One Pot Diastereoselective Synthesis of New Chiral Spiro-1,3,4-thiadiazoles and 1,4,2-Oxathiazoles from (1*R*)-Thiocamphor

Amal Feddouli[a], Moulay Youssef Ait Itto[a], Aïssa Hasnaoui[a], Didier Villemin[b], Paul-Alain Jaffrès[b], [c]Jana Sopkova-De Oliveira Santos, Abdelkhalek Riahi[d], François Huet[e], Jean-Claude Daran[f]

[a]Laboratoire des Substances Naturelles et des Hétérocycles, Département de Chimie, Faculté des Sciences Semlalia, B.P. 2390-Marrakech 40001-Maroc, e-mail : aititto@ucam.ac.ma

[b]ENSICAEN,Université de Caen, 6 Bd du Maréchal Juin, F-14050 Caen, Laboratoire de Chimie Moléculaire et Thioorganique, UMR CNRS 6507, France

[c]Université de Caen, Centre d'Etudes et la Recherche sur le Médicament de Normandie (CERMN), 5 rue Vaubénard, F-14032 Caen, France

[d]Université de Reims, UFR Sciences, UMR 6519, Réactions Sélectives et Applications, B.P. 1039, 51687 Reims Cedex 2, France

[e]Laboratoire de Synthèse Organique UMR CNRS 6011, Faculté des Sciences, Université du Maine, Avenue Olivier Messiaen 72085 Le Mans Cedex 9, France

[f]Laboratoire de Chimie de Coordination, CNRS UPR 8241, 205 route de Narbonne, 31077 Toulouse Cedex 04, France e-mail: daran@lcc-toulouse.fr

Herein we report an efficient one pot synthesis of new chiral 4,5-dihydro-4-arylspiro[1,3,4-thiadiazole]-5,2'-camphane-2-carboxylic acid ethyl esters **5-7** and 4,5-dihydro-3-arylspiro[1,4,2-oxathiazole]-5,2'-camphane **11-13**, using 1,3-dipolar cycloaddition of nitrilimines **2-4** and nitrile oxides **8-10** to (1*R*)-thiocamphor **1** respectively. The structure of the newly prepared 1,3,4-thiadiazoles **5-7** (obtained as pure diastereoisomers) were fully established *via* spectroscopic analysis and X-ray structural analysis which proved the absolute configuration of the C5 spiranic carbon to be (*R*). NMR spectral analysis were also very useful to show the new 1,4,2-oxathiazoles **11-13** are mixtures of two (5*R*)/(5*S*) diastereoisomers with the ratio 6:4, 7:3 and 6:4 respectively.

J. Heterocyclic Chem., **41**, 731 (2004).

Introduction.

Nitrogen and sulfur containing heterocycles are of considerable interest because of their chemistry [1] and potentially benefical biological activities, such as anti-inflammatory [2a], antibacterial [2b], insecticidal [2c], anti-HIV [2d], anticonvulsant [2e] and antitumor [2f]. This prompted us to prepare new nitrogen and sulfur containing heterocyclic systems using the 1,3-dipolar cycloaddition reaction of nitrogen containing 1,3-dipoles with a thiocarbonylated compound.

Since the work of Huisgen [3], 1,3-dipolar cycloaddition reactions remained attractive to organic chemists as these reactions provide a useful and general route to a large variety of five membered heterocyclic systems. While the cycloaddition to substituted alkenes and alkynes has been extensively investigated [3c] the use of thiocarbonyls as dipolarophiles is limited to only few reports [4].

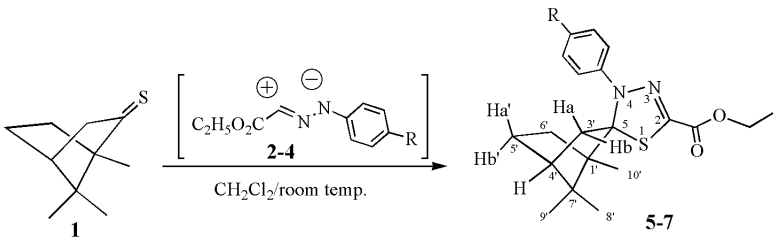
Among these studies, it is worth mentioning that the 1,3-cycloaddition of diazomethane to thiofenchone or thiocamphor leads to the corresponding unstable 1,3,4-thiadiazolines. These intermediates extrude N_2 readily generating the corresponding and more stable, 1-(methylthio)-α-fenchene and 2-(methylthio)-2-bornene [5]. Similarly, diphenylnitrilimine reacts with thioketones, thioamides and thiourethanes to produce the corresponding cycloadducts [4a].

