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(2*S*,3*R*,4*S*,5*R*)-Diethyl 2-(10,10-dimethyl-3,3-dioxo-3λ^6-thia-4-azatricyclo[5.2.1.0^{1,5}]decan-4-ylcarbonyl)-5-phenylpyrrolidine-3,4-dicarboxylate: a novel isomorphous-by-addition compound

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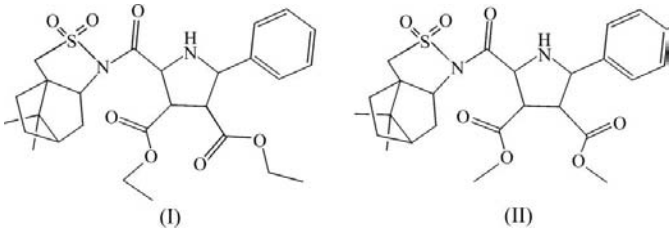
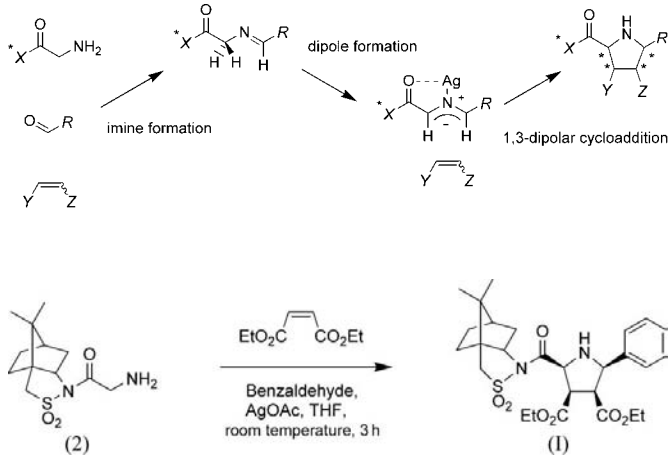
The title compound, $C_{27}H_{36}N_2O_7S$, (I), is isomorphous by addition with the dimethyl ester analogue [Garner, Dogan, Youngs, Kennedy, Protasiewicz & Zaniewski (2001). *Tetrahedron*, **57**, 71–85], (II), by replacing two methyl ester H atoms with two methyl groups. With the exception of the conformation of one of the ester groups, the molecules are almost superimposable. Likewise, apart from a slightly larger *c* axis in (I), few differences in the cell packing of (I) and (II) are found, with both dominated by the same C—H···O hydrogen bonds. Full synthetic and spectroscopic details of (I) are given. The molecular synthesis is important as an example of chiral auxiliary-assisted 1,3-dipolar cycloaddition of an azomethine ylid.

Comment

Pyrrolidine substructures are found in many biologically active compounds, leading to a point where there is a clear need for an arsenal of 'decorated' scaffolds that will enable modern combinatorial access to refined libraries of compounds for (bio)assay and drug development (Schreiber, 2000). The title compound, (I), was prepared as part of a broader research programme designed to explore preparative routes to chiral pyrrolidine scaffolds and to address specifically the potential of chiral auxiliary-assisted 1,3-dipolar cycloaddition of azomethine ylids to various dipolarophiles (see first reaction scheme).



Our work sought to capitalize upon the findings of Garner and co-workers (Garner & Kaniskan, 2005; Garner *et al.*, 2001, 2006) and others (Padwa *et al.*, 1985), who demonstrated that a diastereofacial bias was indeed possible utilizing a chiral auxiliary on an ylid dipole. The synthetic route to (I) employed the glycyl sultam chiral auxiliary, (2), which was prepared from enantiomerically pure (+)-camphor 10-sulfonic acid (Davis *et al.*, 1988; Oppolzer *et al.*, 1989; Hoppe & Beckmann, 1979). The 1,3-dipolar cycloaddition was carried out with diethyl maleate and benzaldehyde in the presence of silver acetate (see second reaction scheme) to yield the title compound, (I). This structural study was undertaken to confirm the relative conformation of the 3,4-ester groups, given that the absolute configuration was established by the stereochemistry of the starting (+)-camphor enantiomer. In this case, the absolute configuration was successfully confirmed by the observed X-ray anomalous dispersion effects [4033 Bijvoet pairs, Flack *x* parameter = 0.00 (7) (Flack, 1983); Hooft *y* parameter = 0.00 (4) (Hooft *et al.*, 2008)].



