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rac-9-Ethyl-12a-hydroxytetradecahydrotriphenylene-1,5(2*H*,4b*H*)-dione: stabilization of a new isomer of a functionalized perhydrotriphenylene through a tandem Michael addition–aldol reaction

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The title compound, $C_{20}H_{30}O_3$, is a new functionalized perhydrotriphenylene derivative formed *via* a tandem Michael addition–aldol reaction. The structural study reveals that the system of fused rings approximates a C_2 point symmetry, with *trans–cis–cis* ring junctions, while highly symmetric all-*trans* perhydrotriphenylene, previously characterized, approximates a D_3 symmetry. The perhydrotriphenylene nucleus of the title compound corresponds to the third stable stereoisomer isolated for this polycyclic system. Considering that the C_s isomer was obtained recently through a similar tandem reaction, a general strategy is proposed which may help to obtain other stable stereoisomers of perhydrotriphenylene.

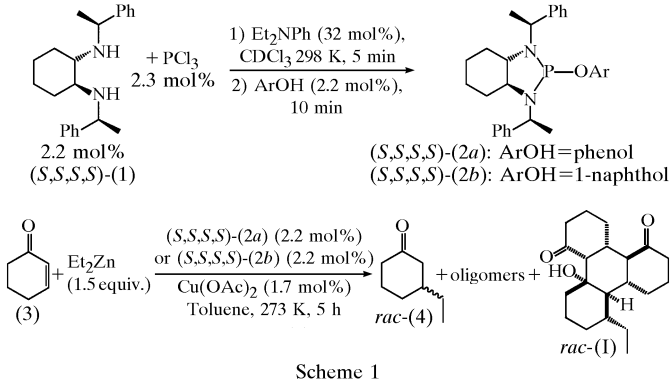
Comment

Perhydrotriphenylene ($C_{18}H_{30}$, abbreviated as PHTP hereinafter) has a complex stereochemistry. There are six enantiomeric pairs and four *meso* forms, as determined by Farina & Audisio (1970*a*). These authors were able to resolve into antipodes the highly symmetrical isomer belonging to the D_3 point group, in which all rings have a chair conformation and all fused-ring junctions have a *trans* configuration (Farina & Audisio, 1970*b*). Following Farina's nomenclature, the D_3 isomer may be described as *anti–trans–anti–trans–anti–trans*, shortened to *ATATAT*. The *trans* descriptors apply to *endo* C—C bonds of the central ring (bonds shared by two rings), while the *anti* descriptors are for C—C *exo* bonds.

Racemic D_3-PHTP has been characterized crystallographically (Harlow & Desiraju, 1990). This isomer generally forms inclusion compounds with small organic molecules (König *et al.*, 1997). In most cases, crystallographic studies of PHTP clathrates are severely complicated due to a tendency towards disorder, with diffraction patterns including incommensurate satellites (Weber *et al.*, 2001; Bürgi *et al.*, 2005). For these reasons, very few PHTP derivatives have been characterized in the solid state. On the other hand, to the best of our knowledge, the possibility of stabilizing other isomers of PHTP has not been addressed, neither through accurate *ab initio* calculations nor by crystallizing such isomers.

The matter may be probed, at least partially, through the synthesis of PHTP derivatives, provided that the starting materials do not include fused rings. With the exception of the abovementioned naked D_3-PHTP, only one guest-free PHTP derivative has been characterized crystallographically to date, namely 9-benzyl-12a-hydroxytetradecahydrotriphenylene-1,5(2*H*,4b*H*)-dione. This derivative was synthesized (Blake *et al.*, 2007) through an original triple cascade reaction involving two Michael additions followed by an intramolecular aldol reaction. The main difficulty for the study of this compound by X-ray diffraction was the very small size of the single crystals available (0.08 × 0.01 × 0.01 mm).

During our work on the copper-catalyzed conjugate addition of Et_2Zn to enones in the presence of chiral phosphoramidites (Feringa, 2000), we found that cyclohex-2-en-1-one, (3), behaves as expected, affording 3-ethylcyclohexanone, (4), but a by-product, the title compound, *rac*-(I), was also produced in a low 6% yield (see Scheme 1 and *Experimental*). Analytical data indicated that (I) is the 9-ethyl analogue of Blake and co-workers' functionalized PHTP. In fact, these authors also detected (I) in their oligomeric mixture, but were unable to isolate it as a pure crystalline solid. We surmise that the formation of *rac*-(I) under our conditions occurred by trapping the enolate of 3-ethylcyclohexanone with cyclohex-2-en-1-one, which afforded the enolate of *trans*-3-ethyl-2-(3-hydroxycyclohex-2-enyl)cyclohexanone. This step was followed by a Michael addition reaction with another equivalent of cyclohex-2-en-1-one, and finally the ring closure proceeded by an aldol reaction, leading to a functionalized-PHTP enolate. Protonation finally afforded the title alcohol, *rac*-(I).



