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Practical resolution of racemic *trans*-2-benzylaminocyclohexanol with di-*p*-toluoyl-L-tartaric acid via diastereomeric salt formation based on the Pope and Peachey method

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ABSTRACT

A new resolution process for racemic *trans*-2-benzylaminocyclohexanol **2**, a key intermediate for chiral pharmaceuticals, was investigated. Di-*p*-toluoyl-L-tartaric acid **15** was found to be a new practical resolving agent in terms of stability and productivity of the resolution system. Resolution conditions were optimized based on the Pope and Peachey method, and the best result was obtained when HCl was added to the resolution system as a supplemental acid; **2**/L-**15**/HCl = 1.0/0.6/0.4 (mol/mol/mol) (yield 92%, 99.5%de, *E* 92%).

1. Introduction

It is well known that enantiopure *trans*-2-aminocyclohexanol **1** is a useful intermediate for various drugs, such as RSD1235 (*anti*-arrhythmic)[1] and OPC-33509 (*anti*-thrombotic).[2] Moreover, the basic skeleton of *trans*-2-aminocyclohexanol is also found in many promising medicines with various indications currently being developed, such as protease inhibitors[3] and an anti-obesity drug.[4] Therefore, the establishment of a practical process for obtaining enantiopure **1** is urgently required (Fig. 1).

To obtain enantiopure **1**, three diastereomeric resolution procedures using di-benzoyl-D-tartaric acid (yield 27%, 80% de, resolution efficiency (*E*) 21%),[5,6] dehydroabietic acid (yield 48%, 81.1%de, *E* 39%),[7] and *N*-pivaloyl proline (Yield 65%, 96%de, *E* 62%)[8] as resolving agents have been reported. Unfortunately, however, these resolution processes may not easily be applied to the industrial-scale production because of their low resolution efficiencies, and the price and availability of the resolving agent.

On the other hand, the resolution of racemic *N*-benzyl derivative **2**, *trans*-2-benzylaminocyclohexanol, with chiral acids such as mandelic acid[9] and di-*p*-toluoyl-L-tartaric acid[1b] has been reported. In both cases, however, these resolution processes need time-consuming multiple salt crystallization steps, and the resolution yields are unsatisfactory for industrial-scale production (yields 60% and 51%, respectively).

As mentioned above, a simple and efficient process for producing enantiopure **2** has not yet been reported. We tried to establish a practical industrial process for obtaining enantiopure **2** via diastereomeric salt formation method since the method is economic, clean, and easier to scale-up to production while keeping the same efficiency from laboratory data. As a result, we found a new practical resolution process for obtaining enantiopure **2** based on the Pope and Peachey method.

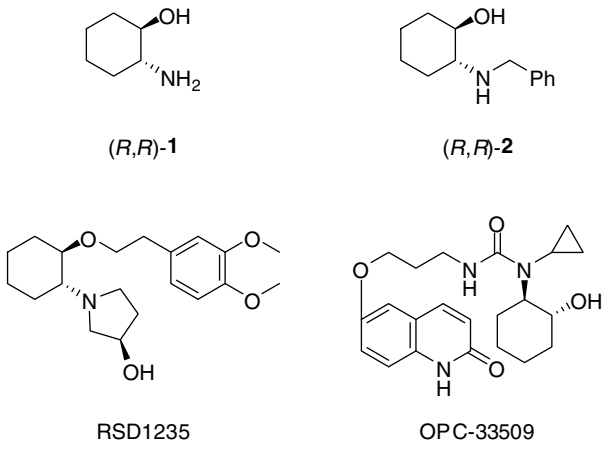

Figure 1.

2. Results and discussion

2.1. Screening of resolving agent for racemic 2

Racemic **2** was prepared according to the reported method[1b] and was used for resolution experiments as a starting material.

