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EFFICIENT RESOLUTION OF SECONDARY ALCOHOLS, CYANOHYDRINS, AND GLYCEROL ACETALS BY COMPLEXATION WITH THE HOST DERIVED FROM TARTARIC ACID

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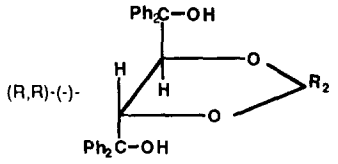
Abstract: Some title hydroxy compounds were resolved efficiently by complexation with the host compounds derived from tartaric acid.

The host compounds (**1**) which are derived from tartaric acid[1] were found to be useful for an efficient resolution of the title hydroxy compounds through inclusion crystal formation.

For example, when a solution of rac-1-phenylethanol (**2a**, 2.62 g, 21.5 mmol) and **1a** (10 g, 21.5 mmol) in 1:1 toluene-hexane (20 ml) was kept at room temperature for 12 h, a 2:1 inclusion complex of (-)-**1a** and (-)-**2a** was obtained as colorless prisms (9.69 g, 85.7%), which upon heating in vacuo gave (-)-**2a** of 75.1% ee (0.95 g, 72.5%). Pure inclusion crystal (7.75 g, 68.4%) obtained by one recrystallization of the crude crystal (9.69 g) was heated in vacuo to give (-)-**2a** of 98.6% ee (0.75 g, 57.3%, $[\alpha]_D$ -37.8 (c 0.36, MeOH). By the same complexation procedure, the secondary alcohols (**2b-g**) were also resolved efficiently, although the resolution of **2b**, **2d**, **2e**, and **2g** was achieved more efficiently by complexation with **1b** instead of **1a** (Table 1). One recrystallization of the 2:1 inclusion complex of **1b** and **2g** of 92.1% ee (4.59 g) from ether-hexane gave pure crystal (2.86 g), and its heating in vacuo gave (-)-**2g** of 100% ee (0.5 g). Although the crude inclusion crystals of **2b**, **2d**, and **2e** with **1b** were decomposed and could not be purified by recrystallization, their optically pure enantiomers would be obtained by repeating the complexation with **1b**. The optical purity of **2a-g** was determined by HPLC on the optically active solid phase, Chiralcel OB or OJ[2] (Table 1).



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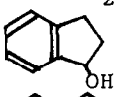
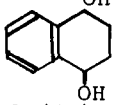
a: R_2=Me_2 **b**: R_2= **c**: R_2=

Table 1. Optical resolution of alcohols (**2a-g**) by complexation with the host **1a** or **1b**

alcohols	hosts			
	1a		**1b**	
	yield(%) $[\alpha]_D$	ee(%) (c MeOH)	yield(%) $[\alpha]_D$	ee(%) (c MeOH)
$PhCH(OH)CH_3$ (**2a**)	72.5 -28.8	75.1[a] (0.22)		
$p\text{-}CH_3C_6H_4CH(OH)C_2H_5$ (**2b**)			79.1 -15.6	63.6[b] (0.55)
$PhCH(OH)C_2H_5$ (**2c**)	39.7 -34.5	91.4[a] (0.37)		
 (**2d**)			79.4 +12.4	78.8[a] (0.40)
 (**2e**)			45.3 +17.7	78.4[a] (0.33)
$PhCH(OH)C{\equiv}CH$ (**2f**)	69.5 +21.1	97.0[b] 0.54)		
$m\text{-}PhOC_6H_4CH(OH)C{\equiv}CH$ (**2g**)			65.0 -22.0	92.1[b] (0.38)

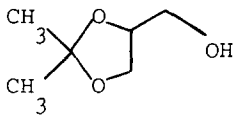
a) Optical purity was determined by HPLC on the optically active solid phase, Chiralcel OB.[2] b) Optical purity was determined by HPLC on the optically active solid phase, Chiralcel OJ.[2]

