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Stereochemistry of Chiral Sulfoxides used for the Synthesis of Antitumor Antibiotic Analogues of Sparsomycin

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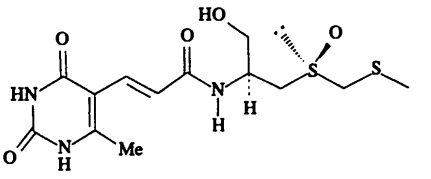
Abstract

The structures of {[(*S*)-(4,5-dihydro-2-phenyloxazol-4-yl)-methyl]-(*S*)-sulfinyl}octane, $C_{18}H_{27}NO_2S$, (2), {[(*S*)-(4,5-dihydro-2-phenyloxazol-4-yl)methyl]-(*R*)-sulfinyl}octane, $C_{18}H_{27}NO_2S$, (3), and 4-{[(*S*)-(4,5-dihydro-2-phenyl-oxazol-4-yl)methyl]-(*S*)-sulfinyl}phenol, $C_{16}H_{15}NO_3S$, (5), have been determined. The known chirality (*S*) at the C10 atom in all three compounds enabled assignment of the absolute configuration at the S13 atom. The C10 chirality was subsequently confirmed by refinement of the Flack parameter. The absolute configuration at S13 for compounds (2), (3) and (5) is *R*, *S* and *S*, respectively. Comparison with the stereochemistry of sparsomycin enables proper choice of diastereomers for analogue development.

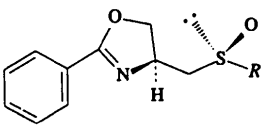
Comment

Sparsomycin, (1), a natural product from bacteria, is a potent inhibitor of protein biosynthesis (Lazaro, San Felix, van den Broek, Ottenheijm & Ballesta, 1991) and has attracted considerable interest as an antibiotic and chemotherapeutic agent (Ottenheijm, van den Broek, Ballesta & Zylicz, 1986). The drug preferentially binds to 'active ribosomes' engaged in polypeptide synthesis on mRNA and blocks the action of peptidyl transferase, a key enzyme which is an integral part of the large ribosomal subunit structure. Valuable information on the structure of this peptidyl transferase centre and of the ribosome as a whole has been obtained from studies using sparsomycin and its analogues.

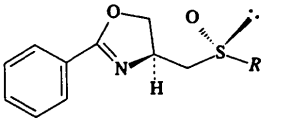
In connection with our syntheses of ribosome inhibitors based on the structure of sparsomycin, we have prepared a novel pair of optically active alkyl *n*-octyl sulfoxides, (2) and (3), and report on their solid-state structures. Curiously, the diastereomeric octyl sulfoxides (2) and (3) can be separated on silica gel, but the related alkyl aryl sulfoxide diastereomers (4) and (5) could not be separated except by selective and repeated crystallizations. We also report on the solid-state structure of compound (5). We have relied on X-ray crystallography for determining the chirality of these sulfoxide centres, since there are no other general methods for compounds that also contain other chiral centres.



(1)



(2) *R* = *n*-octyl
(4) *R* = *p*-(HO)-Ph



(3) *R* = *n*-octyl
(5) *R* = *p*-(HO)-Ph

The molecular structures of the three compounds investigated are presented in Figs. 1, 2 and 3. Compound (2) (Fig. 1) contains two independent molecules in the asymmetric unit, both having the same stereochemistry. The *n*-octyl chains in both molecules of compound (2) and in compound (3) (Fig. 2) all adopt fully extended conformations.

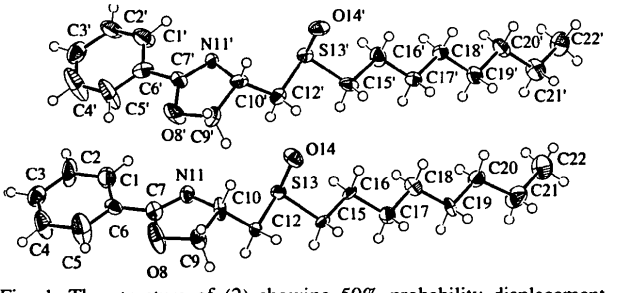


Fig. 1. The structure of (2) showing 50% probability displacement ellipsoids (two independent molecules in the asymmetric unit).

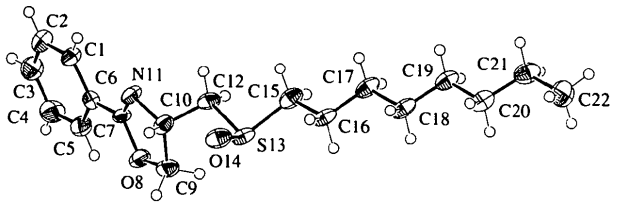


Fig. 2. The structure of (3) showing 50% probability displacement ellipsoids.

