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Pentaspiranes and hexaspiranes with 1,3-dioxane or 1,3-oxathiane rings: synthesis and stereochemistry

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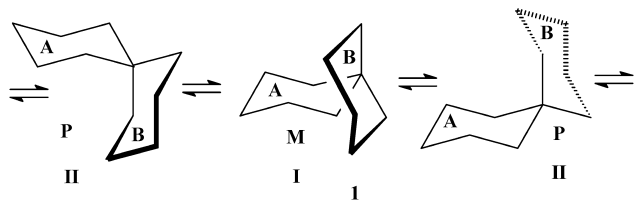
Abstract—The synthesis and stereochemistry of the first reported pentaspiro- and hexaspiro-1,3-dioxane and polyspiro-1,3-oxathiane (from dispiro to hexaspiro) derivatives are described. The crystal structures of a dispiro- and tetraspiro-1,3-oxathiane were determined by X-ray diffraction methods. NMR and chiral column HPLC investigations in solution revealed flexible and semiflexible structures for which *syn*–*anti*, *cis*–*trans* and *d*,*l* isomers were observed.

1. Introduction

Our previous investigations[1–4] of the stereochemistry of spiro-1,3-dioxanes dealt with the helical chirality of those spiranes with six-membered rings. The sequence of a helix which exhibits P or M configuration repeats after every fourth six-membered ring.

The parent compound, spiro[5.5]undecane **1** exhibits a flexible structure in which ring flip (A and B, Scheme 1) causes enantiomeric inversion. [I(M)⇌II(P)].



Scheme 1.

The dispiranes, as well as the higher members of the polyspirane series, can be built up by merging the corresponding monospirane units. For example, dispirane **2** (Scheme 2, Table 1), is made up of monospiranes AB and BC. If the two merged units have the same helix configuration, a dispirane with a M (III) or P (V) configuration is obtained, but if they have different helix configurations, the achiral form (IV) of the dispirane is generated. At the same time marginal rings A and C can be oriented on the same side of the best plane of ring B (defined by bonds C^6–C^1 and C^6–C^5 or C^9–C^{10} and C^9–C^{14}) for which the structures are named 6,9-*syn*. If they are on opposite sides of the reference plane the isomer is 6,9-*anti*. The *syn* or *anti* orientations of marginal rings A and C can be deduced from the values of the dihedral angle described by the planes formed by bonds C^{10}–C^{11}, C^{13}–C^{14} and C^1–C^2, C^4–C^5. The dihedral angle is close to 0° for the *anti* isomer, while for the *syn* isomers the two reference planes are perpendicular. The *syn* isomers are chiral and exhibit M or P configurations while the *anti* isomer is achiral, being centrosymmetric.

The possible stereoisomers of trispirane **3** and tetraspirane **4** (Scheme 3, Table 1) and their chirality may be deduced from the configurations of the three (or four) constituent monospiro units (Table 1). For an odd number of monospiro units all the possible stereoisomers are chiral, while in the case of an even number of monospiro units, achiral forms are also present.

The number of possible stereoisomers increases with the number of monospirane units. The number of possible structures of trispirane **3** is 6 and the tetraspirane **4** and the pentaspirane **5** exhibit 10 and 20 isomers, respectively (Table 1).

Hexaspirane **6** shows 36 possible conformers of the spirane skeleton (found by extending the algorithm discussed for compounds **1**-**5**) four of them being achiral (6,9-*syn*-9,12-*syn*-12,15-*anti*-15,18-*syn*-18,21-*syn*; 6,9-*syn*-9,12-*anti*-12,

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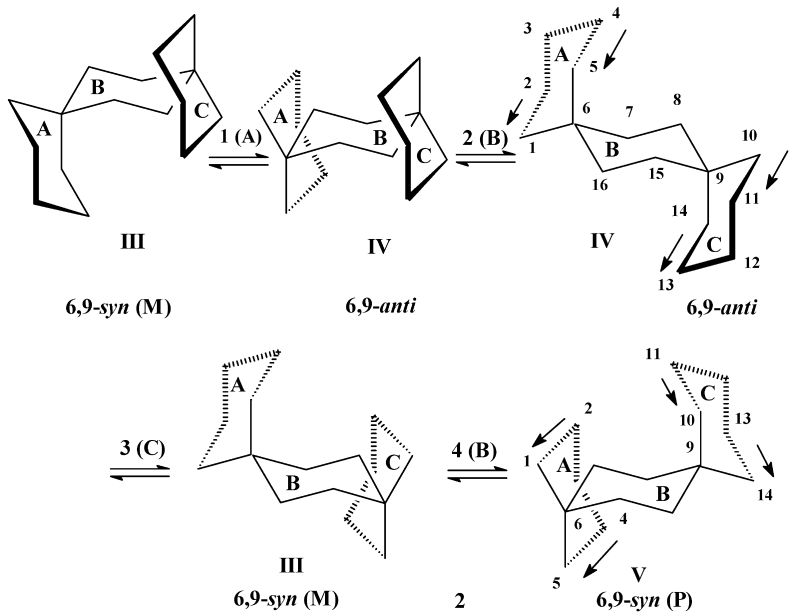
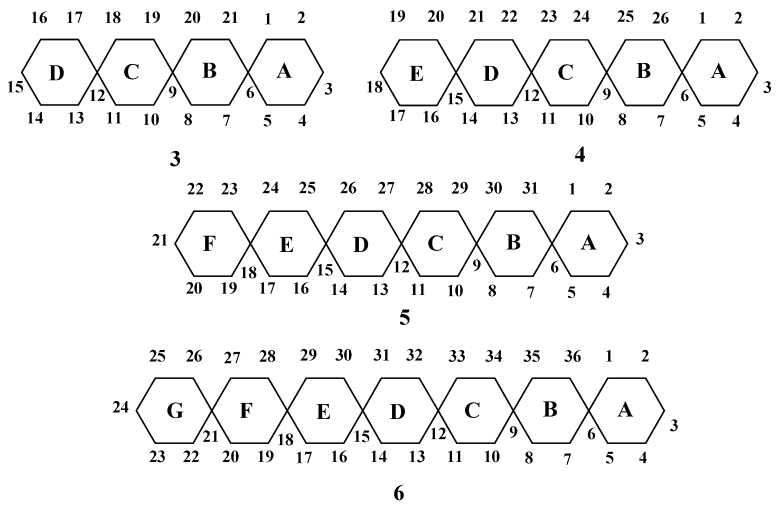


Scheme 2.

Table 1. Possible stereoisomers of spiro (from mono to penta) compounds with six-membered rings

Isomer	Rings orientation 6,9-9,12-12,15-15,18	AB	BC	CD	DE	EF	Helix
I	—	M	—	—	—		M
II	—	P	—	—	—		P
III	*syn*	M	M	—	—		M
IV	*anti*	P(M)	M(P)	—	—		—
V	*syn*	P	P	—	—		P
VI	*syn-syn*	M	M	M	—		M
VII	*syn-syn*	P	P	P	—		P
VIII	*syn-anti*	P	P	M	—		P
IX	*syn-anti*	M	M	P	—		M
X	*anti-anti*	P	M	P	—		P
XI	*anti-anti*	M	P	M	—		M
XII	*syn-syn-syn*	P	P	P	P		P
XIII	*syn-syn-syn*	M	M	M	M		M
XIV	*syn-syn-anti*	P	P	P	M		P
XV	*syn-syn-anti*	M	M	M	P		M
XVI	*anti-syn-anti*	M	P	P	M		P
XVII	*anti-syn-anti*	P	M	M	P		M
XVIII	*anti-anti-syn*	P	M	P	P		P
XIX	*anti-anti-syn*	M	P	M	M		M
XX	*anti-anti-anti*	M(P)	M(P)	P(M)	P(M)		—
XXI	*anti-anti-anti*	M(P)	P(M)	M(P)	P(M)		—
XXII	*syn-syn-syn-syn*	M	M	M	M	M	M
XXIII	*syn-syn-syn-syn*	P	P	P	P	P	P
XXIV	*syn-syn-syn-anti*	M	M	M	M	P	M
XXV	*syn-syn-syn-anti*	P	P	P	P	M	P
XXVI	*syn-syn-anti-syn*	M	M	M	P	P	M
XXVII	*syn-syn-anti-syn*	P	P	P	M	M	P
XVIII	*syn-syn-anti-anti*	M	M	M	P	M	M
XXIX	*syn-syn-anti-anti*	P	P	P	M	P	P
XXX	*syn-anti-syn-anti*	M	M	P	P	M	M
XXXI	*syn-anti-syn-anti*	P	P	M	M	P	P
XXXII	*syn-anti-anti-syn*	M	M	P	M	M	M
XXXIII	*syn-anti-anti-syn*	P	P	M	P	P	P
XXXIV	*anti-syn-syn-anti*	M	P	P	P	M	P
XXXV	*anti-syn-syn-anti*	P	M	M	M	P	M
XXXVI	*syn-anti-anti-anti*	M	M	P	M	P	M
XXXVII	*syn-anti-anti-anti*	P	P	M	P	M	P
XXXVIII	*anti-syn-anti-anti*	M	P	P	M	P	P
XXXIX	*anti-syn-anti-anti*	P	M	M	P	M	M
XL	*anti-anti-anti-anti*	M	P	M	P	M	M
XLI	*anti-anti-anti-anti*	P	M	P	M	P	P

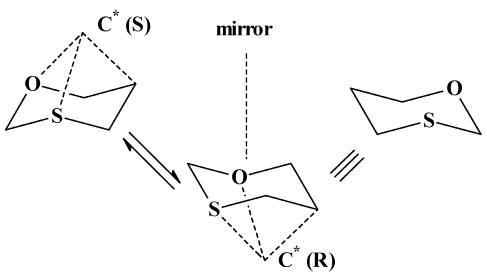


Scheme 3.

15-*anti*-15,18-*anti*-18,21-*syn*; 6,9-*anti*-9,12-*syn*-12,15-*anti*-15,18-*syn*-18,21-*anti* and 6,9-*anti*-9,12-*anti*-12,15-*anti*-15,18-*anti*-18,21-*anti*).

Earlier studies[5,6] of the monocycle and spiro-1,3-oxathianes determined that the peculiar chirality of the unsubstituted heterocycle involves a virtual tricoordinated chiral center (Scheme 4)[5] and we also disclosed *cis*–*trans* equilibration of some of the spiro-derivatives via ring-chain tautomerism (Scheme 5).[6]

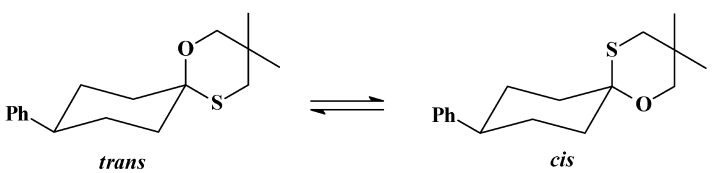
We decided to extend our structural investigation to include the synthesis of a new series of compounds involving larger spiro-1,3-dioxane (penta and hexaspiro) and polyspiro-1,3-oxathiane derivatives (up to hexaspiro) given the interesting configurational and conformational aspects (revealed by variable temperature NMR experiments) of six-membered ring spiro compounds observed in previous studies. These were performed with spiro-1,3-dioxanes, spiro-1,3-oxathiane and polyspiro-1,3-dioxanes (up to tetraspiranes).[1–10] Also we wished to gain a better understanding of the observations concerning the stereochemistry of these derivatives. As far as we know, only a few penta and hexaspiranes have already been reported[11–25] (all of them from the 'rotan' family; i.e., all spiro atoms being located on the same ring) and no studies of the higher spiranes were found. Our target spiranes are among the largest described in the literature and the first ones of this size to have 1,3-dioxane or 1,3-oxathiane rings.



