Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Optically active diaryl tetrahydroisoquinoline derivatives

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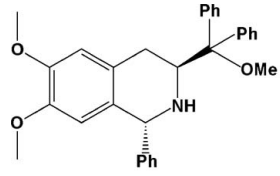
Received 23 October 2010
Accepted 20 December 2010
Online 8 February 2011

In (1*R*,3*S*)-6,7-dimethoxy-3-(methoxydiphenylmethyl)-1-phenyl-1,2,3,4-tetrahydroisoquinoline, $C_{31}H_{31}NO_3$, (I), and (1*R*,3*S*)-2-benzyl-3-[diphenyl(trimethylsiloxy)methyl]-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline, $C_{40}H_{43}NO_3Si$, (II), the absolute configurations have been confirmed to be *R* and *S* at the isoquinoline 1- and 3-positions, respectively, by NMR spectroscopy experiments. Both structures have monoclinic ($P2_1$) symmetry and the N-containing six-membered ring assumes a half-chair conformation. The asymmetric unit of (I) contains one molecule, while (II) has two molecules within the asymmetric unit. These structures are of interest with respect to the conformation around the exocyclic C—C bond: (I) displays an *ap* (antiperiplanar) conformation, while (II) displays an *sc-exo* (synclinal) conformation around this bond. These conformations are significant for stereocontrol when these compounds are used as catalysts. Various C—H$\cdots\pi$ and C—H$\cdots$O bonds link the molecules together in the crystal structure of (I). In the crystal structure of (II), three intermolecular C—H$\cdots\pi$ hydrogen bonds help to establish the packing.

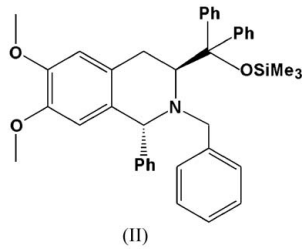
Comment

The tetrahydroisoquinoline (TIQ) molecule and its derivatives have been widely investigated due to their biological and pharmaceutical properties. Given our recent success with TIQ-based ligands for catalytic asymmetric transfer hydrogenation of prochiral ketones, Henry reactions and hydrogenation of olefins (Peters *et al.*, 2010). We decided to investigate the potential of TIQ derivatives as organocatalysts. Compound (I) has recently been synthesized and evaluated as a novel iminium-activated organocatalyst in an asymmetric Diels–Alder reaction (Naicker, Petzold *et al.*, 2010). Compound (II) is novel and is the precursor to the same class of organocatalysts based on a (1*R*,3*S*)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline backbone.

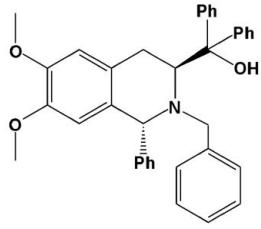
Derived from commercially available L-DOPA, the absolute stereochemistry of (I) and (II) was confirmed to be *R* and *S* at the C1 and C9 positions by ^{1}H NMR, as shown in Figs. 1 and 2, respectively.



(I)



(II)



(III)

Both structures have monoclinic ($P2_1$) symmetry. Compound (I) has a single molecule in the asymmetric unit, while (II) has two molecules within the asymmetric unit. Molecule (I) has a methyl group at the O3 position, whilst (II) has a trimethylsilyl group in this position. In addition, (II) has a benzyl group on the N atom.

In the structure of (I), intermolecular C—H$\cdots\pi$ and C—H$\cdots$O interactions involving atoms O1 and O2 link the molecules into extended chains which run parallel to the *b* axis (Table 1 and Fig. 3). In the chain, the molecules are arranged so that their tails, linked by the C—H$\cdots$O interactions, point towards the core of the chain and their heads protrude to the outer edges of the chain, with adjacent molecules alternating from side-to-side. The C—H$\cdots\pi$ interactions link the heads of those molecules lying on the same side of the chain core.

