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# (4*S*,1′*R*)-Diethyl 6-methyl-2-[(1′-phenylethylimino)methyl]-4-(2-thienyl)-1,4-dihydropyridine-3,5-dicarboxylate

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**Key indicators**

Single-crystal X-ray study
*T* = 183 K
Mean σ(C–C) = 0.002 Å
*R* factor = 0.038
*wR* factor = 0.096
Data-to-parameter ratio = 29.0

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.



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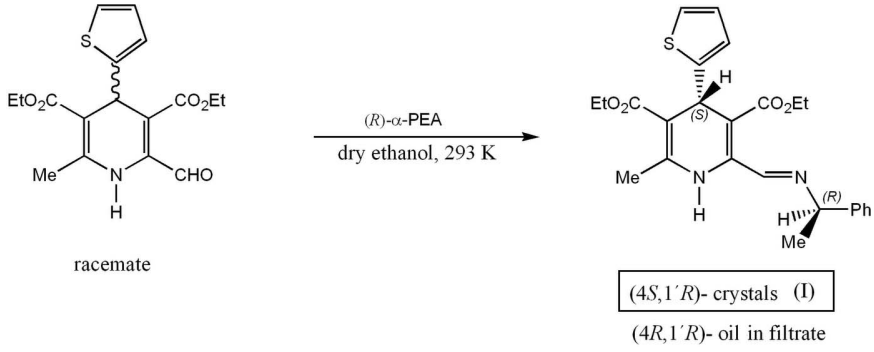
The absolute configuration of the title compound, $C_{25}H_{28}N_2O_4S$, has been determined. The molecules are interconnected by weak C—H···O hydrogen bonds. The 1,4-dihydropyridine (1,4-DHP) ring adopts the usual shallow boat conformation. The thiophene ring is nearly planar.

## Comment

Substituted 4-aryl-1,4-DHPs (1,4-DHP is 1,4-dihydropyridine) are biologically active, showing a wide range of effects, and have found applications in pharmacology as they affect cardiovascular diseases (hypertension, angina pectoris and cardiac arrhythmias), serve as calcium channel blockers (Goldmann & Stoltefuss, 1991), and show neurotropic, antidiabetic, antiviral, antibacterial and anticancer effects (Klusa, 1995; Gorlitzer *et al.*, 2000; Sobolev *et al.*, 2004).




It has been recognized that the absolute configuration at the C4 position of the 1,4-DHP nucleus is crucial in modulating the biological activity (Triggle *et al.*, 1980; Fossheim *et al.*, 1982). Indeed, pairs of enantiomers that differ in their substituents at the C3 and C5 positions of 1,4-DHP usually differ in their biological properties; sometimes they can act in opposite directions, *e.g.* as calcium antagonist–calcium agonist (Kongsamut *et al.*, 1985). The different biological activities of 1,4-DHP enantiomers and diastereomers can cause problems in drug development (Strong, 1999).

Three general methods have been reported for the preparation of enantiomeric 4-aryl-1,4-DHPs: (i) the optical resolution of 1,4-DHP-monocarboxylic acids (Goldmann & Stoltefuss, 1991); (ii) chemoenzymatic hydrolysis of the alkyl ester groups at the C3 and C5 positions of substituted 1,4-DHPs (Sobolev *et al.*, 2004); (iii) the enantioselective Hantzsch-type synthesis using a chiral auxiliary on the 1,4-DHP N atom or the ester group (Kosugi *et al.*, 1994; Peri *et al.*, 2000). In our case, the third method was applied (Marchalín *et al.*, 2004) for the preparation of the title compound, (I).

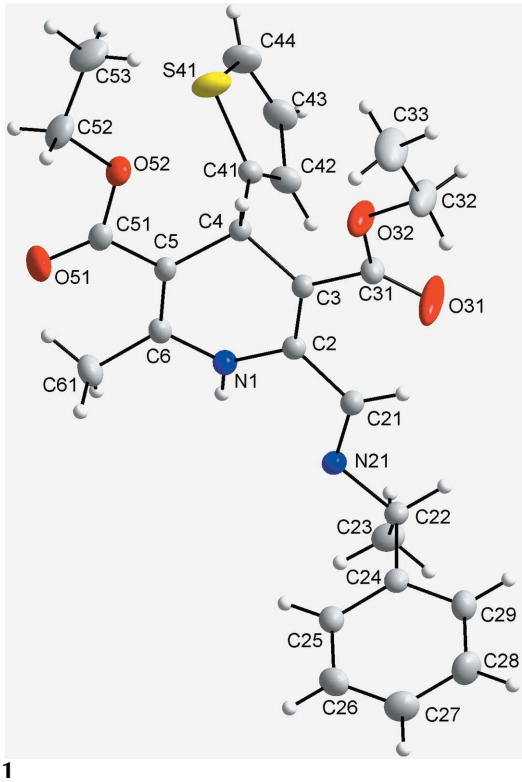



**Figure 1**
The molecular structure of (I), showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

The expected stereochemistry of atoms C4 and C22 was confirmed as *S* and *R*, respectively (Fig. 1). There are intra- and intermolecular C—H···O hydrogen bonds in the crystal structure (Table 2). The 1,4-DHP ring adopts a shallow boat conformation, with atoms C4 and N1 deviating by 0.413 (1) and 0.181 (1) Å, respectively, from the planar base of the boat [the deviations from the mean plane are 0.0005 (17), 0.0005 (17), 0.0004 (16) and 0.0004 (17) Å for C2, C6, C3 and C5, respectively].