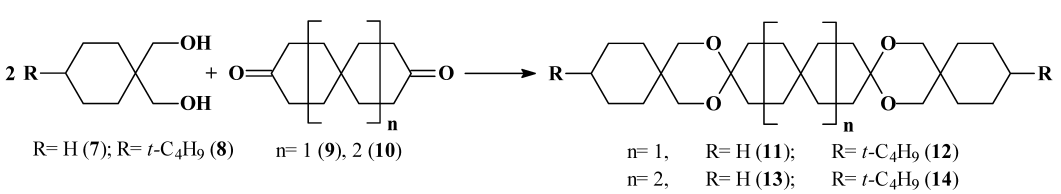
Scheme 4.

2. Results and discussion

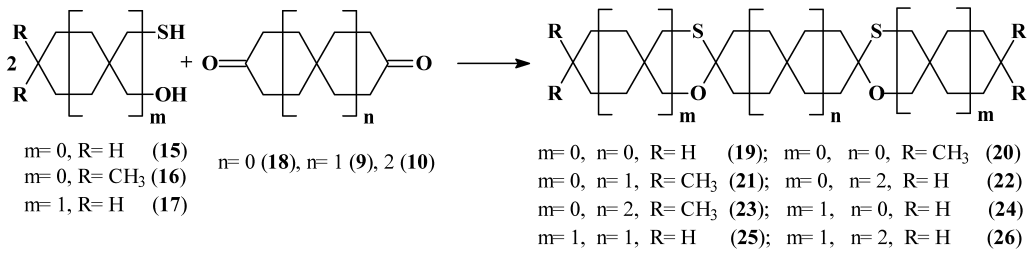
New polyspiro 1,3-dioxanes **11**-**14** and oxathianes **19**-**26** were obtained by condensation reactions of a dicarbonyl compound with a 1,3-diol or a 3-mercapto-alcohol (Schemes 6 and 7).



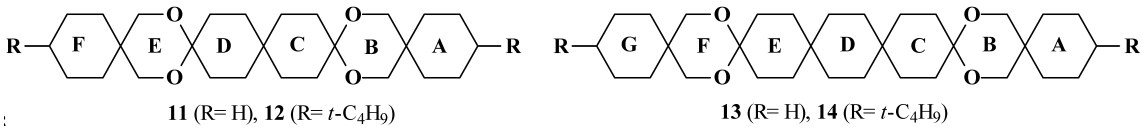
Scheme 5.



Scheme 6.



Scheme 7.



Scheme 8.

2.1. Penta and hexaspiro-1,3-dioxanes

Compounds **11** and **13** have flexible structures (R=H, Scheme 8). All the rings are flipping and all the possible structures of the spirane are in equilibrium. The NMR spectra of these compounds at rt show singlets for the methylene protons of the 1,3-dioxane rings (Table 2). At low temperature (180 K), the changes in the shape of the spectra (broad bands instead of the singlets) suggest that ring flip is frozen.

Table 2. NMR data (CH_2–O moiety, CD_2Cl_2) for **11**-**14**

Compound	**11**	**12**	**13**	**14**
δ (–CH_2O–), ppm	3.54	3.38 3.67	3.46	3.38 3.67

Compounds **12** and **14** (Scheme 8, R=*t*-C_4H_9) exhibit semiflexible structures, the marginal rings being anancomeric[26] ('rigid') while the middle part of the spiranes is flipping (**12**: rings B, C, D, E; **14**: B, C, D, E, F; Scheme 8). The conformational equilibria in **12** involve, on one side, 10 possible structures XXII, XXV, XXVI, XXIX, XXX, XXXIII, XXXV, XXXVI, XXXIX and XL and, on the other side, the other 10 possible conformers (Table 1). To transform a structure of one of these groups into a structure belonging to the other group it is necessary to break and to remake bonds with the opposite stereochemistry. This transformation is not possible via conformational equilibrium, so two separable stereoisomers are possible. A comparison of the configuration of the chiral elements of the isomers of **12** shows that they are enantiomers.

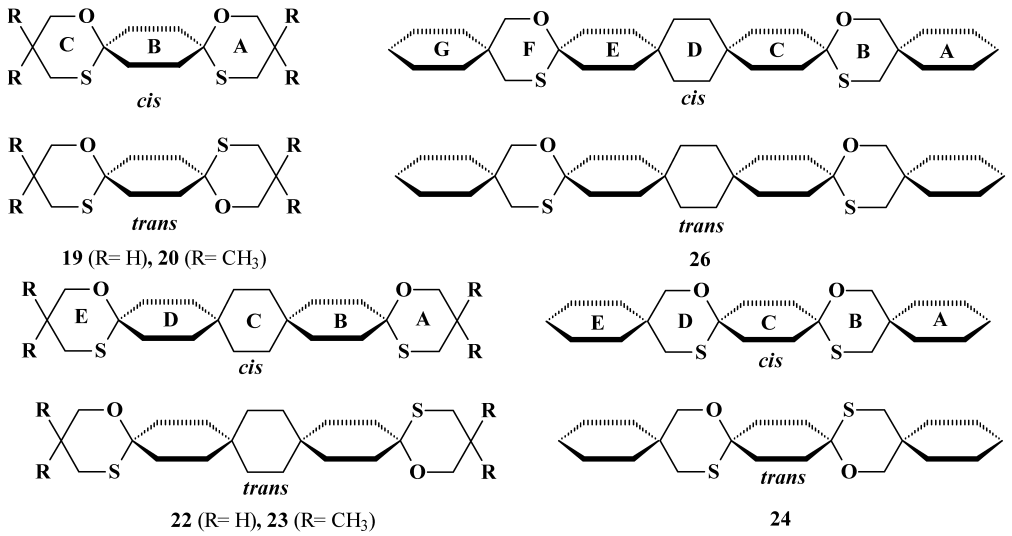
In order to observe the enantiomers of **12**, the compound (racemate) was subjected to resolution on chiral column HPLC. A partial resolution (t_{R1}=24.9 min and t_{R2}= 25.8 min) was observed on CHIRALCEL OD column, using an isocratic mobile phase (*n*-hexane) and polarimetric, mass spectrometry (ESI-MS) and evaporative light scattering detection (ELSD).

Investigations of the conformational equilibria of **14** demonstrated the possibility of having two separable diastereoisomers (as can be deduced from the configurations of the chiral elements). As for **12**, there are two groups of conformers (one of 19 and the other of 17 possible structures for a total of 36). To transform one member of a group into another of the same group, ring flips are sufficient, while to change from a structure of one group into one of the other requires the breaking and remaking of bonds with inverted stereochemistry. The pentaspirane with fixing groups at its extremities and other substituted spiranes with an odd number of spiro units (e.g., monospirane and trispirane),[1,2] have separable enantiomers, while those with an even number of spiro units (e.g., substituted dispiranes, tetraspiranes and hexaspiranes)[3,4] exhibit separable diastereoisomers. In the NMR spectra of **12** and **14** (mixtures of diastereoisomers), recorded at rt, the protons of the 1,3-dioxane rings show up as two singlets (Table 2). The low temperature spectra (180 K, CD_2Cl_2) of these compounds reveal that the flipping of the rings is frozen and rather than the above two singlets, four groups of unresolved signals (bands) are observed from 3.0 to 4.2 ppm. These signals belong to the axial and equatorial protons of the various structurally frozen diastereoisomers.

2.2. Polyspiro-1,3-oxathianes

The stereochemistry of polyspiro-1,3-oxathianes **19**-**26** correlates with the total number of spiro units and with the number of cyclohexane rings separating the two heterocycles. If the two 1,3-oxathiane rings are separated by an odd number of carbocycles, the compound exhibits *cis* and *trans* isomers, whereas, if the number of intervening cyclohexane rings is even, the polyspiro-1,3-oxathiane has separable enantiomers.

2.2.1. Stereochemistry of compounds 19, 20, 22-24 and 26. Compounds **19**, **20**, **22**-**24** and **26** were separated by flash-chromatography into the two possible diastereoisomers (*cis* and *trans*, Scheme 9) and these were investigated as single compounds. In most of the syntheses, the major isomer was *trans* (Table 3). The two isomers have very similar NMR spectra and, in the majority of cases, they could not be differentiated (in their mixture) by NMR. The ratios were calculated using the already determined amounts of separated isomers.



Scheme 9.

Table 3. *trans*/*cis* or $(D^1/D^2)^*$ ratio of compounds **19**, **20**, **22**-**24** and **26**

Compound	**19**	**20**	**22**	**23**	**24**	**26**
trans/*cis* (D^1/D^2)	0.94	1.35	1.44	1.52	1.50	1.04

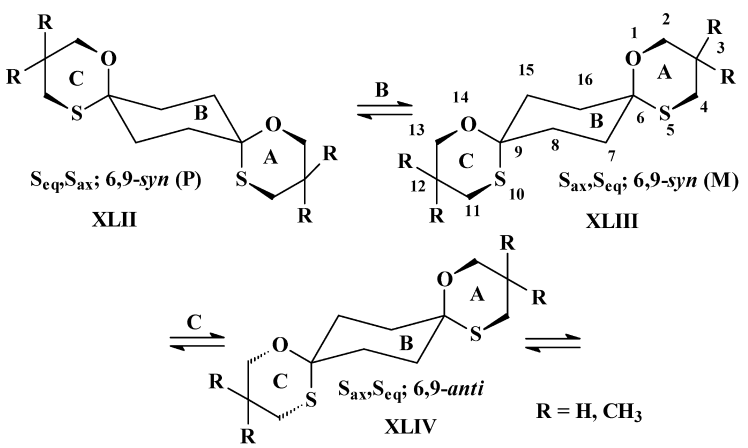
The assignment for the *trans* and *cis* structures could not be performed unambiguously; D^1 for **23** and **26** is only assumed to be the *trans* isomer.

The possible conformational equilibria for the *cis* and *trans* isomers of dispiranes **19** and **20** are shown in Schemes 10 and 11. There are three *cis* structures corresponding to the *syn* (P and M helix) and *anti* orientations of the spirane skeleton. In all of these structures one of the sulfur atoms (on the middle cyclohexane ring) is equatorial and the other, axial. Sulfur is the reference atom since it has priority. The number of possible conformers for the *trans* isomers of **19** and **20** is higher (six) because both sulfur atoms must either be equatorial (main case) or axial (minor case), and each of these is either *syn* (P or M configuration) or *anti*.