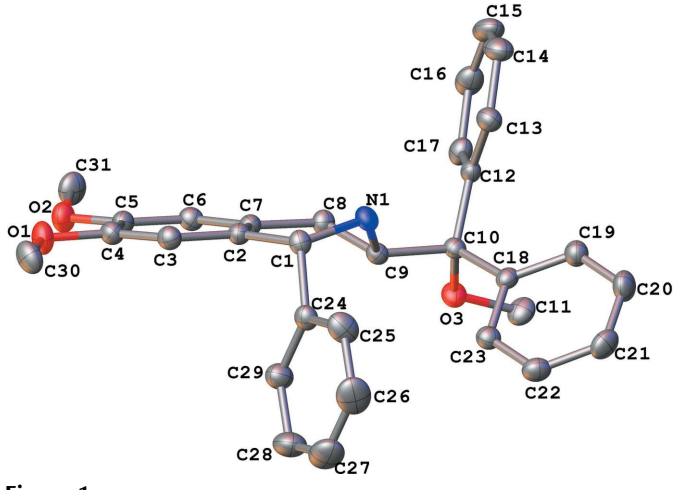


Figure 1
The molecular structure of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms have been omitted for clarity.

  doi:10.1107/S0108270110053357

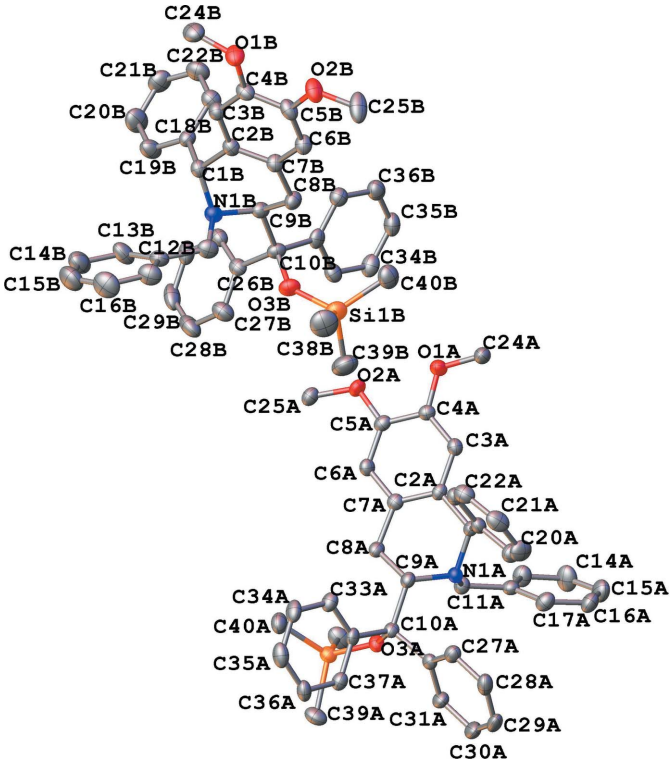


Figure 2
The molecular structure of (II), showing the atom-numbering scheme. There are two molecules in the asymmetric unit, labelled with suffixes *A* and *B*. Displacement ellipsoids are drawn at the 50% probability level. H atoms and some atom labels have been omitted for clarity.

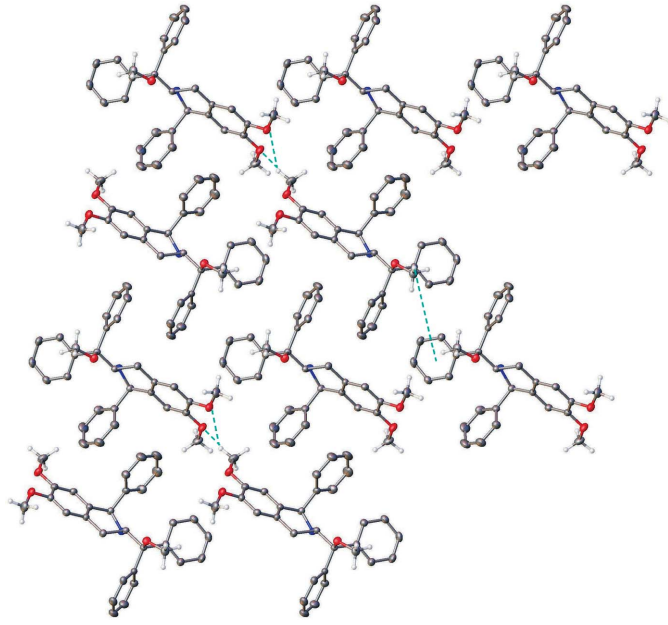


Figure 3
A partial projection of the structure of (I), viewed along [010]. Dashed lines indicate intermolecular interactions. H atoms not involved in intermolecular interactions have been omitted for clarity.

