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Design, synthesis and enzymatic evaluation of N^1-acyloxyalkyl- and N^1-oxazolidin-2,4-dion-5-yl-substituted β-lactams as novel inhibitors of human leukocyte elastase

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This section includes the synthesis procedure for compound **11**, all spectroscopic data for compounds **9-12** and the crystal data for the minor diastereomeric pair of enantiomers of **6d**

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3,3-Diethyl-4-phenoxyazetidin-2-one (9). Purified by column chromatography using DCM-ethyl acetate (95:5) as eluant; white crystals (37 %); m.p. 53-56 ºC; ν_{max} (film) 3258, 2970, 1763, 1494, 1231 cm $^{-1}$; δ ^{1}H-NMR 1.03 (3H, *t*, *J* = 7.5 Hz), 1.07 (3H, *t*, *J* = 7.5 Hz), 1.73-1.85 (3H, *m*), 1.96 (1H, *dq*, *J* = 7.5, 15.1 Hz), 5.37 (1H, *s*), 6.56 (1H, brs), 6.88 (2H, *d*, *J* = 7.7 Hz), 7.04 (1H, *t*, *J* = 7.4 Hz), 7,32 (2H, *t*, *J* = 7.5 Hz); δ ^{13}C-NMR 8.64, 8.90, 21.72, 23.80, 64.68, 83.41, 115.87, 122.41, 129.84, 156.40, 172.57; ESI-MS, *m/z* 219 (MH^+).

4-(1,3-Benzoxazol-2-ylthio)-3,3-diethylazetidin-2-one (10a). [1] Recrystallized from DCM-light petroleum; white crystals (55 %); m.p. 178-179 ºC; ν_{max} (film) 3239, 2969, 1766, 1362, 1321, 1140 cm $^{-1}$; δ ^{1}H-NMR 0.85 (3H, *t*, *J* = 7.5 Hz), 1.15 (3H, *t*, *J* = 7.5 Hz), 1.47 (1H, *dq*, *J* = 7.3, 14.8 Hz), 1.67 (1H, *dq*, *J* = 7.4, 15.2 Hz), 1.85-2.07 (2H, 2 x *dq*, *J* = 7.5, 15,2 Hz), 6.23 (1H, *s*), 6.43 (1H, brs), 7.22-7.60 (4H, *m*); δ ^{13}C-NMR 8.02, 8.76, 21.49, 24.12, 67.62, 70.36, 110.76, 111.94, 124.52, 125.14, 131.15, 146.98, 172.15; EI-MS *m/z* 277 (MH^+).

3,3-Diethyl-4-(phenylthio)azetidin-2-one (10b). [1] Purified by column chromatography using light petroleum-diethyl ether (60:40) as eluant; yellow oil (53 %); ν_{max} (film) 3240, 2968, 1755 cm $^{-1}$; δ ^{1}H-NMR 0.95 (3H, *t*, *J* = 7.2 Hz), 1.10 (3H, *t*, *J* = 7.2 Hz), 1.68-2.05 (4H, *m*), 4.79 (1H, *s*), 6.73 (1H, *s*), 7.26-7.44 (5H, *m*); δ ^{13}C-NMR 8.56, 8.88, 22.84, 24.48, 66.95, 77.20, 127.89, 129.44, 132.16, 134.82, 171.10; EI-MS *m/z* 235 (M^+).

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1. Clemente, A.; Domingos, A.; Grancho, A.P.; Iley, J.; Moreira, R.; Neres, J.; Palma, N.; Santana, A. B.; Valente, E. Design, Synthesis and Stability of *N*-Acyloxymethyl- and *N*-Aminocarbonyloxymethyl-2-Azetidinones as Human Leukocyte Elastase Inhibitors. *Bioorg. Med. Chem. Lett*. **2001**, *11*, 1065-1068.

3,3-Diethyl-4-(phenylsulfonyl)azetidin-2-one (11). [1] To a stirred solution of **10b** (1 g, 4.3 mmol) in DCM, previously cooled in an ice bath during 10 min, 55% MCPBA (3.4 g, 10.6 mmol) was added. After 30 min in an ice bath the mixture was allowed to reach room temperature and stirred for 2.5 h. After completion of the reaction, as monitored by TLC, DCM (40 ml) and diethyl ether (20 ml) were added to the mixture. This organic layer was successively washed with 4.6% $NaHCO_3$ solution (2x50 ml), brine (50 ml), then dried ($MgSO_4$) and evaporated. The residue was subjected to chromatographic purification using diethyl ether-light petroleum (80:20) and diethyl ether as eluants to afford **11** as white crystals (71%); mp 156-158 ºC; ν_{max} (film) 3215, 3063, 2970, 1763, 1582, 1458, 1295, 1150 cm $^{-1}$; δ ^{1}H-NMR 0.96 (3H, *t*, *J* = 7.5 Hz), 1.09 (3H, *t*, *J* = 7.5 Hz), 1.71(1H, *dq*, *J* = 7.5, 14.7 Hz), 1.94 (1H, *dq*, *J* = 7.5, 14.8 Hz), 2.06 (1H, *dq*, *J* = 7.5, 14.9 Hz), 2.39 (1H, *dq*, *J* = 7.5, 14.9 Hz), 4.32 (1H, *s*), 6.26 (1H, br*s*), 7.62 (2H, *t*, *J* = 7.3 Hz), 7.72 (1H, *d*, *J* = 7.3 Hz), 7.93 (2H, *d*, *J* = 7.3 Hz); δ ^{13}C-NMR 8.57, 8.59, 20.32, 24.85, 67.85, 74.29, 128.55, 129.75, 134.84, 138.15, 171.73; EI-MS *m/z* 268 (MH^+).