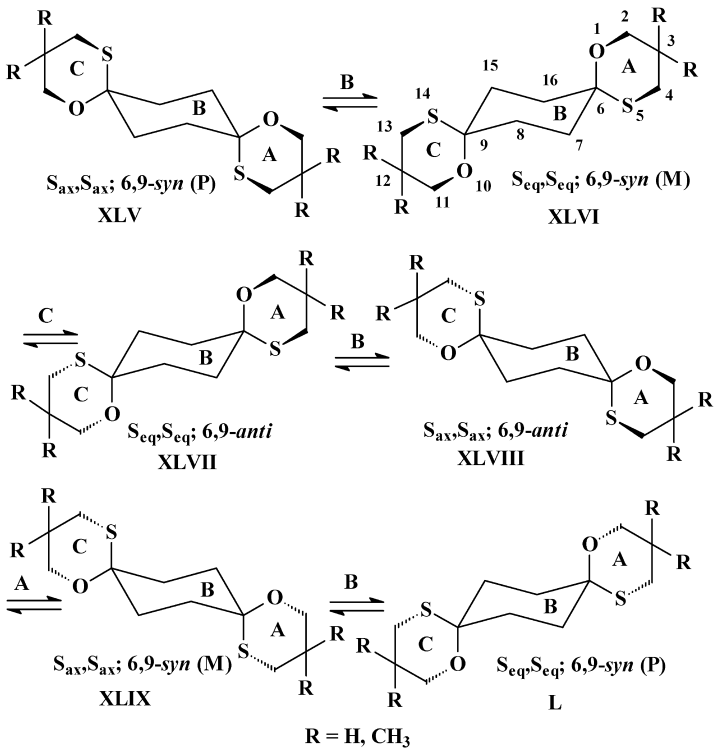
At rt, all possible conformers of each diastereoisomer (*cis* or *trans*) are in equilibrium. The NMR spectra recorded at this temperature are very simple (e.g., the spectra of the *trans* and *cis* isomers of **20** only show two singlets for the protons of the heterocycles; *trans*: δ_{O-CH2}=3.40 ppm and δ_{S-CH2}=2.61 ppm; *cis*: δ_{O-CH2}=3.42 ppm and δ_{S-CH2}=2.59 ppm; Table 4). The ^{1}H NMR spectra of the *cis* and *trans* isomers of dispiro-1,3-oxathianes are very similar. Nonetheless, some differences were observed for the protons of the middle cyclohexane ring. The flipping of the rings in both isomers produces isochronous carbon resonances at positions 7, 8, 15 and 16 (one signal in ^{13}C NMR spectra). However, the protons at these positions are not all equivalent in the conformational equilibrium (Scheme 12).

Four of the eight protons at these positions are *pro-cis*(denoted with c), being oriented on the same side of the middle ring as the two sulfur atoms in the *cis* isomer or on the same side as the closer sulfur atom in the *trans* isomer. The other four protons are oriented on opposite sides of the middle ring with respect to the reference sulfur atoms and, thus, are *pro-trans* (denoted with t).

In the NMR spectrum of the *trans* isomer, the protons of the cyclohexane ring correspond to two doublets at δ 1.80 and 2.1 ppm with an average coupling constant of 10.0 Hz, while in the spectrum of the *cis* isomer, the signals at δ 1.85–2.05 ppm are unresolved doublets of doublets (Figs. 1a and 2a). The low temperature spectra of the isomers of



Scheme 10. Conformational equilibria for *cis* isomers of **19** and **20**.



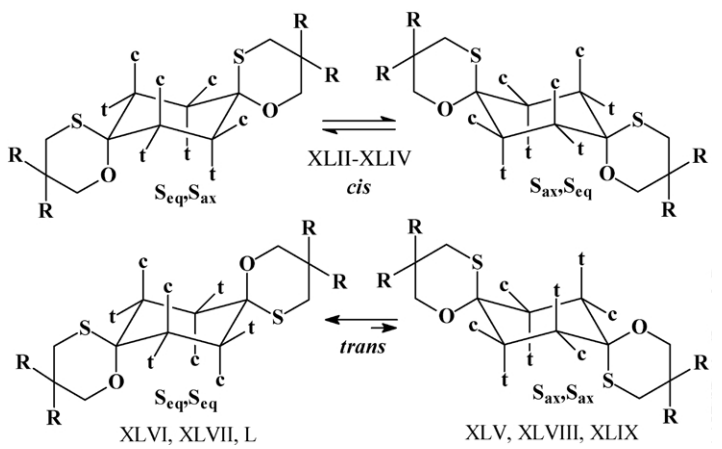
Scheme 11. Conformational equilibria for *trans* isomers of **19** and **20**.

Table 4. NMR data (rt, CD_2Cl_2, δ, ppm) of compounds **19**-**26**

Compound	Isomer	O–CH_2	S–CH_2	CH_3
19	*cis*	3.88	2.83	—
	trans	3.85	2.86	—
20	*cis*	3.42	2.59	1.05
	trans	3.40	2.61	1.05
21	—	3.39	2.57	1.02
22	*cis*	3.74	2.72	—
	trans	3.74	2.72	—
23[*]	D^2	3.30	2.49	0.93
	D^1	3.30	2.48	0.93
24	*cis*	3.47	2.66	—
	trans	3.45	2.68	—
25	—	3.47	2.65	—
26[*]	D^2	3.46	2.65	—
	D^1	3.46	2.65	—

20 (Figs. 1b and 2b) show the signals arising from the frozen diastereoisomers.

The ^{1}H NMR spectrum of the *trans* isomer run at 187 K (Fig. 1) exhibits four sets of signals with different intensities assigned to the six frozen conformations (four which form two pairs of enantiomers) of this isomer. Two sets of high intensity signals were assigned to the *syn* (XLVI, L) and *anti* (XLVII) conformers bearing the equatorial sulfur atoms on the middle cyclohexane ring while the other two sets of low intensity signals belong to the minor conformers for which the sulfur atoms are axial (*syn*: XLV, XLIX; *anti*: XLVIII). The *syn* and *anti* conformers could not be differentiated due to the overlap of the signals belonging to the protons of the cyclohexane rings. This is despite the theoretically different shapes of the spectra anticipated for these protons. In both conformers of the *trans* isomer (*syn* and *anti*), the two heterocycles of the spirane are equivalent.



Scheme 12.

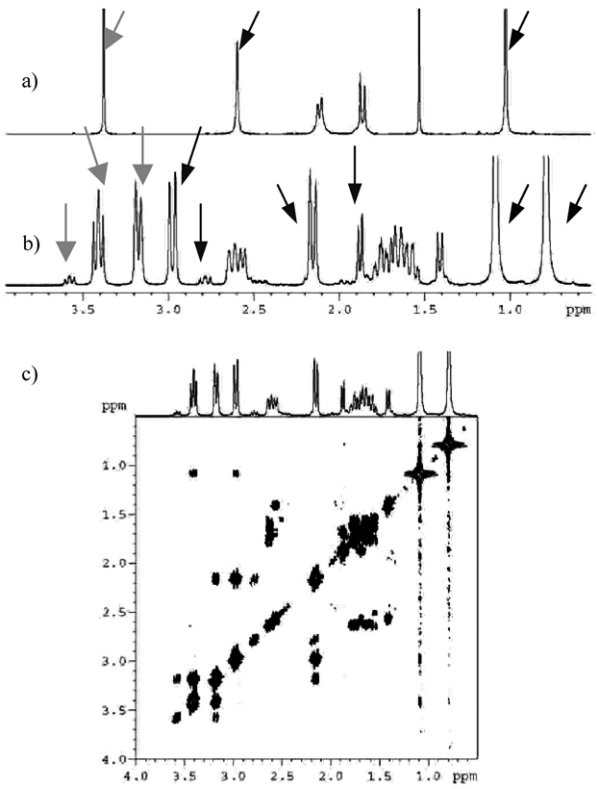


Figure 1. [1]H NMR spectra of the *trans* of **20**; (a) at rt; (b) at 187 K; (c) COSY at 187 K.

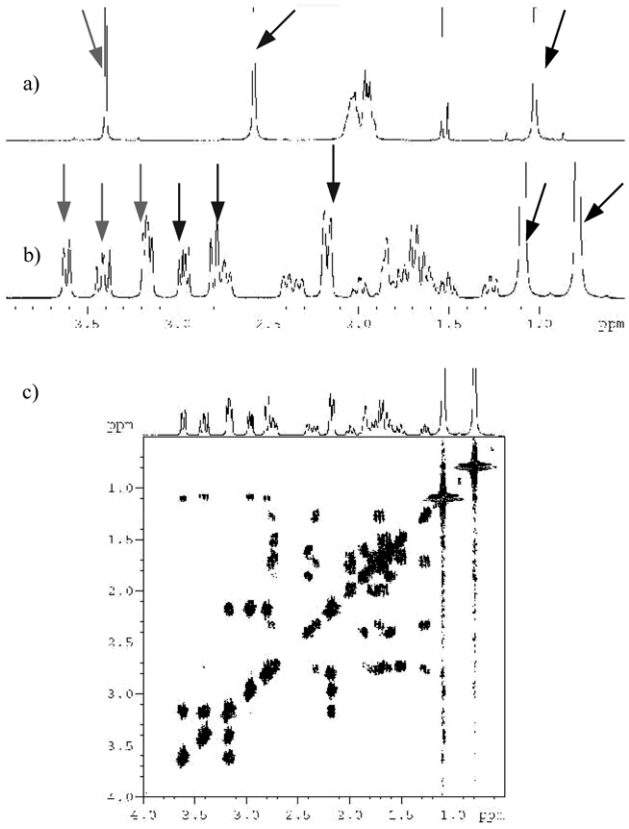


Figure 2. [1]H NMR spectra of the *cis* of **20**; (a) at rt; (b) at 187 K; (c) COSY at 187 K.

The part of the spectrum belonging to the protons of the heterocycles shows, for each diastereoisomer, two AB (AX) systems which were assigned to the axial and equatorial protons of the $O-CH_2$ and $S-CH_2$ moieties, respectively (Fig. 1, Table 5). At low temperature, well separated signals were observed which could be attributed to axial (δ_{ax}=1.080, 1.085 ppm) and equatorial (δ_{eq}=0.789 ppm) protons. However, it was not possible to differentiate the signals belonging to the different stereoisomers.

The [1]H NMR spectrum of *cis* isomer run at 187 K (Fig. 2) is as complex as the spectrum recorded for *trans* isomer, despite the lower number of stereoisomers (in fact only two, the *syn* and *anti* diastereoisomers, which are present in an almost 1/1 ratio). The complexity of the spectrum is due to the non-equivalence of the two 1,3-oxathiane rings A and C. Each isomer has one 1,3-oxathiane ring with an axial sulfur atom while the other one has an equatorial sulphur. The low temperature spectrum shows four sets of signals of similar intensity (some of which overlapped).

The NMR spectra recorded at rt for the *cis* and *trans* isomers of **24** exhibit, for the heterocyclic protons as well as for those of the middle cyclohexane ring, sets of signals similar to those of **20**. Low temperature spectra of the isomers of **24** are more complex due to the higher number of possible structures, but the part of the spectra belonging to the protons of the heterocycles shows groups of signals similar to those attributed to the diastereoisomers of **20**.

The differences observed between the spectra (either at rt or at low temperature) of the *cis* and *trans* isomers of **22**, **23** and **26** are not as significant as those for **19**, **20** and **24**. Thus, structural assignment (*cis* and *trans*), by NMR, for the two isolated isomers of each compound was not possible. However, an assignment was possible for compound **22** via the X-ray diffraction of the crystalline *trans* isomer. In the other cases (compounds **23** and **26**) it was assumed that the less polar product (i.e., the highest R_f on silica gel) was the *trans* isomer (as in the case for **19**, **20**, **22** and **24**). However, without other experimental support, it was preferred to mark the isolated isomers as D^1 and D^2 (in the order of their elution on silica gel, they are assumed to be either the *trans* or the *cis* form of a compound).

