Enantiopure *trans*- and *cis*-3-Aminoindan-1-ols: Preparation and Application as Novel Basic Resolving Agents

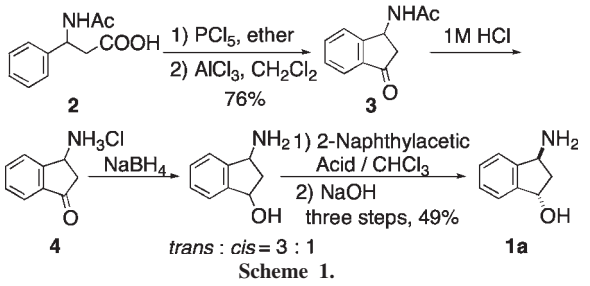
Kazushi Kinbara, Yoshiyuki Katsumata, and Kazuhiko Saigo*
Department of Integrated Biosciences, Graduate School of Frontier Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-8656

(Received November 8, 2001; CL-011123)

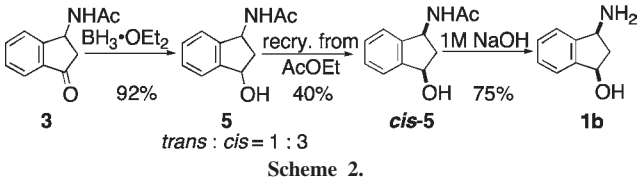
trans- and *cis*-3-Aminoindan-1-ols were prepared by moderately selective reductions of 3-aminoindan-1-one derivatives and separated into enantiopure forms. The enantiopure *trans*-isomer had a moderate resolving ability for 2-arylalkanoic acids having a naphthalene ring at the α-position. The X-ray crystallographic analysis showed that an infinite hydrogen-bond sheet was formed in the less-soluble salt, suggesting that the skeleton of these indanols would be favorable for the stabilization of the less-soluble salt by hydrogen-bonding interaction.

Amino alcohols are versatile compounds as chiral auxiliaries in asymmetric syntheses, resolving agents, etc. We have been focusing our attention on amino alcohols as resolving agents, putting the final goal on the rational design of novel high-performance basic resolving agents fit to target acidic racemates. In the course of our studies on the diastereomeric resolution of systematically-selected racemates by acidic resolving agents,[1] we have found that the formation of a hydrogen-bond sheet in less-soluble diastereomeric salts was important to achieve high efficiency of resolution.[2] On the basis of the results, it is expected that the similar strategy would be applicable for the design of basic resolving agents.[3] After several systematic studies,[3] we now reached to an idea that an indane derivative, in which an amino group and a hydroxy group exist apart from each other, would be suitable for the formation of a stable hydrogen-bond sheet in the less-soluble salts with acidic racemates. Thus, as a candidate having the above-mentioned suitable skeleton, we chose 1,3-amino alcohol, i.e. 3-aminoindan-1-ol in the present study. Here we report the first preparation of enantiopure *trans*- and *cis*-1-aminoindan-3-ols (**1a** and **1b**) and discuss whether **1** are favorable as resolving agents on the basis of the crystal structure of the less-soluble diastereomeric salts with acidic racemates.

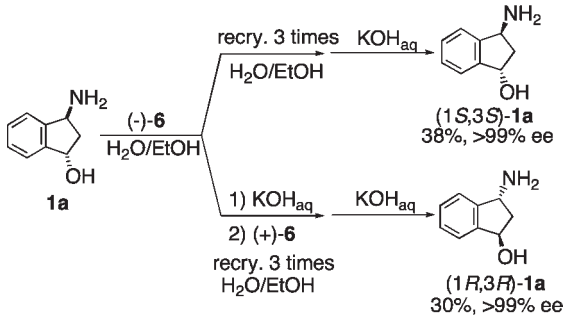
In contrast to the preparation of vicinal cyclic amino alcohols reported so far, that of cyclic 1,3-amino alcohols is rather rare. As a starting compound, which has a skeleton preferable for the construction of a cyclic 1,3-amino alcohol, we selected a β-amino acid derivative. As a result, the preparation of racemic 1-aminoindan-3-ols could be accomplished (Schemes 1 and 2), starting from *N*-acetyl-3-amino-3-phenylpropanoic acid (**2**) which could be easily prepared by the acetylation of 3-amino-3-phenylpropanoic acid.[4] The Friedel-Crafts cyclization of **2** afforded 3-acetamidoindan-1-one (**3**), which was treated with hydrochloric acid to give the amino ketone **4** in good yield. The reduction of **4** by sodium borohydride afforded amino alcohols **1** as a 3 : 1 mixture of **1a** and **1b**. Pure racemic **1a** could be obtained by conversion of this mixture to the salt with naphthylacetic acid, followed by recrystallization from dichloromethane. The total yield of racemic **1a** from **3** was 47%.



Scheme 1.



Scheme 2.



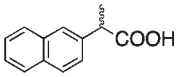
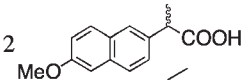
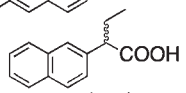
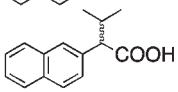
Scheme 3.

