

Tetrameric aggregate of 1,*c*-3-diphenyltetran-*r*-1-ol via an $R_4^4(8)$ homodromic ring

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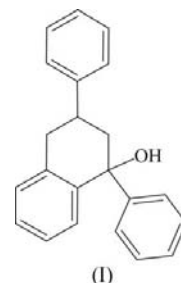
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The compound 1,*c*-3-diphenyltetran-*r*-1-ol (systematic name: 1,*c*-3-diphenyl-1,2,3,4-tetrahydro-*r*-1-naphthol), $C_{22}H_{20}O$, which possesses the tetrahydronaphthalene core that is found in a large number of natural products, crystallizes with $Z' = 4$ and with the four molecules forming a hydrogen-bonded cyclic aggregate. The aliphatic six-membered rings are present with two different conformations in the molecules of the asymmetric unit. A comparison with similar fragments reveals their conformational flexibility. In addition, the structure demonstrates the relative stereochemistries of the chiral centers, which are important since the title compound is used in the stereoselective synthesis of compounds with therapeutic activity.

Comment

The molecule of the title compound, (I), contains a tetrahydronaphthalene core that is often found in a large number of natural products (Bates *et al.*, 1997), as well as bioactive and pharmaceutically interesting substances (Wang *et al.* 2006). We have been studying the synthesis and configurational properties of indanic and tetranilic derivatives (Aguirre *et al.*, 1998, 1999; Alesso *et al.*, 2002, 2003; Vega *et al.*, 2006). In particular, we have been seeking alternative routes to stereoselective synthesis of tetranilic derivatives *via* hydrogenolysis of corresponding tetranols that can be used as intermediates in the synthesis of analogues of bioactive molecules. To progress in stereoselective syntheses, the elucidation of relative configuration at the chiral centers is necessary. The structure of (I) is also of interest for its supramolecular assembly (*vide infra*), which may be of interest in crystal engineering, as aphorized in Lehn's analogy that 'supramolecules are to

molecules and the intermolecular bond what molecules are to atoms and the covalent bond' (Desiraju, 1995).



The title compound has two chiral centers, C1 and C3 (Fig. 1); its synthesis has been reported (Hanaya *et al.*, 1981). There have been attempts to assign the configuration by IR spectroscopy (Hanaya *et al.*, 1981) and NMR (Mufato *et al.*, 2007). Nevertheless, these two results have not been confirmed. The aim of the present work is to provide experimental information about the configuration and also about the conformation and supramolecular aggregation of the title compound. There are four molecules (*A*, *B*, *C* and *D*) in the asymmetric unit, constituting a racemic tetrameric aggregate (Fig. 2). Molecules *A* and *D* have an *SR* configuration, whereas *B* and *C* are *RS*. It is possible to use a different asymmetric unit, with all molecules having an *RS* or *SR* configuration, but that asymmetric unit would not have an integral tetramolecular aggregate.

The selected bond distances, angles and torsion angles listed in Table 1 reveal the main differences among the molecules, which are principally conformational. The two benzene rings (C7–C12 and C17–C22) adopt different relative orientations in each molecule, as expected because the rotations around C3–C12 and C1–C17 are free. To perform a better comparison, the reported torsion angles C2–C3–C12–C7 and C6–C1–C17–C22 for molecules *B* and *C* in Table 1 are from those molecules equivalent to *B* and *C* generated by the center of symmetry, so that we are comparing four molecules with the same *SR* configuration. In particular, the C2–C3–C12–C7 and C6–C1–C17–C22 torsion angles range from