Encouraged by these results we became interested in the 1,3-dipolar cycloadditions of nitrilimines and nitrile oxides with (1*R*)-thiocamphor **1**, which provide new chiral spiro-1,3,4-thiadiazoles and 1,4,2-oxathiazoles.

Results and Discussion.

Nitrilimines **2-4**, which are generated *in situ* from ethyl *N*-arylhydrazo-α-bromoglyoxalates and triethylamine [3a], react at room temperature with (1*R*)-thiocamphor **1** to

Scheme 1



R = CH_3 (**2** and **5**); NO_2 (**3** and **6**); Cl (**4** and **7**)

produce the corresponding cycloadducts **5-7** (Scheme 1) in good yields [**5** (92 %); **6** (80 %); **7** (85 %)].

All compounds **5-7** were fully characterised using standard methods (NMR, mass) of note are the chemical shift values of the spiro carbon (C5) signals (94-96 ppm) in the ^{13}C NMR spectra.

Furthermore, the most salient features of the **5-7** ^{1}H NMR spectra is the one proton doublet [with a large coupling constant (J ~ 15 Hz)] at about 2 ppm, and the one proton doubled doublet of doublets (J ~ 15 Hz , J' 3.6-3.8 Hz, J" 3.4-3.7 Hz) which appeared between 2.19-2.32 ppm. The former signal was attributed to the Ha-C3' proton which has an angle of ~ 90° with respect to the adjacent H-C4' proton and therefore, only geminal coupling (15 Hz) was observed. The latter is ascribed to the Hb-C3' proton; its signal multiplicity (doubled doublet of doublets) is likely due to a geminal coupling with Ha-C3' (15 Hz), a vicinal coupling with H-C4' (3.6-3.8) and a *W*-coupling with one of the two protons at C5' position.

Here it is worthy to note that COSY ^{1}H-^{1}H and HMQC experiments were very useful to assign all carbon and hydrogen atoms of **5-7** and all the resulting spectrometric data were consistent with those available from literature [6].

However, the absolute configuration of the newly formed stereogenic centre (C5 spiranic carbon) was so far unknown. This prompted us to carry out X-ray crystal structural analysis which allowed an unambiguous assignment of the absolute configuration (*R*) to the spiranic carbon, as established by anomalous dispersion effects in diffraction measurements on the crystals (Refinement of the Flack's enantiopole parameter).

In addition, a search in the Cambridge Structural Database [7] shows that the overall geometry of the 1,3,4-thiadiazoline ring fits well with the values reported in the literature [8-13].

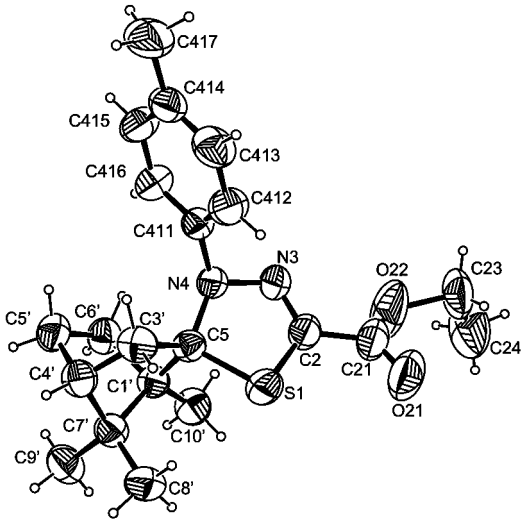


Figure 1: ORTEP view of the molecular structure of **5** with atoms labelling scheme. Ellipsoids are drawn at 50% probability.

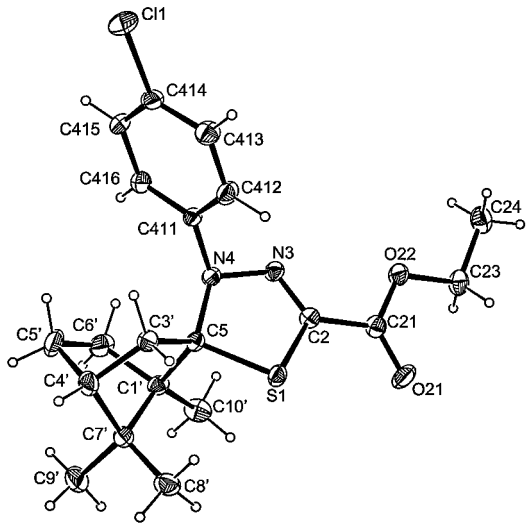


Figure 2: ORTEP view of the molecular structure of **7** with atoms labelling scheme. Ellipsoids are drawn at 50% probability.

