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Resolution of β-aminoalcohols and 1,2-diamines using fractional crystallization of diastereomeric salts of dehydroabietic acid

Zhang Guangyou,† Liao Yuquing, Wang Zhaohui, Hiroyuki Nohira and Takuji Hirose*

Department of Applied Chemistry, Faculty of Engineering, Saitama University, 255 Shimo-ohkubo, Sakura, Urawa, Saitama 338-8570, Japan

Received 30 May 2003; accepted 27 August 2003

Abstract—(*S*)-(+)-1-Amino-3-phenyloxy-2-propanol, (*R*)-(−)-2-amino-1-phenylethanol, (*S*)-(+)-1-amino-2-propanol, (1*S*,2*S*)-(+)-2-aminocyclohexanol and (1*S*,2*S*)-(+)-1,2-diaminocyclohexane were resolved using dehydroabietic acid. It was shown that good to high enantiomeric purity, between 81∼>99% ee, was obtained and that dehydroabietic acid could be easily and efficiently recovered in a reusable form.

1. Introduction

Resolution and asymmetric synthesis are the major methodologies[1] used to obtain synthetic homochiral compounds. The most practical and widely used method is resolution. We have worked on resolution using not only diastereomeric salt formation but also preferential crystallization and developed various kinds of chiral compounds useful as molecular recognition reagents,[2] liquid crystals and related materials.[3] Among chiral compounds, β-aminoalcohols and 1,2-diamines are the most useful starting materials for the preparation of pharmaceuticals and ligands.[4,5] As a result it is important in asymmetric synthesis to search for rapid and efficient resolving agents for aminoalcohols and 1,2-diamines.

Dehydroabietic acid, DAA, is one of the main components of disproportionated rosin and is very easy to obtain as an ethanolamine salt by fractional crystallization.[6] Compared with abietic acid, DAA is more stable under acidic conditions and also withstands auto-oxidation. To our knowledge, DAA has rarely been used as a resolving agent. Herein it is shown that some β-aminoalcohols and 1,2-diaminocyclohexane can be successfully resolved.

* Corresponding author. Tel./fax: +81-48-858-3522; e-mail: hirose@apc.saitama-u.ac.jp

† Permanent address: Department of Chemical Engineering, Jinan University, 106 Jiwei Road, Jinan, Shandon Province 25002, PR China.

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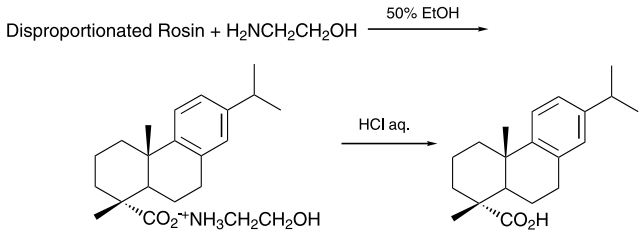
2. Results and discussion

A series of β-aminoalcohols, that is 1-amino-3-phenyloxy-2-propanol **1**, 2-amino-1-phenylethanol **2**, 1-amino-2-propanol **3** and 2-aminocyclohexanol **4**, were obtained via the reaction of ammonia with the corresponding epoxides at 15–20°C. At higher temperatures, more by-products were formed by the competing reaction of the ammonia at the 1-position of the substituted epoxides and/or by the reaction of the product aminoalcohols with epoxides to give the 1:2 adduct.

1-Amino-3-phenyloxy-2-propanol was purified by recrystallization from ethyl acetate. All other aminoalcohols were purified by distillation under vacuum. The yield of 2-aminocyclohexanol was much higher than other products, probably because it was more difficult to react a second time with cyclohexene oxide to form di(2-hydroxycyclohexyl)- amine due to its sterically hindered character. Dehydroabietic acid was prepared from disproportionated rosin according to the literature[6] as shown in Scheme 1.

The salts of β-aminoalcohols or 1,2-diaminocyclohexane with DAA were easily recrystallized from various organic solvents such as ethanol, methanol, acetonitrile, 2-propanol, THF and so on, but only crystals from ethanol or methanol were of significantly higher enantiomeric purity. The process and results of fractional recrystallization are summarized in Scheme 2.



