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New access to enantiopure *O,O′*-dibenzoyltartaric acid: resolution of the mixed calcium methoxyacetate by preferential crystallization

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Abstract

A convenient resolution of racemic *O,O′*-dibenzoyltartaric acid by preferential crystallization of its mixed calcium salt formed with methoxyacetic acid is described. The separation of the partially prepared salt **2** followed by a subsequent recrystallization results in a simple and effective resolution of the title compound during which pure enantiomers of **1** can be obtained even on a large scale. The crystal structure of the conglomerate forming complex **2** is also reported. © 1998 Elsevier Science Ltd. All rights reserved.

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1. Introduction

The enantiomers of *O,O′*-dibenzoyltartaric acid **1** are widespread resolving agents for bases.[1] Recently we have been extensively investigating the development of new applications of tartaric acid derivatives in resolutions, with special interest to the resolution of non-basic compounds. As a result of these studies we showed that calcium complexes of *O,O′*-dibenzoyltartaric acid can be used for the resolution of carboxylic acids[2] and carboxylic acid esters.[2,3] We have also reported the resolution of **1** itself by preferential crystallization of its calcium salt–methoxyethanol complex.[4] In this paper we present a new route to the enantiomers of the title compound in which the conglomerate forming derivative is the mixed calcium salt **2** formed with methoxyacetic acid.

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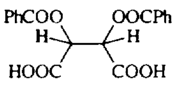

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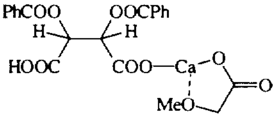

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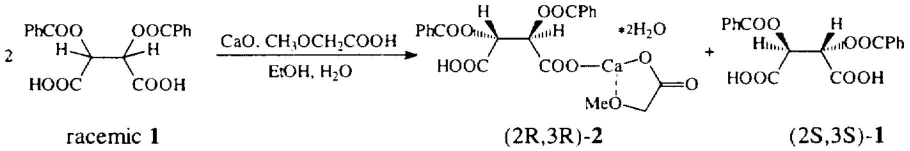
2. Results and discussion

As part of our research concerning metal complexes of *O*,*O*′-dibenzoyltartaric acid, our attention was captured by the outstanding crystallization ability of the mixed calcium methoxyacetate **2**. It is well known that the separation of enantiomers by preferential crystallization without use of chiral reagents is possible only if the compound forms a conglomerate.[5] In order to exploit this excellent crystallization ability we had to check whether the complex forms a conglomerate or not. Of the methods available for the identification of conglomerates,[6] we have chosen the method based on the comparison of the IR spectra (as KBr pellets) of the racemate with that of the enantiomer. The identity of the spectra revealed that we have found a conglomerate type derivative of **1**.[7]

The resolution is based on the reaction of CaO and methoxyacetic acid (equal amounts) with an excess of racemic **1** (containing (2*R*,3*R*)-**1** in 5–15% excess) and subsequent crystallization of (2*R*,3*R*)-**2** induced by seeding with 0.2% of the same complex. Thus the separating salt was more abundant in the (2*R*,3*R*)-enantiomer, whereas the ethanolic solution was enriched in (2*S*,3*S*)-**1** (Scheme 1).



Scheme 1. Resolution of racemic *O*,*O*′-dibenzoyltartaric acid **1** with partial complex formation

The resolution process was continued following the usual steps of a cyclic resolution with induced crystallization:[8] the mother liquor was converted to the initial concentration by dissolving racemic *O*,*O*′-dibenzoyltartaric acid, CaO and methoxyacetic acid (an equal amount to that of the crystallized salt), and the crystallization of (2*S*,3*S*)-**2** was conducted analogously. The crystalline complex salts were purified by a further recrystallization step. The enantiomers of the title compound were liberated from the corresponding enantiomers of **2**. The resolution was optimized by modifying the crystallization time (with continuous stirring) at two salt formation ratios (Q, the amount of **2** ÷ total amount of dibenzoyltartaric acid). The optimized parameter was the so-called 'Fogassy parameter' S.[9]

X-Ray structure analysis was carried out on (2*R*,3*R*)-**2**[12] to investigate the interactions causing the excellent crystallizing ability and to provide reasoning for the conglomerate formation. The ORTEP drawing of (2*R*,3*R*)-**2** is shown in Fig. 1(a). The coordination around the calcium atom [Fig. 1(b)] indicates that the coordination geometry at the Ca^{2+} ion is a distorted trigonal bipyramid (seven-coordinated Ca^{2+}).