3,3-Diethyl-*N*-[(1-ethoxycarbonyl-1-hydroxy)methyl]azetidin-2-one (12a). Yellow oil (85%); ν_{max} (film) 3433, 2970, 1729, 1662, 1242 cm $^{-1}$; δ ^{1}H-NMR 0.94 (3H, *t*, *J* = 7.5 Hz), 0.95 (3H, *t*, *J* = 7.2 Hz), 1.30 (3H, *t*, *J* = 7.2 Hz), 1.62-1.70 (4H, *m*), 2.96 (1H, *d*, *J* = 5.3 Hz), 3.19 (1H, *d*, *J* = 5.3 Hz), 4.21-4.40 (3H, *m*), 5.47 (1H, *s*); δ ^{13}C-NMR 8.73, 14.01, 25.24, 45.94, 60.13, 62.85, 71.31, 169.24, 172.65; ESI-MS *m/z* 230 (MH^+).

4-(1,3-Benzoxazol-2-ylthio)-3,3-diethyl-*N*-[(1-ethoxycarbonyl-1-hydroxy)methyl]azetidin-2-one (12b). Colorless oil (92%) as a mixture of two diastereomeric pairs of enantiomers; ν_{max} (film) 3423, 3082, 1777, 1751, 1360, 1323, 1283 cm $^{-1}$; δ ^{1}H-NMR 0.82 and 0.83 (3H, 2 x *t*, *J* =

7.4 Hz), 1.08 and 1.41 (3H, 2 x *t*, *J* = 7.2 Hz), 1.14 and 1.15 (3H, 2 x *t*, *J* = 7.4 Hz), 1.37-2.03 (4H, *m*), 3.54-4.50 (2H, *m*), 3.78 and 4.11 (1H, 2 x *d*, *J* = 7.7 and 8.3 Hz), 5.12 and 5.33 (1H, 2 x *d*, *J* = 7.7 and 8.1 Hz), 6.32 and 6.46 (1H, 2 x *s*), 7.22-7.70 (4H, *m*); δ ^{13}C-NMR 8.03, 8.69, 13.62, 14.10, 20.59, 20.85, 24.02, 63.05, 63.85, 66.55, 71.03, 72.31, 72.67, 110.53, 112.75, 124.54, 124.74, 130.77, 146.92, 167.69, 171.54; 180.77; ESI-MS *m/z* 379 (MH^+).

3,3-Diethyl-*N*-[(1-ethoxycarbonyl-1-hydroxy)methyl]-4-phenoxyazetidin-2-one (12c). Colorless oil (74%) as a mixture of two diastereomeric pairs of enantiomers; ν_{max} (film) 3404, 3065, 1749, 1492, 1225, 1084 cm $^{-1}$; δ ^{1}H-NMR 1.02 and 1.03 (3H, 2 x *t*, *J* = 7.5Hz), 1.05 and 1.05 (3H, 2 x *t*, *J* = 7.5 Hz), 1.30 and 1.31 (3H, 2 x *t*, *J* = 7.2 Hz), 1.65-1.99 (4H, *m*), 3.92 and 5.17 (1H, 2 x *d*, *J* = 5.7 and 6.8 Hz), 4.17-4.42 (2H, *m*), 5.51 and 5.52 (1H, 2 x *s*), 5.49-5.55 (1H, m), 6.85-7.36 (5H, *m*); δ ^{13}C-NMR 8.64, 9.08, 13.97, 22.14, 23.77, 63.12, 64.62, 69.90, 71.54, 85.16, 86.92, 116.36, 122.76, 129.82, 156.92, 169.23, 170.00, 171.54; ESI-MS *m/z* 321 (M^+).

