Chiral Recognition of Alcohols in the Crystal Lattice of Simple Metal Complexes of *O,O′*-Dibenzoyltartaric Acid: Enantiocomplementarity and Simultaneous Resolution

András Mravik,* Zsolt Böcskei, Kálmán Simon, Ferenc Elekes, and Zoltán Izsáki

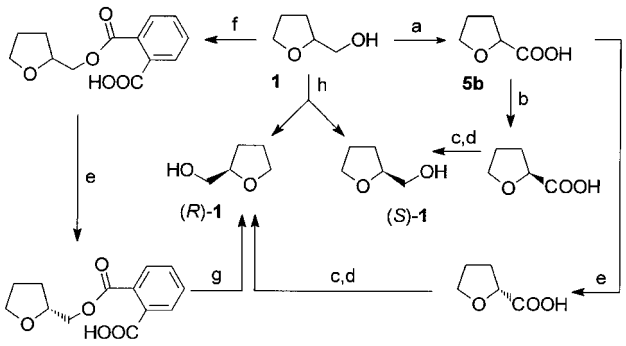
Abstract: A simple preparative method for the enantiomeric enrichment of alcohols is reported. Crystallization of the complexes of alcohols formed with calcium and zinc *O,O′*-dibenzoyltartrates led to effective resolutions of the alcohols. However, zinc and calcium dibenzoyltartrates are complementary resolving agents upon coordinative resolution of less-hindered alkoxy alcohols. Mixed copper(II) salts of *O,O′*-dibenzoyltartaric acid formed with carboxylic acids can also be applied to the resolution of alkoxy alcohols, thereby providing the simultaneous resolution of an alcohol and a carboxylic acid. Zinc dibenzoyltartrate can form coordination compounds with alkoxy alcohols as well as lattice inclusion compounds with simple alcohols as revealed by the four X-ray structures reported here.

Keywords: alcohols · chiral recognition · enantiomeric resolution · inclusion compounds

Introduction

The access to enantiopure alcohols on a preparative scale is performed most frequently by optical resolution. Apart from enzymatic methods[1] and selective inclusion compound formation,[2, 3a] however, most of the resolutions are achieved by a traditional route involving fractional crystallization of the diastereoisomeric salts of a derivative (for example, phthalic monoester) formed with optically active amines.[3] The most important chemical methods for the preparation of enantiopure alcohols, applied particularly to tetrahydrofurfuryl alcohol (**1**), are shown in Scheme 1.

The optical resolution through a derivative requires additional steps to be included into the procedure (acylation of the racemic alcohol, purification of the racemic acid phthalate, diastereomer crystallizations, decomposition of the salt obtained, hydrolysis of the half-ester, and recovery of the enantiomeric alcohol), which cause a drastic decrease in the final yield. Furthermore, the resolving agent itself is often expensive and/or toxic. Primary alcohols can be resolved in the form of the corresponding carboxylic acid, which must be reduced to give the desired alcohol. More advantageous is the resolution of the alcohol itself, which can be achieved by inclusion crystallization.[2, 3a] However, the appropriate chiral host compounds are very expensive and generally available on a gram scale only. In contrast, enantiopure *O,O′*-dibenzoyltartaric acid is available on an industrial scale at a relatively low price.



Scheme 1. The main chemical routes to enantiomeric tetrahydrofurfuryl alcohol (a short review of the methods can be found in ref. [8b]). a) Jones's reagent; b) ephedrine; c) CH_2N_2; d) LAH; e) brucine; overall yields for steps a,b,c,d and a,e,c,d: 7%;[4a] f) phthalic anhydride/pyridine; g) aqueous NaOH; f,e,g: involve several crystallization steps, yield not given ref. [4b]; h) resolution by inclusion crystallization, yield: 15%;[4c] yields are based on half of the starting racemic **1**.

We report here the application of simple metal complexes of *O,O′*-dibenzoyltartaric acid (**4**) as new *resolving agents for*

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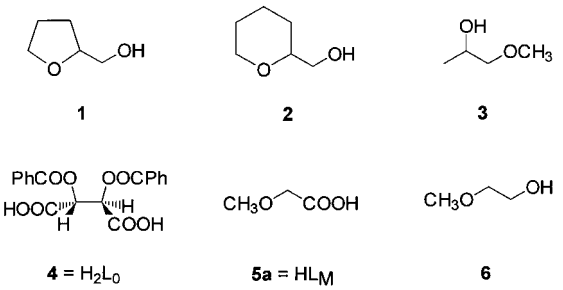
alcohols. Based upon the coordinating ability of metal ions for alcohols, efficient enantiomeric resolutions can be performed by using enantiopure *O*,*O*′-dibenzoyltartrate ions (HL_0^-, L_0^{2-}) as chiral modifiers. Furthermore, the *O*,*O*′-dibenzoyltartrate moieties play an important role in the formation of complexes that crystallize well.



Results and Discussion

Previously we reported on the use of calcium complexes $Ca(L_0)$ (**7**) and $Ca(HL_0)_2$ (**8**) for the resolution of carboxylic acids and hydroxy acid esters.[5] The neutral calcium salt **7** can be applied, however, to the resolution of certain alcohols by crystallizing the complexes **9**-(L), where L stands for the alcohol (currently **1**–**3**) to be resolved.