The puckering of the 1,4-DHP ring at C4 and N1 affects the biological activity of this class of compounds to a great extent (Triggle *et al.*, 1980; Fossheim *et al.*, 1982); see pertinent torsion angles involving atoms C4 and N1 (Table 1). The planar thiophene ring [maximum deviation from the mean plane is 0.005 (1) Å for atom C42] is approximately perpendicular to the 1,4-DHP ring. The dihedral angle between the plane of the five-membered ring and the plane of the base of the boat (C2/C3/C5/C6) is 86.98 (5)° (Nardelli, 1995). The C2—C3—C31—O31 and C6—C5—C51—O51 torsion angles are 13.4 (2) and 8.5 (2)°, respectively, reflecting the synperiplanar (*sp*, *sp*) conformations of the carbonyl C=O bonds.

## Experimental

The title compound was prepared by the reaction of the racemic aldehyde and chiral (*R*)-α-phenylethylamine [(*R*)-α-PEA] in dry ethanol. The title compound precipitated as crystals while the diastereomer diethyl (4*R*,1′*R*)-6-methyl-2-[(1′-phenylethylimino)-methyl]-4-(2-thienyl)-1,4-dihydropyridine-3,5-dicarboxylate remained in the filtrate. Full details of the synthetic procedure have been published by Marchalín *et al.* (2004). Yellow prism-like single crystals were prepared by recrystallization from an ethanol solution (1:1).

### *Crystal data*

$C_{25}H_{28}N_2O_4S$
$M_r$ = 452.55
Monoclinic, $P2_1$
$a$ = 10.3023 (2) Å
$b$ = 8.1925 (1) Å
$c$ = 14.3279 (2) Å
$\beta$ = 90.420 (1)°
$V$ = 1209.27 (3) Å$^3$
$Z$ = 2
$D_x$ = 1.243 Mg m$^{-3}$
Mo $K\alpha$ radiation
$\mu$ = 0.17 mm$^{-1}$
$T$ = 183 (2) K
Prism, yellow
0.60 × 0.28 × 0.10 mm

### *Data collection*

Siemens SMART CCD diffractometer
ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2002)
$T_{min}$ = 0.902, $T_{max}$ = 0.984
21384 measured reflections
8488 independent reflections
7741 reflections with $F^2 > 2\sigma(F^2)$
$R_{int}$ = 0.025
$\theta_{max}$ = 32.9°

### *Refinement*

Refinement on $F^2$
$R[F^2 > 2\sigma(F^2)]$ = 0.038
$wR(F^2)$ = 0.096
$S$ = 1.05
8488 reflections
293 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0718P)^2 + 0.1736P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.29 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.25 e Å$^{-3}$
Absolute structure: Flack (1983), 3679 Friedel pairs
Flack parameter: −0.02 (5)

**Table 1**
Selected geometric parameters (Å, °).

| | | | |
|---|---|---|---|
| N1—C6 | 1.3830 (14) | C21—N21 | 1.2730 (15) |
| N1—C2 | 1.3853 (14) | C41—S41 | 1.7220 (12) |
| C2—C3 | 1.3599 (15) | S41—C44 | 1.7098 (15) |
| | | | |
| C6—N1—C2 | 122.35 (9) | C41—C4—C5 | 110.95 (9) |
| C3—C2—C21 | 126.19 (10) | C21—N21—C22 | 115.87 (10) |
| C2—C3—C31 | 122.86 (10) | C24—C22—C23 | 111.18 (10) |
| C3—C4—C41 | 109.57 (9) | C44—S41—C41 | 92.51 (7) |
| | | | |
| C6—N1—C2—C3 | −18.34 (16) | C2—N1—C6—C5 | 17.82 (16) |
| N1—C2—C3—C4 | −9.11 (16) | N1—C2—C21—N21 | −8.78 (16) |
| C2—C3—C4—C41 | −89.68 (12) | N21—C22—C24—C25 | 45.16 (15) |
| C2—C3—C4—C5 | 32.53 (14) | C41—S41—C44—C43 | 0.23 (13) |
| C3—C4—C5—C6 | −33.13 (14) | C5—C51—O52—C52 | 179.05 (11) |

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

| *D*—H···*A* | *D*—H | H···*A* | *D*···*A* | *D*—H···*A* |
|---|---|---|---|---|
| C52—H52*B*···O31$^{i}$ | 0.99 | 2.61 | 3.043 (2) | 107 |
| C22—H22···O51$^{ii}$ | 1.00 | 2.41 | 3.403 (2) | 171 |
| C21—H21···O31 | 0.95 | 2.31 | 2.898 (2) | 120 |
| C4—H4···O32 | 1.00 | 2.26 | 2.699 (1) | 105 |
| C4—H4···O52 | 1.00 | 2.31 | 2.671 (1) | 100 |
| C61—H61*C*···O51 | 0.98 | 2.35 | 2.903 (2) | 115 |

Symmetry codes: (i) $x-1, y, z$; (ii) $x+1, y, z$.

The majority of the H atoms were visible in a difference Fourier map, including the methyl H atoms. H atoms were placed in idealized positions (N—H = 0.88 Å, methyl C—H = 0.98 Å, methylene C—H =

0.99 Å, methine C—H = 1.00 Å and aromatic C—H = 0.95 Å)and refined as riding, with $U_{iso}(H) = 1.2U_{eq}$(parent atom).

Data collection: *SMART* (Siemens, 1995); cell refinement: *SAINT* (Siemens, 1995); data reduction: *SAINT*; program(s) used to solve structure: *SHELXTL* (Bruker, 2001); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *DIAMOND* (Brandenburg, 2002); software used to prepare material for publication: *SHELXL97*.

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