The crystal structure of (2*R*,3*R*)-**2** (see the packing in Fig. 2) is made up of alternating hydrophobic layers, composed of the phenyl moieties of the benzoyl groups, and hydrophilic layers, composed of the Ca^{2+} ions and their coordinating ligands including the methoxyacetate ion. The hydrophilic layer can be further divided into alternating strips of hydrogen bonds and Ca^{2+}-coordination polyhedrons. The axial positions of the bipyramid are occupied by the carbonyl oxygen atoms of one of the two benzoyl groups (O18) and of the deprotonated carboxylate group (O6) of the symmetry equivalent molecule in the same

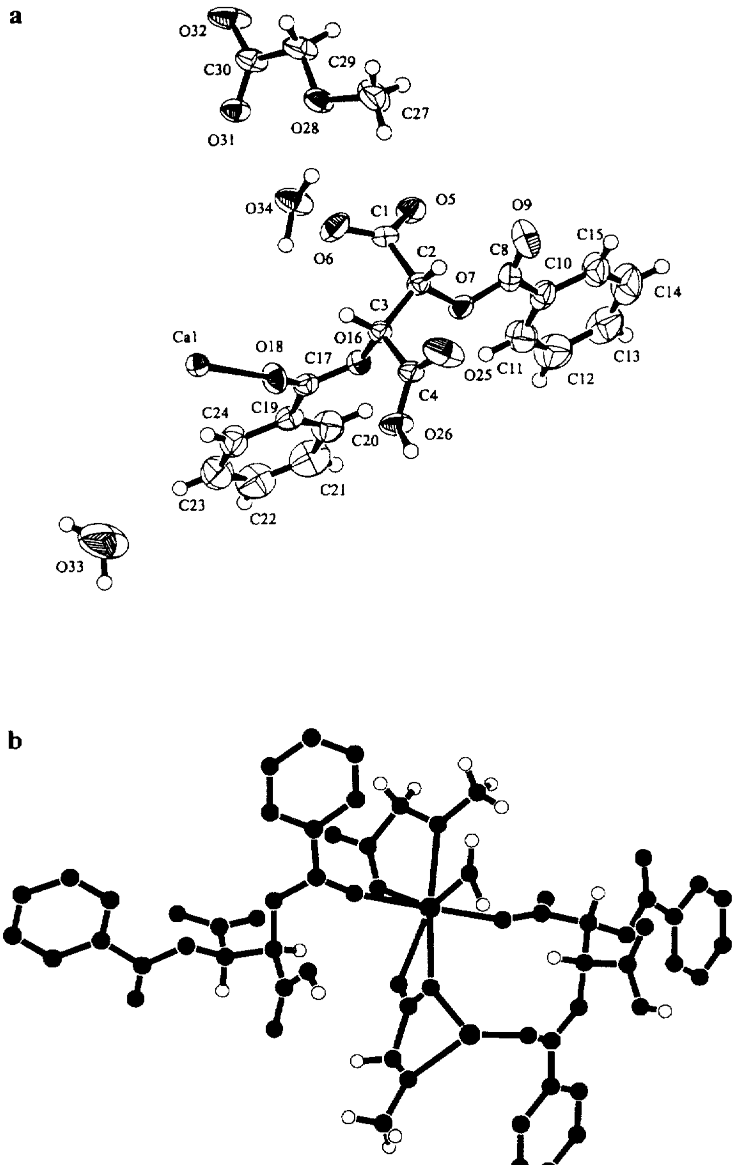


Fig. 1. (a) ORTEP drawing of (2*R*,3*R*)-**2** with atomic numbering; (b) coordination around the calcium ion