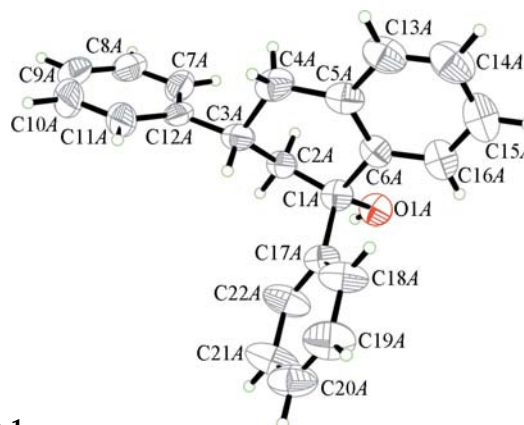
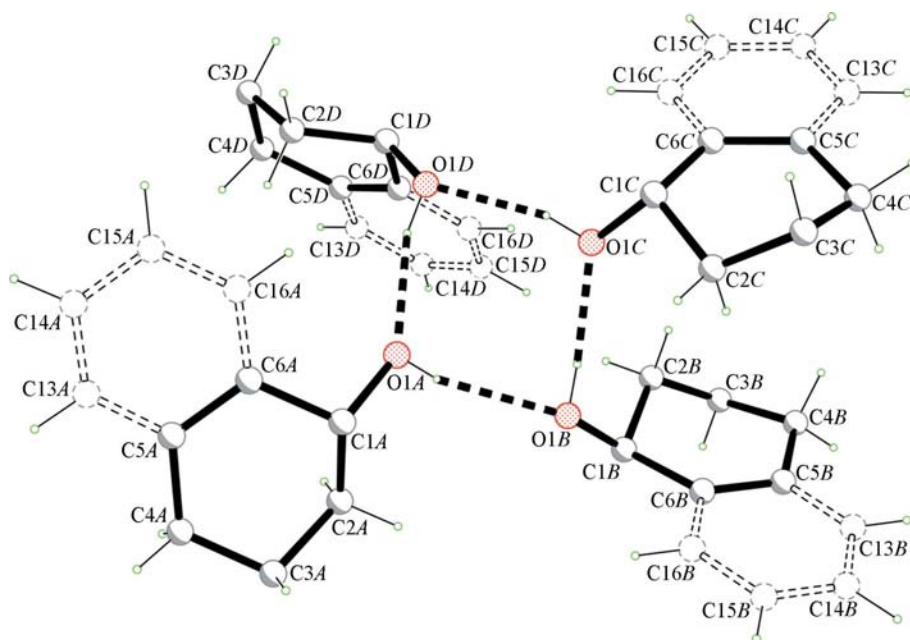


Figure 1
Molecule *A* of (I) (*SR* configuration), with displacement ellipsoids shown at the 30% probability level.


Figure 2

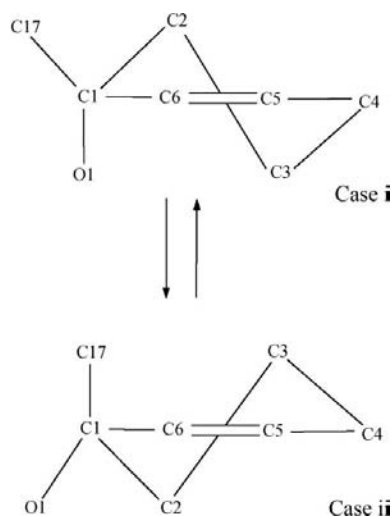
A view of the tetramer, showing the atom-labelling scheme. The benzene rings attached to atoms C1 and C3 have been omitted. The benzene rings fused to the central rings (at C5 and C6) are depicted with open dashed lines. The hydrogen bonds that determine the tetramer are drawn as solid dashed lines.

-30 to -55° and from -160 to 177° (equivalent to -183°), respectively, which establishes the differences in the relative orientations of the rings in the different molecules.

An extra conformational difference is observed when the puckering of the central six-membered C1–C6 ring is analyzed. This ring can be best described as a half-chair in molecules *A* and *D*, but it is twisted in molecules *B* and *C*. The puckering parameters (Cremer & Pople, 1975) are $Q = 0.506$ (4) and 0.494 (4) Å, $\theta = 132.2$ (5) and 133.3 (5) $^\circ$, and $\varphi = 225.3$ (7) and 226.4 (6) $^\circ$ for molecules *A* and *D*, respectively, and $Q = 0.473$ (4) and 0.521 (4) Å, $\theta = 134.6$ (6) and 130.9 (4) $^\circ$, and $\varphi = 211.0$ (8) and 210.6 (6) $^\circ$ for those molecules equivalent to *B* and *C* generated by the center of symmetry.

