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Assessment of the absolute configuration of a series of (3*R*)-3-hydroxy-3-alkyl-β-lactams

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Abstract

The absolute stereochemistry of a series of (3*R*)-3-hydroxy-3-alkyl-β-lactams has been determined by circular dichroism and NMR spectroscopies. The sign of the circular dichroism band between 250 and 220 nm was related to the stereochemistry by applying the β-lactam sector rule. The NMR analysis unambiguously determines the relative configuration at C3 and C4 of the β-lactam ring. The reliability of the method has been proved by X-ray analysis of two of the examined compounds. The obtained results are in agreement with the mechanism proposed for the employed synthetic route.

1. Introduction

β-Lactams with defined stereochemistry represent important synthetic targets as a number of biologically active compounds contain this heterocyclic moiety. In particular, β-lactam antibiotics have attracted the interest of synthetic and medicinal chemists.[1a–g] Furthermore, enantiopure β-lactams are nowadays widely used, according to the 'β-lactam synthon method' (β-LSM), as versatile intermediates for the asymmetric synthesis of compounds of medicinal interest such proteinogenic and non-proteinogenic-amino acids.[2a–c] The development of new synthetic methods, as well as the study of the structure–activity relationship of the target compounds, requires the stereochemistry of these synthons to be fully characterised. Nuclear magnetic resonance (NMR) has been widely used for the determination of the relative configuration (*E* or *Z*) at C3 and C4 of disubstituted β-lactams,[3a–d] while circular dichroism (CD) has been usefully applied to determine the absolute configuration at the two stereogenic centres.[4a–d] The

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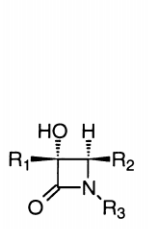
β-lactam sector rule has indeed been successfully applied to derivatives which bear one substituent at C4 and/or at C3. According to this rule, the sign of the observed CD in the 250–220 nm spectral region correctly relates to the stereochemistry of the β-lactams. The CD spectroscopy appears useful to determine the absolute configuration of 3-hydroxy-3-alkyl-β-lactams which bear a quaternary C3 atom, due to a growing interest in their synthesis as precursors to taxol side-chains (isoserine analogues).[5a–c] Independent systems, i.e. X-ray structure analysis and chemical correlation, have also been employed in order to verify the reliability of the CD analysis in predicting their stereochemistry.

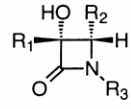
2. Results and discussion

A series of 3-hydroxy-3-alkyl-lactams **1a** and **1c–l** and a 3-hydroxy-3-aryl-lactam **1b** have been recently synthesised by the addition reaction of imines to lithium enolates of acetal type derivatives of chiral α-hydroxy substituted carboxylic acids[6,7] (Fig. 1).



(3R,4R)-E -**1a-i**

	R_1	R_2	R_3
1a	Me	C_6H_5	C_6H_5
1b	C_6H_5	C_6H_5	C_6H_5
1c	*i*-Pr	C_6H_5	C_6H_5
1d	CH_2CO_2H	C_6H_5	C_6H_5
1e	Me	C_4H_3O	H
1f	Me	$\equiv$—$SiMe_3$	H
1g	*i*-Pr	$\equiv$—$SiMe_3$	H
1h	Me	C_6H_5	H
1i	Me	CO_2Me	C_6H_4-*p*-OMe
1l	*i*-Pr	CO_2Me	C_6H_4-*p*-OMe



(3R,4S)-Z -**1a-i**

Fig. 1.

