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Resolution of racemic *cis*-1-amino-2-indanol by diastereomeric salt formation with (*S*)-2-phenylpropionic acid

Rumiko Sakurai[a] and Kenichi Sakai[b,*]

[a]*Department of Biomolecular Engineering, Graduate School of Engineering, Tohoku University, Sendai 980-8579, Japan*
[b]*R & D Division, Yamakawa Chemical Industry Co., Ltd., Kitaibaraki 319-1541, Japan*

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Abstract—Resolution of racemic *cis*-1-amino-2-indanol **1**, a key intermediate for the synthesis of indinavir, is reported. The conditions were optimized for an industrial-scale resolution of racemic *cis*-**1** using (*S*)-2-phenylpropionic acid **6** as the resolving agent and ethanol as the solvent. The less-soluble diastereomeric salt, (1*R*,2*S*)-**1**·(*S*)-**6**, was obtained in 35% yield with 99% de (*E* >69%) by crystallization. Resolving agent **6** was efficiently recovered from the salt and the mother liquor.

It is well known that enantiopure *cis*-1-amino-2-indanol **1** is a valuable chiral ligand and an auxiliary for asymmetric synthesis[1] and the (1*S*,2*R*)-isomer is a key intermediate for the synthesis of indinavir, an HIV protease inhibitor.[2] To obtain enantiopure *cis*-**1**, various methods, such as stereoselective hydrogenation of an oxime,[3] stereoselective Ritter reaction of *cis*- or *trans*-1,2-diol,[4] stereoinversion of enantiopure *trans*-**1**,[5] enzymatic resolution of 1-azideindan-2-ol[6] or a *N*-Cbz derivative,[7] and direct resolution with L-tartaric acid,[8] have been devised. Among them, the direct resolution via diastereomeric salt formation could be the most convenient method to produce a single enantiomer for an industrial-scale production. The resolution of racemic *cis*-**1** with L-tartaric acid is not appropriate for industrial-scale production because of low recovery of L-tartaric acid due to its high solubility in various solvents and heat-instability in alcohols. Hence, we tried to find a better resolving agent suitable for an industrial-scale resolution of racemic *cis*-**1** (Scheme 1).

At first, we used *O*-substituted tartaric acids, dibenzoyl-D-tartaric acid **2** and ditoluoyl-D-tartaric acid **3** as the resolving agent for racemic *cis*-**1**, because their solubilities in water or other solvents are much lower than that of tartaric acid and hence their efficient recovery can be expected. The results are summarized in Table 1. As shown in Table 1, surprisingly poor results were obtained compared with the literature data[9] using L-tartaric acid. Next, we focused our attention on α-substituted phenylacetic acids such as (*S*)-mandelic acid **4**, (*R*)-2-methoxyphenylacetic acid **5** and (*S*)-2-phenylpropionic acid **6** as the resolving agents, which are very often used in industrial-scale productions. The results are summarized in Table 2. The highest diastereomeric excess (de) and resolution efficiency (*E*) were obtained (>99% de, *E* 69%)[10] when (*S*)-**6** was used as the resolving agent (Table 2, entry 6) and ethanol was used as a solvent whereas other resolving agents were totally ineffective; the resolution in 2-propanol showed the highest resolution efficiency but the de was not sufficient (Table 2, entry 7; 95% de, *E* 70%). The fine crystals obtained from the resolution with (*S*)-**6** was (1*R*,2*S*)-**1**·(*S*)-**6**.[11] The final product (1*R*,2*S*)-**1** can be separated from the salt according to the reported method (liberation and crystallization from water at pH 12.5) by Askin et al.[8a] Resolving agent (*S*)-**6** was recovered from the mother liquor by extraction and evaporation of the solvent in 93% recovery.

In conclusion, 2-phenylpropionic acid **6** has been found to serve as a new efficient resolving agent for racemic *cis*-**1** and is suited for an industrial-scale production. We also confirmed that (*S*)-**6** could be recovered with sufficient quality in good recovery.

* Corresponding author. E-mail: sakai@yamakawa-chemical.co.jp

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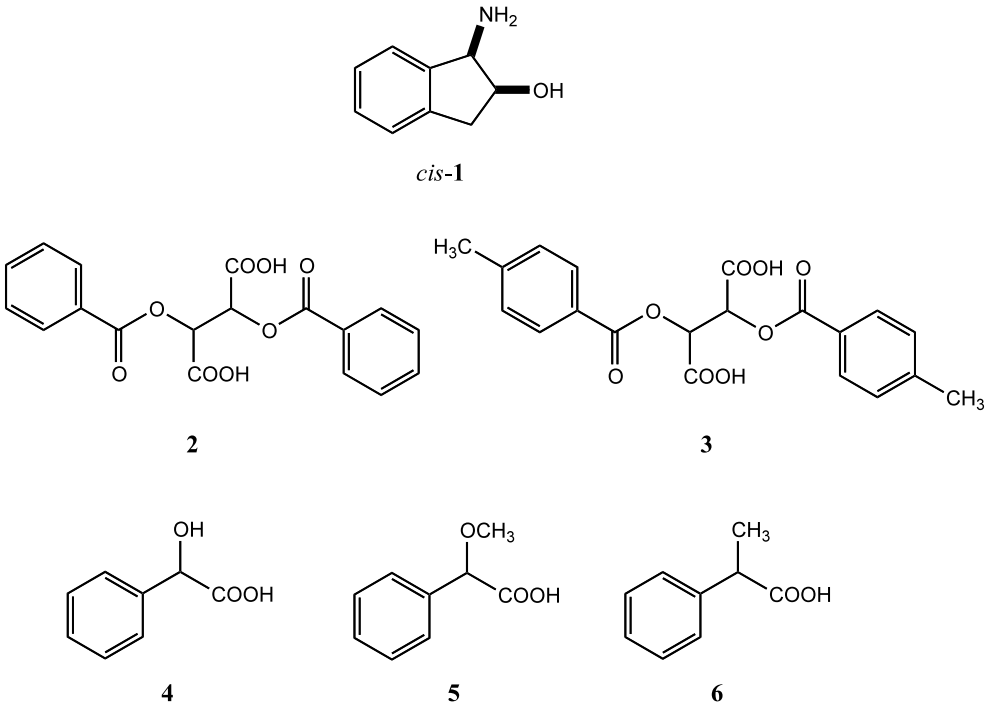