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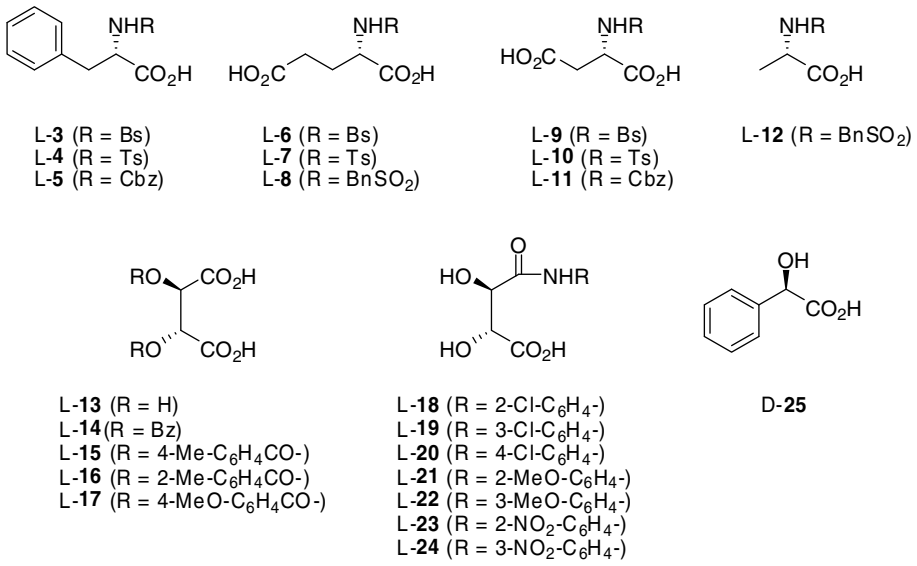

Figure 2. Resolving agents.

To find the most suitable resolving agent for racemic **2**, 23 kinds of commercially available acidic resolving agents were examined: L-amino acid derivatives **3–12**, L-tartaric acids **13** and its derivatives **14–17**, and L-tartranilic acid derivatives **18–24.** D-Mandelic acid **25**[7] was also examined as a reference. The molecular structures of the resolving agents **3–25** used in the experiments are illustrated in Figure 2. Screening of these resolving agents was performed using approximately 1.5 mmol of racemic **2** (0.2 g) and an equimolar resolving agent. The resolution solvent was chosen from water, methanol, or their mixed solvent, and its volume was roughly determined by the respective solubility of the solutes (racemic **2** and resolving agent) charged in each experiment at 65 °C. The reaction mixture was heated to give a clear solution followed by slowly cooling to ambient temperature without stirring. The precipitated crystals were filtrated off and dried in the atmosphere. Diastereomeric excess (%de) of the salts obtained was determined by HPLC (CAPCELL PAK C18 SG120, Shiseido). A sample for analysis was treated with GITC prior to analysis. Each experimental result was evaluated by the resolution efficiency (*E*, %).[5] The screening results are summarized in Table 1.

As shown in Table 1, salt crystals were precipitated with resolving agent L-**9**, L-**12**, L-**15**, L-**16**, L-**20**, and D-**25**, while no crystal or scaled solid was obtained with the other resolving agents. The absolute configuration of amine **2** in the salts was the (*R,R*)-isomer,

Table 1
Resolution of racemic **2** with resolving agents in methanol and water

Entry	Structure	Resolving agent	Solvent (mL)[a]		Solubility[b]	Crystallization[c]	Absolute configuration	Yield (%)	de (%)	E (%)[d]
			MeOH	H2O						
1	Amino acid	L-**3**	5	0	B	b				
2		L-**4**	5	0	B	b				
3		L-**5**	3	0	A	b				
4		L-**6**	3	0	A	b				
5		L-**7**	12	0	C	NA				
6		L-**8**	10	5	B	b				
7		L-**9**	3	0	A	a	R	87	80	63
8		L-**10**	3	0	A	b				
9		L-**11**	3	0	A	b				
10		L-**12**	5	0	B	a	S	68	66	38
11	Tartaric acid	L-**13**	3	0	A	b				
12		L-**14**	5	0	B	b				
13		L-**15**	3	0	B	a	R	72	96	68
14		L-**16**	5	0	B	a	R	11	95	10
15		L-**17**	3	0	A	b				
16	Tartranilic acid	L-**18**	3	0	A	b				
17		L-**19**	3	0	A	b				
18		L-**20**	3	0	A	a	R	110	49	41
19		L-**21**	3	0	A	b				
20		L-**22**	5	1	B	b				
21		L-**23**	5	1	B	b				
22		L-**24**	5	2	B	b				
23	Mandelic acid	D-**25**	3	0	A	b				
24		D-**25**	0	2	B	a	S	78	86	62

