Optical resolution of racemic alcohols by diastereoisomeric complex formation with *O,O'*-dibenzoyl-(2*R*,3*R*)-tartaric acid; the crystal structure of the (−)-(1*R*,2*S*,5*R*)-menthol·*O,O'*-dibenzoyl-(2*R*,3*R*)-tartaric acid complex

Dávid Kozma,*[a] Zsolt Böcskei,[b] Csaba Kassai,[a] Kálmán Simon[b] and Elemér Fogassy[a]

[a] *Department of Organic Chemical Technology, Technical University of Budapest, Budapest POB 91, H-1521 Hungary*
[b] *Chinoin Pharmaceuticals, Budapest POB 110 H-1325 Hungary*

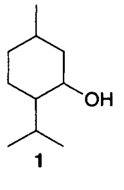
_O,O'_-dibenzoyl-(2_R_,3_R_)-tartaric acid resolves racemic alcohols by complex formation; the X-ray crystal structure of the (−)-(1_R_,2_S_,5_R_)-menthol·_O,O'_-dibenzoyl-(2_R_,3_R_)-tartaric acid complex is reported which was obtained by reacting _O,O'_-dibenzoyl-(2_R_,3_R_)-tartaric acid monohydrate and racemic menthol.

The optical resolution of racemic alcohols on a preparative scale can be achieved through diastereoisomeric salt formation of, for example, an ester derivative of an alcohol or by complex formation with an optically active host.[1] The latter is much simpler, since it does not require derivatization of the racemate. A large number of host compounds have been used as resolving agents,[2–6] but their application is not widespread, their availability is limited and their price relatively high.

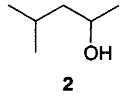
The simplest chiral building blocks[7] are the optically active natural acids such as lactic acid and tartaric acid. Their non-acidic derivatives are known as efficient complex forming agents.[2,4] Recently we found that the optical resolution of the basic *N*-alkylpipecolic acid-anilides by tartaric acid (**TA**) and *O,O'*-dibenzoyl-(2*R*,3*R*)-tartaric acid (*DBTA*) sometimes goes through complex formation rather than salt formation.[8] This led us to the conclusion that underivatized **TA** and **DBTA** may be used for the resolution of racemates having no basic groups. This idea was tested on five racemic alcohols as guest compounds (**1**–**5**).

Both **TA** and **DBTA** were treated with all of the five alcohols by the suspension method described by Toda.[9] For example, finely pulverized **DBTA**·H_2O (2.4 g, 0.0064 mol) was suspended in the solution of racemic menthol (2.0 g, 0.0128 mol in hexane (10 cm^3). Standing overnight at room temperature, the solid phase transformed into large transparent prisms. The solid phase was filtered then heated in a sublimating apparatus at 80 °C *in vacuo*. The sublimate contains the (−)-(1*R*,2*S*,5*R*)-**1** in 83.2 ee%. The other alcohols reacted similarly to form complexes except they were distilled and not sublimated.

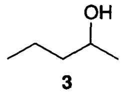
TA does not form complexes with any of the alcohols, while the **DBTA** forms complexes with all of them. Using anhydrous **DBTA** the achieved enantiomeric purities are: **1**: 69.0%; **2**: 20.6%; **3**: 24.3%; **4**. 4.7%, while **5** complexed in racemic form. The change of the anhydrous **DBTA** to **DBTA** monohydrate increased the enantiomeric purity for **1** from 69.0 to 83.2%, and for **2** from 20.6 to 28.5%, while for **3** it decreased from 24.3 to 3%.



1

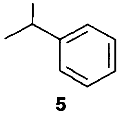


2



3

4



5

The crystal structure of the complex formed on reacting **DBTA** monohydrate and racemic menthol (**MEDBTA**) was determined (Fig. 1).† The monoclinic crystal contains one molecule of **DBTA** and one molecule of (−)-(1*R*,2*S*,5*R*)-**1** as might be predicted from the experimental results, but no water molecules were found in the crystal. The hydrate of the **DBTA** facilitates the complex formation between the **DBTA** and the menthol.

The crystal structure of **MEDBTA** contains carboxylic acids in their protonated state, and is built by alternating hydrophilic and hydrophobic layers. It is a feature of the hydrophobic layers that the cyclohexane moieties of the menthol are sandwiched in between two phenyl rings of two neighbouring **DBTA** molecules. The hydrophilic layers are composed of chains of hydrogen-bonded carboxylic acid moieties. The O···O distance between head-to-tail arranged hydrogen-bonded carboxylic acid moieties is 2.635(4) Å [Etter symbol[10] for the hydrogen bond chain is *C*(7)]. The chains are interconnected by hydrogen bonds formed from the OH groups of the menthol molecules,