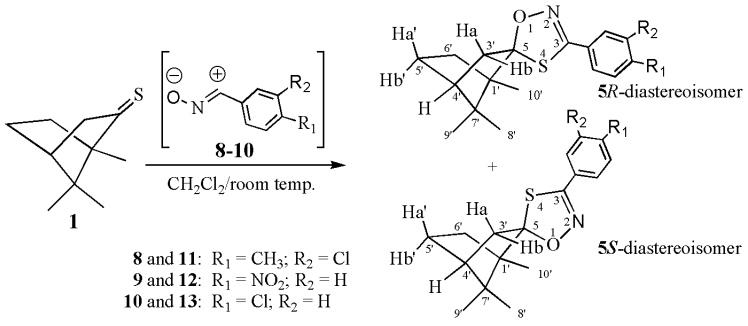
In an attempt to understand the stereospecific nature of the 1,3-dipolar cycloaddition of nitrilimines **2-4** to (1*R*)-thiocamphor **1**, a rapid calculation (geometry optimisation) using the semi-empiric PM3 method [14] compounds **5-7** (R = H and the alkyl chain on the ester function is a methyl group) indicates that the 5*R* stereoisomer is 2.8 Kcal mol^{-1} thermodynamically more stable than the 5*S* stereoisomer. A single point calculation (the conformations obtained from PM3 geometry optimisation were used) of the energies of two stereoisomers by using Hartree-Fock methods (6.31G*) leads to a similar order (3.2 Kcal mol^{-1} energy difference between the two stereoisomers in favour of 5*R* isomer). Furthermore, the *Re* face of the (1*R*)-thiocamphor is much more sterically hindered than the *Si* face. Therefore the approach of the nitrilimine on the (1*R*)-thiocamphor should be favoured on the *Si* face thus producing the experimentally observed stereoisomer.

The reaction of **1** with arylonitrile oxides **8-10**, generated *in situ* from the corresponding arylhydroximinoyl chlorides [3b] on the other hand, afforded inseparable diastereomeric mixtures of spiro 1,4,2-oxathiazoles **11-13** (Scheme 2) albeit in good yields [**11** 6:4 (83 %); **12** 7:3 (90 %); **13** 6:4 (85 %)].

Conclusion.

In summary, we have described a simple one-step synthesis of new spiro 1,3,4-thiadiazoles **5-7** and spiro 1,4,2-oxathiazoles **11-13** *via* 1,3-dipolar cycloaddition of *N*-aryl-*C*-ethoxycarbonyl nitrilimines **2-4** and arylonitrile

Scheme 2



oxides **8-10**, to (1*R*)-thiocamphor respectively. The reaction has proven to be efficient as the desired nitrogen and sulfur containing heterocyclic systems **5-7** and **11-13** were obtained with good yields (≥ 80 %). The synthesis of **5-7** was revealed to be highly diastereoselective as all the new 1,3,4-thiadiazoles were isolated as pure diastereoisomers. Using NMR and X-Ray structural studies, we have demonstrated that the newly formed chiral center (C5) possesses an (*R*) absolute configuration. A brief theoretical study, carried out using semi-empiric PM3 method confirmed the established result. In contrast, the newly prepared 1,4,2-oxathiazoles **11-13** were obtained as inseparable diastereoisomeric mixtures easily identified from the corresponding NMR spectra which revealed 5*R*/5*S* diastereoispmeric ratio of about 7/3 or 6/4.

EXPERIMENTAL

General Remarks.

Melting points (mp) were determined using a capillary apparatus and are uncorrected. Analytical TLC was performed on plates precoated with E. Merck silica gel 60 F_{254} of 0.25 mm thickness. The optical rotations were measured (chloroform) with Perkin Elmer 241 polarimeter. Mass spectra were registered on a JEOL D 300 spectrometer. ^1H and ^{13}C nmr spectra were recorded in $CDCl_3$ with a Bruker AM 400 instrument. Chemical shifts (δ) are expressed in ppm with TMS as internal standard. The elemental analyses were carried out on a CHN2400 Perkin-Elmer analyser.

Typical Experiment.

To a solution of (1*R*)-thiocamphor **1** (0.23 g, 1.37 mmol) and ethyl *N*-aryl hydrazo-α-bromoglyoxalates, precursors of nitrilimines **2-4** (or arylhydroximinoyl chlorides, precursors of arylonitrile oxides **8-10**) (1.37 mmol) in dichloromethane (20 mL), triethylamine (0.3 mL) in dichloromethane (2 mL) was added slowly at room temperature. The reaction mixture was then, stirred at room temperature for two days (monitoring by tlc), filtered and concentrated under reduced pressure. The resulting residue was purified by chromatography (SiO_2, hexane/ethyl acetate 95:5) and recrystallised from hexane.

Ethyl (5*R*,1'*R*,4'*R*)-4,5-Dihydro-4-(*p*-methylphenyl)spiro[1,3,4-thiadiazole-5,2'-camphane]-2-carboxylate (**5**).