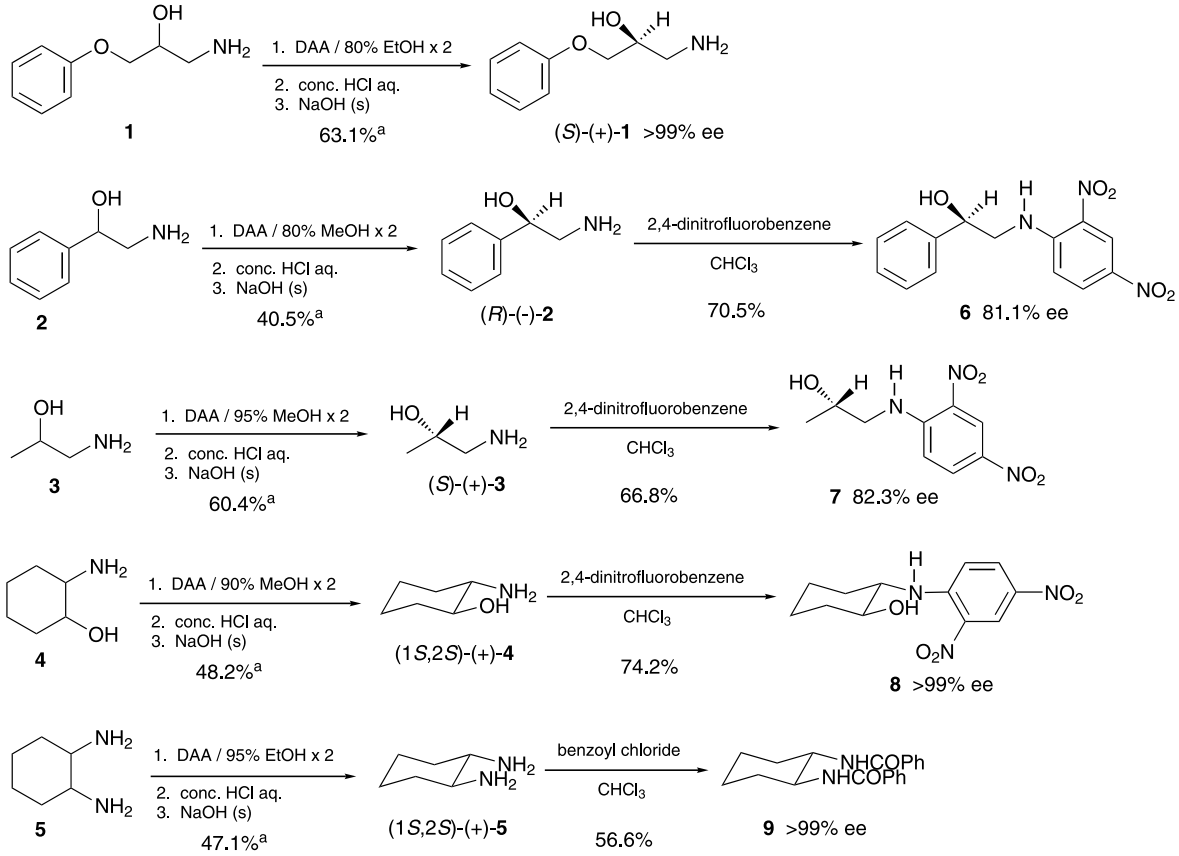
Scheme 1. Preparation of dehydroabietic acid (DAA).

The absolute configurations of the resolved β-aminoalcohols and 1,2-diaminocyclohexane were determined by comparing their specific rotation signs with those in the literature.[7] The enantiomeric purities were determined by chiral HPLC analysis.

The absolute configurations of resolved **1**, **2**, **3**, **4** and **5** were found to be (*S*)-(+), (*R*)-(−), (*S*)-(+), (1*S*,2*S*)-(+) and (1*S*,2*S*)-(+), respectively, as follows. Resolved (*S*)-(+)-**1** was directly analyzed with HPLC and the enantiomeric purity was determined to be >99% ee. This result showed that the entire process was an easy and practical method to obtain (*S*)-(+)-**1**. The resolving agent was easily recovered as a precipitate by acidification of the aqueous solution obtained during liberation of the aminoalcohols and diamine. The unchanged enantiomeric purity of the resolving agent was confirmed by measuring the specific rotation.