Scheme 1

The molecular structure of compound (I) is illustrated in Fig. 1. The relative stereochemistry at the six chiral C atoms of the central *A* ring is 1a*RS*,4a*RS*,5a*SR*,8a*RS*,9a*RS*,12a*SR*. This configuration corresponds to ring junctions *trans–cis–cis* for *A*/*C*, *A*/*B* and *A*/*D*, respectively (Scheme 2 and Fig. 1). All the

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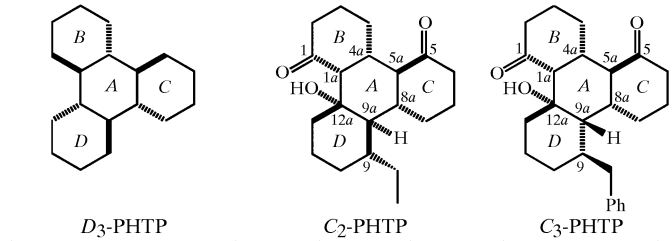
exo central C—C bonds are *anti*. All six-membered rings have chair conformations, with small deviations from ideal geometry, which can be attributed to polycyclic strain [puckering parameters (Cremer & Pople, 1975) θ = 177.67 (16), 5.31 (18), 176.33 (17) and 1.36 (17)° for rings *A*, *B*, *C* and *D*, respectively]. Assuming ideal chair conformations for rings *A*–*D*, the PHTP core structure of *rac*-(I) corresponds to the *rac-ATACAC* isomer in Farina's nomenclature, and belongs to point group C_2.



D_3-PHTP (Harlow & Desiraju, 1990) — C_2-PHTP (This work) — C_3-PHTP (Blake *et al.*, 2007)

Scheme 2

Interestingly, Blake *et al.* (2007) isolated a third isomer for the core PHTP structure, namely *meso-STACAT*, which includes a *syn* C8a—C9a *exo* bond and a *trans* C9a—C12a *A*/*D* ring junction (Scheme 2). The central *A* ring has a twist-boat conformation (θ = 89.9° and φ = 146.3°), as does ring *B* (θ = 85.9° and φ = 153.6°). The other peripheral rings have distorted chair conformations (ring *C*: θ = 167.5°; ring *D*: θ = 169.4°). The PHTP nucleus of this isomer approximates a C_s symmetry, assuming ideal boat and chair conformations. However, considering departures from ideal geometry, the actual symmetry is rather C_1 and the molecule is not a true *meso* form.

As discussed above, a reasonable assumption is that both C_2 and C_s isomers are produced following identical routes. The stabilization of different isomers should then be related to the nature of the functional group at C9 rather than to the reaction conditions. If the proposed tandem mechanism is correct, the differentiation takes place during the first Michael addition, forming the C8a—C9a bond. In the case of 3-benzylcyclohexanone enolate addition, a *syn–exo* C—C bond is formed. The benzyl group is then equatorial, avoiding 1,3-diaxial interactions. With the ethyl analogue, the opposite enolate enantiomer is more favourably added, leading to an axially oriented ethyl group. The second Michael addition, forming the C4a—C5a bond and the final ring closure, is identical regardless of the substituent at C9. In both cases, it seems that the aldol reaction, forming the C1a—C12a bond, is assisted by the formation of a weak intramolecular hydrogen bond involving the hydroxy and carbonyl functional groups at C12a and C1, respectively. Other noncovalent interactions seem to have very little influence on the observed structure. For (I), the crystal packing features centrosymmetric dimers formed through weak C=O···H hydrogen bonds (Table 1). NMR data [COSY (correlation spectroscopy) and HSQC (heteronuclear single quantum coherence)] are consistent with the configuration observed in the solid state. We thus consider that the stereochemistry of (I) is induced by the Zn catalyst formed *in situ*, and not by intermolecular interactions in the solid state.

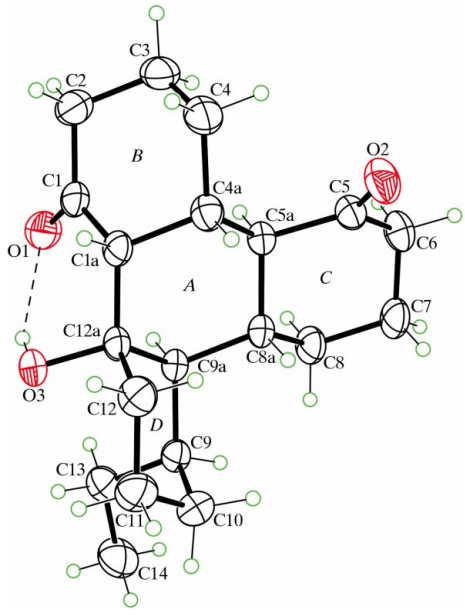


Figure 1
The molecular structure of compound (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 40% probability level and H atoms are shown as small spheres of arbitrary radii. The intramolecular hydrogen bond is indicated as a dashed line (see also Table 1).