Assignment of the stereostructures was based on X-ray analyses, on chemical correlation, and on a combined NMR and circular dichroism spectroscopic study. In particular, the *E/Z* relative configuration of the β-lactams **1a**, **1c**, **1d**, and **1e** was established from a study of their ^{1}H NMR spectra. The methyl protons of *E*-**1a** and *E*-**1e**, the proton resonance of the Me_2C*H* group of *E*-**1c**, and the methylene protons of *E*-**1d** are in the shielding cone of the aromatics C4-phenyl and C4-furyl substituents. Their signals are therefore more upfield than the corresponding signals of the *Z*-diastereomers, which have the hydroxy group in the shielding cone of the aromatic substituents. The relative configuration was also confirmed by a qualitative homonuclear NOE difference spectra performed on the β-lactams **1a** and **1c–l**. In particular, the irradiation of the signals of the *Z*-diastereomers showed a large enhancement (8.0–11.0%) of the neighbouring C4–H protons, while the corresponding *E*-isomers showed enhancements in the range 1.0–3.0%.[8] The *E/Z* relative configuration of β-lactams **1b** was assigned by a comparison of their physical and spectroscopic characteristics with those reported for the racemic forms.[9] Interestingly, a consistent trend in the ^{13}C NMR resonances of the C3 and C4 carbon atoms was observed. As a general rule the isomers that have *E*-configuration display the ^{13}C NMR resonances both at C3 and C4 at a lower field than the corresponding *Z*-isomers (Table 1). The maximum separation observed in the C4 resonances of the diastereomeric pairs was 4.8 ppm (**1c**). The minimum separation was 0.1 ppm (**1f**). As far as the separations observed in the C3 resonances of the diastereomeric pairs are concerned, the maximun value observed was 2.3 ppm (**1a**), the minimum value was 0.9 ppm (**1i** and **1l**). A crossing over of the *E/Z* resonances occurred in the case of the β-lactam **1b** (−1.6 ppm).

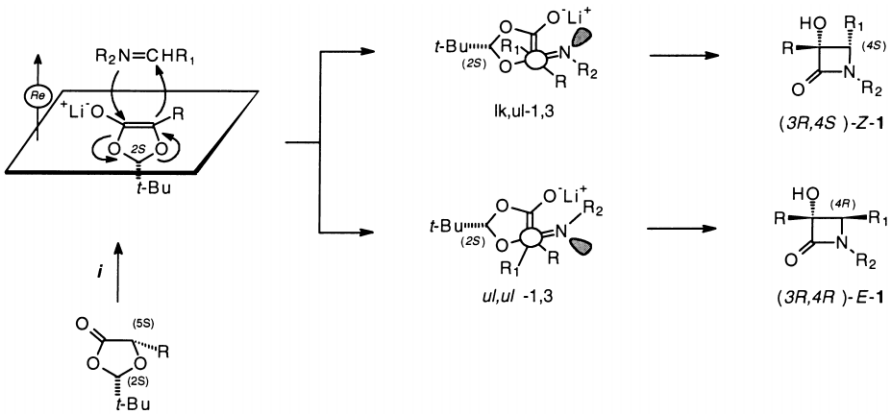
Table 1
^{13}C NMR and CD data of β-lactams *E*/*Z*-**1a–l**

Sample	λ(nm)	Δε (e.e. %)	^{13}CNMR (C3)	^{13}CNMR (C4)
2	244	-6.0 (94)		
Z-**1a**			83.5	68.9
E-**1a**	248	-8.4 (94)	85.8	69.3
Z-**1b**			86.8	70.3
E-**1b**	248	-15.6 (99)	85.2	73.5
Z-**1c**	248	10.6 (97)	89.1	65.2
E-**1c**	248	-13.7 (97)	90.5	70.0
Z-**1d**	248	13.5 (99)	84.4	67.4
E-**1d**			86.6	69.9
Z-**1e**	230	1.8 (96)	86.2	59.3
E-**1e**			87.4	60.0
Z-**1f**	218	2.2 (98)	85.3	53.7
E-**1f**	222	-5.8 (98)	86.9	53.8
Z-**1g**	222	3.4 (96)	91.4	50.6
E-**1g**	225	-6.8 (96)	92.6	53.3
Z-**1h**	243	2.8 (98)	86.7	64.2
Z-**1i**	250	+3.8 (94)	84.3	65.5
E-**1i**			85.2	66.0
Z-**1l**	246	+1.3 (62)	90.3	62.4
E-**1l**			91.2	66.0

On the basis of the mechanism proposed for the employed synthetic route (Scheme 1), an (*R*) absolute configuration should be assigned to C3, the (*S*) being the absolute configuration of the starting hydroxy carboxylic acid.[6,7] Thus the NMR data should allow us to assign the absolute stereochemistry to all the synthesised compounds.

