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Optical Resolution of Pantolactone by Inclusion Crystallization with (R,R)-(-)-trans-2,3-Bis(diphenylhydroxymethyl)-1,4-dioxaspiro[4.5]decane, and Crystal Structure of the Resulting 1:1 Complex

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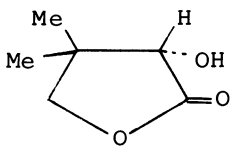
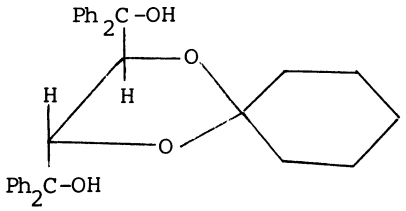
Pantolactone was resolved very efficiently by complex formation of its (S)-(-) isomer with the title host compound. The structure of the 1:1 complex was elucidated by X-ray crystallography.

Pantolactone, dihydro-3-hydroxy-4H-dimethyl-2(3H)-furanone (1), is an important intermediate in the synthesis of pantothenic acid. Optical resolution of 1 by the usual diastereomeric method is complicated and the efficiency is not high.[1] We have developed a very efficient procedure for the resolution of 1 by inclusion complex formation with the title host compound (2), which is readily available from tartaric acid according to the literature method.[2]

For example, when a solution of racemic 1 (2.6 g, 20 mmol) and 2 (5.5 g, 9.93 mmol) in benzene-hexane (1:1, 20 ml) was kept at room temperature for 1 h, a 1:1 complex (3) (2.54 g) of (S)-(-)-1 (the absolute configuration was first established by the present crystal structure analysis) and 2 was obtained as colorless needles. The crude product was recrystallized twice from benzene-hexane (1:1) to give pure 3 (2.05 g), which upon heating in vacuo yielded (S)-(-)-1 of 99% ee [0.39 g, 30%, $[\alpha]_D$ -50.0° (c 0.5 in H_2O)]. The optical purity of (-)-1 was determined by comparison of its $[\alpha]_D$ value with that reported for pure (S)-(-)-1.[1]



1, S isomer shown



(R,R)-(-)-2

The crystal structure of 3 was determined in order to establish the absolute configuration of 1 and to elucidate the nature of the inclusion complexation. Crystal data: $C_{34}H_{34}O_4 \cdot C_6H_{10}O_3$, FW = 636.78, monoclinic, space group $P2_1$, a =

10.563(2), $\underline{b}$ = 9.692(1), $\underline{c}$ = 17.008(2)Å, β = 98.86(1)°, $\underline{V}$ = 1720.4(4)Å, $\underline{Z}$ = 2, $\underline{F}$(000) = 680, $\underline{D}_m$ (flotation in KI/H_2O) = 1.225, $\underline{D}_c$ = 1.229 g cm^{-3}, Mo-$\underline{K}\alpha$ radiation ($\bar{\lambda}$ = 0.71073Å), μ = 0.08 mm^{-1}, crystal size 0.40 x 0.32 x 0.22 mm^3, $2\theta_{max}$ = 50°, 3247 unique reflections collected on a Nicolet R3m/V diffractometer at 20 °C.[3] The structure was solved by direct phase determination based on random starts and negative quartets.[4] All C and O atoms were subjected to anisotropic refinement. The phenyl, methine, methylene, and methyl H atoms were generated geometrically, and the methyl groups were treated as rigid groups; these H atoms were included in structure-factor calculations with assigned isotropic temperature factors. Full-matrix least-squares refinement of 2503 observed data [$|\underline{F}_o| > 4\sigma(|\underline{F}_o|)$] on 423 variables using the weighting scheme $\underline{w} = [\sigma^2(|\underline{F}_o|) + 0.0012|\underline{F}_o|^2]^{-1}$ converged to $\underline{R}_F$ = 0.066 and $\underline{R}_{wF}2$ = 0.085. All computations were perfomed on a DEC MicroVAX-II system with the SHELXTL PLUS package.[5,6]

A perspective view of the asymmetric unit of complex $\underset{\sim}{3}$ with atom numbering[7] is illustrated in Fig. 1. Bond distances and angles of both molecular components are all normal. The hydroxyl groups of each host molecule $\underset{\sim}{2}$ are linked by an intramolecular hydrogen bond. Every pair of host molecules related by the 2_1 symmetry operation is bridged by a guest molecule $\underset{\sim}{1}$ by hydrogen bonds involving its carbonyl and hydroxyl groups, resulting in a helical spiral parallel to the $\underline{b}$ axis. Parameters which describe the geometry of hydrogen bonding are given in