[a] 1.5 mmol of racemic **2** and resolving agent were dissolved in methanol and/or water.
[b] Solubility = A: dissolved at room temperature, B: dissolved at less than 65 °C, C: not dissolved.
[c] Crystallization = a: crystallized, b: not crystallized, NA: not applicable.
[d] Resolution efficiency (*E*, %) = yield (%) × de (%)/100.

except for the resolution with L-**12**. As shown in these screening results, diacidic resolving agents L-**9** and L-**15** showed relatively higher resolution efficiency (E >60%) (entries 7 and 13). To our surprise, these resolving agents formed the acidic salt with a 1:1 molar ratio (diacidic resolving agent **9** or **15**/amine **2**), despite using an equimolar amount of diacidic resolving agents. Although this phenomenon of acidic salt formation has not yet been clarified at present, it is clear that the acidic salt is much more stable than the neutral salt (**9** or **15**/**2** = 1:2 molar ratio).

On the basis of these experimental results, it is concluded that enantiopure **2** could be resolved by using diacidic resolving agent L-**9** or L-**15** as a new resolving agent. However, the chiral purity of the salt with L-**9** (80% de) was relatively low compared with that with L-**15** (95% de), and therefore multiple salt recrystallization would not be avoided. From an industrial point of view, a lesser number of operation steps was desirable and so the resolution condition using L-**15** was further optimized as shown below.

2.2. Optimization of resolution conditions for racemic 2 with L-15

In order to fairly optimize resolution condition suited for practical operation on an industrial scale, we focused on (1) solute concentration, (2) molar ratio of resolving agent, and (3) further optimization based on the Pope and Peachey method.

2.2.1. Effect of solute concentration

In order to know stability of resolution reaction and to maximize productivity (product kg/batch), the effect of solute concentration was examined. Experimental results are summarized in Table 2.

Table 2
Effect of solute concentration in MeOH solvent

Entry	Substrate concentration % (w/w)	MeOH/**2** % (w/w)	Yield (%)	de (%)	E (%)
1	30	7.2	83	>99.5	83
2	40	4.3	87	99.3	86
3	50	2.9	86	98.8	85

As shown in Table 2, it was found that resolution efficiency (E) remained unchanged in a range of solute concentrations between 30% and 50% (w/w). This result suggests that the resolution system is extremely stable. Therefore, optimization of the resolution condition was performed in a range of solute concentrations between 40% and 50% (w/w).

2.2.2. Effect of molar ratio of resolving agent L-15

In order to find economic conditions without any deterioration of productivity, the effect of molar ratio of resolving agent L-**15** was examined. Experimental results are summarized in Table 3.

Table 3
Effect of molar ratio of resolving agent L-**15** in MeOH solvent

Entry	Molar ratio of **15** to racemic **2**[a]	Solute concentration % (w/w)	Salt composition ratio (*R,R*)-**2**/L-**15** (mol/mol)	Yield (%)	de (%)	E (%)
1	1.0	50	1/1	86	98.8	85
2	0.7	43	1/1	35	96.8	34
3	0.5	45	2/1	56	95.5	54

[a] Scale of racemic **2**: 30 mmol.

As shown in Table 3, it was found that a decrease in the molar ratio of L-**15** leads to a decrease in the resolution yield, whereas the chiral purity remained at a higher level (96–99%de). To our surprise, it was also found that molar ratio of (*R,R*)-**2**/L-**15** in the salt remained at 1:1, although L-**15** is less prevalent than **2** (entry 2, L-**15**/**2** = 0.7 (mol/mol)). On the other hand, when the molar ratio of L-**15** decreased to 0.5 (mol/mol), neutral conditions based on acid-base equilibrium, the molar ratio of (*R,R*)-**2**/L-**15** changed to neutral 2:1 as previously reported (entry 3).[1b] To our surprise, the chiral purity of the 2:1 salt remained higher than that observed in the 1:1 salt, although the resolution efficiency (E) was insufficient for industrialization.