However, CD spectra of compounds **1a–l** were carried out (Table 1) in order to obtain stereochemical information by their analysis. All of the *E*-samples (**1a–c**, **1f–g**) showed a negative CD band between 250 and 220 nm, while a positive CD contribution, in the same spectral region, was observed for the *Z*-diastereomers (**1c–l**). A negative CD is expected for a (3*R*,4*R*) stereochemistry, i.e. for the *E*-diastereomers, if the β-lactam octant rule (Fig. 2) is applied. In this case indeed, the substituent at C4 is located in a negative octant, while the disubstitution at C3 determines the presence of a group in both the positive and negative octants.

In addition, the substituent at C4 is expected to give a stronger contribution if the C4 is outside the plane determined by the C=O bond and the N1 and C3 atoms, as reported for structural analogues.[4b]



Scheme 1. Formation of β-lactams (3*R*,4*S*)-*Z*-**1** and (3*R*,4*R*)-*E*-**1** from (2*S*,5*S*)-dioxolanones

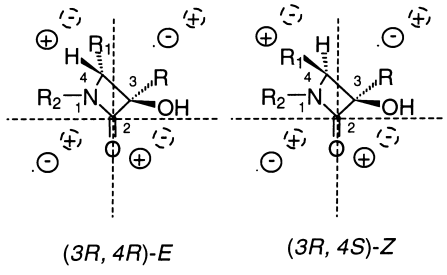


Fig. 2. Application of the β-lactam octant rule to *E*- and *Z*-**1**

Thus, a (4*R*) absolute configuration can be assigned, for example, to the analysed stereoisomer of **1a** (Table 1) and then, on the basis of the CD and NMR data, the absolute stereochemistry of this compound is (3*R*,4*R*)-*E*-**1a**.

The reliability of the absolute stereochemistry assigned by CD for C3-disubstituted-3-hydroxy-β-lactams was confirmed by the X-ray analysis of *E*-**1a** which proved the relative *E*-configuration. The Ortep drawing of *E*-**1a** is reported in Fig. 3. The X-ray analysis also illustrated the non-planarity of the β-lactam ring. The internal torsion angles indicate the non-planarity of the β-lactam ring, in agreement with literature data on structural analogues.[10]

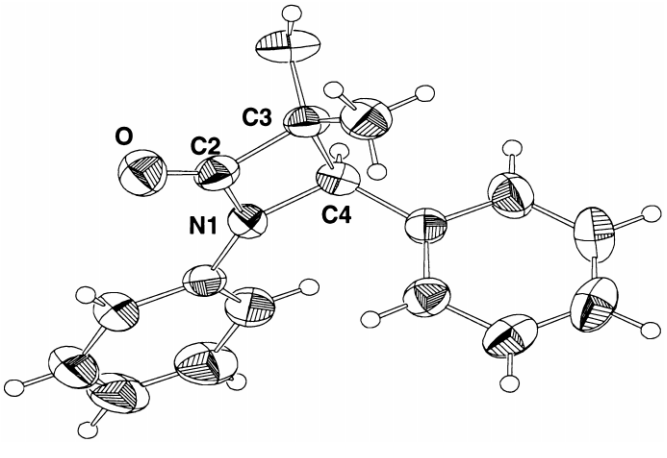


Fig. 3. ORTEP diagram of (3*R*,4*R*)-*E*-**1a**

The absolute configuration was confirmed by the chemical correlation of (3*R*,4*R*)-*E*-**1a** with the β-lactam 1,4-diphenyl-3-methylazetidinone (3*S*,4*S*)-*Z*-**2**[6] (Fig. 4).