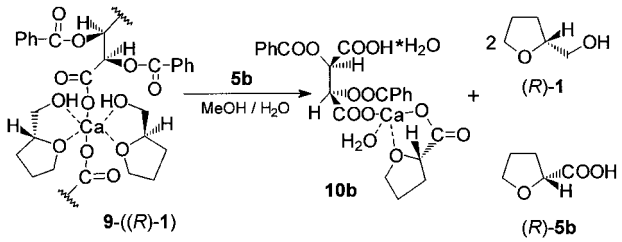
$[Ca(L)_2](L_0)$ **9**-(L)

The best results were obtained when one mole of **7** and four (or more) moles of the racemic alcohol were allowed to react in 96% ethanol, followed by the crystallization of **9**-(L) from ethanol or an ethanol/acetone mixture (see Table 1). Crystalline complexes of type **9** were obtained with alkoxy alcohols only. A very stable complex (**9**-(**6**)) formed with 2-methoxyethanol (**6**) is the key compound upon the enantiomeric resolution of *O*,*O*′-dibenzoyltartaric acid by preferential crystallization.[6] A simple, mild work-up involves the transformation of **9**-(L) into the mixed calcium salt[5, 7] (**10a**) formed with methoxyacetic acid (HL_M), (**5a**) [Eq. (1)].

$$[Ca(L)_2](L_0) + HL_M \longrightarrow [Ca(H_2O)](HL_0)(L_M) \cdot H_2O + 2L \quad (1)$$

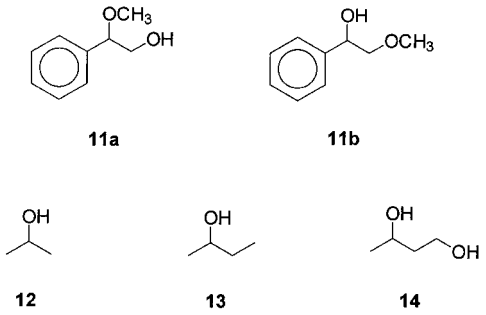
Abstract in Hungarian: *Alkoholok rezolválásának egy új, egyszerű, gyakorlati módszerét ismerteti jelen közleményünk. Az eljárás alapja az a megfigyelés, hogy bizonyos alkoholok, elsősorban alkoxi-alkoholok kristályos komplexet alkotnak az O,O′-dibenzoil-borkősav fémsóival. E komplexek kristályosítása segítségével az illető alkoholok enantiomerjei elválaszthatók egymástól. Figyelemre méltó az a tény is, hogy egyszerűbb alkoxi-alkoholok esetében a kalcium- és cink-dibenzoiltartarát ellentétes konfigurációjú alkoholokkal képez stabilabb komplexet, így e két fém-tartarát egymást kölcsönösen kiegészítő rezolváló ágens. A dibenzoil-borkősav és egy α-halogénkarbonsav vegyes rézsója szintén alkalmas alkoholok enantiomerjeinek elválasztására, lehetővé téve ezáltal az illető alkohol és karbonsav egyidejű rezolválását.*

The liberated alcohol can be obtained[8a] from the mother liquor after removal of salt **10a** (90–95% yield). Enantiopure tetrahydrofurfuryl alcohol (*R*)-**1** was obtained in 52% overall yield. This procedure involves three crystallization steps, in contrast to that with the acid phthalate, which requires five or six crystallization steps to provide the enantiopure phthalic monoester.[4b] As an alternative method, the one presented here seems to be the simplest procedure for the preparation of enantiopure tetrahydrofurfuryl alcohol.[8b] However, in the work-up reaction [Eq. (1)] methoxyacetic acid can be replaced with racemic tetrahydrofuroic acid (**5b**) (Scheme 2).



Scheme 2.

During this second reaction the resolution of tetrahydrofuroic acid and the recovery of the optically active tetrahydrofurfuryl alcohol can be achieved in one step.



In order to expand the range of such coordinative resolutions, we changed the central metal ion. The zinc complexes studied next exhibit substantial differences to the calcium complexes. First of all, an *enantiocomplementary effect* occurs, which means that the configuration of the alkoxy alcohol forming the less soluble complex with $Zn(L_0)$ (**15**) changes to the opposite one when the *O*,*O*′-dibenzoyltartrate ion of the same configuration is used. In addition, the zinc ion readily coordinates other molecules (water, ethanol) to form crystalline compounds. In most cases only one molecule of alkoxy alcohol is coordinated. Thus, tetrahydrofurfuryl alcohol (**1**) and 1-methoxy-2-propanol (**3**) form crystalline complexes **16**-(L), where L stands for (*S*)-**1** or (*S*)-**3**.

$[Zn(H_2O)_2(EtOH)(L)](L_0) \cdot H_2O$ **16**-(L)

X-ray crystallographic analysis of **16**-((*S*)-**1**) and **16**-((*S*)-**3**) showed similar structures. The molecular structure of **16**-((*S*)-**1**) is shown in Figure 1. A stereoview of the packing in **16**-((*S*)-**1**) is given in Figure 2.

