, racemization didn't work in water or alcohol. Temperature had a notable impact on the racemization, and should not be kept below 130°C (Table 2, entry 11). Thus, it is easy to understand why H_2O or EtOH was not a suitable

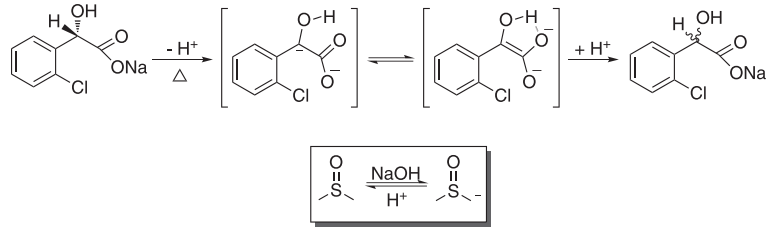

Fig. 2. Mechanism of the racemization in DMSO.

solvent for the racemization. Under the existence of 5 equiv of sodium hydroxide, only a slight amount of racemization occurred even when refluxing for 5 h (Table 2, entries 9–10).

It is interesting that trace water in DMSO contributes to improve the degree of racemization (Table 2, entry 26). The reason would be that trace water improved the dissolution of sodium salt and NaOH during the racemization. When only 3 equiv of sodium hydroxide was used, almost all of the racemization occurred at 160°C after 2 h ($[\alpha]_{product} = 0$).

It should be pointed out that there is no need to use enantiomerically pure *(S)*-**1** for the racemization experiment. The optically enriched compound from the mother liquid of the resolution can also be directly used for the method. *(R)*-**1** can also be racemized into *rac*-**1** under the same condition.

A plausible mechanism of the racemization is now proposed. As described in Figure 2, the proton at the stereogenic center of *(S)*-**1** could be removed by strong alkalinity. The five-membered ring intermediate could be formed through a hydrogen bond between α-hydroxyl and carboxyl group, and the process is the same as benzoin isomerization in basic media.[29] In the 2-chloromandelic acid example, carboxylate ion is formed and shows a better ability to be acceptor of a hydrogen bond. Thus, equal amounts of base have to be used for converting carboxyl acid to carboxylate ion and more base is used for racemization. Increasing the temperature makes the carboxyl and hydroxyl groups closer through the carbon–carbon bond torsion. The removal of the proton at the stereogenic center of *(S)*-**1** by a strong base affords a carbanion that conjugated with the benzene ring. Protonation of the planar carbanion or alkene would definitely produce a racemic compound due to equal probabilities of access of the proton on both faces of the plane. We also propose that sodium hydroxide first reacts with DMSO to form a more reactive anion species (sodium methylsulfinyl methide),[30–32] which then reacts with **1** to form the intermediate anion, thus the dramatic solvent effect can be understood (Fig. 2). Finally, the racemic **1** was obtained by acidification and could be used for further resolution.

A carefully designed experiment would support our proposed mechanism. When the mixture of *(S)*-**1** and 2 equiv of sodium hydroxide was stirred for 2 h at 160°C in the deuterated solvent (DMSO-d_6), ^{1}H NMR analysis of the reaction system showed that a deuterium atom was incorporated at the stereogenic center of **1**, which means that a carbanion formed during the racemization. Thus, the racemization of *(S)*-**1** is easily achieved under certain conditions.

CONCLUSION

The successful methods of coordination-mediated resolution and racemization for the preparation of *(R)*-**1** have been described. The effective resolving agent DTTA was quickly found by "Dutch resolution" in the tartaric acid derivates. Moreover, racemization of *(S)*-**1** was extensively studied and the best condition was found. The mechanism for the racemization was also proposed. The proton at the stereogenic center of *(S)*-**1** could be removed by strong alkalinity affording a five-member ring intermediate through hydrogen-bond between the α-hydroxyl and carboxyl group. A carbanion was formed during the racemization.

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REFERENCES

1. Feliste R, Delebassee D, Simon MF, Chap H, Defreyn G, Vallee E, Dousteblazy L, Maffrand JP. Brroad-spectrum anti-platelet activity of ticlopidine and PCR-4099 involves the suppression of the effects of released ADP. Thromb Res 1987;48:403–415.
2. Bousquet A, Calet S, Heymes A. 2-Thienylglycidsäurederivat, verfahren zu seiner herstellung und seine verwendung als synthesezwischenprodukt. EP patent 0465358. 1992.
3. Blacker AJ, Houson IN. Preparation of mandelic acid derivatives. WO patent 02066410. 2002.
4. Fell R, Korb M, Decker D, Kirschbaum B, Degend M, Bieder G, Kratzer M. Optically active mixtures comprising vanadyl-salen complexes. WO patent 2004055028. 2004.
5. Kurono N, Yoshikawa T, Yamasaki M, Ohkuma T. Enantioselective hydrocyanation of aldehydes catalyzed by Li{Ru(phgly)(2)(binap)} X (X = Cl, Br). Organ Lett 2011;13:1254–1257.
6. van Langen LM, van Rantwijk F, Sheldon RA. Enzymatic hydrocyanation of a sterically hindered aldehyde. Optimization of a chemoenzymatic procedure for (R)-2-chloromandelic acid. Org Process Res Dev 2003;7:828–831.
7. van Langen LM, Selassa RP, van Rantwijk F, Sheldon RA. Cross-linked aggregates of (R)-oxynitrilase: A stable, recyclable biocatalyst for enantioselective hydrocyanation. Organ Lett 2005;7:327–329.
8. Zhang T, Nguyen D, Franco P, Isobe Y, Michishita T, Murakami T. Cellulose tris(3,5-dichlorophenylcarbamate) immobilised on silica: a novel chiral stationary phase for resolution of enantiomers. J Pharm Biomed Anal 2008;46:882–891.
9. Endo T, Tamura K. Process for producing R(−)-mandelic acid and derivatives thereof. US patent 5223416. 1993.
10. Mitsuhashi K, Yamamoto H. Method for producing optically active mandelic acid derivatives. EP patent 1316613. 2003.
11. Osprian I, Fechter MH, Griengl H. Biocatalytic hydrolysis of cyanohydrins: an efficient approach to enantiopure alpha-hydroxy carboxylic acids. J Mol Catal B: Enzym 2003;24:89–98.
12. Huang HR, Xu JH, Xu Y, Pan J, Liu X. Preparation of (S)-mandelic acids by enantioselective degradation of racemates with a new isolate Pseudomonas putida ECU1009. Tetrahedron: Asymmetry 2005;16:2113–2117.
13. Wang PY, Chen TL, Tsai SW. Kinetic resolution of (R,S)-ethyl 2-chloromandelate in biphasic media using hydrolase of Klebsiella oxytoca. Enzyme Microb Technol 2006;39:930–935.