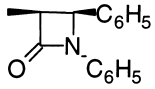


Fig. 4. (3*R*,4*S*)-*Z*-**2**

The CD spectra of (3*R*,4*R*)-*E*-**1a** and (3*S*,4*S*)-*Z*-**2** show the same CD behaviour, with a negative CD band of comparable intensity at about 245 nm (Fig. 5). The intensity of the CD of (3*S*,4*S*)-*Z*-**2** is a little lower with respect to that of (3*R*,4*R*)-*E*-**1a**. This result fits well with the prediction of the sector rule since (3*S*,4*S*)-*Z*-**2** has a proton instead of a hydroxyl group in the negative octant.

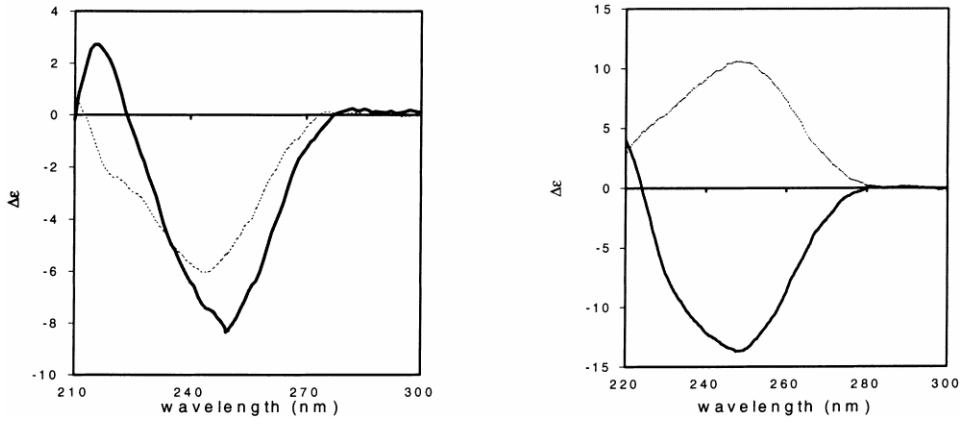


Fig. 5. Left: CD spectra of (3*R*,4*R*)-*E*-**1a** (—) and of (3*S*,4*S*)-*Z*-**2** (- - -). Right: CD spectra of (3*R*,4*R*)-*E*-**1c** (—) and of (3*R*,4*S*)-*Z*-**1c** (- - -)

Differences in the intensities of the CD bands of alkyl substituted β-lactams were reported[4a] depending on the stereochemistry at C3 and the extent of substitution. These authors showed that the absolute configuration at C4 determines the sign of the CD of C3,C4-disubstituted β-lactams. This behaviour was related to the distortion of the β-lactam ring with the out of plane C4 determined by the carbonyl group. The same CD sign, positive, was indeed obtained for the *Z*-(3*R*,4*S*)-3,4-dimethylazetidin-2-one and the *E*-(3*S*,4*S*)-diastereomer. As expected, the enantiomeric forms, i.e. the *Z*-(3*S*,4*R*)- and the *E*-(3*R*,4*R*)-diastereomers, showed negative CD bands. Our results are in agreement with these data, the CD spectra being negative for all the examined (4*R*)-β-lactams and positive for all the (4*S*)-β-lactams (Table 1). As an example, the CD spectra of (3*R*,4*R*)-*E*-**1c** and (3*R*,4*S*)-*Z*-**1c** are reported in Fig. 5. These CD spectra appear almost enantiomeric. As far as compound **1b** is concerned, the CD analysis suggests a (3*R*,4*R*) absolute stereochemistry on the basis of the negative CD band observed at 248 nm (Table 1). Once again, a (4*R*) configuration and the *E*-stereochemistry fit well with the observed CD spectra since the phenyl substituent at C4 is in a negative octant. The results of the NMR analysis of **1b**, as compared with the literature data,[9] are in agreement with an *E*-stereochemistry. The assignment of absolute configuration was confirmed by X-ray structure analysis of the other diastereomer *Z*-**1b**, as the thioxanthate derivative, **3**. The ORTEP drawing of (3*R*,4*S*)-*Z*-**3** is reported in Fig. 6. The non-planarity of the β-lactam ring was even more pronounced in the case of (3*R*,4*S*)-*Z*-**3**, the internal torsion angles being significantly larger (up to 4.5°) with respect to those observed in the case of (3*R*,4*R*)-*E*-**1a**.