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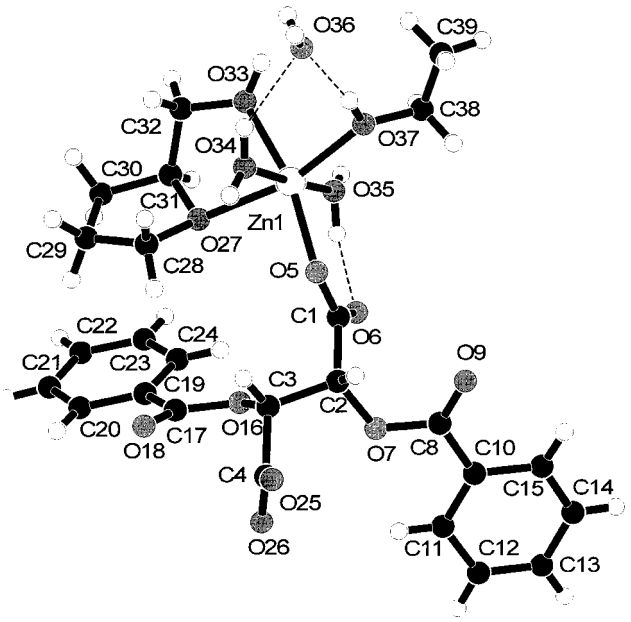

Figure 1. Molecular structure of **16**-((*S*)-**1**).

In contrast to the compounds of type **16**, a complex with two molecules of 2-hydroxymethyltetrahydropyran (**2**) ($Zn(L_0)\cdot 2((S)\text{-}\mathbf{2})\cdot 3H_2O$) was obtained, which may be formulated as **17** considering the structure of **16**-((*S*)-**1**) (see Figure 1).

$$[Zn(H_2O)_2((S)\text{-}\mathbf{2})_2](L_0)\cdot H_2O \qquad \mathbf{17}$$

In the case of tetrahydrofurfuryl alcohol (**1**) the enantiomeric excess can be increased from 39% to 60% by crystallizing the complex **18** in the first step.

$$[Zn(H_2O)(EtOH)((S)\text{-}\mathbf{1})](HL_0)(CH_3COO)\cdot H_2O \qquad \mathbf{18}$$

Complex **18** can be obtained from ethanol in the presence of acetic acid.[9] However, two recrystallizations of **18** from aqueous ethanol afforded pure **16**-((*S*)-**1**). An interesting case is that of the resolution of 2-methoxy-2-phenylethanol (**11a**). Normally, enantiopure **11a** can be obtained by reducing enantiomeric α-methoxyphenylacetic acid,[10a,b] which is available by optical resolution with optically active amines, for example with ephedrine.[11] On the other hand, racemic **11a** can be prepared from styrene oxide by acid-catalyzed methanolysis.[12] The isomeric 2-methoxy-1-phenylethanol (**11b**) (10% in the starting mixture) was excluded during the crystallization. Thus, (*R*)-**11a** (57% *ee*) obtained from **19**[15] contained less than 0.5% **11b** (GC).

$$[Zn(H_2O)_3((R)\text{-}\mathbf{11a})](L_0) \qquad \mathbf{19}$$

This procedure is fully controlled by the concentration of water. Thus, **19** can be crystallized from ethanol or aqueous ethanol (containing less than 10% water), whereas the resolved **11a** can be simply extracted from the aqueous solution of **19**.

Simple alcohols (L, such as 2-propanol or 2-butanol) can also form crystalline complexes[13] of the formula **20**-(L).

$$[Zn(H_2O)_5](L_0)\cdot L \qquad \mathbf{20}\text{-(L)}$$

The X-ray crystal structure of **20**-(**12**) (Figure 3) revealed that, in contrast to the above coordination compounds (**16**, **17**, **18**, and **19**), **20**-(**12**) exists as a true *lattice inclusion compound*. This probably holds for **20**-((*R*)-**13**) as well.

The packing in **20**-(**12**) is shown in Figure 4. A similar inclusion compound (**20**-(THF)) was formed with THF, but decomposed on long standing in air. The X-ray molecular structure of **20**-(THF) is shown in Figure 5. A somewhat different complex (**21**)[14] was obtained from 1,3-butanediol (**14**) in the presence of acetic acid.

$$[Zn(H_2O)_4](HL_0)(CH_3COO)\cdot((S)\text{-}\mathbf{14}) \qquad \mathbf{21}$$

In all four complexes studied by X-ray crystallography the Zn^{2+} ion is coordinated by one of the carboxylate oxygen

