Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 8, pp. 2387-2390, 1996

0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00294-7

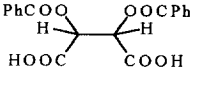
Simple Resolution of O,O'-Dibenzoyltartaric Acid by Preferential Crystallization of its Calcium Salt-Methoxyethanol Complex

András Mravik,* Zsolt Lepp and Elemér Fogassy

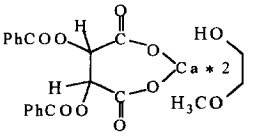
Department of Organic Chemical Technology, Technical University of Budapest,
H-1521 Budapest, POB 91. HUNGARY

Abstract: The enantiomers of the title compound can be obtained in a simple two-step crystallization procedure starting from the racemate. The compound **2** of the calcium O,O'-dibenzoyl-tartrate formed with two molecules of 2-methoxyethanol exists as a conglomerate, making a simple enantioseparation possible. Copyright © 1996 Elsevier Science Ltd

Resolution is the most frequently used procedure for the preparation of enantiomers both in the laboratory and industry[1]. Most of the resolving agents are naturally occuring homochiral compounds or their derivatives and therefore the availability is usually confined to one of the enantiomers. In contrast to the wide variety of the basic resolving agents for acids, there are fewer reagents for resolution of bases[2]. Mandelic acid and tartaric acid and their derivatives are the most commonly used resolving agents for bases[2].



1

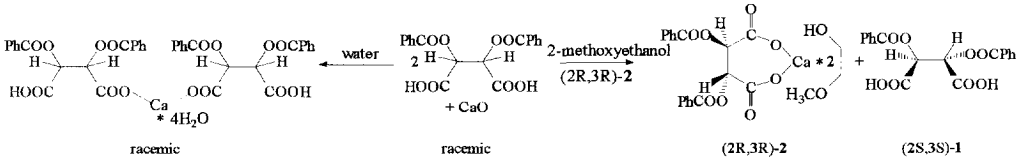


2

O,O'-dibenzoyl-(2R,3R)-tartaric acid prepared from natural tartaric acid on an industrial scale has recently become available at a relatively low price[11]. It is increasingly applied for large scale preparation of optically active compounds. Recently there have been over one hundred examples reported. Due to its much higher price the application of the (S,S)-isomer, however, still remains in the background and used only in some instances[3,4]. In recent years it has been recognized that in some cases dibenzoyltartaric acid forms molecular complexes rather than salts with amines[5]. O,O'-dibenzoyl-(2S,3S)-tartaric acid[4] can be prepared from (2S,3S)-tartaric acid in the same manner, as described for its enantiomer[6]. The unnatural tartaric acid is generally obtained by resolution, is more expensive than the natural form. The loss during the preparation of the benzoylated product[4] makes the O,O'-dibenzoyl-(2S,3S)-tartaric acid even more expensive. From the cheap and synthetically available racemic tartaric acid, racemic **1** can be prepared[7]. The latter may then give either of the enantiomers of **1** by resolution.

Recently we proved that calcium complexes of O,O'-dibenzoyltartaric acid can be used for resolution of compounds of non-basic character. (See for example the resolution of α-hydroxy acid esters[8].)

Among the methods applied for the separation of enantiomers the most favourable one is the direct crystallization of enantiomers. This can be done, if a compound or one of its simple derivatives (in most cases a salt) forms a conglomerate[9]. There are only a limited number of racemates known to exist as a conglomerate. Change in the achiral constituent of a salt, however, can provide a conglomerate forming compound. In this case, however, the salt forming metal ion itself is not the only criterion, since the conglomerate formation highly depends on the solvation of the calcium ion. In fact, a complex of the neutral calcium salt formed with two molecules of 2-methoxyethanol is the key compound. This is a readily crystallizing salt (crystallization is practically complete within 15-20 minutes) in contrast to the hydrated salt, which crystallizes slowly and can be treated only with difficulty. The acid calcium salt of racemic **1** in the presence of water deposits crystals of the hydrated racemic acid salt, whilst in the presence of 2-methoxyethanol the complex **2** of the enantiomeric neutral salt separates leaving behind free acid in the solution (Scheme 1.). This salt separates even in the presence of excess dibenzoyltartaric acid.



Scheme 1. The role of solvation in the conglomerate formation

As a consequence of the above observations, we have developed a very simple and efficient method for the separation of the O,O'-dibenzoyltartaric acid enantiomers. The racemic acid was dissolved in the mixture of ethanol and 2-methoxyethanol, calcium-oxide was then added and dissolved by heating, followed by the crystallization of the enantiomeric salt, induced by seeding with less than 1% of the corresponding complex. In the mother liquor a further portion of the racemic salt (acid + calcium-oxide) was dissolved again and the opposite enantiomer was crystallized analogously. The same mother liquor can be used several times. Currently twelve crystallizations were achieved. The results are in Table 1.