The asymmetric unit of (I) is shown in Fig. 1, with selected dimensions compared with the dimethyl ester analogue, (II) [Garner *et al.*, 2001; Cambridge Structural Database (Version 5.29, with November 2007 updates; Allen, 2002) refcode MIPPOQ], in Table 2. The cell dimensions, molecular packing and alignment of (I) are closely related to those of the dimethyl analogue (Figs. 2 and 3). As the opposite enantiomer was reported for (II), all comparisons here involve using the inverted molecule [conversion (x, $1-y$, z)] for (II); atom labelling here does not match the arbitrary labelling found in the archived CIF of (II) (there were no labels given in the original paper). The two structures are isomorphous through replacement of one H atom of each of the ester methyl groups with a methyl group (Fig. 2). To the best of our knowledge, this is a novel case; more usual isomorphous organic crystals involve larger group 'interchanges', such as Cl for CH_3 in 2,2′-derivatives of 5′,5′-dipropoxybenzidines (El-Shafei *et al.*, 2004)

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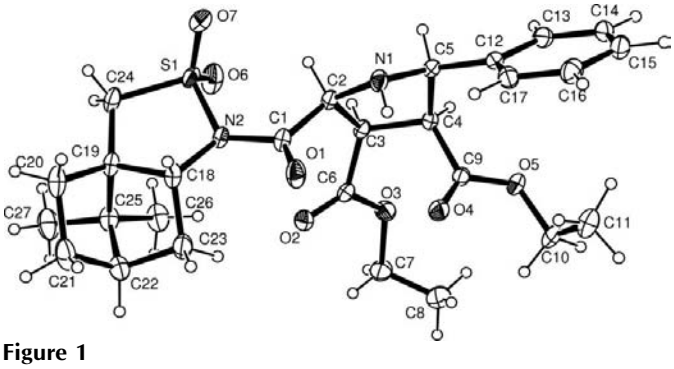

Figure 1
The molecular structure of the asymmetric unit of (I). Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

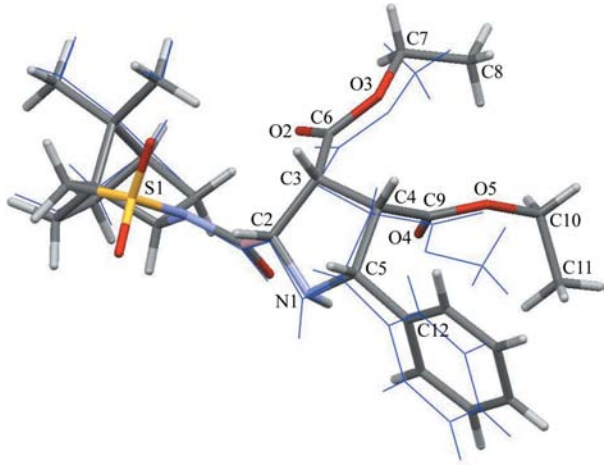

Figure 2
Overlapped view of (I) (thick bonds, shaded) and the inverted enantiomer of (II) (thin bonds). Selected labels are given. Note the conformational difference along the C4—C9—O5—C10—C11 ester chain.

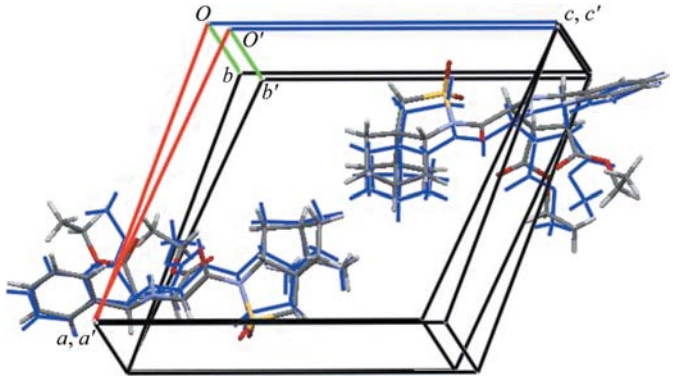

Figure 3
Cell packing diagram of (I) and the inverted cell of (II), using the same bond styles as in Fig. 2. The axes of (I) and (II) are unprimed and primed, respectively. The view with overlap of the *ac* diagonal and the *b* axis illustrates that the cell expansion is mainly along the *c* axis in (I).

or, more commonly, of related transition metals such as Co^{II}/Ni^{II} (*e.g.* Li *et al.*, 2007). It is possible that our literature survey has not picked up previous cases of this phenomenon, though we note there have been many studies of polymorphs of the same compound (*e.g.* Kálmán *et al.*, 2004).