Some cyanohydrins were also resolved efficiently by complexation with the host **1a** or **1b**. For example, when a solution of **1a** (5.0 g, 10.7 mmol) and rac-**3a** (0.76 g, 10.7 mmol) in 1:1 toluene-hexane (20 ml) was kept at room temperature for 12 h, a 2:1 inclusion complex crystal of **1a** and (+)-**3a** was obtained as colorless prisms (4.20 g, 78.1%), which upon heating in vacuo gave (+)-**3a** of 65.1% ee. Pure inclusion crystal (3.06 g, 56.9%) obtained by one recrystallization of the crude crystal (4.20 g) was heated in vacuo to give (+)-**3a** of 100% ee (0.20 g, 52.6%, $[\alpha]_D$ +44.1 (c 0.34, MeOH)). The same complexation of **1a** (0.5 g, 10.7 mmol) and rac-**3b** (1.53 g, 10.7 mmol) gave, after one recrystallization, a pure 2:1 inclusion crystal of **1a** and (+)-**3b** (3.08 g, 54.0%), which upon heating in vacuo gave finally (+)-**3b** of 100% ee (0.34 g, 47.6%, $[\alpha]_D$ +33.7 (c 0.43, MeOH)). By the same method, **3c** was resolved by a complexation with **1b** to give (-)-**3c** of 72.5% ee in 70% yield ($[\alpha]_D$ -12.0 (c 1.0, benzene)). The optical purity of **3a-c** was determined by measuring the ^1H NMR spectrum in the presence of the chiral shift reagent **1a**.[3]

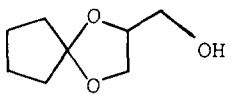
$CH_3CH(OH)C{\equiv}N$ $PhCH(OH)C{\equiv}N$ $m\text{-}PhOC_6H_4CH(OH)C{\equiv}N$

3a **3b** **3c**

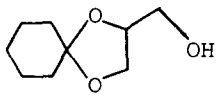
The most interesting application of the resolution method by the complexation with **1a-c** was achieved for glycerol acetals, **4a-c**. When a solution of **1b** (3.55 g, 7.24 mmol) and rac-**4a** (1.45 g, 10.98 mmol) in 1:1 ether-hexane (20 ml) was kept at room temperature for 12 h, a 2:1 inclusion complex of **1b** and (+)-**4a** was obtained as colorless needles (3.57 g, 75%). One recrystallization of the crude crystal gave pure one (2.42 g, 51%), and its heating in vacuo gave (+)-**4a** of 100% ee (0.14 g, 30%, $[\alpha]_D$ +10.73 (c 1.025, MeOH)). The same efficient resolution was also achieved by a complexation with **1c**. Complexation of **1c** (10 g, 19.76 mmol) and rac-**4a** (5.5 g, 41.67 mmol) in 1:1 toluene-hexane (40 ml) at room temperature for 12 h gave, after two recrystallizations, a pure 1:1 complex of **1c** and (+)-**4a** as colorless needles (8.5 g, 67%). Heating of the complex in vacuo gave (+)-**4a** of 100% ee (1.04 g, 40%, $[\alpha]_D$ +11.39 (c 1.03, MeOH)). However, complexation of rac-**4a** and **1a** gave (+)-**4a** of only 24% ee. The optical purity of **4a** was determined by comparison of its $[\alpha]_D$ value with that reported.[4]



4a



4b



4c

For the resolution of **4b**, the host **1b** is the most useful. When a solution of **1b** (3.0 g, 6.10 mmol) and rac-**4b** (1.93 g, 12.22 mmol) in 1:1 ether-petroleum ether (20 ml) was kept at room temperature for 12 h, a 1:1 inclusion complex of **1b** and (+)-**4b** was obtained, after one recrystallization, as colorless needles (2.85 g, 72%), which upon heating in vacuo gave (+)-**4b** of 100% ee (0.77 g, 80%, $[\alpha]_D$ +1.52 (c 1.18, MeOH)). For the resolution of **4c**, however, **1c** is the most effective. Keeping a solution of **1c** (3 g, 5.9 mmol) and rac-**4c** (2 g, 1.16 mmol) in 1:1 toluene-hexane (20 ml) at room temperature for 12 h, a 1:1 inclusion complex of **1c** and (+)-**4c** was obtained, after one recrystallization, as colorless needles (1.78 g, 44%). Heating of the inclusion crystal in vacuo gave (+)-**4c** of 100% ee

(2 g, 20%, $[\alpha]_D$ +7.65 (c 0.81, MeOH)). The optical purity of **4b** and **4c** was determined by comparison of their $[\alpha]_D$ values with those reported.[5].

The efficient resolution of **4a-c** by the simple complexation method with the host **1a-c** is valuable, because the preparative method for optically active glycerol acetals which have been reported so far are very complicated. For example, optically active **4a** has been prepared from L-ascorbic acid [6] or D-mannitol[7] via several reaction steps.

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