In conclusion, we propose that the MiMiRC tandem reaction (Mi = Michael addition; RC = ring closure) may be extended to libraries of substituted enones, allowing new stereoisomers of PHTP derivatives to be stabilized. By using suitable easily removable functional groups, new pure or racemic PHTP stereoisomers would then be achievable.

Experimental

(1*S*,2*S*)-*trans*-*N*,*N*′-Bis[1-(*S*)-phenylethyl]-1,2-diaminocyclohexane, (*S*,*S*,*S*,*S*)-(1) (18 mg, 2.2 mol%) (Anaya de Parrodi *et al.*, 1998), diethylaniline (13 ml, 32 mol%), $CDCl_3$ (0.5 ml) and PCl_3 (4.6 *M* solution in CH_2Cl_2, 12 µl, 2.3 mol%) were placed with vigorous stirring in a NMR tube and the reaction was followed by ^{31}P NMR analysis. After 5 min, the chlorodiazaphospholidine was formed *in situ*. Immediately after, phenol or naphthol (2.2 mol%) were added to the reaction mixture with vigorous stirring, ^{31}P NMR spectra were recorded, showing that the chiral phosphoramidite ligands (*S*,*S*,*S*,*S*)-(2*a*) or (*S*,*S*,*S*,*S*)-(2*b*) were produced. Phosphoramidites (*S*,*S*,*S*,*S*)-(2*a*) and (*S*,*S*,*S*,*S*)-(2*b*) were added directly from the NMR tube, without purification, to a solution of $Cu(OAc)_2$ (7.7 mg, 1.7 mol%) in toluene (3 ml). The solution was stirred under N_2 at 298 K for 30 min and then cooled to 273 K. Et_2Zn (1.0 *M* solution in hexane, 3.8 ml, 3.8 mmol, 1.5 equivalents) and cyclohex-2-en-1-one, (3) (0.24 ml, 2.5 mmol, 1 equivalent), were added to the reaction mixture. After 5 h at 273 K, the reaction was quenched with aqueous NH_4Cl and the mixture was extracted with CH_2Cl_2 (2 × 20 ml). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on deactivated silica gel (Et_3N/SiO_2, 2.5% *v*/*v*) with hexane as eluent, affording *rac*-3-ethylcyclohexanone, (4) (47 mg, 15%), a mixture of non-

isolated oligomers, and *rac*-(I) as colourless crystals (48 mg, 6%), which were recrystallized from hexane–CH_2Cl_2 (10:1 *v*/*v*). Analytical data for *rac*-(I) are available in the archived CIF.

Crystal data

$C_{20}H_{30}O_3$
M_r = 318.44
Triclinic, $P\overline{1}$
a = 8.6898 (10) Å
b = 9.2312 (12) Å
c = 12.3633 (14) Å
α = 72.377 (11)°
β = 73.574 (10)°
γ = 67.681 (9)°
V = 858.41 (18) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.08 mm^{-1}
T = 298 (2) K
0.60 × 0.44 × 0.18 mm

Data collection

Bruker *P*4 diffractometer
6729 measured reflections
3878 independent reflections
2728 reflections with $I > 2\sigma(I)$
R_{int} = 0.018
3 standard reflections
every 97 reflections
intensity decay: 1%

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.042
$wR(F^2)$ = 0.118
S = 1.05
3878 reflections
213 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.21 e Å^{-3}
$\Delta\rho_{min}$ = −0.16 e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
O3—H3···O1	0.82 (2)	2.01 (2)	2.7081 (16)	143 (2)
C8a—H8aA···O2^{i}	0.98	2.52	3.4381 (18)	156

Symmetry code: (i) $-x+1, -y, -z+1$.

Hydroxyl atom H3 was located in a difference Fourier map and refined freely, with O—H = 0.82 (2) Å. The remaining H atoms were included in calculated positions and treated as riding atoms, with C—H = 0.96–0.98 Å and U_{iso}(H) = 1.2 or 1.5U_{eq}(C).

Data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXTL-Plus* (Sheldrick, 2008); program(s) used to refine structure: *SHELXTL-Plus*; molecular graphics: *SHELXTL-Plus*; software used to prepare material for publication: *SHELXTL-Plus*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SU3020). Services for accessing these data are described at the back of the journal.

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