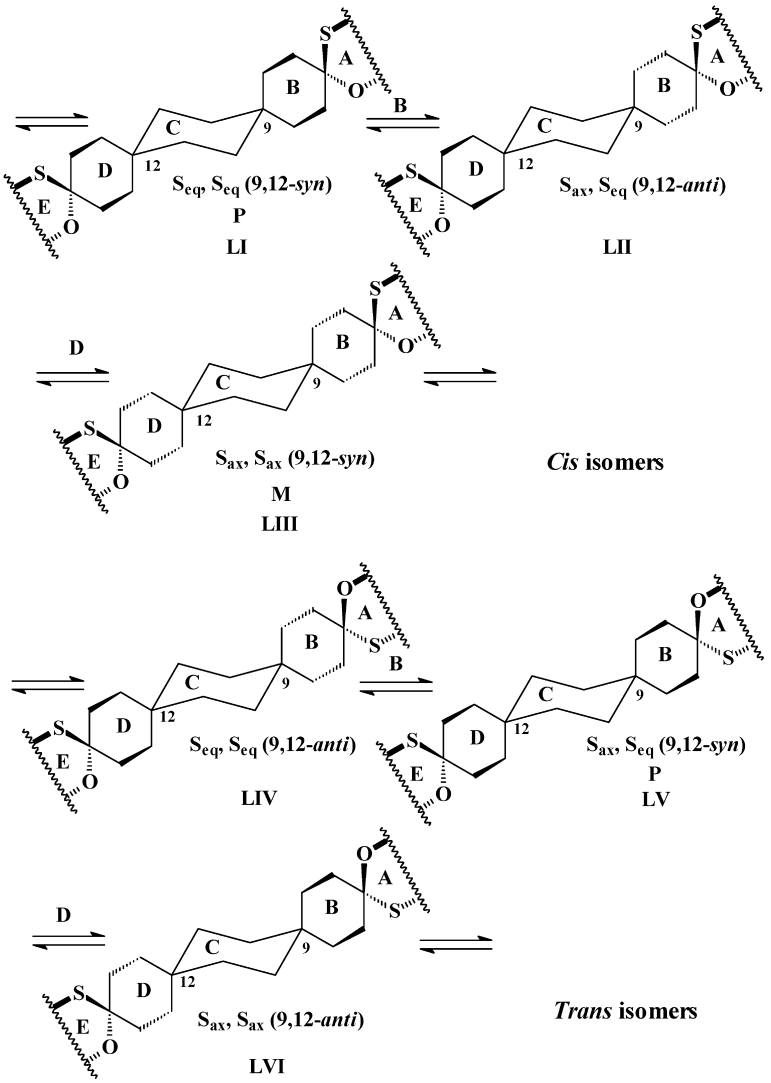
Conformational analysis (Scheme 13) of the middle part of the tetra- (rings B, C and D) and hexaspiranes (rings C, D and E) had markedly different results than those of **19**, **20** and **24**.

The conformational equilibria for the *cis* and *trans* diastereoisomers involving the flipping of rings B, C and D (compounds **22** and **23**, Scheme 13) or C, D and E (compound **26**) lead to conformations in which both sulphur atoms are either both equatorial or both axial or in which there is one axial and one equatorial sulphur (Scheme 13). The different axial and equatorial positions of the sulphur atoms (which dictate the differences in NMR spectra) observed for the *cis* and *trans* isomers of **19**, **20** and **24** do not exist for the *cis* and *trans* isomers of **22**, **23** and **26**. The small steric differences between the *cis* and *trans* isomers of these compounds explain their very similar NMR spectra

Table 5. NMR data[a] (187 K, CD_2Cl_2, δ, ppm) of *trans* and *cis* isomers of **20**

Isomer	O–CH_2		S–CH_2		CH_3	
	eq	ax	eq	Ax	eq	ax
trans (major) *syn* and *anti*	3.17	3.42, 3.39	2.15	2.97	1.085, 1.080	0.789
trans (major) *syn* and *anti*	3.17	3.59, 3.56	2.17	2.79, 2.77	1.08	0.79
cis (all rings of *syn* and *anti* structures)	3.15, 3.17	3.61, 3.43, 3.39	2.16	2.97, 2.95, 2.80	1.097, 1.083	0.795, 0.784

[a] The COSY spectra show long range couplings of the axial proton of the heterocycles with the axial methyl groups (the more deshielded ones).



Scheme 13.

(some minor differences are observed for the signals assigned to the cyclohexane).

The low temperature spectra (180 K) of the isomers of compounds **22**, **23** and **26** do not allow for the differentiation of the signals belonging to their many frozen structures, related to the three different arrangements of the sulfur atoms (eq.,eq.; eq.,ax.; and ax.,ax.). Nonetheless, they do show separate signals for the protons of the 1,3-oxathiane rings with both axial or equatorial sulfur atoms. Thus, the low temperature spectra of these compounds show two sets of signals of different intensities (ratio 3/2). The main set belongs to the protons of the heterocycles bearing an equatorial sulfur atom on the neighbouring cyclohexane ring. This finding is consistent with a higher *A*-value for the cyclohexane ring having the S–R group than for that having the O–R group[27] and it is in agreement with the results of previous conformational determinations involving monospiro-1,3-oxathianes.[6] However, the low temperature spectra of compounds **22** and **23** (Figs. 3 and 4) are quite different. It is known that the presence of geminal methyl groups at position 5 of the 1,3-oxathiane ring increases the barrier for the flipping of the heterocycle. This is contrary to geminal substitution at position 2 which diminishes $\Delta^{\#}G^{\circ}$

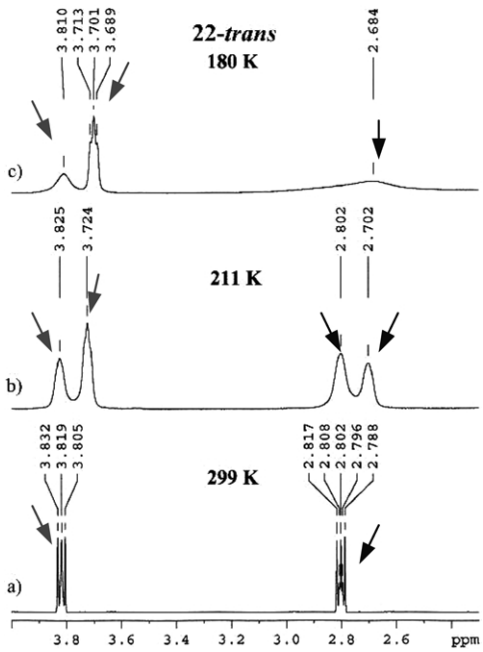


Figure 3. Variable NMR spectra (CD_2Cl_2) of *trans* isomer of compound **22**: (a) 299 K, (b) 211 K and (c) 180 K.

(e.g., the $\Delta^{\#}G^{\circ}$ values for 1,3-oxathiane, for 2,2-dimethyl-1,3-oxathiane and 5,5-dimethyl-1,3-oxathiane are 38.9, 33.4 and 43.5 kJ/mol, respectively).[28] Two factors determine the amount of ring flip for these compounds: an increase in the energy of the ground state (which lowers the barrier of inversion due to the axial substituent) and an increase in the energy of the transition state (half-chair conformations, which increase the barrier of inversion) due to greater steric hindrance. The *A*-values for a methyl group at position 5 of the 1,3-oxathiane ring (A=2.7–3.7 kJ/mol)[29,30] are considerably lower than for that at position 2 (A=13.6 kJ/mol)[29,30] which explains the differences between the values for the inversion barriers. As has been previously observed for the higher barrier of inversion of 5,5-dimethyl-1,3-oxathiane versus 1,3-oxathiane itself the conformational behaviours of compounds **22** and **23** are indeed different. The inversion barrier of the 1,3-oxathiane rings in **23** is high enough that the flipping of the heterocycle freezes at 180 K. This effect can be attributed to the presence of methyl groups. On the other hand, the NMR spectrum of **22** at the same temperature, shows only the beginning of the coalescence related to conformational equilibrium. Variable temperature NMR experiments of the *trans* isomer of **22** (Fig. 3) revealed that the flipping of the cyclohexane part of the spirane (rings B, C and D) froze at 211 K. Two sets of broad and unresolved signals are obtained instead of the two multiplets recorded at 299 K (δ_{CH2-O}=3.81 ppm and δ_{CH2-S}=2.80 ppm). The set of higher intensity signals (δ_{CH2-O}=3.72 ppm and δ_{CH2-S}=2.80 ppm) corresponds to those 1,3-oxathiane rings with an equatorial sulfur atom on the neighboring cyclohexane ring, while the set of lower intensity signals (δ_{CH2-O}=3.82 ppm and δ_{CH2-S}= 2.70 ppm) belong to 1,3-oxathiane rings bearing an axial sulfur. The spectrum run at 180 K shows the coalescence of the signals due to the heterocycles and thus the freezing in space of the 1,3-oxathiane rings.

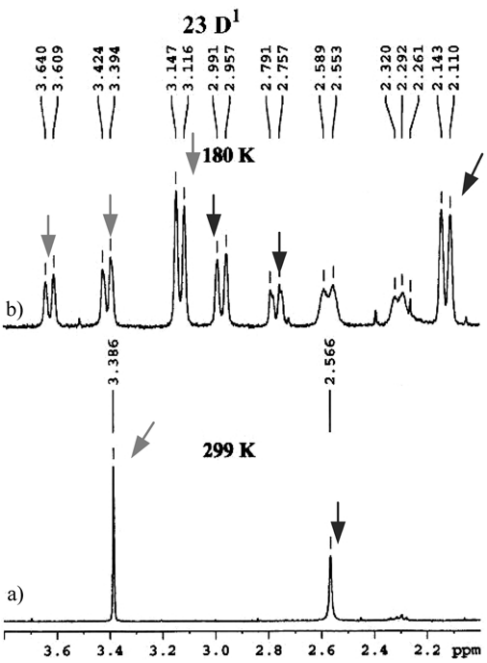


Figure 4. Variable temperature NMR spectra of D^1 isomer of compound **23**: (a) 299 K and (b) 180 K.

Variable temperature NMR experiments of diastereomer D^1 of compound **23** show the freezing in space of both the cyclohexane and the 1,3-oxathiane rings. The two singlets recorded at 299 K (δ_{CH2-O}=3.38 ppm and δ_{CH2-S}= 2.56 ppm), which may be attributed to the protons of the heterocycles, change in the spectrum run at 180 K. Signals belonging to the two types of 1,3-oxathiane rings (equatorial sulfur atom, main case; axial sulfur atom, minor case) and to the axial and equatorial positions of these protons are observed. The signals assigned to the axial protons of each moiety are well separated for each type of ring (CH_2–O moiety: δ_{ax}=3.40 ppm (S_{eq} rings), δ_{ax}=3.62 ppm (S_{ax} rings); CH_2–S moiety: δ_{ax}=2.97 ppm (S_{eq} rings), δ_{ax}=2.77 ppm (S_{ax} rings), while those due to the equatorial protons overlapped (CH_2–O moiety: δ_{eq}=3.13 ppm; CH_2–S moiety: δ_{eq}=2.12 ppm). The other two signals (δ=2.57 ppm and 2.31 ppm) of Figure 4 belong to the protons of the cyclohexane rings. The conclusion that freezing of the flipping of the 1,3-oxathiane rings has occurred was also supported by the recording of different signals for the axial (δ_{ax}=1.11, 1.09 ppm) versus equatorial (δ_{eq}=0.80 ppm) methyl groups at the extremities of the spirane. Variable temperature experiments of the other isomers of **22** and **23** gave similar results.

Low temperature spectra of the isomers of **26** were similar to those observed for the isomers of **23**. That is, the freezing in space of the 1,3-oxathiane rings as well as the central carbocycle occur.

Crystals of the *trans* isomers of compounds **20** and **22** were investigated by X-ray diffraction methods. The ORTEP diagrams (Figs. 5 and 6) show a chair conformation for all six-membered rings, a 6,9-*anti* conformation for dispirane **20** and a 6,9-*syn*-9,12-*anti*-12,15-*syn* conformation of the spirane skeleton for **22**.