3,3-Diethyl-*N*-[(1-ethoxycarbonyl-1-hydroxy)methyl]-4-(phenylsulfonyl)azetidin-2-one (12d). Colorless oil (86%) as a mixture of two diastereomeric pairs of enantiomers; ν_{max} (film) 3451, 2975, 1775, 1756, 1327, 1312, 1263 cm $^{-1}$; δ ^{1}H-NMR 0.73 and 0.81 (3H, 2 x *t*, *J* = 7.4 Hz), 0.98 and 1.00 (3H, 2 x *t*, *J* = 7.4 Hz), 1.30 and 1.32 (3H, 2 x *t*, *J* = 7.2 Hz), 1.53-2.41 (4H, *m*), 4.04 and 5.04 (1H, 2 x *d*, *J* = 8.4 and 7.2 Hz), 4.15-4.40 (2H, *m*), 4.60 and 4.63 (1H, 2 x *s*), 5.17 and 5.49 (1H, 2 x *d*, *J* = 8.4 and 7.2 Hz), 7.58 (2H, *t*, *J* = 7.4 Hz), 7.70 (1H, *t*, *J* = 7.4 Hz), 7.98 (2H, *d*, *J* = 7.4 Hz); δ ^{13}C-NMR 8.15, 8.30, 8.76, 14.03, 20.00, 20.07, 24.09, 24.21, 63.14, 63.50, 65.93, 67.09, 72.42, 72.68, 76.92, 77.69, 129.03, 129.48, 134.67, 137.69, 167.69, 169.23, 171.15; 171.92; ESI-MS *m/z* 387 (MNH_4^+).

Table S1. Combustion analysis data for compounds **4-6**.

Compound	Formula	Elemental analyses	
		Required %	Found %
4a	$C_{19}H_{25}NO_6$	C, 62.80; H, 6.93; N, 3.85	C, 62.70; H, 6.94; N, 3.74
4b	$C_{26}H_{28}N_2O_7S$	C, 60.92; H, 5.51; N, 5.47	C, 60.91; H, 5.50; N, 5.38
4c	$C_{25}H_{29}NO_8S$	C, 59.63; H, 5.80; N, 2.78	C, 59.94; H, 5.65; N, 2.86
5c	$C_{25}H_{30}N_2O_6$	C, 66.06; H, 6.65; N, 6.16	C, 66.03; H, 6.65; N, 5.92
5f [a]	$C_{26}H_{30}N_2O_9S$	C, 57.13; H, 5.53; N, 5.13	C, 57.18; H, 5.67; N, 5.08
5f [b]	$C_{26}H_{30}N_2O_9S$	C, 57.13; H, 5.53; N, 5.13	C, 57.15; H, 5.73; N, 4.98
6a	$C_{17}H_{20}N_2O_4$	C, 64.54; H, 6.37; N, 8.86	C, 64.41; H, 6.44; N, 8.66
6b	$C_{24}H_{23}N_3O_5S$	C, 61.92; H, 4.98; N, 9.03	C, 61.90; H, 5.10; N, 8.71
6c [a]	$C_{23}H_{24}N_2O_5$	C, 67.63; H, 5.92; N, 6.98	C, 67.78; H, 5.71; N, 6.68
6c [b]	$C_{23}H_{24}N_2O_5$	C, 67.63; H, 5.92; N, 6.98	C, 67.81; H, 6.07; N, 6.67
6d [a]	$C_{23}H_{24}N_2O_6S$	C, 60.51; H, 5.30; N, 6.13	C, 60.55; H, 5.38; N, 6.13
6d [b]	$C_{23}H_{24}N_2O_6S$	C, 60.51; H, 5.30; N, 6.13	C, 60.39; H, 5.38; N, 5.93
6e [a]	$C_{23}H_{24}N_2O_7S$	C, 58.46; H, 5.12; N, 5.93	C, 58.46; H, 5.25; N, 5.55
6e [b]	$C_{23}H_{24}N_2O_7S$	C, 58.46; H, 5.12; N, 5.93	C, 58.46; H, 5.21; N, 5.66

[a] major diastereomer; [b] minor diastereomer

Crystallographic data (excluding structure factors) for the minor diastereomeric pair **6d**, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC262210. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Table S2. Crystal data and structure refinement for the minor diastereomeric pair of **6d**.

Identification code	**6d**	
Empirical formula	$C_{23}H_{24}N_2O_6S$	
Formula weight	456.50	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 12.4900(8) Å	α = 90°
	b = 17.5457(13) Å	β = 101.760(4)°
	c = 20.2917(12) Å	γ = 90°
Volume	4353.5(5) Å^3	
Z	8	
Density (calculated)	1.393 Mg / m^3	
Absorption coefficient	0.192 mm^{-1}	
F(000)	1920	
Crystal	Block; Colourless	
Crystal size	0.25 × 0.12 × 0.10 mm^3	
θ range for data collection	2.92 – 27.48°	
Index ranges	$-16 \le h \le 14$, $-22 \le k \le 22$, $-25 \le l \le 26$	
Reflections collected	38243	
Independent reflections	9874 [R_{int} = 0.1287]	
Completeness to θ = 27.48°	99.0 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9810 and 0.9535	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9874 / 0 / 581	
Goodness-of-fit on F^2	0.964	
Final R indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0680, *wR2* = 0.1246	
R indices (all data)	*R1* = 0.2052, *wR2* = 0.1654	
Largest diff. peak and hole	0.472 and –0.381 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). S**tructure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). S**tructure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** *ORTEP3 for Windows* (L. J. Farrugia, J. Appl. Crystallogr. 1997, 30, 565).