Enantiomerically enriched **2**, **3**, **4** and **5** were further derived to **6**, **7**, **8** and **9**, respectively, for HPLC analysis. The enantiomeric purities of **6** and **7** were 81% and 82% ee, respectively and the result which after only one recrystallization was not satisfactory. It is noteworthy however, that the small and flexible aminoalcohol **4** was resolved in good yield and reasonable purity. The rigid structure of DAA seems to be one source of its resolution ability. However the absolute configurations of **1**, **2** and **3** are not consistent in spite of their structural similarities. At the present time, rigidity or bulkiness around the asymmetric center is expected to affect the chirality discrimination. This is consistent with the flexibility of **1** and **3** versus the rigidity of **2** due to its phenyl group. The purity of **8** was >99% ee, which means that the preparative yield and purity of (1*S*,2*S*)-(+)-**4** is as good as that of the enzymatic method reported by Takada et al.[8]

It is well known that chiral 1,2-diaminocyclohexane is a versatile synthon of chiral salen complexes.[9] The high enantiomeric purity of **9** (>99% ee) shows that the preparation of enantiomerically pure (1*S*,2*S*)-(+)-**5** presented here is also efficient practically.[10] However, the



Scheme 2. Optical resolution of β-chiral aminoalcohols and 1,2-diamine by dehydroabietic acid and their derivation. a: Based on half the amount of racemate.

resolution of 1,2-diaminopropane failed in spite of the results with **3**, **4** and **5**.

In summary it has been shown that DAA is a useful resolving agent. Its versatility is probably due to the following factors: (1) Face discrimination by one carboxyl group and two axial methyl groups; (2) its rather rigid planar structure, and (3) its aromatic structure as an additional interacting part for amines like **1** and **2** which have an aromatic group. Although the resolutions of some *o*-aminomethylphenols were tried using DAA, satisfactory results have yet to be obtained.

3. Experimental

3.1. General

^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker AM-400 spectrometer. Enantiomeric excess determinations were carried out using a set of JASCO LC 900 series with a chiral column 'Chiralcel OB-H' (Daicel Chem. Ind. Ltd., 4.6 mm×250 mm). Optical rotations were measured with a JASCODIP-370 polarimeter. Melting temperatures were determined on a Mel-Temp melting point apparatus (Laboratory Devices, MA) and are reported uncorrected. For recrystallization, all solvents were used as received.

3.2. Preparation of DAA

Dehydroabietic acid was prepared according to the literature,[6] mp 170–171.5°C, $[\alpha]_D^{20}=+62.5$ (*c* 2.0, 95% ethanol). (Lit.[6]: mp 170–171.5°C, $[\alpha]_D^{20}=+62.5$.)

3.3. General method for the preparation of β-aminoalcohols

Epoxide (0.1 mol) and 25% NH_3 aq. (1 mol) were mixed together after which methanol was added until the reaction mixture became clear with stirring. The reaction mixture was then further stirred overnight at 15–20°C. Methanol, water and excess NH_3 were removed under reduced pressure. The residue was recrystallized for **1** and distilled under vacuum for **2**, **3** and **4**. Pure **1** was obtained from ethyl acetate in 71% yield. The yields of **2**, **3** and **4** were 32, 45 and 90%, respectively.

3.4. Fractional recrystallization of β-aminoalcohols and 1,2-diaminocyclohexane dehydroabietate

DAA (10 mmol) was dissolved in methanol (50 mL), and then either β-aminoalcohols or **5** (10 mmol) added. After the evaporation of methanol, the residue was recrystallized from the solvent. The crystals were isolated, dried under vacuum, and recrystallized once more. Ordinarily recrystallization overnight was required. The other salts were resolved in the same way with various solvent systems (Scheme 2).

The salts of (*S*)-(+)-**1** (3.34 g) and DAA (6.01 g): 190 mL of 80% ethanol was used for the first recrystallization and then 96 mL for the second to obtain crystals (4.11 g) in 63.1% yield based on half the amount of racemate, $[\alpha]_D^{23}=+40.9$ (*c* 1.0, methanol).

The salts of (*R*)-(−)-**2** (1.94 g) and DAA (4.24 g): 80% methanol (50 and 25 mL) was used for every 1 g of the salt to give a yield of 40.5% (82.3% ee) based on half the amount of racemate, $[\alpha]_D^{25}=+20.5$ (*c* 1.0, methanol).