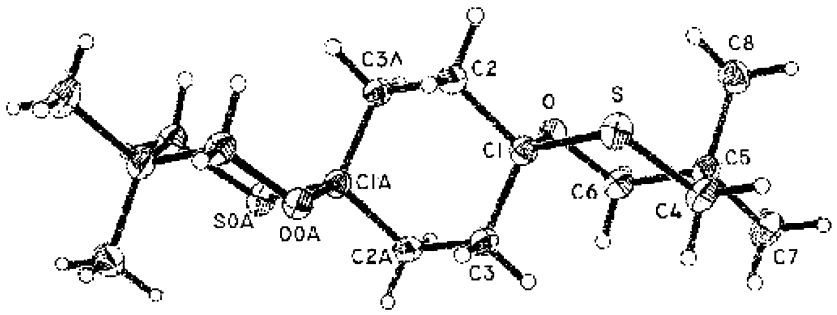


Figure 5. Labelled diagram of the *trans* isomer of compound **20**.

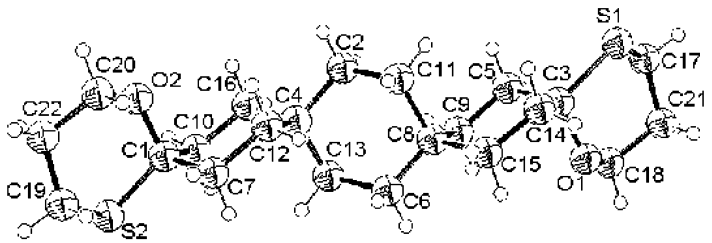
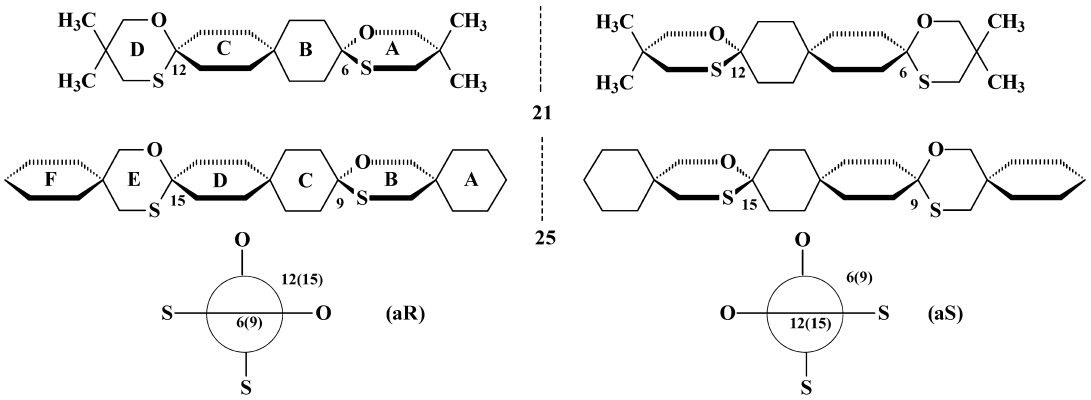


Figure 6. ORTEP diagram of *trans* isomer of compound **22**.



Scheme 14.

These conformations were determined from the values of the reference dihedral angles [**20**: $C^4SC^6O/C^{4A}S^AC^{6A}O^A$=0.0° (the molecule is centrosymmetric); **22**: ($C^{18}O^1S^1C^{17}/C^2C^{11}C^6C^{13}$=99.6°; $C^5C^9C^{14}C^{15}/C^7C^{12}C^{10}C^{16}$=17.9°; $C^2C^{11}C^{13}C^6/C^{20}O^2S^2C^{19}$=96.9°].

2.2.2. Stereochemistry of compounds 21 and 25. Compounds **21** and **25** exhibit separable enantiomers (Scheme 14). In addition to the chiral elements specific to the spirane skeleton (helical chirality) and those specific to the 1,3-oxathiane ring (a virtual tricoordinated chiral center) these compounds also contain a chiral axis (C^6–C^{12} for compound **21** and C^9–C^{15} for compound **25**). The best planes of rings A and D in **21** and B and E in **25** remain perpendicular regardless of the ring flips producing conformational equilibria.

The presence of different heteroatoms (oxygen and sulfur) in these cycles gives the parent structures axial chirality. In fact, the chirality of these molecules is similar to that of spiro[5.5]undecane derivatives bearing different substituents at their extremities.

The different configurations arising from helicity and the virtual chiral center are inverted during ring flip, while the configuration of the chiral axis remains unchanged and compounds **21** and **25** exhibit only enantiomers. The racemic of **25** was solved on HPLC using a chiral column (Fig. 8). The flexible behaviour of the compounds was seen in the NMR spectra which show singlets for the CH_2–O (**21**: δ=3.38 ppm; **25**: δ=3.46 ppm) and the CH_2–S (**21**: δ=2.56 ppm; **25**: δ=2.65 ppm) moieties (Fig. 7). All methyl groups in **21** are detected as one singlet at δ=1.01 ppm (Fig. 8).

Stereochemical analysis of the moiety containing the middle part of the spiranes and the heteroatoms (Scheme 15) reveals that, for each enantiomer, three arrangements are feasible. These would correspond to the axial–axial, equatorial–equatorial or axial–equatorial orientations of

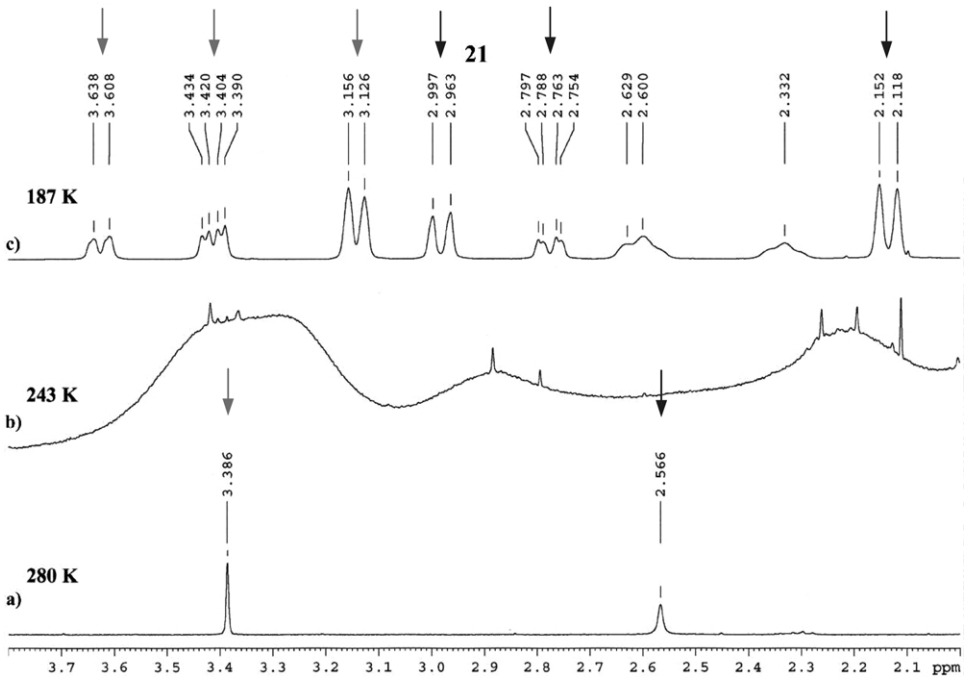


Figure 7. Variable temperature NMR spectra (CD_2Cl_2) of **19**: (a) 280 K, (b) 243 K and (c) 187 K.

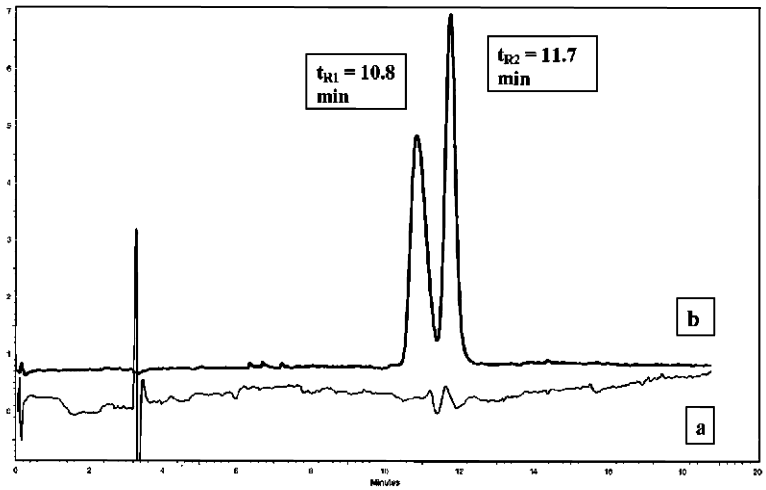


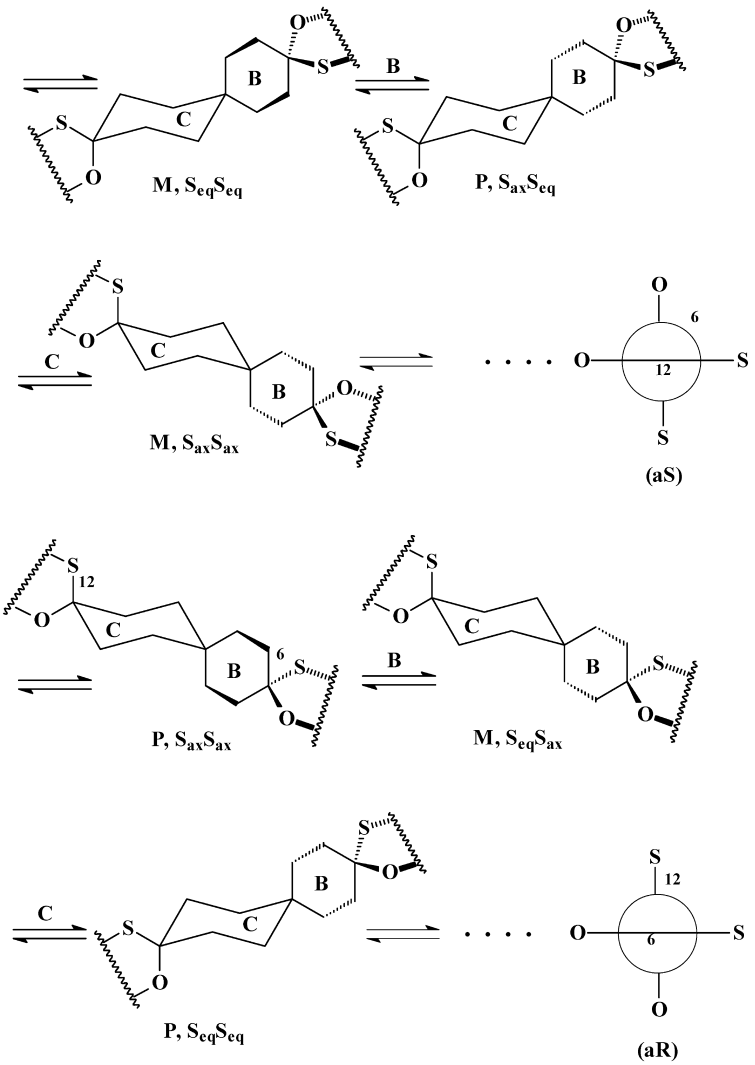
Figure 8. Chromatograms of the resolution of **25** on a CHIRACEL OD column using a chiral detector (polarimeter, a) and evaporative light scattering detection (b).

the sulphur atoms. Low temperature NMR spectra could not differentiate between the large number of stereoisomers of the frozen structures. Nonetheless, different signals for the two types of 1,3-oxathiane rings, that is, either having an equatorial (main case) or axial (minor case) sulfur atom, are observed. The ratio for the two types of rings is about 3/2. The signal for the axial protons of each moiety are well separated for each type of ring (CH_2–O moiety: δ_{ax}=3.41, 3.40 ppm (S_{eq} rings), δ_{ax}=3.62 ppm (S_{ax} rings); CH_2–S moiety: δ_{ax}=2.98 ppm (S_{eq} rings), δ_{ax}=2.77, 2.28 ppm (S_{ax} rings). On the other hand, the equatorial protons belonging to different type of rings overlapped (CH_2–O moiety: δ_{eq}=3.14 ppm; CH_2–S moiety: δ_{eq}=2.13 ppm). The axial and equatorial methyl groups produce different signals. (δ_{ax}=1.16, 1.17 ppm; δ_{eq}=0.86 ppm).