Table 1. Crystallizations of the Enantiomeric Salts Starting from Racemic Dibenzoyltartaric Acid

Run	Racemic DBTA[a]		CaO		Ethanol	Water	Mece[b]	Isolated complex		
	m (g)	*n* (mmol)	*m* (g)	*n* (mmol)	*V* (ml)	*V* (ml)	*V* (ml)	*m* (g)	*n* (mmol)	$[\alpha]_D$ [c]
1.a	60.00	152	2.13	38.0	75	8	50	17.90	32.7	–59.9
1.b	12.00	30.5	1.71	30.5	--	-	10	16.90	30.8	+65.6
2.a	12.00	30.5	1.71	30.5	20	-	10	16.07	29.3	–39.7
2.b	12.00	30.5	1.71	30.5	20	-	10	15.10	27.6	+61.0
3.a	12.00	30.5	1.71	30.5	--	-	10	15.36	28.0	–59.0
3.b	12.00	30.5	1.71	30.5	10	-	10	14.47	26.4	+63.7
4.a	12.00	30.5	1.71	30.5	10	-	10	13.75	25.1	–64.5
4.b	12.00	30.5	1.71	30.5	10	-	10	12.53	22.9	+66.8
5.a	12.00	30.5	1.71	30.5	10	-	10	15.23	27.8	–62.5
5.b	12.00	30.5	1.71	30.5	10	-	--	12.30	22.4	+64.7
6.a	--	--	1.60	28.6	10	-	--	12.89	23.5	–61.0
6.b	--	--	1.60	28.6	10	-	10	17.04	31.1	+55.7
7[d]	-30.00[e]	-76.1	--	--	--	-	--	--	--	
Total	138.00	350	20.72	371	185	8	140	179.5	328	

a) racemic dibenzoyltartaric acid, dihydrate; b) 2-methoxyethanol; c) 22 °C, c=0.5, methanol; d) recovery of the dibenzoyltartaric acid; e) ee.: -5.5%; total yield: 93.6%; yield of the (-)-salt: 91.20g, 47.5%; yield of the (+)-salt: 88.34g, 46.1 %;
Yields are based on the total amount of the racemic acid corrected with that of the recovered material. Seed crystals: 0.10 g each.

The enantiomerically enriched (+) and (-) fractions were recrystallized to give pure enantiomers of **2**. Because of the low solubility of the complexes **2** a slight excess of the free racemic dibenzoyltartaric acid was used during the recrystallizations.

In summary, O,O'-dibenzoyltartaric acid enantiomers are now readily available by a simple crystallization procedure that can easily be applied to large scale production. The price difference between the enantiomers may disappear, making the resolution procedures easier.

EXPERIMENTAL

Optical rotations were measured on a Perkin-Elmer polarimeter model No. 241. Melting points were measured on a Gallenkamp Apparatus and are uncorrected. Solvents (technical grade 96% ethanol, methanol and toluene) were redistilled before use, Merck (99%) 2-methoxyethanol was used.

Racemic O,O'-dibenzoyltartaric acid dihydrate. To a suspension of 183.0 g (538 mmol) racemic O,O'-dibenzoyltartaric anhydride (m.p.: 183-184 °C, Lit.[7]: 182 °C) in 800 ml of water 25 ml of cc. hydrochloric acid was added, and the stirred mixture was heated to maintain 80-85 °C for 3.5 hours. After the mixture was cooled down, the crystalline acid was filtered off, washed with little cold water and air-dried to give 199.7 g (507 mmol, 94%) of the acid. M.p.: 112.5-114 °C and 169-172 °C. Lit.[7]: m.p.: 112-113 °C.

Seed crystals (2R,3R)-2 and (2S,3S)-2. Enantiomeric O,O'-dibenzoyltartaric acid (monohydrate or anhydrous) was dissolved in 85-90% ethanol, calcium-oxide dissolved by heating followed by the addition of large excess of 2-methoxyethanol. The solution was cooled down to room temperature and allowed to stand. The crystals were filtered off and air-dried. Yields ranged between 85 and 92%. (2R,3R)-**2**: $[\alpha]_D^{22} = -65.8 \pm 1$ (c:0.5,methanol), (2S,3S)-**2**: $[\alpha]_D^{22} = +66.0 \pm 1$ (c:0.5,methanol).