The salts of (*S*)-(+)-**3** (2.50 g) and DAA (10.00 g): 95% methanol (40 and 20 mL) was used for every 1 g of the salt to give a yield of 60.4% based on half the amount of racemate, $[\alpha]_D^{22}=+44.4$ (*c* 1.0, methanol).

The salts of (1*S*,2*S*)-(+)-**4** (2.77 g) and DAA (7.23 g): 90% methanol (50 mL and then 20 mL) was used to obtain crystals (2.52 g) in 48.2% yield (81.1% ee) based on half the amount of racemate, $[\alpha]_D^{23}=+37.9$ (*c* 1.0, methanol).

The salts of (1*S*,2*S*)-(+)-**5** (1.14 g) and DAA (3.01 g): 95% ethanol (20 and 10 mL) was used for every 1 g of the salt to give a yield of 47.1% based on half the amount of racemate, $[\alpha]_D^{23}=+50.7$ (*c* 1.0, methanol).

3.5. Liberation of resolved aminoalcohols and 1,2-diaminocyclohexane from their salts of DAA

General method: 1 mmol of the crystals obtained was dissolved in 20 mL of methanol after which 2.5 mmol (3.5 mmol in case of 1,2-diaminocyclohexane) *c*. HCl aq. was added. After the evaporation of methanol, 10 mL of water was added and the mixture was stirred for 10 min. Dehydroabietic acid was filtered off and washed with 10 mL of water. To the filtrate, 2.5 mmol (3.5 mmol in case of 1,2-diaminocyclohexane) NaOH was added. After the evaporation of water from the mixture, precipitated NaCl was removed by filtration and washed with THF. The THF solution was dried over K_2CO_3 and removed by filtration. The solvent was removed to yield either the resolved β-aminoalcohol or 1,2-diaminocyclohexane.

(*S*)-(+)-**1**; 96.2% yield, $[\alpha]_D^{29}=+2.4$ (*c* 1.0, methanol), >99% ee (OD-H, hexane:2-propanol = 7:3).

(*R*)-(−)-**2**; 97.0% yield, $[\alpha]_D^{26}=-31.6$ (*c* 1.0, methanol).

(*S*)-(+)-**3**; 94.2% yield, $[\alpha]_D^{26}=+5.4$ (*c* 1.0, methanol).

(1*S*,2*S*)-(+)-**4**; 95.6% yield, $[\alpha]_D^{24}=+8.2$ (*c* 1.0, methanol).

(1*S*,2*S*)-(+)-**5**, yield in 95.4%, $[\alpha]_D^{30}=+41.2$ (*c* 1.0, methanol).

3.6. Reaction of resolved β-aminoalcohols and 2,4-dinitrofluorobenzene[8]

β-Aminoalcohol (0.5 mmol), 2,4-dinitrofluorobenzene (1.0 mmol) and triethylamine (1.0 mmol) were added to chloroform (20 mL) and the mixture stirred at room temperature for 2 h. Chloroform was removed by evap-

oration and the residue purified by chromatography (silica gel, chloroform:ethyl acetate = 5:1). After concentration of the eluent, the residue was washed with water and then with methanol, and fed to HPLC analysis.

6; 70.5% yield, 81.1% ee (Chiralcel OB-H, 25% 2-propanol in hexane).

7; 66.8% yield, 82.3% ee (Chiralcel OB-H, 30% 2-propanol in hexane).

8; 74.2% yield, >99% ee (Chiralcel OB-H, 30% 2-propanol in hexane).

3.7. Benzoylation of (1*S*,2*S*)-(+)-1,2-diaminocyclohexane

(1*S*,2*S*)-(+)-1,2-Diaminocyclohexane (0.5 mmol), benzoyl chloride (1.2 mmol) and triethylamine (1.2 mmol) were added to THF (20 mL) and the mixture stirred at room temperature for 2 h. The mixture was then poured into 5% NaOH aq. (100 mL) and stirred for 1 h. The solid was filtered out and washed successively with water and methanol to give 0.28 mmol of the product, **9**, in 56.6% yield, >99% ee (Chiralcel OB-H, 10% 2-propanol in hexane).

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