This compound was obtained as colourless crystals in 92% yield, mp 89-90 °C; $[\alpha]_D^{25}$ = +1035 (c = 5, $CHCl_3$); ^1H nmr (deuteriochloroform): δ 0.89 (s, 3H, H_3C8'), 0.91 (m, 1H, *Ha*-C5'), 1.03 (s, 3H, H_3C9'), 1.05 (s, 3H, H_3C10'), 1.35 (t J=7 Hz, 3H, CH_3-CH_2O), 1.44 (ddd J = 13.5, 11.4 and 4.0 Hz, 1H, *H*-C6'), 1.70 (m, 2H, *H*-C4' and *Hb*-C5'), 1.92 (d J=15.3 Hz, 1H, *Ha*-C3'), 2.19 (ddd J = 15.3, 3.8 and 3.7 Hz, 1H, *Hb*-C3'), 2.35 (s, 3H, CH_3-Ar), 2.47 (ddd J = 13.5, 9.8 and 3.7 Hz, 1H, *H*-C6'), 4.34 (m, 2H, CH_2-O), 7.10-7.30 (m, 4H, *H*-Ar); ^{13}C nmr (deuteriochloroform): δ 11.94 (H_3C8'), 14.19 (H_3C-CH_2O), 20.77 (H_3C9'), 21.06 (H_3C10'), 20.61 (H_3C-Ar), 26.42 (H_2C5'), 27.70 (H_2C6') 42.67 (H_2C3'), 45.26 (HC4'), 48.98 (C7'), 58.17 (C1'), 62.06 (CH_2-O), 94.31 (C5), 129.49 and 129.12 (*C*H Ar), 137.67 (C Ar), 140.94 (N4-C Ar), 142.08 (C2), 160.74(C=O); ms: (EI^+) m/z 372 (64 %, M^+), 357 (45), 301 (83), 263 (71), 249 (43), 118 (33), 105 (35), 95 (100), 91 (81), 67 (55), 65 (50), 55 (50).

Anal. Calcd. for $C_{21}H_{28}N_2O_2S$: C 67.71, H 7.58, N 7.52. Found: C 67.80, H 7.69, N 7.46.

Ethyl (5*R*,1'*R*,4'*R*)-4,5-Dihydro-4-(*p*-nitrophenyl)spiro[1,3,4-thiadiazole-5,2'-camphane]-2-carboxylate (**6**).

This compound was obtained as colourless oil in 80% yield; $[\alpha]_D^{25}$ = +1250 (c = 10, $CHCl_3$); ^1H nmr (deuteriochloroform): δ 0.92 (s, 3H, H_3C8'), 1.07 (s, 3H, H_3C9'), 1.08 (s, 3H, H_3C10'), 1.15 (m, 1H, *Ha*-C5'), 1.39 (t J=7 Hz, 3H, CH_3-CH_2O), 1.52 (m, 1H, *H*-C6'), 1.76 (m, 2H, *H*-C4' and *Hb*-C5'), 2.11 (ddd J = 13.6, 9.4 and 3.7 Hz, 1H, *H*-C6'), 2.17 (d J=15.6 Hz, 1H, *Ha*-C3'), 2.32 (ddd J = 15.6, 3.6 and 3.4 Hz, 1H, *Hb*-C3'), 4.38 (m, 2H, CH_2-O), 7.47-8.24 (m, 4H, *H*-Ar); ^{13}C nmr (deuteriochloroform): δ 11.69 (H_3C8'), 14.02 (H_3C-CH_2O), 20.61 (H_3C9'), 20.80 (H_3C10'), 26.28 (H_2C5'), 28.21 (H_2C6'), 40.66 (H_2C3'), 45.17 (HC4'), 48.65 (C7'), 58.56 (C1'), 62.38 (CH_2-O), 95.48 (C5), 124.15 and 126.68 (*C*H Ar), 145.13.67 and 145.29 (N4-C Ar and NO_2-C Ar), 149.90 (C2), 159.88(C=O); ms: (EI^+) m/z 403 (12 %, M^+), 150 (33), 134 (61), 109 (100), 93 (69), 67 (49), 55 (40).

Anal. Calcd for $C_{20}H_{25}N_3O_4S$: C 59.53, H 6.25, N 10.41. Found: C 59.65, H 6.14, N 10.49.

Ethyl (5*R*,1'*R*,4'*R*)-4,5-Dihydro-4-(*p*-chlorophenyl)spiro[1,3,4-thiadiazole-5,2'-camphane]-2-carboxylate (**7**).