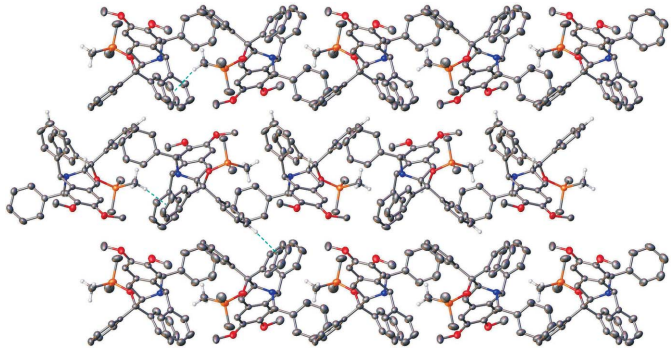


Figure 4
A partial projection of the structure of (II), viewed along [100]. The top and bottom layers contain only *B* molecules, while the central layer contains *A* molecules. Dashed lines indicate intermolecular interactions. H atoms not involved in intermolecular interactions have been omitted for clarity.

In the structure of (II), each independent molecule displays an intramolecular C—H$\cdots\pi$ interaction, while a single intermolecular C—H$\cdots\pi$ interaction involving C35*A*—H links just the two independent molecules (Table 2). An extended network of interactions is not present. The crystal packing of (II) reveals that the pseudosymmetry relates the two independent molecules within the asymmetric unit resulting in a layered packing along the *a* axis (Fig. 4).

From the crystal structures, it is evident that the N-containing six-membered rings assume half-chair conformations (Figs. 1 and 2). This result differs from two analogous compounds, namely (1*R*,3*S*)-methyl 2-benzyl-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate and (1*R*,3*S*)-methyl 6,7-dimethoxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate, which assume half-boat conformations (Naicker *et al.*, 2009; Naicker, Govender *et al.*, 2010*a*). The current study confirms our previous postulation that the change in conformation is a result of the introduction of the phenyl groups at the C1 position.

According to the Cambridge Structural Database (Version 5.31; Allen, 2002), the only other crystal structure of a tetrahydroisoquinoline derivative with diaryl substitution at the C10 position is compound (III) (see Scheme), which we reported recently (Naicker, Govender *et al.*, 2010*b*). In this crystal structure, the methanol O atom is a free OH group. Due to the lack of analogous structures, these diaryl tetrahydroisoquinoline alcohols were compared with proline diaryl alcohols (Seebach *et al.*, 2008). Compound (III) displays a similar conformation to its proline analogue, which displays a *gauche* or *sc-endo* (synclinal) conformation around the O3—C10—C9—N1 bond, with the OH group partially covering the piperidine ring with a torsion angle of −77.0 (2)°.

Compound (I) displays an *ap* (antiperiplanar) conformation around the exocyclic C9—C10 bond, with an O3—C10—C9—N1 torsion angle of 171.5 (1)°. This conformation has only been found in a few examples of *N*-amino prolinol methyl esters (Seebach *et al.*, 2008).

Proline diphenyl OTMS (OTMS is trimethylsiloxy) analogues exhibit an *sc-exo* conformation around the exocyclic ethane bond, with a torsion angle of 61.0°. Both molecules of (II) (Fig. 2) display an *sc-endo* conformation, with torsion angles of −81.1 (3) and −84.8 (2)°. A possible reason for this

change could be that the benzyl group on the N atom forces the phenyl rings at the C10 atom to be the furthest away from it, hence adopting the *sc-endo* conformation.