Special details:
All hydrogen atoms were fixed.

Table S3. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	–589(3)	–1367(2)	6206(2)	26(1)	1
C2	–767(3)	–479(2)	6267(2)	26(1)	1
C3	–1560(3)	–705(2)	6719(2)	27(1)	1
C4	–1396(3)	–2082(2)	7135(2)	28(1)	1
C5	–1485(3)	–1773(2)	7824(2)	26(1)	1
C6	–2972(3)	–2505(2)	7416(2)	31(1)	1
C7	–2902(3)	–1912(2)	8541(2)	37(1)	1
C8	–4022(3)	–1554(2)	8400(2)	30(1)	1
C9	–4713(3)	–1695(2)	8837(2)	34(1)	1
C10	–5737(3)	–1378(2)	8742(2)	36(1)	1
C11	–6117(3)	–922(2)	8189(2)	38(1)	1
C12	–5444(3)	–777(2)	7738(2)	36(1)	1
C13	–4402(3)	–1081(2)	7848(2)	34(1)	1
C14	–708(3)	–2773(2)	5556(2)	31(1)	1
C15	374(3)	–3012(2)	5616(2)	38(1)	1
C16	628(4)	–3768(3)	5723(2)	44(1)	1
C17	–187(4)	–4283(3)	5780(2)	46(1)	1
C18	–1257(4)	–4049(2)	5730(2)	42(1)	1
C19	–1523(3)	–3290(2)	5617(2)	36(1)	1
C20	275(3)	–143(2)	6704(2)	28(1)	1
C21	1220(3)	–69(2)	6342(2)	37(1)	1
C22	–1241(3)	–4(2)	5648(2)	34(1)	1
C23	–1535(3)	802(2)	5830(2)	39(1)	1
N1	–1327(3)	–1481(2)	6670(1)	28(1)	1
N2	–2465(3)	–2042(2)	7935(1)	26(1)	1
O1	–2147(2)	–400(1)	7037(1)	31(1)	1
O2	–2395(2)	–2527(1)	6925(1)	33(1)	1
O3	–831(2)	–1391(1)	8188(1)	36(1)	1
O4	–3807(2)	–2854(2)	7392(1)	39(1)	1
O5	–319(2)	–1512(2)	4988(1)	43(1)	1
O6	–2190(2)	–1741(1)	5185(1)	39(1)	1
S1	–1026(1)	–1806(1)	5399(1)	32(1)	1
C31	–5542(3)	–3347(2)	6201(2)	28(1)	1
C32	–5721(3)	–4231(2)	6239(2)	27(1)	1
C33	–6518(3)	–4025(2)	6689(2)	26(1)	1
C34	–6370(3)	–2663(2)	7131(2)	26(1)	1
C35	–6471(3)	–2978(2)	7818(2)	30(1)	1
C36	–7976(3)	–2248(2)	7405(2)	30(1)	1
C37	–7916(3)	–2866(2)	8518(2)	34(1)	1
C38	–9036(3)	–3222(2)	8354(2)	29(1)	1
C39	–9379(3)	–3693(2)	7799(2)	36(1)	1
C40	–10423(3)	–3998(2)	7667(2)	37(1)	1
C41	–11130(3)	–3856(2)	8091(2)	36(1)	1
C42	–10780(3)	–3400(2)	8653(2)	34(1)	1
C43	–9755(3)	–3079(2)	8777(2)	33(1)	1
C44	–5683(3)	–1910(2)	5583(2)	29(1)	1
C45	–6489(3)	–1415(2)	5692(2)	35(1)	1
C46	–6238(4)	–649(2)	5805(2)	40(1)	1
C47	–5198(4)	–401(2)	5817(2)	44(1)	1

C48	–4389(4)	–899(3)	5717(2)	46(1)	1
C49	–4619(3)	–1657(2)	5605(2)	38(1)	1
C50	–4685(3)	–4591(2)	6669(2)	28(1)	1
C51	–3740(3)	–4652(2)	6314(2)	40(1)	1
C52	–6193(3)	–4681(2)	5596(2)	34(1)	1
C53	–6417(4)	–5514(2)	5740(2)	44(1)	1
N31	–6285(3)	–3255(2)	6668(1)	28(1)	1
N32	–7462(2)	–2708(2)	7924(1)	27(1)	1
O31	–7119(2)	–4358(1)	6990(1)	32(1)	1
O32	–7379(2)	–2228(1)	6918(1)	30(1)	1
O33	–5828(2)	–3361(1)	8187(1)	35(1)	1
O34	–8814(2)	–1911(1)	7375(1)	38(1)	1
O35	–5295(2)	–3165(1)	4983(1)	43(1)	1
O36	–7160(2)	–2956(1)	5199(1)	40(1)	1
S31	–5995(1)	–2884(1)	5406(1)	33(1)	1

Table S4. Bond lengths [Å] and angles [°].