This compound was obtained as colourless crystals in 85% yield, mp 90-91 °C; $[\alpha]_D^{25}$ = +1142 (c = 5, $CHCl_3$); ^1H nmr (deuteriochloroform): δ 0.90 (s, 3H, H_3C8'), 0.91 (m, 1H, *Ha*-C5'), 1.03 (s, 3H, H_3C9'), 1.05 (s, 3H, H_3C10'), 1.36 (t J=7 Hz, 3H, CH_3-CH_2O), 1.47 (ddd J = 13.7, 11.7 and 4.0 Hz, 1H, *H*-C6'), 1.66 (m, 2H, *H*-C4' and *Hb*-C5'), 1.88 (d J=15.3 Hz, 1H,

Ha-C3'), 2.21 (ddd J = 15.3, 3.8 and 3.7 Hz, 1H, *Hb*-C3'), 2.37 (ddd J = 13.7, 10.0 and 4.0 Hz, 1H, *H*-C6'), 4.35 (m, 2H, CH_2-O), 7.25-7.36 (m, 4H, *H*-Ar); ^{13}C nmr (deuteriochloroform): δ 11.82 (H$_3$*C*8'), 14.12 (H$_3$*C*-CH$_2$O), 20.57 (H$_3$*C*9'), 21.71 (H$_3$*C*10'), 26.40 (H$_2$*C*5'), 27.76 (H$_2$*C*6'), 42.26 (H$_2$*C*3'), 45.20 (H*C*4'), 48.91 (C7'), 58.17 (C1'), 62.20 (*C*H$_2$-O), 94.40 (C5), 128.99 and 130.26 (*C*H Ar), 133.27 (Cl-*C* Ar), 142.16 (N4-C Ar), 143.57 (C2), 160.38 (C=O); ms: (EI$^+$) m/z 394 (4.22 %, M+2]$^+$), 392 (11.55 %, M$^+$), 379 (1.91), 377 (4.81), 323 (10.02), 321 (27.27), 111 (15.51), 95 (100), 67 (13.34), 55 (15.46).

Anal. Calcd for $C_{20}H_{25}ClN_2O_2S$: C 61.13, H 6.41, N 7.13. Found: C 61.10, H 6.45, N 7.11.

(5*R*,1'*R*,4'*R*) and (5*S*,1'*R*,4'*R*)-4,5-Dihydro-3-(3"-chloro-4"-methylphenyl)spiro[1,4,2-oxathiazole]-5,2'-camphane (**11**).

This compound was obtained as colourless solid in 83% yield, mp 55-57 °C; ^{1}H nmr (deuteriochloroform): δ 0.92 (s, 1.2H, *H*$_3$C8' 5*S*-diastereoisomer), 0.93 (s, 1.8H, *H*$_3$C8' 5*R*-diastereoisomer), 0.95 (s, 1.2H, *H*$_3$C9' 5*S*-diastereoisomer), 0.97 (s, 1.8H, *H*$_3$C9' 5*R*-diastereoisomer), 1.03 (s, 1.8H, *H*$_3$C10' 5*R*-diastereoisomer), 1.14 (s, 1.2H, *H*$_3$C10' 5*S*-diastereoisomer), 2.06 (d J=14.7 Hz, 0.4H, *Ha*-C3' 5*S*-diastereoisomer), 2.13 (d J=14.7 Hz, 0.6H, *Ha*-C3' 5*R*-diastereoisomer), 2.47 (ddd J = 14.7, 4.5 and 3.3 Hz, 0.6H, *Hb*-C3' 5*R*-diastereoisomer), 2.75 (ddd J = 14.7, 4.4 and 3.4 Hz, 0.4H, *Hb*-C3' 5*S*-diastereoisomer), 2.40 (s, 3H, C*H*$_3$-Ar), 7.24-7.65 (m, 3H, *H*-Ar); ^{13}C nmr (deuteriochloroform): δ 10.23 and 12.74 (H$_3$*C*8'), 19.85 and 20.12 (H$_3$*C*9'), 20.39 and 20.50 (H$_3$*C*10'), 21.21 (H$_3$*C*-Ar), 26.87 and 26.98 (H$_2$*C*5'), 28.94 and 33.08 (H$_2$*C*6'), 45.11 and 45.64 (H$_2$*C*3'), 48.28 and 48.52 (H*C*4'), 49.42 and 49.60 (C7'), 54.95 and 55.51 (C1'), 113.66 and 116.63 (C5), 125.56 and 125.61 (*C*H Ar), 127.76 and 127.84 (*C* Ar), 127.98, 128.02 and 131.07 (*C*H Ar), 134.66 (CH$_3$-*C* Ar), 138.72 and 138.77 (Cl-*C* Ar), 153.38 and 155.40 (C3); ms: (EI$^+$) m/z 337 (4.47 %, M+2]$^+$), 335 (12.16 %, M$^+$), 183 (18.62), 169 (96.53), 127 (75.14), 123 (68.46), 116 (43.70), 109 (92.24), 108 (100), 107 (32.43), 95 (56.22), 93 (28.56), 81 (41.32), 69 (29.00), 67 (46.20), 55 (59.61), 53 (21.60), 43 (24.33).