Proline diaryl alcohols have been used as successful chiral catalysts by exploiting the same rotation along the C9—C10 bond (Diner *et al.*, 2008). This change, which is brought about by different groups on the methanol O atom, makes the current study particularly useful. This feature is found in (I) which, when tested for its catalytic activity in the Diels–Alder reaction, showed poor yields. The structural data demonstrated how we could improve the catalytic reactivity by reducing the steric bulk of the ligand. A successful catalyst was obtained by removing the phenyl moieties from (I) (Naicker, Petzold *et al.*, 2010).

Experimental

To (1*R*,3*S*)-2-benzyl-3-(1,1-diphenylethyl)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (0.4 g, 0.72 mmol), derived from L-DOPA (Naicker, Petzold *et al.*, 2010), in MeOH–THF (1:1 *v*/*v*, 20 ml) was added half an equivalent by mass of 10% palladium on carbon Pd/C under hydrogen (approximately 1 atm). The reaction was stirred for 2 h. The crude product was obtained by filtering the Pd/C through a plug of Celite and the filtrate was then concentrated to dryness. The resulting residue was purified by column chromatography (50:50 EtOAc–hexane, R_F = 0.6) to yield (I) as a white solid [yield 0.2 g, 60%; m.p. 463–465 K; $[\alpha]_D^{20}$ −10.0 (*c* 0.11 in $CHCl_3$)]. Recrystallization from ethyl acetate afforded colourless crystals suitable for X-ray analysis. IR (neat, ν_{max}, cm^{-1}): 2934, 1514, 1448, 1244, 1224, 1063, 698; ^{1}H NMR (400 MHz, $CDCl_3$, δ, p.p.m.): 7.47–7.12 (*m*, 12H), 7.08 (*t*, *J* = 7.6 Hz, 2H), 6.92 (*d*, *J* = 7.6 Hz, 2H), 6.65 (*s*, 1H), 6.40 (*s*, 1H), 5.23 (*s*, 1H), 3.95 (*dd*, *J* = 11.5 and 3.6 Hz, 1H), 3.86 (*s*, 3H), 3.70 (*s*, 3H), 2.92–2.75 (*m*, 4H), 2.52 (*dd*, *J* = 16.2 and 11.5 Hz, 3H).

To a stirred solution of [(1*R*,3*S*)-3-(hydroxydiphenylmethyl)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinolin-2-yl](phenyl)-methanone (0.6 g, 1.1 mmol), derived from L-DOPA (Naicker, Petzold *et al.*, 2010), in dry dichloromethane (20 ml) and triethylamine (0.18 ml, 1.3 mmol), trimethylsilyl trifluoromethanesulfonate (0.24 ml, 1.33 mmol) was added dropwise at 273 K under an inert atmosphere. The mixture was allowed to warm to room temperature and was stirred overnight. The mixture was washed with water, the organic extracts were combined and dried over anhydrous Na_2SO_4, and the solvent was removed *in vacuo*. The resulting residue was purified by column chromatography (20:80 EtOAc–hexane, R_F = 0.55) to afford (II) as a white solid [yield 0.5 g, 75%; m.p. 458–460 K; $[\alpha]_D^{20}$ 57.58 (*c* 0.33 in $CHCl_3$)]. Recrystallization from acetone afforded colourless crystals suitable for X-ray analysis. IR (neat, ν_{max}, cm^{-1}): 2956, 1513, 1245, 839, 696; ^{1}H NMR (400 MHz, $CDCl_3$, δ, p.p.m.): 7.17 (*m*, 14H), 6.84 (*m*, 5H), 6.63 (*m*, 2H), 6.36 (*s*, 1H), 4.57 (*s*, 1H), 4.38 (*d*, *J* = 13.63 Hz, 1H), 4.24 (*dd*, *J* = 3.38 and 12.13 Hz, 1H), 4.00 (*s*, 3H), 3.73 (*s*, 3H), 3.39 (*dd*, *J* = 4.32 and 12.58 Hz, 1H), 3.31 (*d*, *J* = 13.85 Hz, 1H), 2.29 (*dd*, *J* = 3.38 and 16.88 Hz, 1H), 0.0 (*s*, 9H).