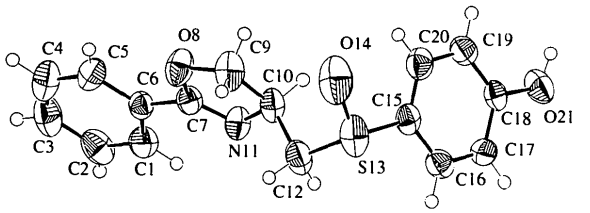


Fig. 3. The structure of (5) showing 50% probability displacement ellipsoids.

The assignments of absolute configuration, made on the basis of known chirality at C10 and in accordance with the priority rules, are S_CS_S, S_CR_S and S_CS_S for compounds (2), (3) and (5), respectively. For compounds (3) and (5), we were able to verify the stereochemistry at C10 using the anomalous dispersion corrections to the atomic scattering factors to calculate the Flack parameter (Flack, 1983) for the three compounds [performed automatically in *SHELXL*93 (Sheldrick, 1993)]. Although the chirality designation for sparsomycin is S_CR_S, because of priority considerations this absolute configuration corresponds to S_CS_S in all of the above compounds. Therefore, compound (2) [as well as the diastereomer of (5)] should be a biologically active sparsomycin analogue after completion of the synthesis.

The crystal packing is similar for compounds (2) and (3); molecules in both crystals are arranged in a head-to-tail fashion parallel to the *b* axis, with only van der Waals interactions between molecules. There is intermolecular hydrogen bonding in the crystal of compound (5), between O21 and N11 (2.72 Å), resulting in a two-dimensional network of hydrogen-bonded molecules perpendicular to the *a* axis.

Experimental

Compounds (2), (3) and (5) were synthesized at the University of Washington, Seattle, USA.

Compound (2)

Crystal data

$C_{18}H_{27}NO_2S$
M_r = 321.47
Mo $K\alpha$ radiation
λ = 0.71073 Å
Monoclinic
$P2_1$
a = 5.188 (1) Å
b = 38.076 (7) Å
c = 9.049 (1) Å
β = 96.32 (1)°
V = 1776.7 (5) Å^3
Z = 4
D_x = 1.202 Mg m^{-3}
D_m not measured
Cell parameters from 25 reflections
θ = 20–30°
μ = 0.189 mm^{-1}
T = 293 (2) K
Plate
0.7 × 0.5 × 0.2 mm
Colourless

Data collection

Siemens *R3m/V* four-circle diffractometer
$2\theta/\theta$ scans
Absorption correction: none
3543 measured reflections
3181 independent reflections
1577 observed reflections [$I > 2\sigma(I)$]
R_{int} = 0.0774
θ_{max} = 25°
$h = 0 \rightarrow 6$
$k = 0 \rightarrow 45$
$l = -10 \rightarrow 10$
3 standard reflections
frequency: 90 min
intensity decay: none

Refinement

Refinement on F^2
$R(F)$ = 0.0781
$wR(F^2)$ = 0.2351
S = 0.947
3180 reflections
401 parameters
H atoms riding on their parent atoms
$w = 1/[\sigma^2(F_o^2) + (0.1097P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = -0.118$
$\Delta\rho_{max}$ = 0.276 e Å^{-3}
$\Delta\rho_{min}$ = −0.306 e Å^{-3}
Extinction correction: none
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)
Absolute configuration: Flack (1983)
Flack parameter = −0.2 (3)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2) for (2)*