C1–N1	1.458(4)	O5–S1	1.429(3)
C1–C2	1.582(5)	O6–S1	1.435(3)
C1–S1	1.791(3)	C31–N31	1.464(4)
C1–H1	1.0000	C31–C32	1.572(5)
C2–C22	1.523(5)	C31–S31	1.791(3)
C2–C3	1.534(5)	C31–H31	1.0000
C2–C20	1.535(5)	C32–C33	1.525(5)
C3–O1	1.197(4)	C32–C52	1.537(5)
C3–N1	1.399(5)	C32–C50	1.541(5)
C4–N1	1.430(4)	C33–O31	1.210(4)
C4–O2	1.459(4)	C33–N31	1.384(4)
C4–C5	1.525(5)	C34–N31	1.419(4)
C4–H4	1.0000	C34–O32	1.461(4)
C5–O3	1.190(4)	C34–C35	1.529(5)
C5–N2	1.373(5)	C34–H34	1.0000
C6–O4	1.203(4)	C35–O33	1.188(4)
C6–O2	1.344(4)	C35–N32	1.382(5)
C6–N2	1.378(5)	C36–O34	1.193(4)
C7–N2	1.461(4)	C36–O32	1.354(4)
C7–C8	1.507(5)	C36–N32	1.377(5)
C7–H7A	0.9900	C37–N32	1.460(4)
C7–H7B	0.9900	C37–C38	1.507(5)
C8–C9	1.379(5)	C37–H37A	0.9900
C8–C13	1.398(5)	C37–H37B	0.9900
C9–C10	1.371(5)	C38–C43	1.384(5)
C9–H9	0.9500	C38–C39	1.393(5)
C10–C11	1.382(5)	C39–C40	1.384(5)
C10–H10	0.9500	C39–H39	0.9500
C11–C12	1.385(5)	C40–C41	1.375(5)
C11–H11	0.9500	C40–H40	0.9500
C12–C13	1.382(5)	C41–C42	1.388(5)
C12–H12	0.9500	C41–H41	0.9500
C13–H13	0.9500	C42–C43	1.374(5)
C14–C19	1.387(5)	C42–H42	0.9500
C14–C15	1.397(5)	C43–H43	0.9500
C14–S1	1.756(4)	C44–C45	1.382(5)
C15–C16	1.369(6)	C44–C49	1.393(5)
C15–H15	0.9500	C44–S31	1.774(4)
C16–C17	1.384(6)	C45–C46	1.389(5)
C16–H16	0.9500	C45–H45	0.9500
C17–C18	1.382(6)	C46–C47	1.365(6)
C17–H17	0.9500	C46–H46	0.9500
C18–C19	1.381(5)	C47–C48	1.381(6)
C18–H18	0.9500	C47–H47	0.9500
C19–H19	0.9500	C48–C49	1.371(6)
C20–C21	1.516(5)	C48–H48	0.9500
C20–H20A	0.9900	C49–H49	0.9500
C20–H20B	0.9900	C50–C51	1.507(5)
C21–H21A	0.9800	C50–H50A	0.9900
C21–H21B	0.9800	C50–H50B	0.9900
C21–H21C	0.9800	C51–H51A	0.9800
C22–C23	1.525(5)	C51–H51B	0.9800
C22–H22A	0.9900	C51–H51C	0.9800
C22–H22B	0.9900	C52–C53	1.528(5)
C23–H23A	0.9800	C52–H52A	0.9900
C23–H23B	0.9800	C52–H52B	0.9900
C23–H23C	0.9800	C53–H53A	0.9800