The low temperature spectra of compound **25**, while showing evidence that conformational equilibrium freezes, are more complex. The complexity arises from the higher number of isomers and greater differentiation between the many types of 1,3-oxathiane rings.

3. Conclusions

The good yielding synthesis of the first reported polyspiro-1,3-oxathianes, from di to hexaspiranes, and of the first penta and hexaspiro-1,3-dioxanes is reported. The *cis* and *trans* isomers of oxathiane derivatives were separated by column chromatography and were investigated as single compounds. The fist crystal structures of polyspiro-1,3-oxathiane derivatives (one dispiro- and another one tetraspiro) were determined by X-ray diffraction and the 6,9-*anti* disposition of the dispirane (**20**) and the



Scheme 15.

6,9-*syn*-9,12-*anti*-12,15-*syn* (**22**) arrangement of the tetraspirane skeleta were revealed. The variable temperature NMR experiments showed the flexible or the semiflexible structure of the investigated polyspiro-1,3-dioxane or polyspiro-1,3-oxathiane derivatives. The semiflexible 1,3-dioxane spiranes bearing an odd number of spirane units were found to have separable enantiomers, while those with an even number of spiro units have separable diastereoisomers. The polyspiro-1,3-oxathiane compounds exhibiting two 1,3-oxathiane rings separated by an odd number of cyclohexane rings have separable *cis* and *trans* isomers, but if the respective number of cyclohexane rings is even, the polyspirane shows separable enantiomers. The chiral HPLC resolution of polyspiranes (pentaspiro-1,3-dioxane and tetraspiro-1,3-oxathiane) is also reported.

4. Experimental

4.1. General remarks

^{1}H and ^{13}C NMR spectra were recorded in CD_2Cl_2 ($CDCl_3$) as solvent in 5 mm tubes on a Bruker AM 400 (Varian Gemini) NMR spectrometer equipped with a dual ^{13}C–^{1}H (multinuclear) head operating at 400 (300) MHz for protons and 100 (75) MHz for carbon atoms. IR spectra were recorded on a JASCO FT-IR 615 spectrometer. Melting points were measured with a Kleinfeld APOTEC melting point apparatus and are uncorrected. Elemental analyses were obtained at the University of Medicine and Pharmaceutics, Cluj-Napoca, Romania or at Université de Rouen, France. The results agreed favorably with the calculated values. Thin-layer chromatography was performed on Merck silica gel 60 F 254. Silica gel Merck (40–63 μm) was used for flash chromatography.

HPLC separations were carried out at 15 °C using a quaternary gradient pump (Spectra Physics P4000) with a Rheodyne Model 7725 injection valve (20 μL sample loop) and a column of 250 mm length and 4.6 mm i.d. containing a CHIRALCEL OD phase (DAICEL Chemical Industries, 10 μm particles). Detection was performed by a DDL 31 Evaporative Light Scattering Detector (ELSD) (Eurosep Instrument), ESI-MS and a chiral detector (polarimeter JASCO Model OR 1590). The sensitivity on the ELSD was adjusted via the photomultiplier gain at 600 V (HT PM

Table 6. Crystal data and data collection information for **20** and **22**

Compound	**20**	**22**
Empirical formula	$C_{16}H_{28}O_2S_2$	$C_{22}H_{36}O_2S_2$
Formula weight	316.50	396.63
Temperature (K)	293(2)	297(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Orthorhombic	Triclinic
Space group	*Pbca*	*P*1 (no. 1)
Unit cell dimensions		
a (Å)	9.8770(10)	6.0808(7)
b (Å)	7.8200(10)	
c (Å)	21.739(2)	9.9635(12)
α (°)	90	112.061(2)
β (°)	90	105.678(2)
γ (°)	90	92.743(2)
Volume (Å^3)	1679.1(3)	525.04(11)
Z	4	1
D_{calc} (g/cm^3)	1.252	1.254
Absorbtion coefficient (mm^{-1})	0.317	0.267
F(000)	688	216
Crystal size (mm)	0.29×0.42×0.31	0.37×0.37×0.48
θ range for the data collection (°)	1.87–2.75	2.26–28.1
Reflections collected	14,189	4004
Independent reflections	1927	1980
Refinement method	Full-matrix on F^2	Full-matrix on F^2
Data/restraints/parameters	1927/0/92	1980/0/235
Goodness-of-fit on F^2	1.059	1.089
Final *R* indices [$F^2>2\sigma(F^2)$]	R_1=0.0321, wR_2=0.0755	R_1 0.0349, wR_2=0.0896
R indices (all data)	R_1=0.0397	R_1=0.0380
Largest difference peak and hole (e Å^3)	0.279 and −0.146	0.19 and −0.21

600). Nitrogen (pressure 1.3 bar) was chosen to nebulise the effluent coming from column and the evaporation temperature was set at 50 °C. The samples were prepared in *n*-hexane. The solutes were analyzed with an isocratic mobile phase (100% *n*-hexane) at a flow rate of 0.7 mL/min. *n*-Hexane (HPLC grade) was obtained from ACROS (Geel, Belgium). A Finnigan Navigator LC–MS system (Manchester, UK) with a Spectra Physics pump (P1000) was used in the Atmospheric Pressure Chemical Ionisation in positive mode (APCI+) for compounds identification in these conditions: source heater=130 °C, APCI heater=550 °C, cone voltage 30 V.

4.2. X-ray crystallographic data

The molecular structure of **20** was determined at Université du Québec à Montréal, Québec, Canada, while the structure of **22** was determined at the National Laboratory of X-ray Diffractometry, 'Babes-Bolyai' University, Cluj-Napoca, Romania. The details of the crystal structure determination and refinement for compounds **20** and **22** are given in Table 6.

The crystals were studied on a Siemens P4 diffractometer (**20**) and on a Bruker SMART-APEX diffractometer (**22**), using graphite-monochromatised Mo Kα radiation. Crystal (**22**) was attached with silicon grease to a cryoloop. The data were collected using the XSCANS program for crystal **20**. The structures were solved by direct methods, and all the other non-hydrogen atoms were found by the usual Fourier methods. The structures were refined with anisotropic thermal parameters. The hydrogen atoms were fixed in a riding model with mutual isotropic thermal parameters. The resolution and the refinement of the structures were done using the Siemens SHELXTL system (**20**)[31] and a software package SHELX-97 (**22**).[32,33] The drawings were created with the Siemens SHELXTL system (**20**) and Ortep program (**22**).[34]

The CIF tables have been deposited with the Cambridge Crystallographic Data File Centre as supplementary publication no. CCDC-2158555 (**20**) and 215677 (**22**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: int. code +44(1223)336-033; e-mail: deposit@ccdc.cam.ac.uk].

4.3. General procedure for the synthesis of compounds 11-14 containing 1,3-dioxane rings

To a solution of 4.4 mmol of diol (**7** or **8**) in 20 mL of toluene and 2 mL of DMSO were added 2.0 mmol of the corresponding diketone (**9** and **10**, respectively) and 0.02 g of *p*-toluenesulfonic acid. The mixture was refluxed and the water that resulted from the reaction was removed using a Dean–Stark trap. When the theoretical amount of water was separated, after cooling at room temperature, the catalyst was neutralised (with stirring) with excess powdered CH_3COONa (ca. 0.05 g). The reaction mixture was washed twice with 20 mL water. The organic layer was dried over Na_2SO_4, then toluene was removed under reduced pressure and the spiro compounds were purified by flash-chromatography on silica gel or by crystallisation from acetone.

The syntheses of the starting diol, **8**, and mercaptoalcohol **17** were devised by our group[35] (being new compounds), while the syntheses of diol **7**[36] and of diketones **9**[37–39] and **10**[40] were performed using procedures described in the literature

4.3.1. 8,16,25,30-Tetraoxapentaspiro[5.2.2.2.2.5.2.2.2.2]-hentriacontane (11). White crystals (0.2 g, 24%), mp 180–182 °C. (Found: C, 74.99; H, 10.32. $C_{27}H_{44}O_4$ requires: C, 74.96; H, 10.25%); δ_H (400 MHz; CD_2Cl_2) 1.25–1.45 (28H, overlapped peaks, 1-H_2, 5-H_2, 19-H_2, 23-H_2; 2-H_2, 4-H_2, 20-H_2, 22-H_2; 3-H_2, 21-H_2; 11-H_2, 13-H_2, 27-H_2, 28-H_2), 1.69 (8H, broad triplet (AA'BB' system), ^3J= 6.0 Hz, 10-H_2, 14-H_2, 26-H_2, 29-H_2) and 3.54 (8H, s, 7-H_2, 17-H_2, 24-H_2, 31-H_2); δ_C (100 MHz; CD_2Cl_2) 21.98, 27.24, 28.64, 32.08, 32.30, 32.49, 32.99 (C-1, C-5, C-19, C-23; C-2, C-4, C-20, C-22; C-3, C-21; C-6, C-18; C-10, C-14, C-26, C-28; C-11, C-13, C-27, C-28), 68.46 (C-7, C-17, C-24, C-31) and 98.91 (C-9, C-15).

4.3.2. 3,21-Di-*t*-butyl-8,16,25,30-tetraoxapentaspiro-[5.2.2.2.2.5.2.2.2.2]hentriacontane (12). White crystals (0.19 g, 18%), mp 290–292 °C. (Found: C, 77.30; H, 11.21. $C_{35}H_{60}O_4$ requires: C, 77.15; H, 11.10%); δ_H (400 MHz; CD_2Cl_2) 0.84 (18H, s, 3-C(CH_3)$_3$, 21-C(CH_3)$_3$), 0.91–1.11 (10H, overlapped peaks, 3-H, 21-H; 2-H_2, 4-H_2, 20-H_2, 22-H_2), 1.35 (8H, m, 11-H_2, 13-H_2, 27-H_2, 28-H_2), 1.59 (4H, m, 1-H_{ax}, 5-H_{ax}, 19-H_{ax}, 23-H_{ax}), 1.69 (8H, m, 10-H_2, 14-H_2, 26-H_2, 29-H_2), 1.87 (4H, m, 1-H_{eq}, 5-H_{eq}, 19-H_{eq}, 23-H_{eq}), 3.38 (4H, s, 7-H_2, 24-H_2) and 3.67 (8H, s, 17-H_2, 31-H_2); δ_C (100 MHz; CD_2Cl_2) 22.68, 28.66, 32.31, 32.49, 32.69, 32.84 (C-1, C-5, C-19, C-23; C-2, C-4, C-20, C-22; 3-*C*(CH_3)$_3$, 21-*C*(CH_3)$_3$; C-6, C-18; C-10, C-14, C-26, C-28; C-11, C-13, C-27, C-28), 27.81 (3-C(*C*H_3)$_3$, 21-C(*C*H_3)$_3$), 49.14 (C-3, C-21), 64.99 (C-7, C-17, C-24, C-31) and 98.92 (C-9, C-15).