Sequential deprotonation of the tertiary alcohol of a sample of (3*R*,4*S*)-*Z*-**1b** with potassium hydride followed by the addition of CS_2, and methylation with an excess of iodomethane gave compound (3*R*,4*S*)-*Z*-**3** (Scheme 2).

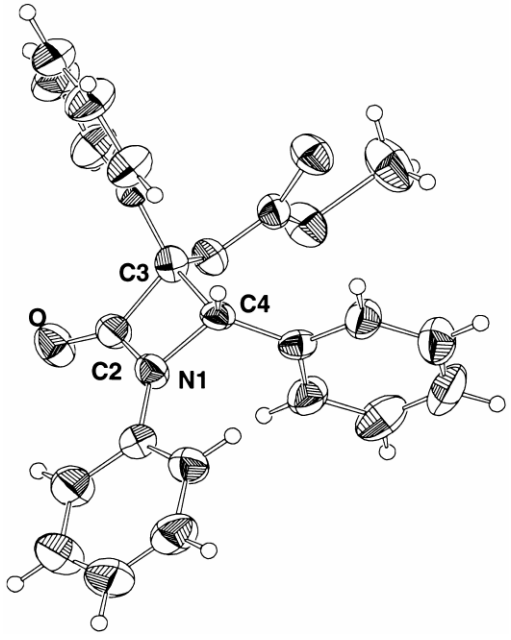
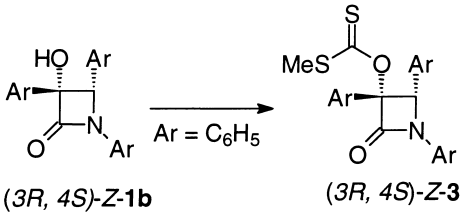


Fig. 6. ORTEP diagram of (3*R*,4*S*)-*Z*-**3**



Scheme 2. Synthesis of (3*R*,4*S*)-*Z*-**3**

The absolute stereochemistry was then tentatively assigned to the compounds **1c**–**l** on the basis of their NMR spectra and of the analysis of their CD, by applying the β-lactam sector rule (Table 1). Both the diastereomers, *E* and *Z*, were analysed in the cases of **1c**, **1f**, and **1g**. The application of this sector rule considers the β-lactam ring as planar. However it has been proposed[4a,d11] that the substitution at C3 and at C4 determines the non-planarity of the ring and then the intrinsic chirality of the β-lactam moiety. In particular, a left handed chirality is expected to determine a positive contribution to the CD spectrum, while a right handed chirality should give a negative CD.[4d] This behaviour is closely connected to the tendency of the substituent at C3 or at C4 to adopt the pseudoequatorial position on the β-lactam ring. The 3-hydroxy-β-lactams **1a**–**l** are disubstituted at C3 and thus the torsion angle O=C–N–R should be mainly determined by the stereochemistry at C4. In practice, the driving force should be the tendency of the substituent at C4 to adopt a pseudoequatorial position. On the basis of the experimental CD data and assuming the intrinsic chirality as the main source of the optical activity, a positive torsion angle O=C–N–R should exist for the *E*-diastereomers (negative CD) and a negative torsion angle should exist for the *Z*-diastereomers (positive CD). This hypothesis was indeed nicely supported by the X-ray analysis, which showed a positive torsion angle (8.98) for (3*R*,4*R*)-*E*-**1a**, and a negative torsion angle (−2.79) for (3*R*,4*S*)-*Z*-**3**.