unit cell, which has the opposite orientation. This means that two *O*,*O'*-dibenzoyltartaric acid molecules are connected through two Ca^{2+} bridges in the crystal lattice in one unit cell. In the equatorial plane of the bipyramid one of the two oxygen atoms of the carboxylate group (O31) of the methoxyacetic acid simultaneously coordinates to two neighboring Ca^{2+} ions to form an endless Ca–O–Ca–O chain through the crystal lattice. On the other hand, both the O31 and O32 oxygen atoms from the same carboxylate group of the methoxyacetic acid are coordinated to the Ca^{2+} in the equatorial plane. This binding constrains the carboxylate carbon atom C30 to a relatively close position to the calcium ion (2.81 Å). Furthermore, one of the equatorial positions of the bipyramid is occupied by the ether oxygen O28 of another methoxyacetic acid molecule. This means that the three oxygen atoms of the methoxyacetate ion are coordinated to two calciums in the same plane, and O31 coordinates to both calcium ions, which

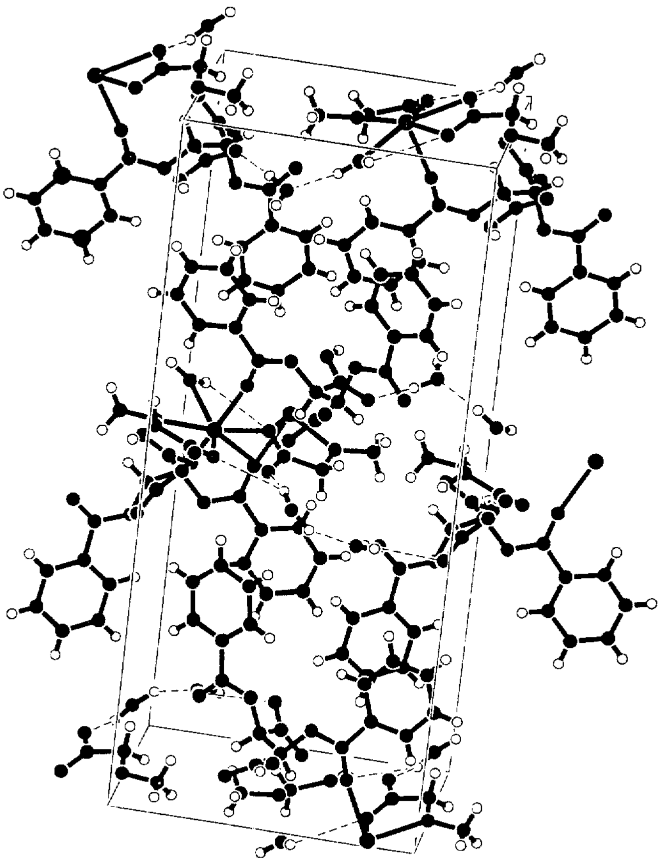


Fig. 2. A packing view of the complex (2*R*,3*R*)-**2**

results in a well ordered position for the methoxyacetate ion in the crystal lattice. The calcium ions themselves are strongly anchored in the crystal structure, which is indicated by the low thermal motion parameter (2.334 Å^2). One of the two water oxygens (O34) is also coordinated to the calcium ion in its equatorial plane.

3. Experimental

Optical rotations were measured on a Perkin–Elmer 241 polarimeter. Infrared spectra were recorded on a Perkin–Elmer FT-IR 1600 instrument with samples as KBr pellets. Melting points were measured on a Gallenkamp apparatus and are uncorrected. Solvents (technical grade 96% ethanol, methanol) were redistilled before use, Merck methoxyacetic acid (>98%) was used.