4.3.3. 8,19,28,35-Tetraoxahexaspiro[5.2.2.2.2.2.5.2.2.2.2.2]hexatriacontane (13). White crystals (0.27 g, 26%), mp 309–311 °C. (Found: C, 76.82; H, 10.99. $C_{33}H_{56}O_4$ requires: C, 76.69; H, 10.92%); δ_H (400 MHz; CD_2Cl_2) 1.25–1.45 (36H, overlapped peaks, 1-H_2, 5-H_2, 22-H_2, 26-H_2; 2-H_2, 4-H_2, 23-H_2, 25-H_2; 3-H_2, 24-H_2; 11-H_2, 16-H_2, 30-H_2, 33-H_2; 13-H_2, 14-H_2, 31-H_2, 32-H_2), 1.69 (8H, m, 10-H_2, 17-H_2, 29-H_2, 34-H_2) and 3.46 (8H, s, 7-H_2, 20-H_2, 27-H_2, 36-H_2); δ_C (100 MHz; CD_2Cl_2) 21.98, 27.24, 28.45, 29.30, 30.27, 32.08, 32.79, 32.99 (C-1, C-5, C-22, C-26; C-2, C-4, C-23, C-25; C-3, C-24; C-6, C-21; C-10, C-17, C-29, C-34; C-11, C-16, C-30, C-33; C-12, C-15; C-13, C-14, C-31, C-32), 68.44 (C-7, C-20, C-27, C-36) and 99.01 (C-9, C-18).

4.3.4. 3,24-Di-*t*-butyl-8,19,28,35-tetraoxahexaspiro-[5.2.2.2.2.2.5.2.2.2.2.2]hexatriacontane (14). White crystals (0.41 g, 33%), mp 310–312 °C. (Found: C, 78.15; H, 11.66. $C_{41}H_{72}O_4$ requires: C, 78.29; H, 11.54%); mixture of diastereoisomers. δ_H (400 MHz; CD_2Cl_2) 0.84 (18H, s, 3-C(CH_3)$_3$, 24-C(CH_3)$_3$), 0.91–1.10 (10H, overlapped peaks, 3-H, 24-H; 2-H_2, 4-H_2, 23-H_2, 25-H_2), 1.29 (8H, s, 13-H_2, 14-H_2, 31-H_2, 32-H_2), 1.33 (8H, m, 11-H_2, 16-H_2, 30-H_2, 33-H_2), 1.58 (4H, m, 1-H_{ax}, 5-H_{ax}, 19-H_{ax}, 23-H_{ax}), 1.68 (8H, m, 10-H_2, 17-H_2, 29-H_2, 34-H_2), 1.87 (4H, m, 1-H_{eq}, 5-H_{eq}, 19-H_{eq}, 23-H_{eq}) and 3.38 (4H, s, 7-H_2, 27-H_2), 3.67 (8H, s, 22-H_2, 36-H_2); δ_C (100 MHz; CD_2Cl_2) 22.67, 28.46, 32.07, 32.48, 32.69, 32.69, 32.79, 32.84 (C-1, C-5, C-22, C-26; C-2, C-4, C-23, C-25; 3-*C*(CH_3)$_3$, 24-*C*(CH_3)$_3$; C-6, C-21; C-10, C-17, C-29, C-34; C-11, C-16, C-30, C-33; C-12, C-15; C-13, C-14, C-31, C-32), 27.80 (3-C(*C*H_3)$_3$, 24-C(*C*H_3)$_3$), 49.14 (C-3, C-24), 64.97 (C-7, C-20, C-27, C-36) and 99.04 (C-9, C-18).

4.4. General procedure for the synthesis of compounds 19-26 containing 1,3-oxathiane rings

A solution of 4.4 mmol of 3-mercapto-propan-1-ol (**15**-**17**), the corresponding diketone (**9**, **10**, **18**) (2.0 mmol) and 0.05 g of *p*-toluenesulfonic acid in 20 mL of toluene was refluxed and the water generated in the reaction was removed using a Dean–Stark trap. When the theoretical water was separated, after cooling at rt, the catalyst was neutralised (with stirring) with an excess of 0.1 M KOH (in order to remove the remaining thiol). The organic layer was then washed twice with water (20 mL). After drying over Na_2SO_4, the toluene was removed under reduced pressure and the oxathianes were purified by flash-chromatography or by crystallisation from acetone.

4.4.1. 5,14-Dioxa-1,10-dithiadispiro[5.2.5.2]hexadecane (19). White crystals (0.43 g, 83%), mixture of *trans* and *cis* isomers, subjected to column chromatography (dichloromethane–petroleum ether–ethyl acetate 5/12/1, ΔR_f=0.14, *trans* isomer with R_f=0.54 and *cis* isomer with R_f=0.40).

trans Isomer. White crystals (0.18 g, 35%), mp 187–188 °C. (Found: C, 55.32; H, 7.56; S, 24.88. $C_{12}H_{20}O_2S_2$ requires: C, 55.35; H, 7.74; S, 24.63%); δ_H (300 MHz, $CDCl_3$) 1.78–1.86 (4H, m, 3-H_2, 12-H_2), 2.00 (4H, d, ^2J= 10.0 Hz, 7-*H*H′, 8-*H*H′, 15-*H*H′, 16-*H*H′), 2.12 (4H, d, ^2J= 10.0 Hz, 7-H*H*′, 8-H*H*′, 15-H*H*′, 16-H*H*′), 2.86 (4H, m, 2-H_2, 11-H_2) and 3.85 (4H, m, 4-H_2, 13-H_2); δ_C (75 MHz, $CDCl_3$) 24.08 (C-3, C-12), 25.51 (C-7, C-8, C-15, C-16), 31.78 (C-2, C-11), 61.63 (C-4, C-13) and 80.19 (C-6, C-9).

cis Isomer. White crystals (0.19 g, 37%), mp 119–120.2 °C. (Found: C, 55.54; H, 7.58; S, 24.72. $C_{12}H_{20}O_2S_2$ requires: C, 55.35; H, 7.74; S, 24.63%); δ_H (300 MHz, $CDCl_3$) 1.78–1.86 (4H, m, 3-H_2, 12-H_2), 1.98–2.16 (8H, m, 7-H_2, 8-H_2, 15-H_2, 16-H_2), 2.83 (4H, m, 2-H_2, 11-H_2) and 3.88 (4H, m, 4-H_2, 13-H_2); δ_C(75 MHz, $CDCl_3$) 24.12 (C-3, C-12), 25.64 (C-7, C-8, C-15, C-16), 32.37 (C-2, C-11), 61.37 (C-4, C-13) and 80.91 (C-6, C-9).

4.4.2. 3,3,12,12-Tetramethyl-5,14-dioxa-1,10-dithiadispiro[5.2.5.2]hexadecane (20). White crystals (0.5 g, 79%), mixture of *trans* and *cis* isomers, subjected to column chromatography (petroleum ether–ethyl acetate 12/1, ΔR_f= 0.11, *trans* isomer with R_f=0.52 and *cis* isomer with R_f=0.41).

trans Isomer. White crystals (0.26 g, 42%), mp 192–193 °C. (Found: C, 60.85; H, 8.99; S, 20.16. $C_{16}H_{28}O_2S_2$ requires: C, 60.71; H, 8.92; S, 20.26%); δ_H (300 MHz, $CDCl_3$) 1.05 (12H, s, 3-CH_3, 12-CH_3), 1.94 (4H, d, ^2J= 10.0 Hz, 7-*H*H′, 8-*H*H′, 15-*H*H′, 16-*H*H′), 2.13 (4H, d, ^2J= 10.0 Hz, 7-H*H*′, 8-H*H*′, 15-H*H*′, 16-H*H*′), 2.61 (4H, s, 2-H_2, 11-H_2) and 3.40 (4H, s, 4-H_2, 13-H_2); δ_C (75 MHz, $CDCl_3$) 24.92 (3-CH_3, 12-CH_3), 28.04 (C-3, C-12), 31.62 (C-7, C-8, C-15, C-16), 36.75 (C-2, C-11), 71.25 (C-4, C-13) and 80.05 (C-6, C-9).

cis Isomer. White crystals (0.19 g, 31%), mp 156 °C. (Found: C, 55.29; H, 7.68; S, 24.81. $C_{16}H_{28}O_2S_2$ requires: C, 60.71; H, 8.92; S, 20.26%); δ_H (300 MHz, $CDCl_3$) 1.05 (12H, s, 3-CH_3, 12-CH_3), 1.92–2.14 (8H, m, 7-H_2, 8-H_2,

15-H_2, 16-H_2), 2.59 (4H, s, 2-H_2, 11-H_2) and 3.42 (4H, s, 4-H_2, 13-H_2); δ_C (75 MHz, $CDCl_3$) 24.93 (3-CH_3, 12-CH_3), 28.09 (C-3, C-12), 32.20 (C-7, C-8, C-15, C-16), 36.81 (C-2, C-11), 71.16 (C-4, C-13) and 80.70 (C-6, C-9).

4.4.3. 3,3,15,15-Tetramethyl-5,17-dioxa-1,13-dithia-trispiro[5.2.2.5.2.2]henicosane (21). White crystals (0.21 g, 27%), mp 189–191 °C. (Found C, 65.64; H, 9.37; S, 16.44. $C_{21}H_{36}O_2S_2$ requires: C, 65.57; H, 9.43; S, 16.67%); δ_H (400 MHz; CD_2Cl_2) 1.02 (12H, s, 3-CH_3, 15-CH_3), 1.25–1.50 (8H, m, 8-H_2, 10-H_2, 19-H_2, 20-H_2), 1.81 (4H, m, 7-*H*H′, 11-*H*H′, 18-*H*H′, 21-*H*H′), 1.98 (4H, m, 7-H*H*′, 11-H*H*′, 18-H*H*′, 21-H*H*), 2.57 (4H, s, 2-H_2, 14-H_2) and 3.39 (4H, s, 4-H_2, 16-H_2); δ_C (100 MHz; CD_2Cl_2) 28.40, 29.94, 32.20, 33.13 (C-3, C-5; C-7, C-11, C-18, C-21; C-8, C-10, C-19, C-20; C-9), 25.14 (3-CH_3, 15-CH_3), 37.09 (C-2, C-14), 71.42 (C-4, C-16) and 82.19 (C-6, C-12).