The definition of isomorphicity is well tested by these two structures. It is obvious that (I) and (II) have different conformations with respect to rotation about the C4—C9 bond, as shown by the dihedral angles (Table 2) and in Fig. 2. Minor 'displacement' differences involving the phenyl ring (C12–C17) and the location of the N1 H atom are noted, although in the latter case the position in (II) was a calculated one rather than its refined position in (I). Indeed, the position of the N1 H atom (H1) in (I) seems to fulfil the distance criteria, but not the expected N—H···O interaction angle criteria based on normal intermolecular interactions [at 110 (2)°; see Desiraju & Steiner, 1999]. Atom H1 is also under the influence of atom O4, with an intramolecular H1···O4 distance of 2.60 (4) Å. The five- and six-membered rings in (I) and (II), as expected from the close overlap (Fig. 2), are almost identical, *e.g.* the N1/C2–C5 ring in (I) is in an envelope conformation, with Cremer & Pople (1975) parameters Q_2 = 0.391 (2) Å and φ_2 = 150.3 (3)°, whilst the inverted molecule of (II) has a slight twist on C5—N1, with Q_2 = 0.397 (4) Å and φ_2 = 160.8 (6)°. The S1/N2/C18/C19/C24 rings are similar, each being in a twisted C18—C19 bond conformation.

Examination of Fig. 3 shows how the *a* and *b* cell axes of (I) and (II) are similar, with a relatively minor alteration in the direction and size of the *c* axis, consistent with the molecular orientation and addition of the extra methyl group. The molecules are in the same relative orientation in the unit cells and details of the three-dimensional cell packing illustrate only minor differences between the two cells. The interactions are mainly of the C—H···O type (the acceptor O atom being either a carboxyl O atom or an O atom bound to S), with one C—H···π interaction (Table 1). We note the differences first. The orientation of the O5—C10 bond in (II) allows a C10—H···O2 interaction which is missing in (I). Likewise, the orientation and presence of methyl C8 only in (I) sets up an interaction with O2 (entry 2, Table 1). The phenyl C16—H16···O5 interaction in (I) (entry 3, Table 1) is found in (II), but changed, with the acceptor atom being O4 (since the ester conformation is rotated; see Fig. 2). One final difference involves a close intramolecular interaction in (I) (entry 9, Table 2) which is missing from (II). The remaining five inter- and intramolecular interactions (Table 1) are duplicated in both structures, under the same symmetry designations, with an average difference in H···acceptor distance of 0.10 (7) Å. Similar methylene C—H···O=S distances have been observed before (*e.g.* H···O = 2.330 Å; James *et al.*, 2005).

In summary, the relationship between the title compound, (I), and the antipode of the previously reported compound, (II), can be described as being a novel case of 'isomorphous by addition', given the subtle though distinct differences in the molecules and packing.

Experimental

Benzaldehyde (69.0 µl, 0.68 mmol) was dissolved in tetrahydrofuran (1 ml) and added to a solution of the glycyl sultam (2) (Davis *et al.*, 1988; Oppolzer *et al.*, 1989; Hoppe & Beckmann, 1979) (185 mg,

0.68 mmol) in tetrahydrofuran (1 ml) (see second reaction scheme in *Comment*). Diethyl maleate (329 µl, 2.04 mmol) was added to the reaction solution, followed by silver acetate (5.70 mg, 34.0 µmol). After being stirred under argon in the dark for 3 h, the reaction mixture was diluted with dichloromethane (100 ml) and washed with saturated ammonium chloride solution (50 ml). The organic layer was dried over magnesium sulfate and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (silica gel, ethyl acetate–petroleum spirit 3:7 *v*/*v*, then 4:6 and 1:1 *v*/*v*) to give (I) (182 mg, 50%) as a pale-yellow solid. Analysis: R_F = 0.18 (ethyl acetate–petroleum spirit 3:7 *v*/*v*); $[\alpha]^{22} = -39.9$ (*c* = 1.5, $CHCl_3$); HRMS (ES^+): calculated for $C_{27}H_{36}N_2{}^{23}NaO_7S$ (MNa^+): 555.2141; found: 555.2127; microanalysis requires: C 60.88, H 6.81, N 5.26%; found: C 60.57, H 6.99, N 5.17%. For details of ^1H and ^{13}C NMR data, see the archived CIF. The crystallization solvent was ethanol.