3.1. *Seed crystals (2R,3R)-2 and (2S,3S)-2*

Compound (2*R*,3*R*)-**1** (monohydrate) (5 g, 13.3 mmol) was dissolved in ethanol (10 mL), then 0.74 g (13.3 mmol) calcium oxide and water (1 mL) were added. After a few minutes of heating with stirring a clear solution was obtained to which 1.20 g (13.3 mmol) methoxyacetic acid was added. The solution was cooled down to room temperature and allowed to stand overnight. The crystalline salt was filtered off and air-dried to yield 4.79 g (9.17 mmol, 69.0%) (2*R*,3*R*)-**2**, $[\alpha]_D^{20}=-76.2$ (c=0.5, methanol), m.p.: 153–157°C, IR (KBr, cm^{-1}): 3566, 3483, 3357, 3212, 1703, 1580, 1345, 1265, 1120, 1105, 715, 664. Starting from (2*S*,3*S*)-**1** monohydrate, (2*S*,3*S*)-**2** was obtained.

Racemic 2 was obtained analogously, starting from racemic **1** (dihydrate). Yield: 84%, m.p.: 141–144°C, the IR spectrum is identical to that of the enantiomeric form.

3.2. Resolution of the racemic O,O′*-dibenzoyltartaric acid (demonstrative procedure)*

A mixture of 9.5 g (24.1 mmol) racemic **1** and 0.5 g (1.3 mmol) (2*R*,3*R*)-**1** was dissolved by heating in ethanol (25 mL), then 0.35 g (6.3 mmol) calcium oxide and water (5 mL) were added. The stirred solution was heated until the calcium oxide dissolved, then 0.57 g (6.3 mmol) methoxyacetic acid was added. The mixture was cooled down to room temperature and seeded with 0.02 g (2*R*,3*R*)-**2**. The solution was stirred at 400 rpm for 60 min. The precipitated crystalline salt was filtered off and air-dried to yield 1.54 g (2.95 mmol, 12%) (2*R*,3*R*)-**2**. $[\alpha]_D^{20}=-69.1$ (c=0.5, methanol). To the mother liquor, 1.16 g (2.95 mmol) racemic **1** and 0.17 g (2.95 mmol) calcium oxide were added. After a clear solution had been obtained by heating, 0.27 g (2.95 mmol) methoxyacetic acid was added with continuous stirring followed by cooling and entrainment with 0.02 g (2*S*,3*S*)-**2**, 1.55 g (2.96 mmol, 12%) (2*S*,3*S*)-**2** was thus obtained. $[\alpha]_D^{20}=+68.9$ (c=0.5, methanol). The cycle was repeated twice leading to complexes of essentially the same yields and enantiopurities.

*3.3. Purification of (*2R,3R*)-2 and (2S,3S)-2*

The homochiral pure complex salts were obtained following a single recrystallization step from a mixture of methanol:water=10:1. The amount of seed crystals was 0.2%. (2*R*,3*R*)-**2**, yield: 78%, $[\alpha]_D^{20}=-76.2$ (c=0.5, methanol). (2*S*,3*S*)-**2**, yield: 79%, $[\alpha]_D^{20}=+76.2$ (c=0.5, methanol).

*3.4. (2S,3S)-*O,O′*-Dibenzoyltartaric acid*

To 1.0 g (1.91 mmol) of (2*S*,3*S*)-**2**, conc. hydrochloric acid (0.4 mL) and water (4 mL) were added. The liberated (2*S*,3*S*)-**1** appeared as an oil which solidified on continuous stirring and cooling. The crystallized acid was filtered off, washed with a small amount of water and air-dried. 0.66 g (92%) of (2*S*,3*S*)-**1** (monohydrate) was obtained; $[\alpha]_D^{20}=+112$ (c=1.0, ethanol) [lit.:[10] $[\alpha]_D^{20}=+114$ (c=1.0, ethanol)].

*3.5. (*2R,3R*)-*O,O′*-Dibenzoyltartaric acid*

The procedure was the same as described above. Starting from (2*R*,3*R*)-**2**, (2*R*,3*R*)-**1** (monohydrate) was obtained in 93% yield. $[\alpha]_D^{20}=-112$ (c=1.0, ethanol) [lit.[11]: $[\alpha]_D^{18}=-115.8$ (c=1.7, abs. ethanol)].