C53–H53B	0.9800	O35–S31	1.432(3)
C53–H53C	0.9800	O36–S31	1.435(3)
N1–C1–C2	88.1(2)	C14–C15–H15	120.2
N1–C1–S1	114.6(2)	C15–C16–C17	119.7(4)
C2–C1–S1	118.2(2)	C15–C16–H16	120.1
N1–C1–H1	111.3	C17–C16–H16	120.1
C2–C1–H1	111.3	C18–C17–C16	121.1(4)
S1–C1–H1	111.3	C18–C17–H17	119.5
C22–C2–C3	116.4(3)	C16–C17–H17	119.5
C22–C2–C20	114.1(3)	C19–C18–C17	119.7(4)
C3–C2–C20	109.2(3)	C19–C18–H18	120.1
C22–C2–C1	120.8(3)	C17–C18–H18	120.1
C3–C2–C1	84.8(2)	C18–C19–C14	119.2(4)
C20–C2–C1	107.9(3)	C18–C19–H19	120.4
O1–C3–N1	129.3(3)	C14–C19–H19	120.4
O1–C3–C2	138.4(3)	C21–C20–C2	113.9(3)
N1–C3–C2	92.3(3)	C21–C20–H20A	108.8
N1–C4–O2	111.4(3)	C2–C20–H20A	108.8
N1–C4–C5	111.6(3)	C21–C20–H20B	108.8
O2–C4–C5	103.9(3)	C2–C20–H20B	108.8
N1–C4–H4	109.9	H20A–C20–H20B	107.7
O2–C4–H4	109.9	C20–C21–H21A	109.5
C5–C4–H4	109.9	C20–C21–H21B	109.5
O3–C5–N2	127.9(3)	H21A–C21–H21B	109.5
O3–C5–C4	126.9(3)	C20–C21–H21C	109.5
N2–C5–C4	105.2(3)	H21A–C21–H21C	109.5
O4–C6–O2	123.3(3)	H21B–C21–H21C	109.5
O4–C6–N2	126.2(4)	C2–C22–C23	112.4(3)
O2–C6–N2	110.6(3)	C2–C22–H22A	109.1
N2–C7–C8	113.4(3)	C23–C22–H22A	109.1
N2–C7–H7A	108.9	C2–C22–H22B	109.1
C8–C7–H7A	108.9	C23–C22–H22B	109.1
N2–C7–H7B	108.9	H22A–C22–H22B	107.9
C8–C7–H7B	108.9	C22–C23–H23A	109.5
H7A–C7–H7B	107.7	C22–C23–H23B	109.5
C9–C8–C13	117.7(4)	H23A–C23–H23B	109.5
C9–C8–C7	118.9(3)	C22–C23–H23C	109.5
C13–C8–C7	123.4(3)	H23A–C23–H23C	109.5
C10–C9–C8	121.8(4)	H23B–C23–H23C	109.5
C10–C9–H9	119.1	C3–N1–C4	129.0(3)
C8–C9–H9	119.1	C3–N1–C1	94.7(3)
C9–C10–C11	120.2(4)	C4–N1–C1	131.1(3)
C9–C10–H10	119.9	C5–N2–C6	111.3(3)
C11–C10–H10	119.9	C5–N2–C7	125.6(3)
C10–C11–C12	119.2(4)	C6–N2–C7	122.9(3)
C10–C11–H11	120.4	C6–O2–C4	108.9(3)
C12–C11–H11	120.4	O5–S1–O6	120.14(16)
C13–C12–C11	120.1(4)	O5–S1–C14	108.14(17)
C13–C12–H12	120.0	O6–S1–C14	108.03(17)
C11–C12–H12	120.0	O5–S1–C1	105.67(16)
C12–C13–C8	120.9(4)	O6–S1–C1	110.08(16)
C12–C13–H13	119.5	C14–S1–C1	103.54(17)
C8–C13–H13	119.5	N31–C31–C32	87.7(2)
C19–C14–C15	120.7(4)	N31–C31–S31	114.0(2)
C19–C14–S1	120.3(3)	C32–C31–S31	118.0(2)
C15–C14–S1	119.0(3)	N31–C31–H31	111.7
C16–C15–C14	119.5(4)	C32–C31–H31	111.7
C16–C15–H15	120.2	S31–C31–H31	111.7