Resolution of the racemic O,O'-dibenzoyltartaric acid. 60 g (152 mmol) racemic **1** was dissolved in a mixture of ethanol (75 ml), water (8 ml) and 2-methoxyethanol (50 ml). 2.13 g (38 mmol) calcium-oxide was dissolved by heating and the stirred solution was cooled continouosly. 0.1 g (2R,3R)-**2** was added at between 35 and 45 °C and the mixture was cooled down to 0 °C, at which temperature it was stirred for additional 15-20 min. The crystalline salt was filtered off and dried to yield 17.90 g (32.7 mmol) of (2R,3R)-**2**. $[\alpha]_D^{22} = -59.9$ (c:0.5,methanol). To the mother liquor 2-methoxyethanol (10 ml) was added and the solution was warmed up. racemic **1** (12.0 g, 30.5 mmol) and calcium-oxide (1.71 g, 30.5 mmol) were dissolved by heating. (2S,3S)-**2** was crystallized as its enantiomer above, using 0.1 g (2S,3S)-**2** for seeding. There was 16.90 g (30.9 mmol) of (2S,3S)-**2** obtained. $[\alpha]_D^{22} = +65.6$ (c:0.5,methanol). The procedure was repeated five times as detailed in Table 1. In the last run calcium-oxide was added instead of the racemic salt. The final mother liquor was evaporated, the residue was taken up in 120 ml of water and acidified with 10 ml of cc. hydrochloric acid. The mixture was stirred for 2 hours, the crystalline dibenzoyltartaric acid was filtered off and dried in the air to give 30.0 g (76 mmol) of nearly racemic **1**, $[\alpha]_D^{20} = -6.0$ (c:1.0,methanol).

(2R,3R)-2 and (2S,3S)-2. To the combined (-)-fractions (91.0 g, 166 mmol) 7.0 g (17.8 mmol) of racemic **1** was added and dissolved in 300 ml of hot methanol, followed by the addition of 100 ml of 2-methoxyethanol.

The solution was cooled and seeded with 0.1 g of (2R,3R)-**2**. The mixture was then stirred for 20 min. at 0 °C, the salt was separated by filtration, washed with a small volume of the mixture of methanol and 2-methoxyethanol (3-1) and dried to give 78.5 g (143 mmol, 86%) of (2R,3R)-**2**. $[\alpha]_D^{22}$ = -65.8 (c:0.5,methanol). Analogously, the combined (+)-fractions (88.0 g, 161 mmol) was recrystallized to give 76.0 g (139 mmol, 86%) (2S,3S)-**2**. $[\alpha]_D^{22}$ = +66.0 (c:0.5,methanol).

O,O'-dibenzoyl-(2R,3R)-tartaric acid. To a suspension of 5.0 g (9.1 mmol) of (2R,3R)-**2** in toluene (15 ml) cc. hydrochloric acid (1.7 ml) and water (10 ml) were added, followed by a gentle warming. The resulting mixture was cooled down, seeded with crystals of dibenzoyltartaric acid monohydrate and allowed to stand. The crystalline acid was filtered off, washed with a little water and air-dried. There was 3.20 g (8.5 mmol, 93%) of (2R,3R)-**1**.H_2O obtained. $[\alpha]_D^{22}$ = -112 (c:1.0, methanol), $[\alpha]_D^{22}$ = -111 (c:1.0, abs. ethanol). (lit.[10]: $[\alpha]_D^{18}$ = -115.8 (c:1.7, abs. ethanol)) m.p.: 88-89.5 °C. (lit.[6]: m.p.: 88-89 °C, lit.[10]: m.p.: 88-90 °C).

O,O'-dibenzoyl-(2S,3S)-tartaric acid. (2S,3S)-**2** was converted to the corresponding acid with a yield of 94% as described above for its enantiomer. $[\alpha]_D^{22}$ = +112 (c:1.0, methanol) (lit.[4]: $[\alpha]_D^{20}$ = +114 (c:1, ethanol)), m.p.: 88-89 °C (lit.[4]: 89-90 °C).

Acknowledgement: The authors thank the Hungarian Research Fund (Operating Grant from the OTKA Committee, No T 014 887) and the Varga József Foundation for financial support.

REFERENCES AND NOTES

1. Crosby, J. *Tetrahedron* **1991**, 47, 4789-4846.
2. Wilen, S. H. *Top. Stereochem.* **1971**, 6, 107-176.
3. a) Bell, K. H.; Portoghese, P. S. *J. Med. Chem.* **1973**, 16, 589-591. b) Grol, C. J.; Jansen, L. J.; Rollema, H. *ibid.*, **1985**, 28, 679-683.
4. Semonský, M.; Černý, A.; Zikán, V. *Collect. Czech. Chem. Commun.* **1956**, 21, 382-390.
5. a) Hatano, K.; Takeda, T.; Saito, R. *J. Chem. Soc. Perkin Trans. 2* **1994**, 579-584. b) Nemák, K.; Ács, M.; Jászay, Zs. M.; Kozma, D.; Fogassy, E. *Tetrahedron*, **1996**, 52, 1637-1642.
6. Butler, C. L.; Cretcher, L. H. *J. Am. Chem. Soc.* **1933**, 55, 2605-2606.
7. Brigl, P.; Grüner, H. *Chem. Ber.* **1932**, 65, 641-645.
8. Mravik, A.; Fogassy, E.; Katona, Z.; Markovits, I. Hung. Pat. Appl. P 96 00187, **1996**.
9. Jaques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolutions,* Wiley-Interscience, New York, 1981.
10. Zetzsche, F.; Hubacher, H. *Helv. Chim. Acta* **1926**, 9, 291-297.
11. Approx. price is 14 USD / kg.

(*Received in UK* 23 *May* 1996)