Anal. Calcd for $C_{18}H_{22}ClNOS$: C 64.36, H 6.60, N 4.17. Found: C 64.48, H 6.64, N 4.02.

(5*R*,1'*R*,4'*R*) and (5*S*,1'*R*,4'*R*)-4,5-Dihydro-3-(4"-nitrophenyl)-spiro[1,4,2-oxathiazole]-5,2'-camphane (**12**).

This compound was obtained as colourless solid in 90% yield, mp 150-152 °C; ^{1}H nmr (deuteriochloroform): δ 0.94 (s br, 3H, *H*$_3$C8'), 0.97 (s, 0.9H, *H*$_3$C9' 5*S*-diastereoisomer), 0.98 (s, 2.1H, *H*$_3$C9' 5*R*-diastereoisomer), 1.04 (s, 2.1H, *H*$_3$C10' 5*R*-diastereoisomer), 1.15 (s, 0.9H, *H*$_3$C10' 5*S*-diastereoisomer), 2.09 (d J=14.8 Hz, 0.3H, *Ha*-C3' 5*S*-diastereoisomer), 2.16 (d J=14.8 Hz, 0.7H, *Ha*-C3' 5*R*-diastereoisomer), 2.49 (ddd J = 14.8, 4.5 and 3.3 Hz, 0.7H, *Hb*-C3' 5*R*-diastereoisomer), 2.79 (ddd J = 14.8, 4.2 and 3.5 Hz, 0.3H, *Hb*-C3' 5*S*-diastereoisomer), 7.80-8.28 (m, 4H, *H*-Ar); ^{13}C nmr (deuteriochloroform): δ 10.18 and 12.74 (H$_3$*C*8'), 19.78 and 20.46 (H$_3$*C*9'), 20.35 and 21.17 (H$_3$*C*10'), 26.83 and 26.97 (H$_2$*C*5'), 28.89 and 33.20 (H$_2$*C*6'), 45.11 and 45.66 (H$_2$*C*3'), 48.32 and 48.55 (H*C*4'), 49.76 and 49.99 (C7'), 55.13 and 55.68 (C1'), 115.14 and 118.15 (C5), 123.89, 128.25 and 128.29 (*C*H Ar), 134.65 and 134.73 (*C* Ar), 148.70 (NO$_2$-*C* Ar), 152.55 and 154.54 (C3); ms: (EI$^+$) m/z 332 (8.91 %, M$^+$), 302 (3.40), 222 (9.47), 180 (14.17), 169 (100), 150 (46.47), 127 (64.26), 123 (58.62), 118 (32.77), 109 (82.81), 108 (95.06), 107 (31.17), 95 (92.94), 93 (35.42), 91 (24.89), 83 (31.78), 81 (65.04), 69 (36.47), 67 (49.93), 55 (79.86), 53 (30.97), 43 (25.74).

Anal. Calcd for $C_{17}H_{20}N_2O_3S$: C 61.42, H 6.06, N 8.43. Found: C 61.40, H 6.11, N 8.41.

(5*R*,1'*R*,4'*R*) and (5*S*,1'*R*,4'*R*)-4,5-dihydro-3-(4"-chlorophenyl)-spiro[1,4,2-oxathiazole]-5,2'-camphane (**13**).

This compound was obtained as colourless solid in 85% yield, mp 78-80 °C; ^{1}H nmr (deuteriochloroform): δ 0.92 (s, 1.2H, *H*$_3$C8' 5*S*-diastereoisomer), 0.93 (s, 1.8H, *H*$_3$C8' 5*R*-diastereoisomer), 0.96 (s, 1.2H, *H*$_3$C9' 5*S*-diastereoisomer), 0.97 (s, 1.8H, *H*$_3$C9' 5*R*-