C33–C32–C52	116.5(3)
C33–C32–C50	109.5(3)
C52–C32–C50	113.8(3)
C33–C32–C31	85.0(2)
C52–C32–C31	119.9(3)
C50–C32–C31	108.7(3)
O31–C33–N31	130.0(3)
O31–C33–C32	137.3(3)
N31–C33–C32	92.6(3)
N31–C34–O32	111.4(3)
N31–C34–C35	111.7(3)
O32–C34–C35	103.4(3)
N31–C34–H34	110.0
O32–C34–H34	110.0
C35–C34–H34	110.0
O33–C35–N32	127.4(4)
O33–C35–C34	127.5(4)
N32–C35–C34	105.1(3)
O34–C36–O32	123.9(3)
O34–C36–N32	126.7(4)
O32–C36–N32	109.5(3)
N32–C37–C38	113.3(3)
N32–C37–H37A	108.9
C38–C37–H37A	108.9
N32–C37–H37B	108.9
C38–C37–H37B	108.9
H37A–C37–H37B	107.7
C43–C38–C39	118.6(4)
C43–C38–C37	118.6(3)
C39–C38–C37	122.8(3)
C40–C39–C38	120.4(4)
C40–C39–H39	119.8
C38–C39–H39	119.8
C41–C40–C39	120.6(4)
C41–C40–H40	119.7
C39–C40–H40	119.7
C40–C41–C42	118.9(4)
C40–C41–H41	120.6
C42–C41–H41	120.6
C43–C42–C41	120.8(4)
C43–C42–H42	119.6
C41–C42–H42	119.6
C42–C43–C38	120.7(4)
C42–C43–H43	119.7
C38–C43–H43	119.7
C45–C44–C49	121.1(4)
C45–C44–S31	120.0(3)
C49–C44–S31	118.9(3)
C44–C45–C46	119.1(4)
C44–C45–H45	120.4
C46–C45–H45	120.4
C47–C46–C45	119.6(4)
C47–C46–H46	120.2
C45–C46–H46	120.2
C46–C47–C48	121.2(4)
C46–C47–H47	119.4
C48–C47–H47	119.4
C49–C48–C47	120.2(4)
C49–C48–H48	119.9
C47–C48–H48	119.9
C48–C49–C44	118.8(4)
C48–C49–H49	120.6
C44–C49–H49	120.6
C51–C50–C32	114.0(3)
C51–C50–H50A	108.7
C32–C50–H50A	108.7
C51–C50–H50B	108.7
C32–C50–H50B	108.7
H50A–C50–H50B	107.6
C50–C51–H51A	109.5
C50–C51–H51B	109.5
H51A–C51–H51B	109.5
C50–C51–H51C	109.5
H51A–C51–H51C	109.5
H51B–C51–H51C	109.5
C53–C52–C32	112.4(3)
C53–C52–H52A	109.1
C32–C52–H52A	109.1
C53–C52–H52B	109.1
C32–C52–H52B	109.1
H52A–C52–H52B	107.9
C52–C53–H53A	109.5
C52–C53–H53B	109.5
H53A–C53–H53B	109.5
C52–C53–H53C	109.5
H53A–C53–H53C	109.5
H53B–C53–H53C	109.5
C33–N31–C34	130.5(3)
C33–N31–C31	94.5(3)
C34–N31–C31	130.7(3)
C36–N32–C35	112.0(3)
C36–N32–C37	122.9(3)
C35–N32–C37	125.0(3)
C36–O32–C34	109.9(3)
O35–S31–O36	120.03(17)
O35–S31–C44	108.43(17)
O36–S31–C44	108.17(18)
O35–S31–C31	105.32(17)
O36–S31–C31	109.89(17)
C44–S31–C31	103.81(17)

Table S5. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	18(2)	40(2)	19(2)	–3(2)	4(2)	–3(2)
C2	24(2)	27(2)	29(2)	1(2)	7(2)	–4(2)
C3	21(2)	35(2)	25(2)	0(2)	5(2)	2(2)
C4	22(2)	31(2)	30(2)	2(2)	3(2)	–4(2)
C5	24(2)	27(2)	26(2)	1(2)	3(2)	3(2)
C6	25(2)	37(2)	30(2)	4(2)	6(2)	5(2)
C7	39(3)	51(3)	23(2)	4(2)	13(2)	7(2)
C8	29(2)	35(2)	28(2)	–2(2)	10(2)	–1(2)
C9	37(3)	36(2)	33(2)	2(2)	12(2)	4(2)
C10	35(3)	37(2)	42(2)	–1(2)	18(2)	–2(2)
C11	32(3)	30(2)	52(3)	–9(2)	8(2)	0(2)
C12	33(3)	35(2)	39(2)	0(2)	9(2)	3(2)
C13	35(3)	37(2)	33(2)	5(2)	13(2)	1(2)
C14	22(2)	49(3)	24(2)	–13(2)	9(2)	–6(2)
C15	30(3)	52(3)	32(2)	–10(2)	6(2)	–3(2)
C16	23(3)	65(3)	41(3)	–3(2)	3(2)	12(2)
C17	52(3)	50(3)	35(2)	1(2)	5(2)	15(2)
C18	38(3)	49(3)	40(2)	2(2)	12(2)	–3(2)
C19	30(3)	42(3)	35(2)	–9(2)	8(2)	–1(2)
C20	27(2)	32(2)	25(2)	3(2)	5(2)	–1(2)
C21	30(2)	41(2)	42(2)	–8(2)	11(2)	–3(2)
C22	33(3)	42(3)	27(2)	6(2)	7(2)	–6(2)
C23	34(3)	40(2)	40(2)	7(2)	7(2)	2(2)
N1	27(2)	34(2)	24(2)	–1(1)	11(1)	–1(1)
N2	25(2)	34(2)	19(2)	–1(1)	6(1)	–3(1)
O1	29(2)	37(2)	29(1)	4(1)	11(1)	5(1)
O2	33(2)	39(2)	29(1)	–5(1)	9(1)	–5(1)
O3	31(2)	37(2)	37(2)	2(1)	0(1)	–6(1)
O4	29(2)	49(2)	39(2)	1(1)	7(1)	–10(1)
O5	51(2)	52(2)	30(2)	–1(1)	18(1)	–7(1)
O6	30(2)	47(2)	37(2)	–5(1)	–1(1)	0(1)
S1	29(1)	42(1)	24(1)	–4(1)	7(1)	–3(1)
C31	27(2)	36(2)	23(2)	4(2)	9(2)	2(2)
C32	26(2)	36(2)	19(2)	–3(2)	5(2)	2(2)
C33	23(2)	32(2)	21(2)	–2(2)	1(2)	0(2)
C34	18(2)	32(2)	28(2)	–1(2)	7(2)	–2(2)
C35	32(3)	24(2)	30(2)	–7(2)	–1(2)	–6(2)
C36	26(2)	35(2)	28(2)	–6(2)	2(2)	–5(2)
C37	34(3)	44(2)	29(2)	–2(2)	13(2)	–3(2)
C38	34(2)	30(2)	25(2)	2(2)	8(2)	0(2)
C39	33(3)	41(2)	37(2)	–3(2)	16(2)	1(2)
C40	39(3)	34(2)	38(2)	–3(2)	7(2)	–5(2)
C41	24(2)	39(2)	47(3)	6(2)	12(2)	–2(2)
C42	29(2)	37(2)	40(2)	3(2)	17(2)	4(2)
C43	37(3)	32(2)	32(2)	1(2)	14(2)	2(2)
C44	30(3)	37(2)	21(2)	3(2)	5(2)	–3(2)
C45	25(2)	49(3)	31(2)	7(2)	10(2)	6(2)
C46	42(3)	42(3)	37(2)	4(2)	14(2)	5(2)
C47	55(3)	42(3)	33(2)	0(2)	5(2)	–12(2)
C48	36(3)	52(3)	47(3)	4(2)	3(2)	–7(2)
C49	25(3)	52(3)	37(2)	3(2)	6(2)	0(2)
C50	22(2)	32(2)	30(2)	–1(2)	7(2)	2(2)