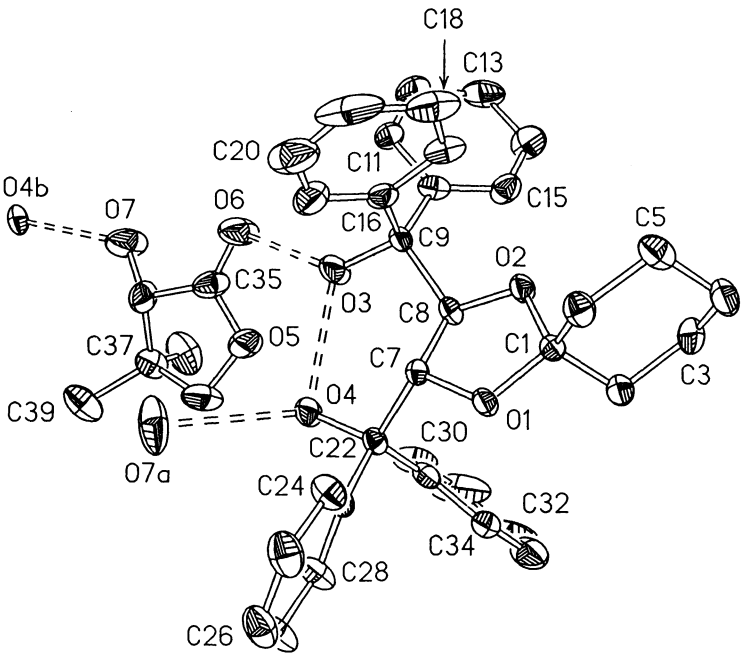


Fig. 1. Perspective view of the two molecular components of complex $\underset{\sim}{3}$. The thermal ellipsoids are drawn at the 30% probability level, and hydrogen bonds are represented by double dashed lines. Symmetry code: $\underline{a}$ -$\underline{x}$, ½+$\underline{y}$, -$\underline{z}$; $\underline{b}$ -$\underline{x}$, -½+$\underline{y}$, -$\underline{z}$. Geometry of hydrogen bonding: O3...O4 2.365Å, O3...O6 2.741Å, O4...O3...O6 106.2°, C9-O3...O4 116.4°, C9-O3...O6 136.7°, O4...O7$\underline{a}$ 2.745Å, O3...O4...O7$\underline{a}$ 105.3°, C22-O4...O3 104.8°, C22-O4...O7$\underline{a}$ 139.5°, C35=O6...O3 103.5°, C37-O7...O4$\underline{b}$ 131.6°.

the legend to Fig. 1. Figure 2 shows that the crystal structure is built of a lateral packing of these spiral columns. In the unit cell the molecules are located close to the $(10\bar{1})$ set of planes, and accordingly the $(10\bar{1})$ reflection has the highest observed intensity.

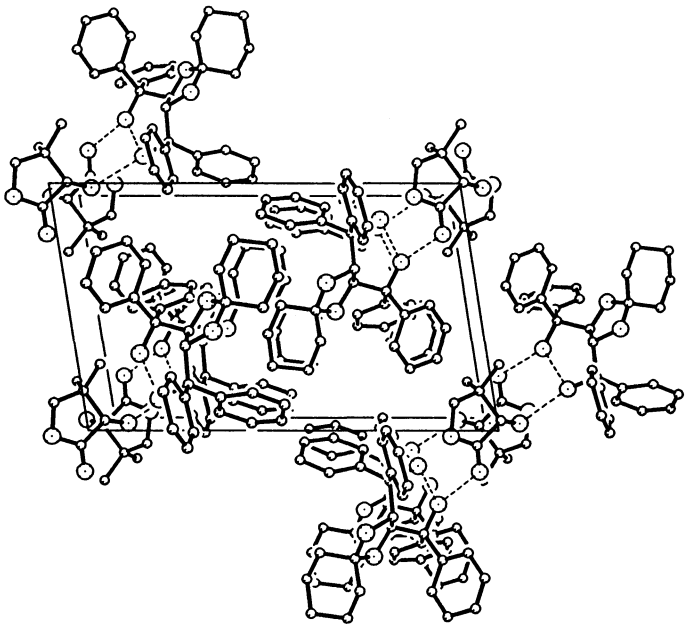


Fig. 2. Perspective view of the molecular packing in 3. The origin of the unit cell lies at the lower left corner, with a pointing upwards, b towards the reader, and c from left to right. Hydrogen bonds are represented by broken lines.

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References

1) E.T. Stiller, S.A. Harris, J. Finkelstein, J.C. Keresz, and K. Folker, J. Am. Chem. Soc., 62, 1785 (1940); C. Hatat, A. Karim, N. Kokel, A. Mortreux, and F. Petit, Tetrahedron Lett., 29, 3675 (1988), and references cited therein.
2) D. Seebach, A.K. Beck, R. Imwinkelried, S. Roggo, and A. Wonnacott, Helv. Chim. Acta, 70, 954 (1987).
3) Experimental procedure is as described in R.A. Sparks, "Crystallographic Computing Techniques," ed by F.R. Ahmed, Munksgaard, Copenhagen (1976), p. 452.
4) G.T. DeTitta, J.W. Edmonds, D.A. Langs, and H. Hauptman, Acta Crystallogr., Sect. A, 31, 472 (1975).

5) G.M. Sheldrick, "Crystallographic Computing 3: Data Collection, Structure Determination, Proteins, and Data bases, ed by G.M. Sheldrick, C. Krüger, and R. Goddard, Oxford University Press, New York (1985), p. 175; G.M. Sheldrick, Acta Crystallogr., Sect. A, 43, supplement, C-320 (1987).
6) G.M. Sheldrick, Acta Crystallogr., Sect. A, 43, Supplement, C-320 (1987).
7) The atomic parameters have been deposited with the Cambridge Crystallographic Data Centre. Structure factors are available on request from the last author.

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