The selectivity could be switched by changing the order of reduction and deprotection of **3** (Scheme 2). The reduction of **3** by BH_3•THF gave 3-acetamidoindan-1-ol (**5**) as a mixture of the isomers (*trans* : *cis* = 1 : 3). Recrystallization of this mixture twice from ethyl acetate afforded pure *cis*-**5**, and the deprotection of *cis*-**5** with aqueous sodium hydroxide gave **1b** in good yield. The total yield of racemic **1b** from **3** was 31%.

Enantiopure forms of **1a** could be obtained by the diastereomeric resolution using (−)-dibenzoyl-L-tartaric acid ((−)-**6**) as a resolving agent (Scheme 3). Thus, recrystallization of the diastereomeric salt of **1a** with (−)-**6** three times from aqueous ethanol afforded pure (1*S*, 3*S*)-**1a**•(−)-**6**, which was hydrolized by aqueous KOH to give pure (1*S*, 3*S*)-**1a** in 38% yield.[5]

(1*R*, 3*R*)-**1a** could be obtained in a similar manner to the resolution of (1*S*, 3*S*)-**1a** by using (+)-**6** as a resolving agent: From the mother liquor of the first crystallization, (1*R*, 3*R*)-**1a**-enriched mixture could be recovered, which was treated with (+)-dibenzoyl-D-tatraric acid ((+)-**6**) to afford enantiopure (1*R*, 3*R*)-**1a**. The absolute stereochemistry of (1*S*, 3*S*)-**1a** was determined

Table 1. Resolution of 2-arylalkanoic Acids by (1*S*, 3*S*)-**1a**

entry	racemic acid	yield / %[a]	%ee	yield × ee
1		100	28	0.28
2		90	55	0.50
3		73	48	0.35
4		87	41	0.36

[a]Yield of the crystallized diastereomeric salt baed on the half amount of the racemic acid.

by the X-ray crystallographic analysis of (1*S*, 3*S*)-**1a**•(−)-ditoluoyltartrate.[6]

Concerning **1b**, its enantiopure form was difficult to be obtained by the diastereomeric resolution. Instead, chiral HPLC was found to be effective for the separation of the enantiomers.[7]

The resolution of 2-arylalkanoic acids was performed using enantiopure **1a** as a resolving agent (Table 1). As a result, it was found that the resulting diastereomeric salts had rather high solubility in aqueous alcohol and that the efficiency of resolution was quite low when the aryl group was a substituted phenyl group. In contrast, moderate efficiency of resolution could be achieved in the cases of 2-arylalkanoic acids having a naphthalene ring at the α-position.

The crystal structure of the less-soluble salt of (1*S*, 3*S*)-**1a**•(*S*)-naproxen (entry 2) is shown in Figure 1.[8] This crystal has a quite characteristic hydrogen-bonding pattern, compared with other reported examples.[1–3] At first, the ammonium hydrogen of **1a**•$\mathbf{H}^+$ and the carboxylate oxygen of a naproxen anion form a

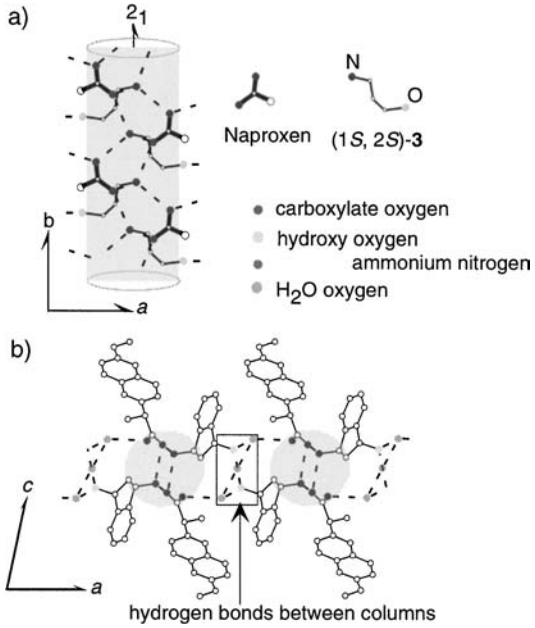


Figure 1. Crystal structure of less-soluble (1*S*, 3*S*)-**1a**•(*S*)-naproxen. a) Schematic representation of the hydrogen-bond column. b) Hydrogen-bond sheet viewed down the *b*-axis. The dotted lines represent hydrogen bonds.

columnar hydrogen-bond network, as were found in less-soluble diastereomeric salts of our previous studies (Figure 1a).[1,2] The remarkable point is the role of the hydroxy group of **1a**•$\mathbf{H}^+$ in the hydrogen-bond network. In this structure, the hydroxy group of **1a**•$\mathbf{H}^+$ directly forms hydrogen-bonds with the carboxylate oxygen, resulting in the formation of an infinite sheet of hydrogen-bonds in the less-soluble salt (Figure 1b). This sheet structure is reinforced by hydrogen-bonds with water molecules incorporated in the less-soluble salt. As a result, a quite stable hydrogen-bond sheet is realized in the less-soluble salt. This is the first example of a less-soluble salt, in which the hydroxy group of an amino alcohol directly interacts with a columnar structure, made by ammonium hydrogens and carboxylate oxygens, to form a hydrogen-bond sheet.