From these test results, it was found that the best resolution condition was L-**15**/**2** = 1.0 (entry 1, E 88%). Moreover, the test results suggest that the composition molar ratio (1:1 or 2:1) of the salt does not affect the chiral purity, although yield was affected by the molar ratio of the resolving agent used. In other words, the molar ratio of the resolving agent is not a decisive factor for obtaining higher chiral purity. This result quickly prompted us to apply the Pope and Peachey method[10] using a supplementary acid while decreasing the molar ratio of L-**15** to racemic **2**.

2.2.3. Optimization of resolution condition based on the Pope and Peachey method

It is well known that the Pope and Peachey method can usually give better results in the salt yield by a salt-out effect with a more soluble salt formed between amine **2** and a supplementary acid (SA) such as HCl or AcOH. Since the present resolution system, composed of amine **2**, resolving agent L-**15**, and methanol, is extremely stable as described above, the resolution conditions were further optimized based on this method. Experimental results are summarized in Table 4.

Table 4
Optimization of resolution of racemic **2** with resolving agent L-**15** based on the Pope and Peachey method

Entry	Molar ratio of **15** to racemic **2**[a]	Supplementary acid		Yield (%)[b]	de (%)	E (%)
		Sort of acid	Molar ratio to **2**			
1	0.6	AcOH	0.4	52	99.4	52
2	0.6	HCl	0.4	92	99.5	92
3	0.5	HCl	0.5	84	98.8	83

[a] Solute concentration: 50% (w/w).
[b] Salt composition: 1:1 (mol/mol).

First, 0.4 M amount of HCl or AcOH was added into the resolution reaction in methanol (**2**/L-**15**/SA = 1.0/0.6/0.4 (mol/mol/mol); Table 4, entries 1 and 2). As a result, it was found that HCl gives a better result compared with that of using AcOH (E 92% and 51%, respectively). The result obtained by using HCl duly improved compared to that without SA (Table 4, entry 2 and Table 3, entry 1). On the other hand, when HCl content was increased to **2**/L-**15**/HCl = 1.0/0.5/0.5 (mol/mol/mol) the yield decreased, whereas the chiral purity remained in a high level (entry 3, 99.8%de, E 83%). These test results suggest that the Pope and Peachey method using HCl as a supplementary acid is extremely effective for obtaining better results compared with the usual resolution process with none of the supplementary acid (Tables 2 and 3).

3. Conclusion

A new resolution process for racemic *trans*-2-benzylaminocyclohexanol **2** was investigated. It was found that resolving agent L-**15** is quite effective as a resolving agent on the basis of stability and productivity of the resolution system for an industrial-scale production. The resolution conditions were optimized based on the Pope and Peachey method, and HCl was selected as a supplementary acid. The best result was obtained with racemic **2**/L-**15**/HCl = 1.0/0.6/0.4 (mol/mol/mol) (yield 92%, 99.5%de, E 92%).

4. Experimental

4.1. General

Racemic 2-benzylaminocyclohexanol **2** was prepared by the conventional method using the ring-opening reaction of cyclohexene oxide with benzylamine based on the proposed procedure.[1b] (*R*)-Mandelic acid **25** was purchased from Yamakawa Chemical Industry Co., Ltd (Tokyo), and was used without further purification. The other acidic resolving agents used in the resolution experiments were all made in Toray Fine Chemicals Co., Ltd (Tokyo)[11] and had high enantiomeric purities with over 99%ee. ^{1}H NMR spectra were recorded on a JEOL JNM-AL400 spectrometer (400 MHz for a proton), using CD_3OD and $CDCl_3$ as a solvent and tetramethylsilane as the internal reference. Elemental analysis was performed on Perkin Elmer CHNS/O 2400 II Analyzer. IR spectra were measured on a JASCO FT/IR-230 spectrometer in KBr pellets. Melting points were obtained on YAMATO apparatus MLDEL MP-21 and were uncorrected.