In conclusion, NMR and CD spectroscopy results are useful to reliably determine the absolute stereochemistry of 3-hydroxy-3-alkyl-β-lactams. In particular, the sign of the CD band between 250 and

220 nm correctly relates the absolute configuration at C4 and NMR analysis unambiguously determines the relative configuration at C3 and C4. The reliability of the method has been proved by X-ray structure analysis and chemical correlation for two of the examined β-lactams. Furthermore, X-ray structure analyses of (3*R*,4*R*)-*E*-**1a** and of (3*R*,4*S*)-*Z*-**3** gave evidence of the non-planarity of the β-lactam ring.

3. Experimental

3.1. Materials

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 200 MHz VXR Varian spectrometer with Me_4Si or $CHCl_3$ (in $CDCl_3$) as internal standards. Mass spectra were recorded on a Finnegan ion trap spectrometer with an ionisation potential of 70 eV. Infrared spectra were recorded on a Nicolet 205-FT spectrometer. Compounds **1a**–**l** were synthesised according to a reported procedure,[6,7] and their spectroscopic data have already been reported.[6,7] Organic solvents were HPLC grade from Merck (Darmstadt, Germany).

Synthesis of (3*R*,4*S*)-*Z*-**3**: A THF (10 ml) solution of β-lactam (3*R*,4*S*)-*Z*-**1b** (0.100 g, 0.32 mmol) and KH (0.150 g) was refluxed while stirring for 30 min. CS_2 (0.3 ml) was added at 0°C and the reaction mixture was stirred at 10°C for 60 min. MeI (1 ml) was added at 25°C and the solution was stirred for 2 h. The solvent was evaporated under reduced pressure to yield the corresponding β-lactam *Z*-**3** (0.097 g, 0.24 mmol, 75%) which was purified by crystallisation. (3*R*,4*S*)-*Z*-**3**: m.p. 187–188°C; $[\alpha]_D^{22}$ −162.0 (*c* 0.3, $CHCl_3$); IR (THF): ν 1765, 1230, 1010 cm^{-1}; MS: *m/z* 359 ($M^+ - SCH_3$), 298, 270, 181, 180; ^{1}H NMR ($CDCl_3$): δ 2.20 (s, 3H, Me), 5.79 (s, 1H, C4–H), 7.00–7.60 (m, 15H, arom); ^{13}C NMR ($CDCl_3$): δ 19.1, 67.3, 94.6, 117.9, 124.8, 126.4, 128.5, 128.7, 128.8, 128.9, 129.2, 133.2, 134.4, 136.6, 161.7, 209.6; $C_{23}H_{19}NO_2S_2$ (405.5): calcd C 68.12, H 4.72, N 4.35; found: C 68.65, H 4.78; N 4.31.

3.2. UV and CD measurements

Absorption (UV) and CD spectra of pure diastereomers [*E*-**1a**–**c**, *E*-**1f**,**g**, *Z*-**1c**–**h**, *Z*-**1i**–**l**, **2**] were carried out by a Cary 4 (Varian, Sidney, Australia) spectrophotometer and a Jasco J-600 (Jasco Instruments, Tokio, Japan) spectropolarimeter, respectively. The measurements were performed with 2-propanol solutions (c 3–5 mM), 1–0.1 mm pathlength, room temperature. Both the instruments were interfaced to personal computers to acquire and elaborate the data. UV (2-propanol): *E*-**1a**, 252 nm; *E*-**1b**, 254 nm; *E*-**1c**, 251 nm; *Z*-**1c**, 252 nm; *Z*-**1d**, 252 nm; *Z*-**1e**, 222 nm; *E*-**1f**, 223 nm (sh); *Z*-**1f**, 223 nm (sh); *E*-**1g**, 225 nm (sh); *Z*-**1g**, 225 nm (sh); *Z*-**1h**, 254 nm; *Z*-**1i**, 257 nm; *Z*-**1l**, 258 nm; **2**, 249 nm. UV and CD spectra of compounds *Z*-**1a**–**b** and *E*-**1d**,**e**,**i**,**l** were not carried out because they were available only as diastereomeric *E/Z* mixtures.