$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
C1	0.365 (4)	0.2898 (4)	0.194 (2)	0.070 (6)
C2	0.479 (4)	0.3217 (4)	0.207 (2)	0.082 (7)
C3	0.369 (3)	0.3500 (4)	0.128 (2)	0.041 (4)
C4	0.161 (3)	0.3444 (4)	0.035 (2)	0.060 (5)
C5	0.040 (3)	0.3118 (4)	0.023 (2)	0.075 (6)
C6	0.150 (3)	0.2843 (3)	0.099 (1)	0.033 (3)
C7	0.032 (3)	0.2491 (4)	0.089 (1)	0.031 (3)
O8	−0.202 (2)	0.2473 (3)	0.003 (1)	0.061 (3)
C9	−0.287 (3)	0.2112 (3)	0.003 (2)	0.036 (3)
C10	−0.064 (2)	0.1925 (3)	0.101 (2)	0.028 (3)
N11	0.118 (2)	0.2206 (3)	0.144 (1)	0.028 (3)
C12	0.058 (3)	0.1623 (3)	0.019 (1)	0.029 (3)
S13	0.3131 (6)	0.1425 (1)	0.1406 (3)	0.024 (1)
O14	0.187 (2)	0.1295 (2)	0.2722 (9)	0.041 (2)
C15	0.377 (2)	0.1051 (3)	0.030 (1)	0.021 (3)
C16	0.567 (3)	0.0818 (3)	0.124 (1)	0.026 (3)
C17	0.650 (3)	0.0497 (3)	0.038 (2)	0.030 (3)
C18	0.847 (3)	0.0271 (4)	0.132 (2)	0.034 (3)
C19	0.946 (3)	−0.0046 (3)	0.051 (2)	0.035 (4)
C20	1.140 (3)	−0.0271 (3)	0.143 (2)	0.034 (3)
C21	1.224 (3)	−0.0607 (4)	0.070 (2)	0.057 (5)
C22	1.400 (4)	−0.0832 (4)	0.169 (2)	0.071 (6)
C1′	0.225 (3)	0.2571 (4)	−0.288 (2)	0.056 (5)
C2′	0.393 (4)	0.2846 (4)	−0.265 (2)	0.067 (6)
C3′	0.354 (3)	0.3147 (4)	−0.348 (2)	0.051 (4)
C4′	0.154 (4)	0.3154 (5)	−0.455 (3)	0.086 (7)
C5′	−0.007 (3)	0.2870 (4)	−0.483 (2)	0.074 (6)

C6′	0.027 (2)	0.2581 (4)	−0.397 (1)	0.030 (3)
C7′	−0.149 (3)	0.2269 (3)	−0.425 (1)	0.028 (3)
O8′	−0.340 (2)	0.2308 (3)	−0.538 (1)	0.052 (3)
C9′	−0.489 (2)	0.1983 (3)	−0.542 (1)	0.031 (3)
C10′	−0.345 (3)	0.1755 (3)	−0.421 (1)	0.029 (3)
N11′	−0.131 (2)	0.1985 (3)	−0.355 (1)	0.030 (3)
C12′	−0.227 (3)	0.1422 (3)	−0.484 (1)	0.032 (3)
S13′	−0.033 (1)	0.1188 (1)	−0.3424 (3)	0.027 (1)
O14′	−0.212 (2)	0.1068 (2)	−0.2334 (9)	0.036 (2)
C15′	0.037 (3)	0.0818 (3)	−0.454 (1)	0.031 (3)
C16′	0.219 (3)	0.0565 (4)	−0.362 (2)	0.036 (4)
C17′	0.314 (3)	0.0262 (3)	−0.450 (1)	0.031 (3)
C18′	0.507 (3)	0.0028 (3)	−0.362 (1)	0.030 (3)
C19′	0.617 (3)	−0.0263 (3)	−0.452 (2)	0.037 (3)
C20′	0.821 (3)	−0.0493 (4)	−0.362 (2)	0.037 (4)
C21′	0.927 (3)	−0.0783 (4)	−0.449 (2)	0.044 (4)
C22′	1.136 (3)	−0.0993 (4)	−0.365 (2)	0.047 (4)

Compound (3)

Crystal data

$C_{18}H_{27}NO_2S$
M_r = 321.47
Monoclinic
$P2_1$
a = 4.828 (1) Å
b = 34.865 (6) Å
c = 5.317 (1) Å
β = 98.93 (1)°
V = 884.2 (3) Å^3
Z = 2
D_x = 1.207 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 25 reflections
θ = 20–25°
μ = 0.190 mm^{-1}
T = 193 (2) K
Needle
0.70 × 0.20 × 0.15 mm
Colourless

Data collection

Siemens *R3m/V* four-circle-diffractometer
$2\theta/\theta$ scans
Absorption correction: none
2237 measured reflections
1638 independent reflections
1065 observed reflections [$I > 2\sigma(I)$]

R_{int} = 0.0400
θ_{max} = 25°
$h = -1 \rightarrow 5$
$k = -6 \rightarrow 41$
$l = -6 \rightarrow 6$
3 standard reflections
frequency: 90 min
intensity decay: none

Refinement

Refinement on F^2
$R(F)$ = 0.0445
$wR(F^2)$ = 0.1326
S = 0.668
1638 reflections
202 parameters
H atoms riding on their parent atoms
$w = 1/[\sigma^2(F_o^2) + (0.1118P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = −0.002

