New chiral ammonium salt hosts derived from amino acids: very efficient optical resolution of 2,2′-dihydroxy-1,1′-binaphthyl by complexation with these host compounds

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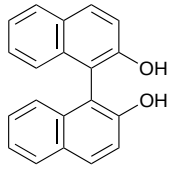
Chiral ammonium salt hosts are prepared from amino acids by transformation of their NH_2 and CO_2H groups into $Me_3N^+Br^-$ and CH_2OH groups, respectively, *via* three simple reaction steps; by complexation with these hosts, 2,2′-dihydroxy-1,1′-binaphthyl is resolved very efficiently.

It has been reported that ′onium salts such as ammonium[1–5] and phosphonium salts[6] form inclusion complexes with alcohol and phenol derivatives *via* hydrogen bond formation between the counter anion of the ′onium salt host and the hydroxy group of the alcohol or phenol guest. In these inclusion complexes, molecular recognition between the host and guest occurred and separation of isomers of the guest was accomplished. When a chiral ′onium salt host is used, *rac*-guest compounds were resolved. For example, *rac*-2,2′-dihydroxy-1,1′-binaphthyl **1**



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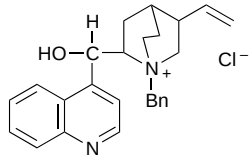
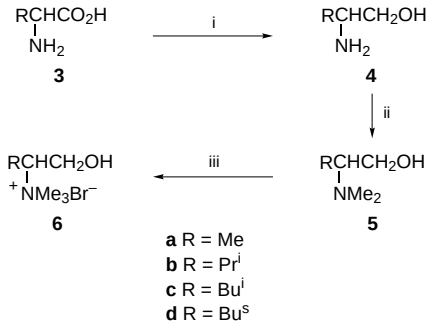


(–)-**2**

was easily resolved by complexation with *N*-benzylcinchonidinium chloride **2**, because **2** forms a 1 : 1 inclusion complex with (*R*)-(+)-**1** selectively.[4] X-Ray crystal structure analysis of the complex showed that the complex is mainly constructed *via* formation of an intermolecular hydrogen bond between Cl^- of **2** and the OH group of **1**. It was also found that an intramolecular hydrogen bond between the OH group of **2** and Cl^- plays an important role in forming the complex.[5] This finding suggests that a chiral compound which has $Me_3N^+X^-$ and OH groups would be a good host for resolution of *rac*-**1**. According to this idea, chiral β-hydroxy trimethylammonium bromide hosts **6a–d** were prepared from the corresponding β-amino acids **3a–d** by transformation of their NH_2 and CO_2H groups into $Me_3N^+Br^-$ and CH_2OH groups, respectively, *via* the three step reaction shown in Scheme 1.



Scheme 1 *Reagents*: i, $LiAlH_4$; ii, HCO_2H, HCHO; iii, MeBr

For example, treatment of L-leucinol **4c**, prepared by $LiAlH_4$ reduction of L-leucine **3c** in 99% yield,[7] with formaldehyde and formic acid according to the reported procedure[8] gave *N*,*N*-dimethyl-L-leucinol **5c** in 98% yield. Treatment of **5c** with MeBr gave the quaternary ammonium salt host, (+)-1-hydroxymethyl-3-methylbutyl(trimethyl)ammonium bromide **6c** in 77% yield as colourless prisms.† By the same procedure, (−)-**6a**, (+)-**6b** and (+)-**6d** were prepared from L-alanine (**3a**), L-valine (**3b**) and L-isoleucine (**3d**), respectively.