Acknowledgements

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References

1. S. H. Wilen, *Top. Stereochem.* **1971**, 6, 107–176.
2. A. Mravik, Zs. Böcskei, Z. Katona, I. Markovits and E. Fogassy, *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 1534–1536.
3. A. Mravik, Zs. Böcskei, Z. Katona, I. Markovits, Gy. Pokol, D. K. Menyhárd and E. Fogassy, *Chem. Commun.* **1996**, 1983–1984.
4. A. Mravik, E. Fogassy and Zs. Lepp, Hung. Pat. Appl. P00185, 1996; A. Mravik, Zs. Lepp and E. Fogassy, *Tetrahedron: Asymmetry* **1996**, 7, 2387–1390.
5. J. Jacques, A. Collet and S. H. Wilen, *Enantiomers, Racemates and Resolutions*, Wiley-Interscience: New York, 1981.
6. Summary of methods in: E. L. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley-Interscience: New York, 1994; p. 301.
7. *O,O′*-Dibenzoyltartaric acid itself forms racemate type crystals.
8. A. N. Collins, G. N. Sheldrake and J. Crosby, *Chirality in Industry*, Wiley & Sons: Chichester, 1992; p. 25.
9. R. A. Sheldon, *Chirotechnology*, Marcel Dekker Inc.: New York, 1993; p. 193.
10. M. Semonský, A. Cerný and V. Zikán, *Collect. Czech. Chem. Commun.* **1956**, 21, 382–390.
11. F. Zetzsche and H. Hubacher, *Helv. Chim. Acta* **1926**, 9, 291–297.
12. All data were collected on a Rigaku AFC6S single crystal diffractometer, using Cu–K$_\alpha$ radiation (λ=1.5418 Å), $\omega-2\theta$ scans, with $3.33° < 2\theta < 75.16°$. $C_{21}H_{22}CaO_{13}$, M=522.47, orthorhombic, a=11.224(2) Å, b=26.556(3) Å, c=8.132(2) Å, V=2423.9(8) Å^3, space group $P2_12_12_1$, Z=4, D_{calc}=1.43 gcm^{-3}, μ=2.83 mm^{-1}. 2774 independent reflections were measured of which 2265 were considered as observed [$F>2\sigma(I)$]. All data were corrected for Lorentz and polar factors. Computations were carried out using the TeXsan package (Molecular Structure Corporation, TeXsan: Crystal Structure Analysis Package, 1992), but final refinement was done with SHELXL-93 (G. M. Sheldrick, SHELXL-93: Program for crystal structure refinement, 1993). The non-hydrogen atoms were refined anisotropically, the hydrogen atom positions were generated via geometric evidence and the isotropic thermal motion parameters were refined, but were allowed to ride on their parent atoms. Refinement was done by full-matrix least squares to give R_1=0.048 for the observed data, wR_2=0.1377 for all the independent reflections $\{(w=1/[\sigma^2(F_o^2)+(0.0766P)^2+1.8231P]$ where $P=(F_o^2+2F_c^2)/3\}$. The maximum and minimum residual electron densities in the final ΔF map were 0.92 and $-0.39e^-$/Å^3 respectively. The maximum and mean shift/error ratios in the final refinement cycle were both 0.00. Hydrogen bond geometry: angle O33...H33A...O25_\$7 174.28 (0.30); distance O33...O9_\$5 3.054 (0.009) Å; angle O33...H33B...O9_\$5 176.06 (0.29); distance O34...O33_S2 2.774 (0.007) Å; angle O34...H34A...O33_\$2 144.13 (0.28); distance O34...O32_\$4 2.604 (0.005) Å; angle O34...H34B...O32_\$4 164.63 (0.25); distance O26...O5_\$4 2.530 (0.005) Å; angle O26...H26A...O5_\$4 174.81 (0.20); \$2: $-x+1/2$, $-y+2$, $z+1/2$; \$4: x, y, $z-1$; \$5: $x+1$, y, $z-1$; \$7: $x+1$, y, z.