$\Delta\rho_{max}$ = 0.129 e Å^{-3}
$\Delta\rho_{min}$ = −0.142 e Å^{-3}
Extinction correction: none
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)
Absolute configuration: Flack (1983)
Flack parameter = −0.20 (17)

Table 2. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2) for (3)*

$U_{eq} = (1/3)\sum_i\sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
C1	0.793 (1)	−0.0262 (2)	0.207 (1)	0.036 (2)
C2	0.913 (1)	−0.0558 (2)	0.090 (1)	0.042 (2)
C3	0.858 (2)	−0.0935 (2)	0.147 (1)	0.048 (2)
C4	0.685 (2)	−0.1011 (2)	0.325 (1)	0.051 (2)
C5	0.568 (1)	−0.0717 (2)	0.442 (1)	0.041 (2)
C6	0.617 (1)	−0.0339 (2)	0.387 (1)	0.032 (1)
C7	0.492 (1)	−0.0019 (2)	0.505 (1)	0.030 (1)
O8	0.3218 (9)	−0.0123 (1)	0.6794 (7)	0.040 (1)
C9	0.214 (1)	0.0228 (2)	0.769 (1)	0.037 (2)
C10	0.347 (1)	0.0546 (2)	0.627 (1)	0.035 (2)
N11	0.514 (1)	0.0334 (1)	0.4603 (9)	0.036 (1)
C12	0.526 (1)	0.0825 (2)	0.801 (1)	0.035 (1)
S13	0.3052 (3)	0.1107 (1)	0.9722 (3)	0.036 (1)
O14	0.1257 (9)	0.1343 (1)	0.7762 (8)	0.043 (1)
C15	0.569 (1)	0.1417 (2)	1.137 (1)	0.039 (2)
C16	0.439 (1)	0.1723 (2)	1.280 (1)	0.037 (2)
C17	0.656 (1)	0.1978 (2)	1.440 (1)	0.039 (2)
C18	0.527 (2)	0.2272 (2)	1.600 (1)	0.040 (2)
C19	0.743 (1)	0.2506 (2)	1.770 (1)	0.040 (2)
C20	0.615 (1)	0.2799 (2)	1.930 (1)	0.043 (2)
C21	0.833 (2)	0.3035 (2)	2.104 (1)	0.050 (2)
C22	0.703 (2)	0.3328 (2)	2.263 (1)	0.055 (2)

Compound (5)

Crystal data

$C_{16}H_{15}NO_3S$
M_r = 301.35
Orthorhombic
$P2_12_12_1$
a = 32.492 (8) Å
b = 7.756 (3) Å
c = 5.817 (2) Å
V = 1465.9 (8) Å^3
Z = 4
D_x = 1.365 Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
λ = 1.54178 Å
Cell parameters from 12 reflections
θ = 30–45°
μ = 2.047 mm^{-1}
T = 293 (2) K
Transparent blocks
0.42 × 0.25 × 0.24 mm
Colourless

Data collection

PICKER FACS-1 four-circle diffractometer
$\theta/2\theta$ scans
Absorption correction: ψ scan (North, Phillips & Mathews, 1968)
T_{min} = 0.54, T_{max} = 0.61
1497 measured reflections
1497 independent reflections

1221 observed reflections [$I > 2\sigma(I)$]
θ_{max} = 65°
$h = 0 \rightarrow 38$
$k = 0 \rightarrow 9$
$l = 0 \rightarrow 6$
3 standard reflections
monitored every 100 reflections
intensity decay: none

Refinement

Refinement on F^2
$R(F)$ = 0.0535
$wR(F^2)$ = 0.1739
S = 1.002
1497 reflections
194 parameters
H atoms riding on their parent atoms
$w = 1/[\sigma^2(F_o^2) + (0.1213P)^2 + 0.362P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = −0.057
$\Delta\rho_{max}$ = 0.244 e Å^{-3}
$\Delta\rho_{min}$ = −0.254 e Å^{-3}

Extinction correction: *SHELXL*93 (Sheldrick, 1993)
Extinction coefficient: 0.0067 (14)
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)
Absolute configuration: Flack (1983)
Flack parameter = 0.00 (6)