The conformational differences between the four molecules observed in the non-aromatic six-membered ring merit further analysis. Considering the expected conformational equilibrium shown in the scheme below, case i and case ii can be characterized by the torsion angles C5–C6–C1–O1 or C5–C6–C1–C2. In the cases described in the scheme, the typical values are around 90 and -30° (case i) and around 150 and 30° (case ii) for the C5–C6–C1–O1 and C5–C6–C1–C2 torsion angles, respectively. This is the case if C1 has an *S* configuration (as shown in the scheme). When C1 has an *R* configuration, negative values should be obtained for C5–C6–C1–O1. A search of the Cambridge Structural Database (CSD, Version 5.29; Allen, 2002) for fragments such as the one described in the scheme below (*S* and *R* configuration at atoms C1 and C3), with a benzene ring fused at C6–C5 and a hydroxy group at the O1 position, gave 141 hits with 204 fragments. As expected, the mean value obtained for the C4–C5–C6–C1 torsion angle is low (sample mean value = -0.9° , s.u. = 5°) because of the aromatic character of the C5–C6 bond.

Fig. 3 shows the C5–C6–C1–O1 and C5–C6–C1–C2 torsion angles as a scatter diagram where, as was mentioned, the negative values for the C5–C6–C1–O1 torsion angle mean that C1 has the *R* configuration. Beyond the obvious correlation between the C5–C6–C1–O1 and C5–C6–C1–C2 torsion angles, Fig. 3 also shows that the C5–C6–C1–C2 torsion angle spans a wide range of values (from -60 to 60°), thus reflecting a quasi-continuous conformational



flexibility. In the present work, the flexibility of the central ring becomes evident when inspecting the torsion angles as shown in Table 1. As before, for the purpose of comparison, the *SR* enantiomers of *B* and *C* were used. The C5–C6–C1–O1 and C5–C6–C1–C2 torsion angles range from 130 to 146° and 18 to 26° , respectively. The subtle flexibility of this ring

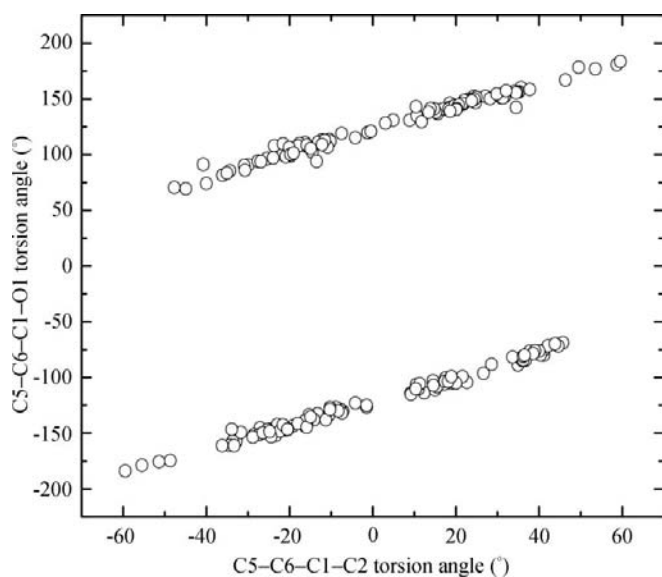


Figure 3

A scatter diagram of the C5–C6–C1–O1 torsion angle versus the C5–C6–C1–C2 torsion angle. Positive and negative values are obtained for the C5–C6–C1–O1 torsion angles when C1 has *S* and *R* configurations, respectively.

becomes evident in the four chemically equivalent molecules.