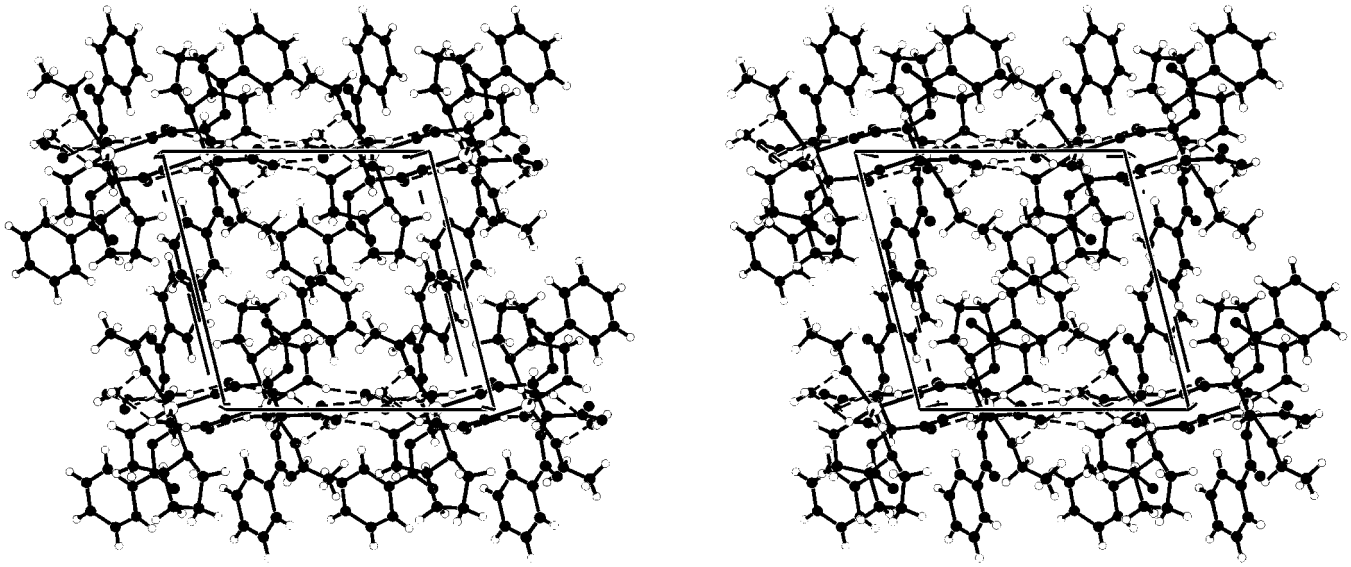

Figure 2. Stereoview of the packing in **16**-((*S*)-**1**).

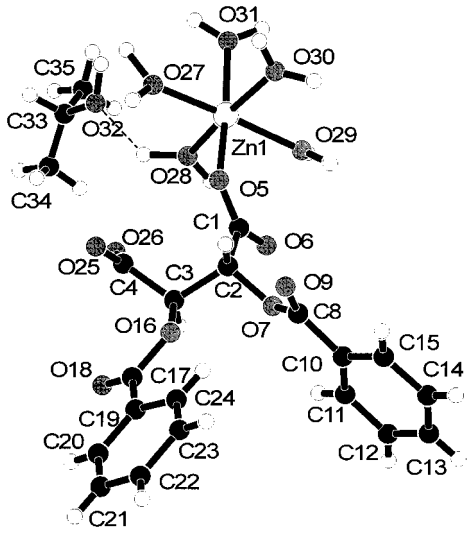

Figure 3. Molecular structure of **20**-(**12**).

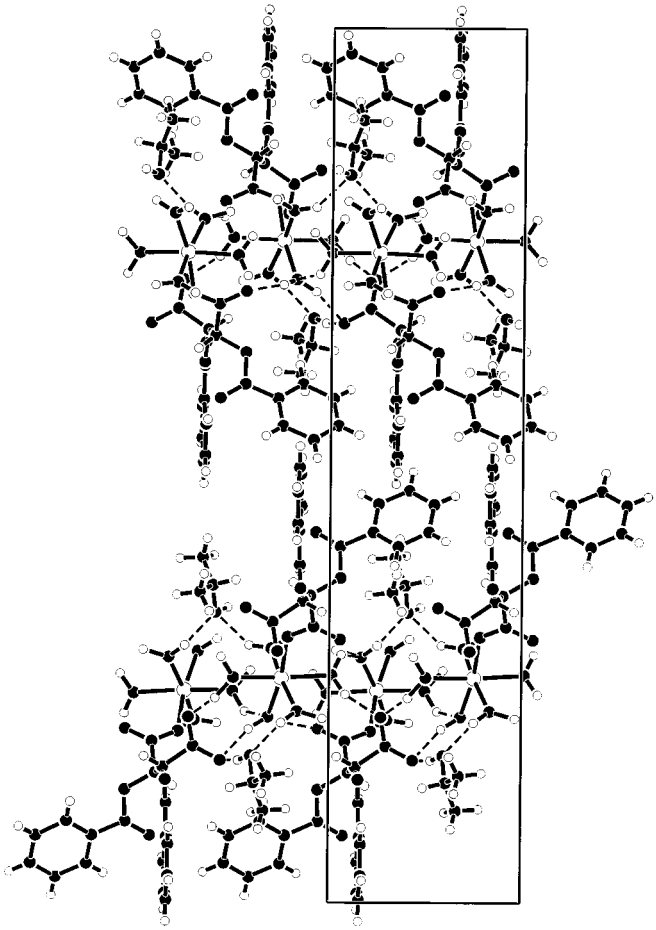

Figure 4. Packing diagram of **20**-(**12**).

atoms of the tartrate ion. In addition, in two of the complexes (**16**-((*S*)-**1**) and **16**-((*S*)-**3**)) Zn^{2+} is also coordinated by the oxygen atoms of the bidentate ligands of tetrahydrofurfuryl alcohol (cf. the molecular structure of **16**-((*S*)-**1**) in Figure 1) and 1-methoxy-2-propanol (in **16**-((*S*)-**3**)), respectively. The remaining three coordination sites are occupied in both complexes by the oxygen atoms of an ethanol as well as two