4.2. Determination of diastereomeric excess of 2 in the salt

The diastereomeric excess (%de) of the salt (=enantiomeric excess (%ee) of **2**) was determined by HPLC, CAPCELL PAK C18 SG120 (ID 4.6 mm × L 150 mm, Shiseido). The salt was treated with sodium hydroxide in water and the liberated amine **2** was extracted with $CHCl_3$. The separated organic layer was treated with GITC (2,3,4,6-tetra-*O*-acetyl-D-glucopyranosylisothiocyanate) prior to HPLC analysis to give an amine-GITC derivative. Analytical conditions were as follows: mobile phase 5 mM SDS (sodium dodecyl sulfate) aqueous solution/MeCN = 60/40 (v/v), detector UV (243 nm), column temperature 40 °C, elution rate 1.0 mL/min. Retention time: (*R*)-enantiomer 11.9 min, (*S*)-enantiomer 14.0 min.

4.3. Resolution of racemic 2 with L-15

A typical resolution procedure is as follows (Table 2, entry 1): To a 1 L flask were added 51.3 g of racemic **2** (250 mmol), 96.6 g of L-**15** (250 mmol), and 345 g of methanol followed by heating under stirring to obtain a clear solution at 65 °C. The solution was gradually cooled to 20 °C for about 3 h, and the precipitated diastereomeric salt was filtered off and washed with methanol (25 g) to yield wet salt crystals, followed by drying at 50 °C to afford (*R*,*R*)-**2**:L-**15** salt (63.7 g, 103.8 mmol, yield 83%, 99.8%de, *E* 83%).

Analytical data of the less-soluble diastereomeric salts obtained by the resolution are shown below. (*R*,*R*)-**2**:L-**15**: $[\alpha]_D^{20} = -110.3$ (*c* 1.0, MeOH); 99.8%de; mp 174–175 °C; IR (KBr) cm^{-1} 3440, 3166, 3068, 2946, 2926, 2862, 1725, 1612, 1541, 1404, 1338, 1266, 1240, 1178, 1111, 848, 754, 696; ^{1}H NMR (CD_3OD, 400 MHz): δ 8.00–8.02 (m, 4H), 7.27–7.46 (m, 9H), 5.88 (s, 2H), 4.23 (dd, *J* = 13.2, 10.8 Hz, 2H), 3.56 (br, 1H), 3.30 (s, 1H), 2.77 (d, *J* = 8.8 Hz, 1H), 2.40 (s, 6H), 2.10 (d, *J* = 10.8 Hz, 1H), 1.95 (s, 1H), 1.67–1.72 (m, 2H), 1.21–1.41 (m, 4H); Anal. Calcd for $C_{33}H_{37}NO_9$: C, 66.99; H, 6.30; N 2.37. Found: C, 66.90; H, 6.40; N, 2.35.

A typical resolution procedure based on the Pope and Peachey method is as follows (Table 4, entry 2): To a 100 mL flask were added 5.91 g of racemic **2** (29 mmol), 7.28 g of L-**15** (18 mmol), 1.25 g of 35% HCl aq (12 mmol), and 10.3 g of methanol followed by heating to obtain a clear solution at 65 °C. The solution was gradually cooled to 20 °C for about 3 h, and the precipitated diastereomeric salt was filtered off and washed with methanol (5 g) to yield wet salt crystals, which were dried at 50 °C to afford (*R*,*R*)-**2**:L-**15** salt (7.86 g, 13.3 mmol, yield 92%, 99.5%de, *E* 92%).

The less-soluble salt was treated with toluene and aqueous sodium hydroxide. The organic layer was separated and concentrated to give the crystalline product (*R*,*R*)-**2** with >99.5%ee. (*R*,*R*)-**2**: $[\alpha]_D^{20} = -91.2$ (*c* 1.0, MeOH); >99.5%ee; mp 90–91 °C (lit.[9] 92 °C); IR (KBr) cm^{-1} 3295, 3110, 3060, 3023, 2937, 2856, 2664, 2359, 2341, 1603, 1451, 1430, 1360, 1339, 1099, 1078, 972, 880, 844, 749, 699; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.21–7.31 (m, 5H), 3.92 (d, *J* = 13.2 Hz, 1H), 3.76 (br, 1H), 3.65 (d, *J* = 13.0 Hz, 1H), 3.18 (dt, *J* = 14.9, 4.9 Hz, 1H), 2.25–2.31 (m, 1H), 2.11–2.15 (m, 1H), 1.97 (br, 1H), 1.68–1.71 (m, 2H), 1.17–1.29 (m, 4H), 0.94–1.03 (m, 1H).

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