The four molecules in the asymmetric unit are linked by as many hydrogen bonds (Table 2) to constitute a tetramer (Fig. 2). Each molecule is hydrogen bonded to two neighbors, once as an acceptor and once as a donor. The four hydrogen bonds determine a homodromic ring with a graph set $R_4^4(8)$ (Bürgi & Dunitz, 1994). Searching the CSD for similar rings developed by a molecule with a hydroxy group attached to a six-membered C-atom ring, we found 140 fragments forming $R_4^4(8)$ patterns. We consider two relevant parameters for these rings, *viz.* the O···O distances and the ring planarity. The O···O distances in the tetramer in (I) have a mean value of 2.712 (6) Å, which seems to be on the low side of the mean found for the 140 fragments (2.79 Å, s.u. = 0.09 Å); therefore good cohesion seems to be established in the tetramer. On the other hand, considering the mean plane through the four O atoms, we find that 57 of the 140 fragments have rigorously planar rings, probably owing to the existence of a crystallographic symmetry element to generate the ring. However, for a few fragments, the O atoms in the ring are far from planarity. In particular, there are 14 fragments with distances from the O atoms to the least-squares plane greater than 0.5 Å (the largest value is 0.85 Å). The ring in (I) has a mean distance from the O atom to the least-squares plane of 0.30 (1) Å.

Experimental

The diastereoisomers 1,3-diphenyltetran-1-ol were synthesized from 3-phenyltetran-1-one and the corresponding Grignard reagent as reported by Hanaya *et al.* (1981). Crystals of (I) suitable for diffraction analysis were obtained after allowing a methanol solution to stand for several weeks at room temperature.

Crystal data

$C_{22}H_{20}O$	$V = 6817 (2) \text{ \AA}^3$
$M_r = 300.38$	$Z = 16$
Monoclinic, $P2_1/c$	Mo $K\alpha$ radiation
$a = 16.546 (3) \text{ \AA}$	$\mu = 0.07 \text{ mm}^{-1}$
$b = 13.124 (3) \text{ \AA}$	$T = 293 (2) \text{ K}$
$c = 31.942 (6) \text{ \AA}$	$0.4 \times 0.2 \times 0.05 \text{ mm}$
$\beta = 100.62 (3)^\circ$	

Data collection

Rigaku AFC6 Diffractometer	$R_{\text{int}} = 0.112$
16186 measured reflections	3 standard reflections
13368 independent reflections	every 147 reflections
3121 reflections with $I > 2\sigma(I)$	intensity decay: 13%

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.063$	835 parameters
$wR(F^2) = 0.202$	H-atom parameters constrained
$S = 0.85$	$\Delta\rho_{\text{max}} = 0.21 \text{ e \AA}^{-3}$
13368 reflections	$\Delta\rho_{\text{min}} = -0.17 \text{ e \AA}^{-3}$

Table 1

Selected geometric parameters (Å, °).

O1A–C1A	1.474 (5)	O1C–C1C	1.464 (5)
O1B–C1B	1.436 (5)	O1D–C1D	1.446 (5)
O1A–C1A–C2A	107.7 (4)	O1C–C1C–C2C	104.2 (4)
O1B–C1B–C2B	108.2 (4)	O1D–C1D–C2D	107.9 (4)
C2A–C3A–C12A–C7A	–39.1 (7)	C5A–C6A–C1A–O1A	142.4 (4)
C2B ⁱ –C3B ⁱ –C12B ⁱ –C7B ⁱ	–54.8 (7)	C5B ⁱ –C6B ⁱ –C1B ⁱ –O1B ⁱ	138.6 (5)
C2C ⁱ –C3C ⁱ –C12C ⁱ –C7C ⁱ	–29.9 (7)	C5C ⁱ –C6C ⁱ –C1C ⁱ –O1C ⁱ	130.1 (5)
C2D–C3D–C12D–C7D	–47.3 (7)	C5D–C6D–C1D–O1D	146.2 (4)
C6A–C1A–C17A–C22A	177.1 (5)	C5A–C6A–C1A–C2A	25.6 (6)
C6B ⁱ –C1B ⁱ –C17B ⁱ –C22B ⁱ	–173.2 (5)	C5B ⁱ –C6B ⁱ –C1B ⁱ –C2B ⁱ	19.7 (7)
C6C ⁱ –C1C ⁱ –C17C ⁱ –C22C ⁱ	–165.9 (4)	C5C ⁱ –C6C ⁱ –C1C ⁱ –C2C ⁱ	18.2 (6)
C6D–C1D–C17D–C22D	–160.3 (4)	C5D–C6D–C1D–C2D	26.1 (6)

Symmetry code: (i) $-x, -y, -z$.