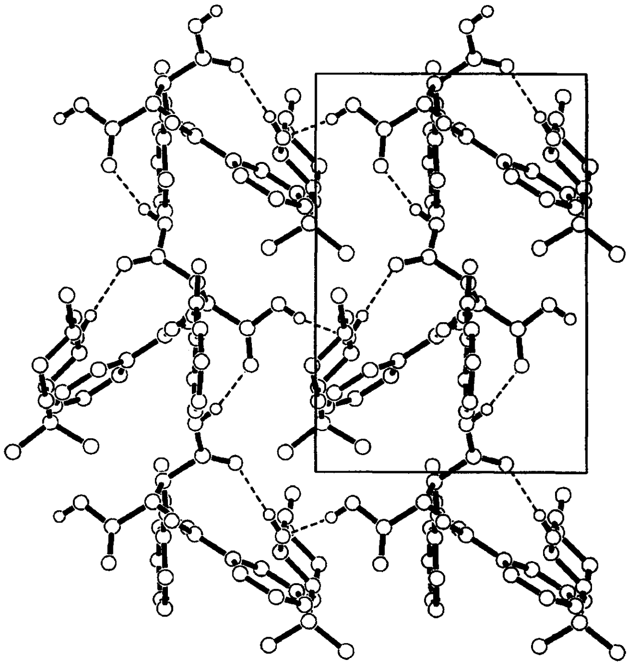


Fig. 1 Crystal packing and hydrogen bonding network in **MEDBTA** (for clarity, all H atoms which do not participate in the H bonding have been removed). Dotted lines represent hydrogen bonds. Hydrogen bond data (Å,°): DBTA chain (vertical on the figure) O7–H···O1 2.635(4), 1.848(36), 160.46(1.26) (1 − *x*, 0.5 + *y*, −*z*); the horizontal chain containing the OH group of the menthol: O8···H33–O33 2.816(5), 2.002(5), 172.11(1.87); O6–H6···O33 2.569(5), 1.777(13), 162.10(3.95) (*x* − 1, *y*, *z*).

both as H-bond donor and acceptor [Etter symbol $C_2^2(7)$]. The two quasi-perpendicular hydrogen bond chains form large rings, which can be characterised by the graph notation $R_6^6(26)$. It appears as though the parallel chains of **DBTA** molecules form a scaffold with hydrophobic empty boxes into which guest molecules of menthol can penetrate. In addition to the non-specific hydrophobic forces in the boxes, the OH groups of the menthol are held firmly by hydrogen bonds formed by two parallel **DBTA** chains.

The experiments prove that one of the cheapest commercially available resolving agents, **DBTA**, can be used not only for optical resolution *via* diastereoisomeric salt formation, but also as a complex-forming agent for the optical resolution of racemic alcohols.

The authors are grateful for financial support to the OTKA foundation [grant numbers: F7386 and F19600 (D. K.) and T14887 (E. F.)] and for the Z. Magyary award for D. K.

Footnote

† *Crystal data*: $C_{10}H_{20}O{\cdot}C_{18}H_{14}O_8$, monoclinic, $P2_1$, $a = 8.738(3)$, $b = 12.753(5)$, $c = 13.036(5)$ Å, $\beta = 97.66(3)°$, $V = 1439.7(9)$ Å^3, $D_c = 1.187$ g cm^{-3}, $Z = 2$, $\mu = 0.733$, $T = 293(2)$ K, crystal dimensions 1.00 × 0.50 × 0.25 mm, 2917 independent reflections, $R_1 = 0.040$ $wR_2 = 0.096$ for reflections with $I > 2\sigma(I)$, maximum final ΔF peak 0.18 e Å^{-3}, Rigaku AFC6S diffractometer, wavelength: 1.54178 Å, $\theta_{max} = 75.14°$. The structure was solved using the TEXSAN program package [TEXSAN: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992)], while the full-matrix least-squares (on F^2) refinement was done with SHELEX-93 (G. M. Sheldrick, SHELEX-93 Program for the Refinement of Crystal Structures, University of Göttingen, 1993) running on a Silicon Graphics R3000 work station. No absorption correction was applied. Hydrogen atoms with known geometry were generated, except the OH atoms which were taken from difference Fourier calculations. Atomic coordinates, bond length and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

References

1 J. Jacques, A. Collet and S. H. Wilen, *Enantiomers, Racemates and Resolutions*, Wiley, New York, 1981.
2 D. Seebach, A. K. Beck, R. Imwinkelried, S. Roggo and A. Wonnacott, *Helv. Chim. Acta*, 1987, **70**, 954.
3 F. Toda, *Top. Curr. Chem.*, 1987, **140**, 44.
4 E. Weber, C. Wimmer, A. L. Llamas-Saiz and C. Forces-Forces, *J. Chem. Soc., Chem. Commun.*, 1992, 733.
5 F. Toda, K. Tanaka, Z. Stein and I. Goldberg, *J. Chem. Soc., Perkin Trans. 2*, 1993, 2359.
6 F. Toda, K. Tanaka, I. Miyahara, S. Akutsu and K. Hirotsu, *J. Chem. Soc., Chem. Commun.*, 1994, 1795.
7 R. A. Sheldon, *Chirotechnology*, Marcel Dekker, New York, 1993.
8 K. Nemák, M. Ács, Zs. Jászai, D. Kozma and E. Fogassy, *Tetrahedron*, 1996, **52**, 1637.
9 F. Toda and Y. Tohi, *J. Chem. Soc., Chem. Commun.*, 1993, 1238.
10 M. C. Etter, *Acc. Chem. Res.*, 1990, **23**, 120.

Received, 28th December 1995; Com. 5/08392C