Table 1

Crystal Data and Structure Refinement for **7** and **5**

	7	**5**
cvbn m,.Formula	$C_{20}H_{25}ClN_2O_2S$	$C_{21}H_{28}N_2O_2S$
M_r	392.93	372.51
T[K]	160(2)	293(2)
Cryst syst., space group	Monoclinic, P2$_1$	Orthorhombic, P2$_1$2$_1$2$_1$
a[Å]	8.6990(11)	8.8526(6) Å
b[Å]	9.9840(10)	10.5985(10) Å
c[Å]	11.4460(16)	21.7152(17) Å
β[deg]	105.869(15)	90.0
Volume [Å^3]	956.2(2)	2034.2(5)
Z, D_{calc} [g cm^{-3}]	2, 1.365	4, 1.214
Cryst. size [mm]	0.62 x 0.4 x 0.32	0.81 x 0.63 x 0.50
μ [mm^{-1}]	0.326	0.176
reflns$_{collected/unique}$	9427 / 3722	20913 / 3984
R_{int}	0.0225	0.0428
$2\theta_{max}$	52.30	52.32
Completness [%]	98.2	98.1
no. of data/restraints/params	3722 / 1 / 240	3984 / 41 / 271
GOF	1.06	1.045
R$_1$/wR$_2$ [>2σ(I)]	0.0236 / 0.0605	0.0349 / 0.0841
R$_1$/wR$_2$ (all data)	0.0251 / 0.0617	0.0430 / 0.0894
Absolute structure parameter	0.00(4) (1734 Friedels's pairs)	0.00(7) (1699 Friedel's pairs)
$\Delta\rho_{fin}$ [e.Å^3]	0.233 / -0.158	0.145 / -0.119

diastereoisomer), 1.03 (s, 1.8H, H_3C10' 5*R*-diastereoisomer), 1.14 (s, 1.2H, H_3C10' 5*S*-diastereoisomer), 2.06 (d J=14.7 Hz, 0.4H, *Ha*-C3' 5*S*-diastereoisomer), 2.13 (d J=14.7 Hz, 0.6H, *Ha*-C3' 5*R*-diastereoisomer), 2.47 (ddd J = 14.7, 4.4 and 3.4 Hz, 0.6H, *Hb*-C3' 5*R*-diastereoisomer), 2.76 (ddd J = 14.7, 4.2 and 3.6 Hz, 0.4H, *Hb*-C3' 5*S*-diastereoisomer), 7.33-7.64 (m, 4H, *H*-Ar); ^{13}C nmr (deuteriochloroform): δ 10.22 and 12.75 (H_3C8'), 19.82 and 20.37 (H_3C9'), 20.50 and 21.18 (H_3C10'), 26.84 and 26.97 (H_2C5'), 28.93 and 33.15 (H_2C6'), 45.10 and 45.62 (H_2C3'), 48.27 and 48.49 (H*C*4'), 49.49 and 49.70 (C7'), 54.92 and 55.49 (C1'), 113.84 and 116.83 (C5), 127.11 and 127.20 (*C* Ar), 128.73, 128.76 and 128.89 (*C*H Ar), 136.47 and 136.52 (Cl-*C* Ar), 153.47 and 155.51 (C3); ms: (EI$^+$) m/z 323 (4.51 %, M+2]$^+$), 321 (10.29 %, M$^+$), 211 (2.38), 184 (5.45), 171 (12.47), 169 (100), 137 (25.07), 127 (51.09), 123 (43.04), 109 (49.51), 108 (48.87), 95 (30.48), 81 (35.01), 69 (19.90), 67 (26.10), 55 (45.23).

Anal. Calcd for $C_{17}H_{20}ClNOS$: C 63.44, H 6.26, N 4.35. Found: C 63.48, H 6.27, N 4.33.

X-Ray Crystallographic Study.

A single crystal of compound **7** was mounted under inert perfluoropolyether at the tip of a glass fibre and cooled in the cryostream of the diffractometer whereas, in contrast a single crystal of compound **5** was fixed at the tip of a glass fiber and maintained at room temperature. Both data were collected on a Stoe IPDS diffractometer operating with monochromatic MoKα radiation (λ= 0.71073).

The structures were solved by direct methods (SIR97 [15]) and refined by least-squares procedures on F^2 using SHELXL-97 [16]. All H atoms attached to carbon were introduced into the calculation in idealised positions [d(CH)= 0.96 Å] and treated as riding models. In **5** the OEt group appears to be spread over two sites in the ratio 0.59/0.41. The disordered model was constrained to chemically reasonable dimensions using the tools available in SHELXL-97 [16]. The drawing of the molecules (Figures 1 and 2) were realised with the help of ORTEP32 [17]. In both compounds, final refinements allowed the fraction contribution of the inverted enantiomer to vary [18], the Flack's parameter quoted being the refined value of this contribution. Crystal data and refinement parameters are shown in Table 1.

Supplementary Information.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC- 215792 & 215793. 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].

REFERENCES AND NOTES

[1a] S. Hamad Elgazwy Abdel-Sattar, *Tetrahedron*, **59**,7445 (2003); [b] N. Fdil, My. Y. Ait Itto, M. Ait Ali, A. Karim and J.-C. Daran, *Tetrahedron Lett*., **43**, 8769 (2002); [c] M. Ait Ali, My. Y. Ait Itto, A. Hasnaoui, A. Riahi, A. Karim and J.-C. Daran, *J. Organometallic Chem*., **619**, 265 (2001); [d] My. Y. Ait Itto, A. Hasnaoui, A. Riahi and F. Huet, *Molecules*, ***5***, M186 (2000).