14. DeSantis G, Short JM, Burk MJ, Wong K, Farwell R, Chatman K. Increased activity and stability at increased pH and temperature. US patent 7608445. 2009.
15. Guo JL, Mu XQ, Zheng CG, Xu Y. A highly stable whole-cell biocatalyst for the enantioselective synthesis of optically active alpha-hydroxy acids. J Chem Technol Biotechnol 2009;84:1787–1792.
16. Noda H, Sakai K, Murakami N. Production of optically active 2-chloromandelic acid and production intermediate. JP patent 2001072644. 2001.
17. Peng Y, He Q, Rohani S, Jenkins H. Resolution of 2-chloromandelic acid with (R)-(+)-N-benzyl-1-phenylethylamine: chiral discrimination mechanism. Chirality 2012;24:349–355.
18. Hyoda T, Nawata H. Method for producing optically active o-chloromandelic acid. JP patent 2002114737. 2002.
19. He Q, Peng YF, Hu ZS, Huangfu PY, Zhao HL. Resolution of o-chloromandelic acid. J East China Univ Sci Technol 2004;30:339–342.
20. Wang P, Zhang E, Zhao P, Ren QH, Guan YY, Liu HM. Diastereomeric resolution of racemic o-chloromandelic acid. Chirality 2012;24:1013–1017.
21. Mravik A, Bocskei Z, Katona Z, Markovits I, Pokol G, Menyhard DK, Fogassy E. A new optical resolution method: Coordinative resolution of mandelic acid esters. The crystal structure of calcium hydrogen (2R,3R)-O,O'-dibenzoyl tartrate-2(R)-(−)-methyl mandelate. Chem Commun 1996:1983–1984.
22. Mravik A, Bocskei Z, Katona Z, Markovits I, Fogassy E. Coordination-mediated optical resolution of carboxylic acids with O,O'-dibenzoyltartaric acid. Angew Chem Int Ed 1997;36:1534–1536.
23. Xu HW, Wang QW, Zhu J, Deng JG, Cun LF, Cui X, Wu J, Xu XL, Wu YL. Copper(II)-mediated resolution of alpha-halo carboxylic acids with chiral O,O'-dibenzoyltartaric acid: spontaneous racemization and crystallization-induced dynamic resolution. Org Biomol Chem 2005;3:4227–4232.
24. Lorenz H, Seidel-Morgenstern A. Processes to separate enantiomers. Angew Chem Int Ed 2014;53:1218–1250.
25. Hu Y, Yu ZE, Zhuang XX, Sun XX, Guo Y, Li L. Green chiral resolution of 2-chloromandelic acid. Chem World 2012;53:364–367.
26. Zhou ZZ, Hu Y, Sun XX, Guo Y, Yao H, Chen HW. Chiral tartaric acids derivatives and preparation method thereof. CN patent 101239913. 2008.
27. Vries T, Wynberg H, van Echten E, Koek J, ten Hoeve W, Kellogg RM, Broxterman QB, Minnaard A, Kaptein B, van der Sluis S, Hulshof L, Kooistra J. The family approach to the resolution of racemates. Angew Chem Int Ed 1998;37:2349–2354.
28. Ebbers EJ, Ariaans GJA, Houbiers JPM, Bruggink A, Zwanenburg B. Controlled racemization of optically active organic compounds: prospects for asymmetric transformation. Tetrahedron 1997;53:9417–9476.
29. Ivonin S, Lapandin A, Shtamburg V. Isomerization of (Het) arylbenzoins in basic media. Chem Heterocycl Com 2004;40:154–160.
30. Exner JH, Steiner EC. Dissoziation zu Monomeren und freien Ionen ist bisher lediglich in DMSO beobachtet worden. J Am Chem Soc 1974;96:1782–1787.
31. Wolfe S, Lajohn LA, Bernardi F, Mangini A, Tonachini G. D-orbital effects and the structure of the alpha-thiocarbanion. Tetrahedron Lett 1983;24:3789–3792.
32. Wolfe S, Stolow A, Lajohn LA. A theoretical reexamination of carbanions adjacent to sulfoxide, sulfone and sulfonium centers. Tetrahedron Lett 1983;24:4071–4074.