Table 2

Hydrogen-bond geometry (Å, °).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
O1A–H1A···O1B	0.82	2.14	2.909 (5)	155
O1B–H1B···O1C	0.82	1.92	2.737 (5)	173
O1C–H1C···O1D	0.82	1.96	2.759 (5)	163
O1D–H1D···O1A	0.82	2.04	2.792 (5)	153

Crystals of (I) yield poor diffraction data at high 2θ values. Data were corrected for decay. All H atoms were treated as riding atoms, located at idealized positions, with C–H distances of 0.97 (CH₂), or 0.93 or 0.98 Å (CH), and O–H distances of 0.82 Å. All H atoms were assigned isotropic displacement parameters, with $U_{\text{iso}}(\text{H})$ values of 1.2 times U_{eq} of the parent non-H atoms for CH₂ and CH groups, and 1.5 times for the OH group.

Data collection: *AFC6S Diffractometer Control Software* (Molecular Structure Corporation, 1993); cell refinement: *AFC6S Diffractometer Control Software*; data reduction: *AFC6S Diffractometer Control Software*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *SHELXTL/PC* (Sheldrick, 2008); software used to prepare material for publication: *SHELXTL/PC* and *PARST* (Nardelli, 1983).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FA3170). Services for accessing these data are described at the back of the journal.

References

- Aguirre, J. M., Alesso, E. N. & Moltrasio, G. Y. (1999). *J. Chem. Soc. Perkin Trans. 1*, pp. 1353–1358.
- Aguirre, J. M., Alesso, E. N., Moltrasio, G. Y. & Mufato, J. D. (1998). *J. Chem. Res. Synop.* pp. 464–465.
- Alesso, E. N., Torviso, R., Finklielsztein, L., Lantaño, B., Moltrasio, G. Y., Aguirre, J. M., Vazquez, P. G., Pizzio, L. R., Caceres, C., Blanco, M. & Ythomas, H. J. (2002). *Synth. Commun.* **32**, 3803–3812.
- Alesso, E. N., Torviso, R., Lantaño, B., Finklielsztein, L., Erlich, M., Moltrasio, G. Y., Aguirre, J. M. & Brunet, E. (2003). *ARKIVOC*, pp. 283–297.
- Allen, F. H. (2002). *Acta Cryst.* **B58**, 380–388.
- Bates, R. B., Caldera, S., Desphande, V. H., Malik, B. L. & Paknikar, S. K. (1997). *J. Nat. Prod.* **60**, 1041–1047.
- Bürgi, H.-B. & Dunitz, J. D. (1994). Editors. *Structure Correlation*, Vol. 2, Part III, ch. 11. Weinheim: VCH.
- Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.
- Desiraju, G. R. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 2311–2327.
- Hanaya, K., Onodera, S., Ikegami, Y., Kudo, H. & Shimaya, K. (1981). *J. Chem. Soc. Perkin Trans. 2*, pp. 944–947.
- Molecular Structure Corporation (1993). *AFC6S Diffractometer Control Software*. Version 4.3.0. Molecular Structure Corporation, The Woodlands, Texas, USA.
- Mufato, J. D., Aguirre, J. M., Vega, D. R., Drago, E. V., Lantaño, B. & Alesso, E. N. (2007). XVI SINAQO Conference, Mar del Plata, Argentina.
- Nardelli, M. (1983). *Comput. Chem.* **7**, 95–97.
- Sheldrick, G. M. (2008). *Acta Cryst.* **A64**, 112–122.
- Vega, D. R., Mufato, J. D., Aguirre, J. M., Alesso, E. N. & Lantaño, B. (2006). *Acta Cryst.* **E62**, o1618–o1620.
- Wang, G., Zheng, G. & Zhao, Z. G. (2006). *Tetrahedron Asymmetry*, **17**, 2074–2081.