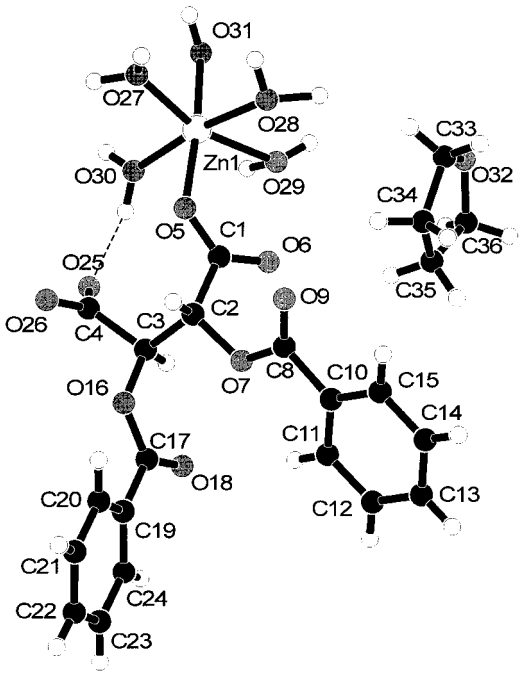

Figure 5. Molecular structure of **20**-(THF).

water molecules. A third water molecule can be found outside the coordination sphere of the Zn^{2+} ion. This water molecule seems to play an essential role by utilizing all of its hydrogen bonding capabilities to interconnect the coordination spheres of three Zn^{2+} ions (by accepting hydrogen bonds from one of the water molecules (O36) and the alcoholic hydroxyl group of the ethanol as well as donating hydrogen bonds to the carboxylate oxygen atoms of two different tartrate anions, none of the carboxylates coordinate Zn^{2+} ions directly). Parallel columns of Zn^{2+} coordination spheres are arranged into layers which are separated again by hydrophobic layers. These are made up of perpendicularly oriented stacked columns of repeating ethyl, phenyl, tetrahydrofurfuryl, phenyl, ethyl, phenyl, tetrahydrofurfuryl etc. moieties (cf. the packing diagram of **16**-((*S*)-**1**), Figure 2). In complexes **20**-(THF) and **20**-(**12**) bidentate ligands are replaced by monodentate analogues. These are unable to get in the coordination sphere of the Zn^{2+} ions, but are present in the holes of the host type crystal structures as guest molecules. Instead of the bidentate ligands two more water molecules show up in the coordination sphere of Zn^{2+} ions resulting in a totally altered intermolecular structure (see the molecular structure of **20**-(**12**) in Figure 3).

The complex **16**-((*S*)-**1**) is isostructural with **16**-((*S*)-**3**), while **20**-(THF) is pseudoisostructural with **20**-(**12**). By the latter we mean that the unit cell constants, the crystal system and space group of **20**-(THF) and **20**-(**12**) are different, but only due to a small deformation of the crystal lattice of **20**-(THF) as compared with **20**-(**12**) and vice versa (see the packing diagrams of **20**-(THF) and **20**-(**12**) in Figure 6 and Figure 4, respectively). The unit cell constants of **16**-((*S*)-**1**) and **16**-((*S*)-**3**) are also almost the same showing a high degree of isostructurality, while in the case of **20**-(**12**) one of the cell constants (*b*) is about twice that of the *c* cell edge of **20**-(THF), while the remaining two are very similar.

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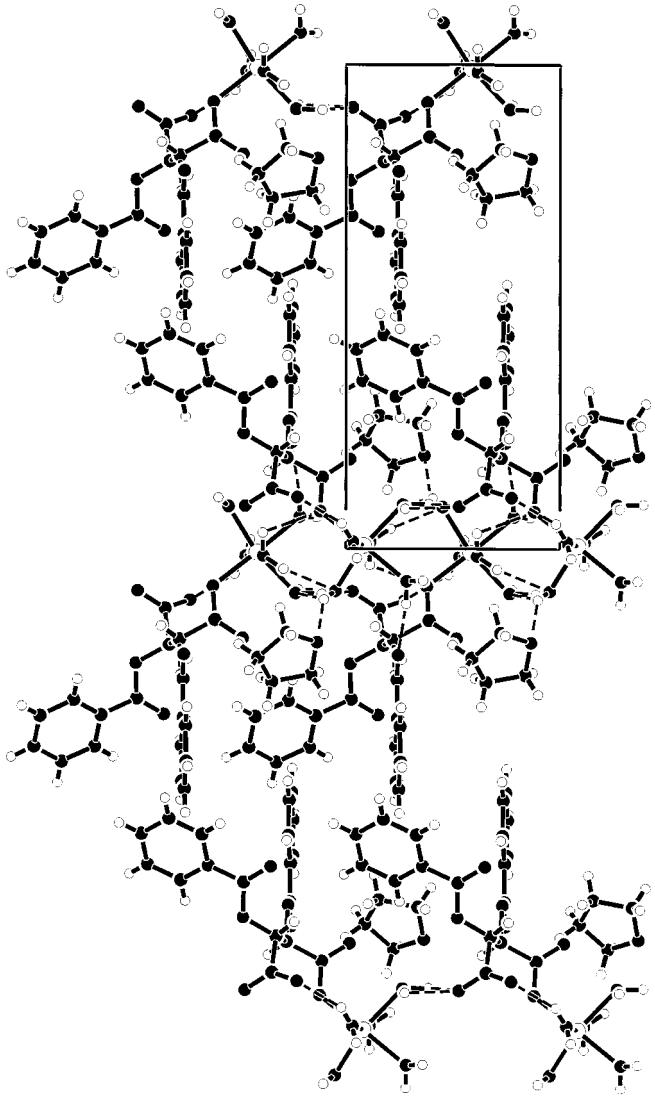
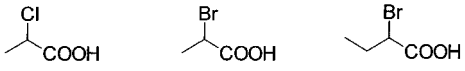


Figure 6. Packing diagram of **20**-(THF).