C51	26(2)	54(3)	41(2)	4(2)	10(2)	5(2)
C52	34(3)	43(3)	25(2)	–6(2)	3(2)	1(2)
C53	45(3)	41(3)	42(2)	–13(2)	0(2)	2(2)
N31	27(2)	32(2)	25(2)	–6(1)	9(1)	–3(1)
N32	23(2)	37(2)	22(2)	1(1)	7(1)	3(1)
O31	30(2)	37(2)	32(1)	–1(1)	11(1)	–4(1)
O32	28(2)	37(2)	26(1)	3(1)	7(1)	5(1)
O33	34(2)	38(2)	33(2)	–1(1)	5(1)	6(1)
O34	29(2)	45(2)	42(2)	4(1)	10(1)	10(1)
O35	54(2)	48(2)	33(2)	1(1)	26(2)	3(1)
O36	36(2)	50(2)	31(2)	5(1)	–3(1)	–4(1)
S31	33(1)	41(1)	25(1)	3(1)	7(1)	1(1)

Table S6. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	176	–1518	6417	31	1
H4	–743	–2422	7179	33	1
H7A	–2393	–1577	8850	44	1
H7B	–2938	–2405	8772	44	1
H9	–4474	–2019	9212	41	1
H10	–6187	–1473	9059	44	1
H11	–6831	–709	8119	46	1
H12	–5700	–470	7353	43	1
H13	–3938	–966	7544	41	1
H15	930	–2654	5583	46	1
H16	1359	–3937	5757	52	1
H17	–8	–4807	5856	56	1
H18	–1807	–4409	5772	50	1
H19	–2256	–3123	5582	43	1
H20A	104	367	6864	34	1
H20B	506	–472	7104	34	1
H21A	1370	–566	6160	55	1
H21B	1871	109	6660	55	1
H21C	1028	299	5974	55	1
H22A	–1906	–259	5393	41	1
H22B	–702	23	5352	41	1
H23A	–2070	778	6122	58	1
H23B	–1848	1083	5418	58	1
H23C	–874	1064	6067	58	1
H31	–4776	–3198	6413	34	1
H34	–5723	–2317	7180	31	1
H37A	–7958	–2383	8764	41	1
H37B	–7414	–3212	8820	41	1
H39	–8892	–3805	7508	43	1
H40	–10653	–4308	7281	45	1
H41	–11846	–4065	8000	43	1
H42	–11254	–3310	8956	41	1
H43	–9537	–2756	9156	39	1
H45	–7207	–1596	5689	41	1
H46	–6786	–300	5874	48	1
H47	–5028	123	5895	53	1

H48	–3670	–715	5726	55	1
H49	–4064	–2004	5543	46	1
H50A	–4453	–4283	7082	33	1
H50B	–4867	–5108	6809	33	1
H51A	–3933	–5000	5930	59	1
H51B	–3096	–4847	6627	59	1
H51C	–3576	–4147	6152	59	1
H52A	–6883	–4438	5365	41	1
H52B	–5672	–4659	5288	41	1
H53A	–5724	–5773	5920	66	1
H53B	–6782	–5764	5323	66	1
H53C	–6888	–5539	6071	66	1

Figure S1. ORTEP view of the crystal structure determined for the minor diastereomeric pair of enantiomers of compound **6d**; the right-hand enantiomer has 4*S*,5'*R* chirality and the left-hand enantiomer has 4*R*,5'*S* chirality.