Crystal data

$C_{27}H_{36}N_2O_7S$
M_r = 532.64
Monoclinic, $P2_1$
a = 13.7194 (9) Å
b = 6.9464 (4) Å
c = 14.9703 (9) Å
β = 107.148 (2)°
V = 1363.25 (14) Å^3
Z = 2
Mo *Kα* radiation
μ = 0.17 mm^{-1}
T = 122 (2) K
0.45 × 0.24 × 0.06 mm

Data collection

Bruker–Nonius APEXII CCD area-detector diffractometer
Absorption correction: multi-scan (Blessing, 1995)
T_{min} = 0.665, T_{max} = 1.000
(expected range = 0.658–0.990)
28357 measured reflections
9045 independent reflections
6778 reflections with $I > 2\sigma(I)$
R_{int} = 0.058

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.056
$wR(F^2)$ = 0.152
S = 1.03
8865 reflections
342 parameters
1 restraint
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.44 e Å^{-3}
$\Delta\rho_{min}$ = −0.23 e Å^{-3}
Absolute structure: Flack (1983), with 4033 Friedel pairs
Flack parameter: 0.00 (7)

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

*Cg*1 represents the centroid of the C12–C17 phenyl ring.

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C7—H7*B*···O1^{i}	0.99	2.46	3.230 (3)	134
C8—H8*B*···O2^{ii}	0.98	2.49	3.420 (4)	158
C16—H16···O5^{iii}	0.95	2.59	3.474 (3)	155
C24—H24*A*···O6^{iv}	0.99	2.40	3.366 (3)	166
C24—H24*B*···O7^{v}	0.99	2.37	3.313 (4)	159
C5—H5···*Cg*1^{vi}	1.0	2.74	3.679 (2)	157
N1—H1···O1	0.83 (4)	2.32 (4)	2.723 (3)	110 (2)
C7—H7*A*···O2	0.99	2.33	2.729 (3)	103
C26—H26*B*···O2	0.98	2.39	3.339 (3)	164

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

A total of 11 reflections within $2\theta = 50°$ were omitted either as outliers or because they were partially screened by the backstop. The H atom on N1 was located and refined with an isotropic displacement parameter. All C-bound H atoms were constrained to their expected geometries, with C—H = 0.98, 0.99 or 1.00 Å. Methyl H atoms were refined with $U_{iso}(H) = 1.5U_{eq}(C)$; all other H atoms were refined with $U_{iso}(H) = 1.2U_{eq}(C)$.

Data collection: *SMART* (Bruker, 2006); cell refinement: *SAINT* (Bruker, 2006); data reduction: *SAINT* and *SADABS* (Bruker, 2006); program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEP-3* (Farrugia, 1997) and *Mercury* (Macrae *et al.*, 2006); software used to prepare material for publication: *SHELXL97*, *PLATON* (Spek, 2003) and *Mercury*.

Table 2
Comparison of selected bond lengths and angles (Å, °) in (I) and (II).

	(I)	(II)
S1—O6	1.426 (2)	1.423 (4)
S1—N2	1.6733 (18)	1.687 (3)
O3—C6	1.335 (3)	1.341 (5)
O3—C7	1.463 (3)	1.441 (5)
N1—C2	1.473 (3)	1.454 (5)
O6—S1—O7	116.45 (15)	116.4 (2)
C1—N2—S1	124.26 (16)	122.8 (3)
N2—C1—C2—N1	148.7 (2)	148.2 (3)
O1—C1—C2—C3	90.5 (3)	89.2 (5)
S1—N2—C1—O1	153.6 (2)	151.1 (4)
C2—C3—C6—O3	−166.8 (2)	−165.2 (3)
C3—C6—O3—C7	175.5 (2)	−179.4 (3)
C6—O3—C7—C8	−129.8 (3)	
C2—C3—C6—O2	15.8 (3)	17.1 (6)
C5—C4—C9—O5	−104.7 (2)	69.8 (4)
C10—O5—C9—C4	177.9 (2)	−177.7 (4)
C5—C4—C9—O4	73.7 (3)	−107.4 (5)

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3280). Services for accessing these data are described at the back of the journal.

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