Recovery of the resolved alcohols can be achieved by extraction or in certain cases by distilling off the low-boiling azeotrope of the alcohol formed with water. A special work-up may involve ligand exchange, that is, conversion of the complex into another species, by which the previously complexed alcohol is freed. The results obtained with calcium and zinc (2*R*,3*R*)-*O*,*O*′-dibenzoyltartrates are given in Table 1.

The copper(II) complexes of *O*,*O*′-dibenzoyltartaric acid may exhibit an interesting new field of optical resolution.



22 **23** **24**

A series of copper(II) complexes of the general formula[15] **25**-(L,A) exists that can be applied to the enantiomeric resolution of the coordinated ligands L and A (as A^-).

$[Cu(L)_{n_l}(H_2O)_{nw}](HL_0)(A)$ **25**-(L,A)

Table 1. Complex salts of calcium and zinc (2*R*,3*R*)-*O*,*O*′-dibenzoyltartrates obtained with alcohols.

L	M	Solvent[a]	Complex	Yield[%][b]	*ee* [%][c]
1	Ca	EtOH/acetone	**9**	90	67(*R*)
2	Ca	EtOH/acetone	**9**	89	28(*R*)
3	Ca	EtOH	**9**	81	69(*R*)
6	Ca	EtOH/**6**	**9**	92[d]	–
1	Zn	EtOH/water	**16**	78	39(*S*)
1	Zn	EtOH/(AcOH)	**18**	84	60(*S*)
2	Zn	EtOH/water	**17**	41	33(*S*)
3	Zn	EtOH/water	**16**	71	81(*S*)
6	Zn	EtOH/**6**	**16**	95[d]	–
11[e]	Zn	EtOH	**19**	92[f]	57(*R*)
12	Zn	water/**12**	**20**	89[d]	–
13	Zn	water	**20**	82	30(*R*)
14	Zn	water/(AcOH)	**21**	93	12(*S*)

[a] EtOH: 96% ethanol. [b] Yield of the complex based on half of the starting racemic alcohol. [c] Enantiomeric excess and configuration (in parentheses) of the optically active alcohol obtained from the complex were determined by comparing the specific rotation value and the sign of rotation to those of the pure enantiomer. [d] Yield based on the amount of $M(L_0)$. [e] 90% **11a** and 10% **11b**. [f] Yield based on half of the racemic **11a**.

In the formula for **25**-(L,A), L stands for an alcohol (n_l generally equal to 1), and A stands for an acid (HA) anion (A^-). That is, a mixed copper(II) salt (generally more stable than the corresponding zinc salt) of *O*,*O*′-dibenzoyltartaric acid formed with HA will be the resolving agent for the alcohol L. On the other hand, a stable mixed salt exists (mixed salts with acetic acid and α-halogeno acids were investigated; compare to the mixed calcium salts[5]), which can be applied to the resolution of HA. However, the enantiomeric compositions of L and HA obtained from **25** are mutually affected by A and L, respectively. In conclusion, L and HA can be resolved in one crystallization step, even when starting from the racemic forms of both compounds. This simultaneous resolution phenomenon is demonstrated by a few examples given in Table 2.

Table 2. Copper complexes **25**-(L,A) obtained with one (L or A) and two (L and A) resolvable ligands.

L[a]	HA[b]	Yield[%][c]	ee_L[%][d]	ee_{HA}[%][e]
1	AcOH	74	11(*S*)	–
EtOH	**24**	66	–	14(*R*)
1	**24**	41	44(*S*)	11(*R*)
EtOH	**23**	66	–	3(*R*)
1	**23**	60	55(*S*)	19(*R*)
2	**23**	81	62(*S*)	29(*R*)
2	AcOH	75	31(*R*)	–
EtOH	**22**	86	–	32(*S*)
1	**22**	35	8(*S*)	33(*S*)

[a] Starting (racemic) alcohol; EtOH: ethanol. [b] Starting (racemic) acid; AcOH: acetic acid. [c] Yield of the complex **25** based on half of the starting racemic ligand (L or HA); in other cases equimolar amounts of racemic L and racemic HA were used. [d] Enantiomeric excess and configuration (in parentheses) of the alcohol (L) isolated from **25** were determined by comparing the specific rotation value and the sign of rotation to those of the pure enantiomer. [e] Enantiomeric excess and configuration (in parentheses) of the acid (HA) isolated from **25** were determined by comparing the specific rotation value and the sign of rotation to those of the pure enantiomer.

Conclusion

New, simple resolving agents can be obtained from *O,O′*-dibenzoyltartaric acid by complexing it with metals. The methods presented here along with those applied to the enantioseparation of other nonbasic compounds may provide an opportunity for the development of simple procedures which yield pure compounds.

Experimental Section

General: Commercially available chemicals (> 98 %) were used except for **11**, which was prepared as reported previously.[12] Solvents were purified by standard methods; 96 % ethanol was redistilled. Melting points were measured on a Gallenkamp apparatus and are uncorrected. IR spectra (KBr) were recorded on a Perkin-Elmer 1600 FT-IR spectrometer. Optical rotations were measured on a Perkin – Elmer 241 polarimeter. GC/MS: Hewlett – Packard HP 5890; HP-5 column (25 m × 0.2 mm × 0.5 μm) methyl-phenyl(5 %) polysiloxane; He, 35 cm min^{-1}, 75 kPa; *T* program: 50 °C (5 min), 50 to 300 °C (10 °C min^{-1}). MS: Hewlett – Packard HP-5971, 70 eV, *T* = 150 °C, scan mode, 2.2 scans s^{-1}.