[2a] E. Palaska, G. Sahin, P. Kelicen, N. T. Durlu and G. Altinok, *Il Farmaco*, **57**, 101 (2002); [b] A. Foroumadi, Z. Kiani and F. Soltani, *Il Farmaco*, **58**, 1073 (2003); [c] B. Chai, S. Cao, Q. Wu, G.-H. Song and X.-H. Qian, *Indian J. Pharmac*., **22**, 113 (1990); [d] K. Ijichi, M. Fujiwara, H. Nagano, Y. Matsumoto, Y. Hanasaki, T. Ide, K. Katsuura, H. Takayama, S. Shirakawa, N. Aimi, S. Shigeta, K. Konno, M. Matsushima, T. Yokota and M. Baba, *Antiviral Research*, **31**, 87 (1996); [e] B. Masereel, S. Rolin, F. Abbate, A. Scozzfava and C. T. Supuran, *J. Med. Chem*., **45**, 312 (2002); [f] M. Kawakami, K. Koya, T. Ukai, N. Tatsuta, A. Ikegawa, K. Ogawa, T. Shishido and L. B. Chen, *J. Med. Chem*., **41**, 130 (1998).

[3a] R. Huisgen and H. J. Koch, *Liebigs Ann. Chem*., **591**, 200 (1955); [b] R. Huisgen, W. Mack and E. Anneser, *Angew. Chem*., **73**, 656 (1961); [c] R. Huisgen, *Angew. Chem. Int. Ed. Engl*., **2**, 565 and 633 (1963); [d] R. Huisgen, R. Grashey and J. Sauer, The Chemistry of Alkenes, Vol. **1**, Patai, S., Ed.; John Wiley: New York, 1964, pp 806–878; [e] R. Huisgen, 1,3-Dipolar Cycloaddition Chemistry; Padwa, A. Ed., John Wiley: New York, 1984.

[4a] R. Huisgen, R. Grashey, M. Seidel, H. Knupfer and R. Schmidt, *Liebigs Ann. Chem*., **658**, 169 (1962); [b] H. M. Hassaneen, A. S. Shawali, D. S. Farag and E. M. Ahmed, *Phosph. Sulfur and Silicon*, **113**, 53 (1996); [c] B. Kelmendi, G. Mloston and H. Heimgartner, *Heterocycles,* **52**, 475 (2000); [d] K. A. Kandeet and A. S. A. Youssef, *Molecules*, , **6**, 510 (2001).

[5] R. Huisgen, G. Mloston and A. Proebstl, *Heteroat. Chem*., **12**, 136 (2001).

[6] B. N. Brousse, A. G. Moglioni, M. M. Alho, Á. Álvarez-Larena, G. Y. Moltrasio and N. B. D´Accorso, *ARKIVOC*, **Part (X)**, 14 (2002).

[7] F. H. Allen and O. Kennard, *Chem. Des. Autom. News*, **8**, 31(1993).

[8] R.-J. Kuban and B. Schulz, *Cryst. Res. and Technol*., **22**, 799 (1987).

[9] G. V. Boyd, T. Norris and P. F. Lindley, *J. Chem. Soc., Perkin Trans. 1*, 1673 (1976).

[10] H. Dehne, A. Scheunemann, M. Michalik, H. Hartung and F. Heinemann, *Sulfur Letters*, **18**, 135 (1995).

[11] G. Rabe, J. Sundermeyer, H. W. Roesky, H.-G. Schmidt and M. Noltemeyer, *Chem. Ber*., **123**, 691 (1990).

[12] J. B. F. Dunstan, G. M. Elsey, R. A. Russell, G. P. Savage, G. W. Simpson and E. R. T. Tiekink, *Aust. J. Chem*., **51**, 499 (1998).

[13] H. Dehne, K. Drexler, K. Martens, H. Reinke and M. Michalik, *Sulfur Letters*, **24**, 29 (2000).

[14] J. J. P. Stewart, *J. Computational Chem*., **10**, 209 (1989).

[15] A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori and R. Spagna, *SIR97*, program for automatic solution of crystal structures by direct methods. *J. Appl. Cryst*. **32**, 115 (1999).

[16] G. M. Sheldrick, *SHELXL97*, program for crystal structure refinement. Universityof Göttingen, Germany, (1997).

[17] L. J. Farrugia, *ORTEP-32* for Windows, *J. Appl. Cryst*. **30**, 565 (1997).

[18a] H. D. Flack, *Acta Cryst*. **A39**, 876 (1983); [b] G. Bernardinelli and H. D. Flack, *Acta Cryst*. **A41**, 500 (1985).