Table 3. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²) for (5)*

$U_{eq} = (1/3)\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
C1	0.0811 (2)	−0.3988 (8)	0.264 (1)	0.052 (1)
C2	0.0609 (2)	−0.5401 (8)	0.349 (1)	0.062 (2)
C3	0.0288 (2)	−0.6143 (9)	0.225 (1)	0.070 (2)
C4	0.0183 (2)	−0.5470 (9)	0.020 (1)	0.068 (2)
C5	0.0384 (2)	−0.4059 (8)	−0.073 (1)	0.054 (1)
C6	0.0701 (1)	−0.3299 (7)	0.050 (1)	0.042 (1)
C7	0.0909 (1)	−0.1767 (7)	−0.0436 (9)	0.042 (1)
O8	0.0748 (1)	−0.1151 (5)	−0.2399 (7)	0.059 (1)
C9	0.0970 (2)	0.0413 (8)	−0.294 (1)	0.061 (2)
C10	0.1318 (2)	0.0448 (7)	−0.113 (1)	0.050 (1)
N11	0.1215 (1)	−0.1000 (6)	0.0418 (8)	0.048 (1)
C12	0.1347 (2)	0.2139 (8)	0.020 (1)	0.058 (2)
S13	0.1595 (1)	0.3806 (2)	−0.1489 (4)	0.0641 (6)
O14	0.1461 (1)	0.3538 (7)	−0.3908 (9)	0.086 (2)
C15	0.2112 (1)	0.3036 (6)	−0.1279 (9)	0.043 (1)
C16	0.2332 (2)	0.3419 (7)	0.066 (1)	0.047 (1)
C17	0.2742 (2)	0.2896 (7)	0.083 (1)	0.046 (1)
C18	0.2923 (1)	0.2032 (7)	−0.1007 (9)	0.042 (1)
C19	0.2699 (2)	0.1647 (7)	−0.297 (1)	0.049 (1)
C20	0.2290 (2)	0.2165 (7)	−0.307 (1)	0.051 (1)
O21	0.3323 (1)	0.1572 (7)	−0.0749 (7)	0.060 (1)

The crystals were not of high quality, especially those of compound (2) as evidenced by the high R_{int} value. This is not unexpected in crystals of structures with long hydrophobic chains of atoms. Data for compounds (2) and (3) were collected using $\theta/2\theta$ scans. The scan width was (1.0 + 0.14tanθ)°, with a θ-scan rate of 0.8° min^{-1} and background counts for 5 s on each side of every scan. Data for compound (5) was collected using a $\theta/2\theta$ scan mode, with a scan width of 1.8°, a scan rate of 1.0° min^{-1} and background counts for 20 s on each side of every scan. Scattering factors, dispersion corrections and absorption coefficients were taken from *International Tables for Crystallography* (1992, Vol. C, Tables 6.1.1.4, 4.2.6.8 and 4.2.4.2, respectively). The absolute configuration at S13 has been assigned to agree with the known chirality at C10. Confirmation of the assignments of the C10 configuration of the investigated crystals was established as described by Flack (1983) and Flack & Schwarzenbach (1988). The relatively high *wR* values are due to crystal quality and to the fact that *wR* values are calculated on F^2 using all data.

Data collection: Siemens *P*3 software for (2) and (3); Picker software for (5). Cell refinement: Siemens *P*3 software for (2) and (3); Picker software for (5). Data reduction: Siemens *P*3 software for (2) and (3); Picker software for (5). For all compounds, program(s) used to solve structures: *SHELXS*86 (Sheldrick, 1990); program(s) used to refine structures: *SHELXL*93 (Sheldrick, 1993); molecular graphics: *ZORTEP* (Zsolnai, 1995); software used to prepare material for publication: *SHELXL*93.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: SX1014). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Methyl (1*R*,2*R*)- and (1*S*,2*S*)-1-Cyano-2-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]cyclopropane-1-carboxylate

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Abstract

In the title diastereomeric compounds, $C_{11}H_{15}NO_4$, the methyl ester group adopts a bisecting conformation with the carbonyl O atom eclipsing the cyclopropane ring. In the crystals of both compounds, the molecules are piled up along one of the crystallographic axes.

Comment

Cyclopropane amino acids are particularly interesting because they constitute a unique form of 'conformationally constrained' amino acid which has been found in nature, generally in the unbound form or, in some cases, as a constituent of small peptides. When introduced into a peptide chain, the peculiar nature of this kind of amino acid residue is expected to cause profound changes in the proximal peptide conformation, which may affect the ability of the peptide to fit an enzyme active site and/or its intended bioreceptor.

Our interest in the asymmetric synthesis of cyclopropane amino acids (Cativiela, Díaz-de-Villegas & Jiménez, 1994, 1995*a*,*b*,*c*, 1996) has prompted us to use a chiral cyano ester as a synthetic precur-