9-((*R*)-1): (2*R*,3*R*)-*O,O′*-Dibenzoyltartaric acid monohydrate (30.1 g, 80 mmol) was dissolved in ethanol and then CaO (4.48 g, 80 mmol) was added. The mixture was briefly refluxed until a clear (or almost clear) solution was obtained. To the warm solution, racemic tetrahydrofurfuryl alcohol (32.6 g, 320 mmol) and acetone (16 mL) were added. The solution was seeded, slowly cooled, and finally allowed to stand for 10 h at 5 °C. The crystalline precipitate was filtered off (43.0 g, 71.7 mmol) and recrystallized twice from a mixture of ethanol/acetone (5:1). The air-dried material (33.6 g, 56 mmol, 70 %) melted at 65 – 67 °C. A pure sample of **9**-((*R*)-**1**) obtained from a solution containing (*R*)-**1** in excess had a melting point of 73 – 76 °C. IR (KBr): ν = 3406, 2977, 1718, 1618, 1389, 1270, 1116, 1071, 720 cm^{-1}.

(*R*)-Tetrahydrofurfuryl alcohol ((*R*)-**1**): Methoxyacetic acid (3.8 g, 42 mmol) and water (8 mL) were added to a warm solution of **9**-((*R*)-**1**) (20 g, 33.3 mmol) in ethanol (40 mL). The stirred solution was cooled to 15 °C, at which temperature it was stirred for an hour. The crystals (**10a**) were removed by filtration, and the mother liquor was distilled at atmospheric pressure until the head temperature had increased to 90 °C. Anhydrous sodium carbonate (2.0 g) was added to the residue, and the mixture was stirred for 30 min followed by the addition of chloroform (100 mL) and anhydrous sodium sulfate (6 g). Vigorous stirring was continued for an hour. After all solids were filtered off, the solution was evaporated, and the residue was fractionated at reduced pressure. Pure (*R*)-tetrahydrofurfuryl alcohol (5.0 g, 49 mmol, 74 %) was obtained. $[\alpha]_D^{22} = -2.18$ (neat), $[\alpha]_D^{22} = -18.5$ (*c* = 1.0 in chloroform), $[\alpha]_D^{22} = -17.1$ (*c* = 5.4 in chloroform). *ee* > 98 %. Ref. [4b]: $[\alpha]_D^{20} = -2.18$ (neat), $[\alpha]_D^{20} = -17.1$ (*c* = 5.4 in chloroform).

(*R*)-2-Methoxy-2-phenylethanol ((*R*)-**11a**): To a hot solution obtained by dissolving (2*R*,3*R*)-*O,O′*-dibenzoyltartaric acid monohydrate (5.64 g, 15 mmol) and zinc acetate dihydrate (3.29 g, 15 mmol) in ethanol (25 mL), racemic **11**[12] (3.8 g, 25 mmol) was added, and the stirred solution was seeded at 40 – 50 °C. The mixture was slowly cooled to 10 °C and allowed to stand. The crystalline complex (6.5 g, 10.4 mmol) was filtered off and recrystallized twice from aqueous ethanol (6 % and 10 % water). The air-dried material (**19**) (3.1 g, 4.9 mmol) had a melting point of 202 – 206 °C (decomp). The complex was suspended in water (15 mL), and toluene (25 mL) was added. Upon stirring the solid dissolved, and the organic layer was separated. The aqueous layer was extracted with a second portion of toluene (20 mL). The organic layers were combined and dried over sodium sulfate. The solvent was removed at reduced pressure, and the residue was distilled to give pure (**11a** > 99.5 %) (*R*)-**11a** (0.61 g; 4.0 mmol). B.p.$_{0.1}$ 60 – 62 °C. (Retention time *t* = 14.40 min.) $[\alpha]_D^{22} = -132$ (*c* = 1.0 in acetone). *ee* > 98 %. Ref. [10b]: $[\alpha]_D^{20} = -129.5$ (neat), ref. [10c]: $[\alpha]_D^{20} = -133$ (*c* = 1 in acetone).

Simultaneous resolution of 2-hydroxymethyltetrahydropyran and 2-bromopropionic acid: Racemic 2-bromopropionic acid (6.6 g, 43 mmol), racemic 2-hydroxymethyltetrahydropyran (5.0 g, 43 mmol) and water (9 mL) were added to a solution of (2*R*,3*R*)-*O,O′*-dibenzoyltartaric acid monohydrate (9.0 g, 24 mmol) and copper(II) acetate hydrate (4.80 g, 24 mmol) in ethanol (18 mL),. The solution was allowed to stand at room temperature, then cooled to 5 °C to complete the crystallization. The crystalline complex was filtered off and air-dried (12.62 g). This material was suspended in water (12 mL), and concentrated NH_3 was added until a clear solution was obtained. The aqueous solution was extracted three times with chloroform (35 mL each). The combined organic phase was dried and evaporated. The residual oil was fractionated to give (*S*)-2-hydroxymethyltetrahydropyran (1.60 g, 13.8 mmol, 64 %) (**2** > 99.5 %, retention time *t* = 9.49 min). $[\alpha]_D^{22} = +11.9$ (*c* = 1.0 in water). *ee* = 62 %. Ref. [19]: $[\alpha]_D^{22} = +19.2$ (*c* = 1 in water). To the aqueous solution, water (15 mL), toluene (50 mL), and excess concentrated hydrochloric acid were added; the mixture was warmed for a short period, cooled to 10 °C, and allowed to stand until the solid material completely separated. The solution was filtered, the toluene layer was separated, and the aqueous layer was extracted with ethyl acetate (50 mL). The organic phases were combined, dried over sodium sulfate, and concentrated in vacuo. The residue was distilled to give (*R*)-2-bromopropionic acid (2.48 g, 16.2 mmol, 75 %). (**23** > 99.5 %, retention time *t* = 11.11 min). $[\alpha]_D^{22} = +8.7$ (*c* = 1.0 in methanol). *ee* = 29 %. Ref. [20] for the (*S*) isomer: $[\alpha]_D^{21} = -29.8$ (*c* = 1 in methanol).