3.3. Chromatographic measurements

The HPLC system consisted of a Jasco PU-980 pump and a Jasco MD 910 multiwavelength detector (Jasco, Tokyo, Japan). The eluents were also monitored with a Jasco J 710 spectropolarimeter equipped with a micro HPLC cell (8 μL volume) and lenses to focus the light beam in the sample compartment. This detection system allows both the absorption and the circular dichroism signal to be simultaneously detected. The chromatographic retention of the solutes were monitored by measuring the absorption and the CD at 250 nm (**1a**–**e**, **1h**–**l**) and at 230 nm (**1f**–**g**). All chromatographic resolution data are reported

as capacity factor ($k'=t-t_o/t_o$, where t is the retention time of the fraction and t_o is the retention time of the solvent), and enantioselectivity factor ($\alpha=k'2/k'1$, where $k'1$ and $k'2$ are the capacity factors of the second and of the first eluted enantiomers. The chromatographic resolution of compounds **1a–c**, **1h**, and **1e** was obtained with a Chiralpack AD column (Daicel 25×0.46 cm i.d). The mobile phase was *n*-hexane:2-propanol (80:20–95:5), 1 ml/min. Compounds **1d**, **1f**, **1g**, and **1i** were analysed on a Chiralcel OJ column (Daicel 25×0.46 cm i.d.). The mobile phase was *n*-hexane:2-propanol:acetic acid (75:25:1.5) in the case of **1d**, while mixtures of *n*-hexane and 2-propanol (90:10–97.5:2.5) were used in all the other cases. The flow was 0.8–1 ml/min. Finally, a Chiralcel OD column (Daicel 25×0.46 cm i.d.) was used for the resolution of compounds **1h** and **1l**. The mobile phase was hexane:2-propanol, and the flow was 1 ml/min.

3.4. X-Ray crystallography

Analyses were carried out on single crystals of *E*-**1a** and *Z*-**3** obtained after slow evaporation of an ethyl acetate solution. Crystal data were collected at 293 K with an Enraf–Nonius CAD4 single crystal diffractometer with the Mo-Kα radiation (λ=0.71073 Å). The structures were solved by direct method using SHELXS. The test for crystal chirality was carried out by using the Flack parameter. Expected values are 0 (within 3 esds) for correct and +1 for inverted absolute structure. In **1a** the absolute structure was not possible to determine reliably and the Friedel opposites were merged and the imaginary term of the anomalous dispersion was not applied. In **3** the absolute structure was determined and the Flack parameter of 0.03(12) suggested that the assignment of the crystal chirality was correct. Refinements were carried out by full-matrix least squares of F^2 for all data using SHELXL-97.

E-**1a** ($C_{16}H_{15}NO_2$, M=253.29), orthorhombic, space group $P2_12_1$, a=5.9940(4) Å, b=14.703(2) Å, c=15.663(2) Å, V=1380.4(3) Å^3, Z=4, D_c=1.219 g/cm^3, μ(Mo-Kα)=0.081 mm^{-1}, final R1, wR2 and S are 0.0353, 0.0763 and 0.995 for 175 parameters and 1927 unique observed reflections with $I>2\sigma(I)$.

Z-**3** ($C_{23}H_{19}NO_2S_2$, M=405.51), orthorhombic, space group $P2_12_1,2_1$ a=6.050(1) Å, b=17.992(3) Å, c=19.135(1) Å, V=2082.9(5) Å^3, Z=4, D_c=1.293 g/cm^3, μ(Mo-Kα)=0.274 mm^{-1}, final R1, wR2 and S are 0.0439, 0.0796 and 1.020 for 255 parameters and 3245 unique observed reflections with $I>2\sigma(I)$. Tables of crystal data and structure refinement, final positional parameters, anisotropic thermal parameters, bond lengths and angles, are available as supplementary material (Tables 2–13, 19 pages).

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