When a solution of (+)-**6c** (0.5 g, 2.08 mmol) and *rac*-**1** (1.19 g, 4.16 mmol) in EtOH (6 ml) was kept at room temperature for 24 h, a 1 : 1 inclusion complex of (+)-**6c** and (+)-**1** was obtained as colourless prisms. The crude complex was recrystallised from diethyl ether to give pure complex crystals‡ and then the pure complex crystals were dissolved in a mixture of diethyl ether and water. From the diethyl ether solution, (+)-**1** (100% ee)§ was obtained (0.42 g, 70% yield). From aqueous solution, **6c** was recovered (0.43 g, 86% yield). By the same complexation experiments of *rac*-**1** with (−)-**6a**, (+)-**6b** and (+)-**6d**, (−)-**1** (100% ee, 68% yield), (+)-**1** (100% ee, 36% yield) and (−)-**1** (100% ee, 48% yield) were obtained, respectively. In all cases, host compounds were recovered in almost quantitative yield and could be reused.

In comparison to the resolution of *rac*-**1** by complexation with **2**, the present resolution with **6** of about half mole of **2** has many advantages. Since **6** can easily be prepared in large quantities from cheap L-amino acid *via* a simple three step reaction, the present resolution method is more economical than that *via* the relatively expensive **2**. Furthermore, either (+)-**1** or (−)-**1** can be obtained according to demand, as (−)-**6a** and (+)-**6d** include (−)-**1** and (+)-**6b** and (+)-**6c** include (+)-**1**.

By using the precise chiral recognition between **1** and **6** in the inclusion complex, *rac*-**6** can also be resolved by optically active **1**. For example, when a solution of *rac*-**6d** (0.34 g, 1.40 mmol), prepared from *rac*-isoleucine (*rac*-**3d**) and (−)-**1** (0.2 g, 0.69 mmol) in EtOH (3.5 ml) was kept at room temperature for 24 h, a 1 : 1 complex of (−)-**1** and (+)-**6d** was obtained, after recrystallisation from EtOH, as colourless prisms (0.28 g, 76% yield). The pure complex crystals were dissolved in a mixture of diethyl ether and water. From aqueous solution, (+)-**6d** (100% ee) was obtained (0.13 g, 76% yield). From diethyl ether solution, (−)-**1** was recovered (0.15 g, 76% yield).

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Footnotes

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† *Selected data* for (−)-**6a**: no clear mp; $[\alpha]_D$ −4.6 (*c* 0.5, MeOH); ν_{max} (Nujol)/cm^{-1} 3292 (OH); Calc. for $C_6H_{16}ONBr$: C, 36.38; H, 8.14; N, 7.07. Found: C, 36.35; H, 8.12; N, 7.10%. For (+)-**6b**: mp 153–160 °C; $[\alpha]_D$ +6.9 (*c* 0.5, MeOH); ν_{max}(Nujol)/cm^{-1} 3275 (OH); Calc. for $C_8H_{20}ONBr$: C, 42.49; H, 8.91; N, 6.19. Found: C, 42.19; H, 8.91; N, 6.33%. For **6c**: mp 153–156 °C; $[\alpha]_D$ +18.0 (*c* 0.5, MeOH); ν_{max}(Nujol)/cm^{-1} 3290 (OH); Calc. for $C_9H_{22}ONBr$: C, 52.56; H, 7.35; N, 5.11. Found: C, 52.49; H, 7.09;

N, 5.03%. For (+)-**6d**: mp 156–157 °C; $[\alpha]_D$ + 8.9 (*c* 0.5, MeOH); ν_{max}(Nujol)/cm^{-1} 3275 (OH); Calc. for $C_9H_{22}ONBr$: C, 52.56; H, 7.85; N, 5.11. Found: C, 52.30; H, 7.10; N, 5.30%.

‡ *Selected data* for complex of (+)-**6c** and (+)-**1**: 0.96 g, 88% yield; no clear mp; $[\alpha]_D$ +33.2 (*c* 0.5, THF), ν_{max}(Nujol)/cm^{-1} 3200 (OH); Calc. for $C_{12}H_{20}ONBr$: C, 65.91; H, 6.98; N, 2.63. Found: C, 65.80; H, 6.90; N, 2.90%.

§ All optical purities of (+)- and (−)-**1** were determined by HPLC using a column containing an optically active solid phase (Chiralpak AS) and hexane–EtOH (95 : 5) as eluent. The Chiralpak AS is available from Daicel Chemical Industries Ltd., Himeji, Japan.

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