Although the resolution ability of this amino alcohol is not high enough for practical use, the crystal structure of the less-soluble salts shows that the geometrical relationship between the hydroxy group and the amino group is very important for the formation of a stable hydrogen-bond sheet. Thus, it is expected that this structure would become a potential candidate for a novel basic resolving agent; upon introducing a suitable substituent on the aromatic group of **1a** to realize close packing of less-soluble diastereomeric salts, a more powerful basic resolving agent would be achieved.

Dedicated to Prof. Teruaki Mukaiyama on occasion of his 75th birthday.

References and Notes

1 K. Kinbara, Y. Harada, and K. Saigo, *J. Chem. Soc., Perkin Trans. 2*, **2000**, 1339; K. Kinbara, K. Oishi, Y. Harada, and K. Saigo, *Tetrahedron*, **56**, 6651 (2000).
2 K. Kinbara, K. Sakai, Y. Hashimoto, H. Nohira, and K. Saigo, *J. Chem. Soc., Perkin Trans. 2*, **1996**, 2615.
3 K. Kinbara, Y. Kobayashi, and K. Saigo, *J. Chem. Soc., Perkin Trans. 2*, **2000**, 111; K. Kinbara, Y. Kobayashi, and K. Saigo, *J. Chem. Soc., Perkin Trans. 2*, **1998**, 1767.
4 P. Kuehne, A. Linden, and M. Hesse, *Helv. Chim. Acta*, **79**, 1085 (1996).
5 (1*S*, 3*S*)-**1a**: mp 113.5–114 °C; ^{1}H NMR ($CDCl_3$) $\delta = 1.58$ (br, s, 3H), 2.06 (dt, 1H, $J = 6.3, 13.7$ Hz), 2.46 (ddd, $J = 3.0, 6.3, 13.7$ Hz), 4.64 (t, ^{1}H, $J = 6.3$ Hz), 5.34 (dd, 1H, J = 3.0, 6.3 Hz), 7.31–7.43 ppm (m, 4H); IR (KBr) 3350, 3300, 3125, 2925, 2700, 1650, 1320, 1300, 1040, 990, 770 cm^{-1}; $[\alpha]^{17.2}{}_D = 38.1$ ($c = 1.00$, EtOH). (1*R*, 3*R*)-**1a**: mp 112–113.5 °C; $[\alpha]^{17.2}{}_D = -39.3$ ($c = 1.00$, EtOH); ^{1}H NMR and IR spectra were identical with (1*S*, 3*S*)-**1a**.
6 Crystal data for (1*S*, 2*S*)-**1a**•(−)-ditoluoyl-L-tartrate: $C_{29}H_{29}NO_9$, $M = 535.55$, Orthorhombic, space group $P2_12_12$, $a = 14.994(1)$ Å, $b = 24.595(2)$ Å, $c = 7.927(2)$ Å, $V = 2923.3(3)$ Å^3, $Z = 4$, $Dc = 1.217$ Mg m^{-3}, $R = 0.085$, reflections used = 3970. The details of the refinement was submitted as supporting information.
7 Daicel CrownPak CR+ (eluent: pH1.9 $HClO_4$) was used for the separation of the enantiomers. A small amount of unknown compound cotaminates (+)-**1b**. The details for the separation and characterization of (+)- and (−)-**1b** will be reported elsewhere. (+)-**1b:** The first fraction; Colorless oil; ^{1}H NMR ($CDCl_3$) $\delta = 1.64$ (dt, 1H, $J = 6.0$, 13.2 Hz), 2.13 (br, s, 3H), 2.81 (dt, $J = 6.6$, 14.1 Hz), 4.24 (t, 1H, $J = 6.6$ Hz), 5.05 (t, 1H, $J = 6.0$ Hz), 7.30–7.44 ppm (m, 4H); IR (KBr) 3350, 2950, 1580, 1460, 1340, 1040, 770, 740 cm^{-1}; CD ($CHCl_3$, 7.2×10^{-4} M, 1.0 cm): $\lambda(\Delta\varepsilon) = 280$ (1.5). (−)-**1b:** The second fraction; Colorless oil; CD ($CHCl_3$, 7.2×10^{-4} M, 1.0 cm): $\lambda(\Delta\varepsilon) = 280$ (0.23); ^{1}H NMR and IR spectra were identical with (+)-**1b**.
8 Crystal data for (1*S*, 2*S*)-**1a**•(*S*)-naproxen: Space group, *C*2, $a = 20.516(5)$ (Å), $b = 6.263(1)$ (Å), $c = 19.027(4)$ (Å), $\beta = 119.73(1)$ (°), $V = 2123.0(7)$ Å^3, $Z = 2$, $Dc = 1.272$ Mg m^{-3}, $R = 0.052$, reflections used = 2735. The detail of the refinement was submitted as supporting information.