Scheme 1.

Table 1. Resolution of racemic *cis*-**1** with *O*-substituted tartaric acids

Entry	Resolving agent[a]	Solvent	Solvent versus **1** (w/w)	Yield (%)	Diastereomeric excess[b] (% de)	Resolution efficiency (*E*) (%)	Absolute configuration of **1** in a salt
1	D-**2**	MeOH	×17	32	12	8	(−)-(1*S*,2*R*)
2		EtOH	×40	75	12	18	(−)-(1*S*,2*R*)
3	D-**3**	MeOH	×40	31	15	9	(+)-(1*R*,2*S*)
4		EtOH	×40	79	7	11	(+)-(1*R*,2*S*)

[a] An equimolar amount of resolving agent is used. D-**2**, dibenzoyl-D-tartaric acid; D-**3**, ditoluoyl-D-tartaric acid.
[b] De of **1** presented in the salt was based on the ee of the amine liberated from the salt. Ee of **1** was directly determined by HPLC using Inertsil ODS-2 (GL Science, 5 μm, 4.6×250 mm) (eluent: water/acetonitrile (60/40), UV 254 nm, 40°C). A sample for chiral purity analysis by HPLC was treated with GITC prior to injection.

Table 2. Resolution of racemic *cis*-**1** with α-substituted phenylacetic acids

Entry	Resolving agent[a]	Solvent	Solvent versus **1** (w/w)	Yield (%)	Diastereomeric excess[b] (% de)	Resolution efficiency (*E*) (%)	Absolute configuration of **1** in a salt
1	(*S*)-**4**	MeOH	×5.7	66	1	1	(−)-(1*S*,2*R*)
2		EtOH	×27	76	3	5	(−)-(1*S*,2*R*)
3	(*R*)-**5**	MeOH	×1.0	No crystal was obtained			
4		EtOH	×2.7	No crystal was obtained			
5	(*S*)-**6**	MeOH	×6.7	23	98	45	(+)-(1*R*,2*S*)
6		EtOH	×17	35	>99	>69	(+)-(1*R*,2*S*)
7		2-PrOH	×33	37	95	70	(+)-(1*R*,2*S*)

[a] An equimolar amount of resolving agent is used. (*S*)-**4**, (*S*)-mandelic acid; (*R*)-**5**, (*R*)-2-methoxyphenylacetic acid; (*S*)-**6**, (*S*)-2-phenylpropionic acid.
[b] De of **1** presented in the salt was based on the ee of the amine liberated from the salt. Ee of **1** was directly determined by HPLC using Inertsil ODS-2 (GL Science, 5 μm, 4.6×250 mm) (eluent: water/acetonitrile (60/40), UV 254 nm, 40°C). A sample for chiral purity analysis by HPLC was treated with GITC prior to injection.

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9. Refer to Ref. 8a (examples 10 and 11). Resolution yield = 40% (de% of the salt has not been disclosed). The less-soluble salt was obtained as a methanol solvate. Enantiomerically pure *cis*-**1** is obtained in 93% yield upon liberation of amine from the salt.
10. Resolution efficiency (E) has been calculated using the following equation: E = yield (%)×diastereomeric purity (% de)/100.
11. $[\alpha]_D^{20}$ +20.0 (*c* 1.0, EtOH); mp 167.5–172.0°C; ^{1}H NMR (DMSO): δ 7.40–7.14 (m, 9H), 5.89 (s, 4H), 4.44 (ddd, J = 2.4, 5.6, 6.0 Hz, 1H), 4.28 (d, J = 5.6 Hz, 1H), 3.47 (q, J = 7.2 Hz, 1H), 3.03 (dd, J = 6.0, 16.0 Hz, 1H), 2.84 (dd, J = 2.4, 16.0 Hz, 1H), 1.31 (d, J = 7.2 Hz, 3H); IR (KBr): 3236, 3018, 2976, 2914, 2824, 2708, 2584, 1605, 1540, 1510, 1451, 1393, 1356, 1321, 1280, 1182, 1094, 758, 743, 700, 677 cm^{-1}. Anal. calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.18; H, 7.11; N, 4.68%.