Crystal data for 16-((*S*)-**1**): M_r = 623.89, monoclinic, space group $P2_1$, *a* = 11.187(3), *b* = 11.451(2), *c* = 11.334(1) Å, β = 104.096(14)°, *V* = 1408.2(5) Å^3, *Z* = 2, ρ_{calcd} = 1.471 g cm^{-3}, μ = 1.820 mm^{-1}. A colorless platelike crystal (0.50 × 0.30 × 0.05 mm^3) gave a data set of 3130 reflections (Θ_{max} = 75.14°) of which 2999 were unique with R_{int} = 0.047 and 2086 had intensities higher than 2σ(*I*). A psi-scan correction was applied: min/max transmission: 0.665/1.000. *R*1 = 0.0570, *wR*2 = 0.1457, GOF = 1.000 for those reflections with $I > 2\sigma(I)$. The Flack parameter[16] *x* = 0.04(8) confirms the absolute configuration.

Crystal data for 16-((*S*)-**3**): M_r = 611.88, monoclinic, space group $P2_1$, *a* = 11.193(2), *b* = 11.4997(14), *c* = 11.3151(10) Å, β = 105.234(10)°, *V* = 1405.3(5) Å^3, *Z* = 2, ρ_{calcd} = 1.446 g cm^{-3}, μ = 1.811 mm^{-1}. A colorless needlelike crystal (0.50 × 0.30 × 0.25 mm^3) gave a data set of 3189 reflections (Θ_{max} = 75.09°) of which 3047 were unique with R_{int} = 0.054 and 2626 had intensities higher than 2σ(*I*). No absorption correction was applied. *R*1 = 0.0456, *wR*2 = 0.1185, GOF = 1.047 for those reflections with $I > 2\sigma(I)$. The Flack parameter[16] *x* = −0.01(4) confirms the absolute configuration.

Crystal data for 20-(**12**): M_r = 571.83, orthorhombic, space group $P2_12_12_1$, *a* = 9.091(8), *b* = 36.209(10), *c* = 7.9225(14) Å, *V* = 2607.8(23) Å^3, *Z* = 4, ρ_{calcd} = 1.456 g cm^{-3}, μ = 0.945 mm^{-1}. A colorless needlelike crystal (0.50 × 0.30 × 0.25 mm^3) gave a data set of 3130 reflections (Θ_{max} = 75.14°) of which 2971 were unique and 2290 had intensities higher than 2σ(*I*). *R*1 = 0.0818, *wR*2 = 0.2296, GOF = 1.040 for those reflections with $I > 2\sigma(I)$.

Crystal data for 20-(THF): M_r = 583.83, monoclinic, space group $P2_1$, *a* = 8.845(3), *b* = 8.098(25), *c* = 18.117(25) Å, β = 95.86(5)°, *V* = 1290.8(44) Å^3, *Z* = 2, ρ_{calcd} = 1.502 g cm^{-3}, μ = 1.943 mm^{-1}. A colorless platelike crystal (1.00 × 0.75 × 0.30 mm^3) gave a data set of 2939 reflections (Θ_{max} = 75.26°) of which 2766 were unique with R_{int} = 0.063 and 2656 had intensities higher than 2σ(*I*). *R*1 = 0.0619, *wR*2 = 0.1666, GOF = 1.086 for those reflections with $I > 2\sigma(I)$. The Flack parameter[16] *x* = 0.06(6) confirms the absolute configuration.

Crystal structure determinations: Single crystals of **16**-((*S*)-**1**) and **16**-((*S*)-**3**) were grown from an ethanol/water mixture, whereas crystals of **20**-(**12**) and **20**-(THF) were obtained from water. All data were collected at room temperature with a Rigaku AFC6S diffractometer; $\omega/2\Theta$ scans measured by using graphite-monochromated $Cu_{K\alpha}$ radiation. Three standards monitored every 150 reflections indicated no significant decay in any of the four cases. Lorentz-polarization corrections were applied in all cases. All structures were solved by using the TEXSAN package[17] and refined with SHELXL-93[18] against F^2 using all unique reflections. All non-hydrogen atoms were refined anisotropically. Most hydrogen atoms were generated based upon geometrical evidence, with X–H bond length dependent on the chemical nature of X. Some hydrogen atom positions (for example those belonging to the water molecules) were taken from difference Fourier calculations and reinforced by forming hydrogen bonds with proper geometry. Crystallographic data (excluding structure factors) for the

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structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100599. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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