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

Cg is the centroid of the C18–C23 ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C11—H11*A*···*Cg*^{i}	0.98	2.57	3.45 (2)	150
C30—H30*A*···O1^{ii}	0.98	2.54	3.356 (2)	140
C30—H30*A*···O2^{ii}	0.98	2.59	3.400 (2)	140

Symmetry codes: (i) $x, y+1, z$; (ii) $-x, y-\frac{1}{2}, -z+1$.

Compound (I)

Crystal data

$C_{31}H_{31}NO_3$
M_r = 465.57
Monoclinic, $P2_1$
a = 11.4071 (14) Å
b = 6.4750 (8) Å
c = 16.961 (2) Å
β = 101.707 (2)°
V = 1226.7 (3) Å^3
Z = 2
Mo *K*α radiation
μ = 0.08 mm^{-1}
T = 173 K
0.22 × 0.14 × 0.09 mm

Data collection

Bruker APEXII DUO diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2008)
T_{min} = 0.645, T_{max} = 0.746
11498 measured reflections
3737 independent reflections
3191 reflections with $I > 2\sigma(I)$
R_{int} = 0.051

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.043
$wR(F^2)$ = 0.108
S = 1.05
3737 reflections
320 parameters
2 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.23 e Å^{-3}
$\Delta\rho_{min}$ = −0.23 e Å^{-3}

Compound (II)

Crystal data

$C_{40}H_{43}NO_3Si$
M_r = 613.84
Monoclinic, $P2_1$
a = 11.045 (10) Å
b = 17.008 (15) Å
c = 18.489 (15) Å
β = 105.287 (15)°
V = 3350 (5) Å^3
Z = 4
Mo *K*α radiation
μ = 0.11 mm^{-1}
T = 100 K
0.22 × 0.12 × 0.10 mm

Data collection

Bruker APEXII DUO diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2008)
T_{min} = 0.976, T_{max} = 0.989
37993 measured reflections
17263 independent reflections
11255 reflections with $I > 2\sigma(I)$
R_{int} = 0.064

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.057
$wR(F^2)$ = 0.124
S = 0.99
17263 reflections
812 parameters
1 restraint
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.38 e Å^{-3}
$\Delta\rho_{min}$ = −0.41 e Å^{-3}
Absolute structure: Flack (1983)
Flack parameter: 0.00 (10), 8119 Friedel pairs

Atom H1N on N1 of (I) was located in a difference electron-density map and refined isotropically with a simple bond-length restraint of N1—H1N = 0.96 (1) Å. All remaining H atoms were positioned geometrically, with C—H = 0.95 (aromatic), 0.98 (methyl), 0.99 (methylene) or 1.00 Å (methine), and refined as riding on their

Table 2
Hydrogen-bond geometry (Å, °) for (II).

*Cg*1, *Cg*2, *Cg*3 and the centroids of the C26*B*–C31*B*, C32*A*–C37*A* and C32*B*–C37*B* rings, respectively.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C35*A*—H35*A*···*Cg*1^{i}	0.95	2.80	3.669 (3)	152
C40*A*—H40*A*···*Cg*2	0.98	2.71	3.540 (3)	143
C40*B*—H40*D*···*Cg*3	0.98	2.64	3.449 (4)	140

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

parent atoms, with U_{iso}(H) = 1.5U_{eq}(C) for methyl groups or 1.2U_{eq}(C) otherwise. For (I), the Flack *x* parameter (Flack, 1983) based on refinement with 3080 Friedel pairs was −0.5 (10), which indicated that no conclusions can be drawn regarding the absolute structure. Consequently, the Friedel pairs were merged before the final refinement. For (II), the Flack parameter refined to 0.00 (10) using 8119 Friedel pairs, which indicated that the refined model represents the true absolute configuration and is in accordance with expectation from the known chirality of the starting material in the synthesis.

For both compounds, data collection: *APEX2* (Bruker, 2006); cell refinement: *SAINT* (Bruker, 2006); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *OLEX2* (Dolomanov *et al.*, 2009); software used to prepare material for publication: *SHELXL97*.

The authors thank Dr Hong Su of the Chemistry Department of the University of Cape Town for her assistance with the crystallographic data collection.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SF3143). Services for accessing these data are described at the back of the journal.

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