4.4.4. 5,20-Dioxa-1,16-dithiatetraspiro[5.2.2.2.5.2.2.2]-hexacosane (22). White crystals (0.56 g, 71%), mixture of *trans* and *cis* isomers, subjected to column chromatography (toluene–dichloromethane–ethyl acetate 8/2/0.5, ΔR_f= 0.10, *trans* isomer with R_f=0.34 and *cis* isomer with R_f= 0.23).

trans Isomer. White crystals (0.33 g, 42%), mp 215–217 °C. (Found: C, 66.78; H, 9.12; S, 16.14. $C_{22}H_{36}O_2S_2$ requires: C, 66.62; H, 9.15; S, 16.17%); δ_H (400 MHz, $CDCl_3$) 1.33–1.58 (16H, overlapped peaks, 8-H_2, 13-H_2, 22-H_2, 25-H_2; 10-H_2, 11-H_2, 23-H_2, 24-H_2), 1.64–1.78 (8H, overlapped peaks, 3-H_2, 18-H_2; 7-*H*H′, 14-*H*H′, 21-*H*H′, 26-*H*H′), 1.86 (4H, m, 7-H*H*′, 14-H*H*′, 21-H*H*′, 26-H*H*′), 2.72 (4H, m, 2-H_2, 17-H_2) and 3.74 (4H, m, 4-H_2, 19-H_2); δ_C (100 MHz, $CDCl_3$) 24.47, 26.39, 30.26, 32.52, 32.74 (C-2, C-17; C-3, C-18; C-7, C-14, C-21, C-26; C-8, C-13, C-22, C-25; C-9, C-12; C-10, C-11, C-23, C-24), 61.61 (C-4, C-19) and 82.52 (C-6, C-15).

cis Isomer. White crystals (0.23 g, 29%), mp 206–208 °C. (Found: C, 66.55; H, 9.26; S, 16.30. $C_{22}H_{36}O_2S_2$ requires: C, 66.62; H, 9.15; S, 16.17%); δ_H (400 MHz, $CDCl_3$) 1.19 (4H, s, 10-H_2, 23-H_2), 1.24 (4H, s, 11-H_2, 24-H_2), 1.28–1.34 (8H, overlapped peaks, 8-H_2, 13-H_2, 22-H_2, 25-H_2), 1.64–1.78 (8H, overlapped peaks, 3-H_2, 18-H_2; 7-*H*H′, 14-*H*H′, 21-*H*H′, 26-*H*H′), 1.86 (4H, m, 7-H*H*′, 14-H*H*′, 21-H*H*′, 26-H*H*′), 2.72 (4H, m, 2-H_2, 17-H_2) and 3.74 (4H, m, 4-H_2, 19-H_2); δ_C (100 MHz, $CDCl_3$) 24.47, 26.39, 30.26, 32.52, 32.74 (C-2, C-17; C-3, C-18; C-7, C-14, C-21, C-26; C-8, C-13, C-22, C-25; C-9, C-12; C-10, C-11, C-23, C-24), 61.61 (C-4, C-19) and 82.52 (C-6, C-15).

4.4.5. 3,3,18,18-Tetramethyl-5,20-dioxa-1,16-dithiate-traspiro[5.2.2.2.5.2.2.2]hexacosane (23). White crystals (0.57 g, 63%), mixture of *trans* and *cis* isomers, subjected to column chromatography (toluene–dichloromethane–ethyl acetate 60/1/0.15, ΔR_f=0.09, D^1 isomer with R_f=0.29 and D^2 isomer with R_f=0.20).

D^1 *isomer*. White crystals (0.32 g, 35%), mp 225–227 °C. (Found: C, 68.89; H, 9.61; S, 14.33. $C_{26}H_{44}O_2S_2$ requires: C, 68.97; H, 9.80; S, 14.16%); δ_H (400 MHz, $CDCl_3$) 0.93 (12H, s, 3-CH_3, 18-CH_3), 1.16–1.35 (16H, overlapped peaks, 8-H_2, 13-H_2, 22-H_2, 25-H_2; 10-H_2, 11-H_2, 23-H_2, 24-H_2), 1.73 (4H, m, 7-*H*H′, 14-*H*H′, 21-*H*H′, 26-*H*H′), 1.84 (4H, m, 7-H*H*′, 14-H*H*′, 21-H*H*′, 26-H*H*′), 2.48 (4H, s, 2-H_2, 17-H_2) and 3.30 (4H, s, 4-H_2, 19-H_2); δ_C (100 MHz, $CDCl_3$) 28.40, 32.11, 32.74 (C-3, C-18; C-7, C-14, C-21, C-26; C-8, C-13, C-22, C-25; C-9, C-12; C-10, C-11, C-23, C-24), 25.14 (3-CH_3, 18-CH_3), 37.10 (C-2, C-17), 71.40 (C-4, C-19) and 82.38 (C-6, C-15).

D^2 *isomer*. White crystals (0.21 g, 23%), mp 206–208 °C. (Found: C, 68.99; H, 9.64; S, 14.31. $C_{26}H_{44}O_2S_2$ requires: C, 68.97; H, 9.80; S, 14.16%); δ_H (400 MHz, $CDCl_3$) 0.93 (12H, s, 3-CH_3, 18-CH_3), 1.19 (4H, s, 10-H_2, 23-H_2), 1.23 (4H, s, 11-H_2, 24-H_2), 1.27–1.35 (8H, overlapped peaks, 8-H_2, 13-H_2, 22-H_2, 25-H_2), 1.73 (4H, m, 7-*H*H′, 14-*H*H′, 21-*H*H′, 26-*H*H′), 1.84 (4H, m, 7-H*H*′, 14-H*H*′, 21-H*H*′, 26-H*H*′), 2.49 (4H, s, 2-H_2, 17-H_2) and 3.30 (4H, s, 4-H_2, 19-H_2); δ_C (100 MHz, $CDCl_3$) 28.40, 30.26, 31.15, 32.13, 32.74 (C-3, C-18; C-7, C-14, C-21, C-26; C-8, C-13, C-22, C-25; C-9, C-12; C-10, C-11, C-23, C-24), 25.15 (3-CH_3, 18-CH_3), 37.10 (C-2, C-17), 71.40 (C-4, C-19) and 82.39 (C-6, C-15).

4.4.6. 22,25-Dioxa-8,13-dithiatetraspiro[5.2.2.2.5.2.2.2]-hexacosane (24). White crystals (0.49 g, 62%), mixture of *trans* and *cis* isomers, subjected to column chromatography (toluene–dichloromethane–ethyl acetate 24/2/0.25, ΔR_f= 0.15, *trans* isomer with R_f=0.43 and *cis* isomer with R_f= 0.28).

trans Isomer. White crystals (0.26 g, 33% yield), mp 217–219 °C. (Found: C, 66.47; H, 9.22; S, 16.21. $C_{22}H_{36}O_2S_2$ requires: C, 66.62; H, 9.15; S, 16.17%); δ_H (400 MHz, $CDCl_3$) 1.33–1.58 (20H, overlapped peaks, 1-H_2, 5-H_2, 16-H_2, 20-H_2; 2-H_2, 4-H_2, 17-H_2, 19-H_2; 3-H_2, 18-H_2), 1.85 (4H, d, ^2J=10 Hz, 10-*H*H′, 11-*H*H′, 23-*H*H′, 24-*H*H′), 2.10 (4H, d, ^2J=10 Hz, 10-H*H*′, 11-H*H*′, 23-H*H*′, 24-H*H*′), 2.68 (4H, s, 7-H_2, 14-H_2) and 3.45 (4H, s, 21-H_2, 26-H_2); δ_C (100 MHz, $CDCl_3$) 21.74, 27.17, 30.66, 32.95, 33.56 (C-1, C-5, C-16, C-20; C-2, C-4, C-17, C-19; C-3, C-18, C-6, C-15; C-10, C-11, C-23, C-24), 34.31 (C-7, C-14), 70.69 (C-21, C-26) and 81.77 (C-9, C-12).

cis Isomer. White crystals (0.17 g, 22%), mp 196–198 °C. (Found: C, 66.38; H, 9.18; S, 16.11. $C_{22}H_{36}O_2S_2$ requires: C, 66.62; H, 9.15; S, 16.17%); δ_H (400 MHz, $CDCl_3$) 1.35–1.60 (20H, overlapped peaks, 1-H_2, 5-H_2, 16-H_2, 20-H_2; 2-H_2, 4-H_2, 17-H_2, 19-H_2; 3-H_2, 18-H_2), 1.90–2.07 (8H, overlapped peaks, 10-H_2, 11-H_2, 23-H_2, 24-H_2), 2.66 (4H, s, 7-H_2, 14-H_2) and 3.47 (4H, s, 21-H_2, 26-H_2); δ_C (100 MHz, $CDCl_3$) 21.74, 27.18, 30.60, 32.39, 33.55 (C-1, C-5, C-16, C-20; C-2, C-4, C-17, C-19; C-3, C-18, C-6, C-15; C-10, C-11, C-23, C-24), 34.23 (C-7, C-14), 70.80 (C-21, C-26) and 81.08 (C-9, C-12).

4.4.7. 24,31-Dioxa-7,17-dithia-pentaspiro[5.2.2.2.2.5.2.2.2.2]hentriacontane (25). White crystals (0.19 g, 21%), mp 250–252 °C. (Found: C, 69.95; H, 9.45; S, 13.88. $C_{27}H_{44}O_2S_2$ requires: C, 69.77; H, 9.54; S, 13.80%); δ_H (400 MHz; CD_2Cl_2) 1.32–1.58 (28H, overlapped peaks, 1-H_2, 5-H_2, 19-H_2, 23-H_2; 2-H_2, 4-H_2, 20-H_2, 22-H_2; 3-H_2, 21-H_2; 11-H_2, 13-H_2, 27-H_2, 28-H_2), 1.80 (4H, m, 10-*H*H′, 14-*H*H′, 26-*H*H′, 29-*H*H′), 1.93 (4H, m, 10-H*H*′, 14-H*H*′, 26-H*H*′, 29-H*H*′), 2.65 (4H, s, 7-H_2, 17-H_2) and 3.46 (4H, s,

24-H_2, 31-H_2); δ_C (100 MHz; CD_2Cl_2) 21.76, 27.20, 30.67, 32.18, 32.29, 32.39, 33.60 (C-1, C-5, C-19, C-23; C-2, C-4, C-20, C-22; C-3, C-21; C-6, C-18; C-10, C-14, C-26, C-28; C-11, C-13, C-27, C-28), 34.19 (C-7, C-17), 70.53 (C-24, C-31) and 82.80 (C-9, C-15).

4.4.8. 27,36-Dioxa-7,20-dithia-hexaspiro[5.2.2.2.2.2.5.2.2.2.2]hexatriacontane (26). White crystals (0.62 g, 57% yield), mixture of *trans* and *cis* isomers, subjected to column chromatography (toluene–dichloromethane–ethyl acetate 24/2/0.25, ΔR_f=0.13, D^1 isomer with R_f=0.38 and D^2 isomer with R_f=0.25).

D^1 *isomer*. White crystals (0.24 g, 22% yield), mp 315–317 °C. (Found: C, 72.41; H, 10.11; S, 11.82. $C_{33}H_{56}O_2S_2$ requires: C, 72.20; H, 10.28; S, 11.68%); δ_H (400 MHz, $CDCl_3$) 1.28–1.49 (36H, overlapped peaks, 1-H_2, 5-H_2, 22-H_2, 26-H_2; 2-H_2, 4-H_2, 23-H_2, 25-H_2; 3-H_2, 24-H_2; 11-H_2, 16-H_2, 30-H_2, 33-H_2; 13-H_2, 14-H_2, 31-H_2, 32-H_2), 1.80 (4H, m, 10-*H*H′, 17-*H*H′, 29-*H*H′, 34-*H*H′), 1.84 (4H, m, 10-H*H*′, 17-H*H*′, 29-H*H*′, 34-H*H*′), 2.65 (4H, s, 7-H_2, 20-H_2) and 3.46 (4H, s, 27-H_2, 36-H_2).

D^2 *isomer*. White crystals (0.23 g, 21%), mp 324–326 °C. (Found: C, 72.34; H, 10.11; S, 11.81. $C_{33}H_{56}O_2S_2$ requires: C, 72.20; H, 10.28; S, 11.68%); δ_H(400 MHz, $CDCl_3$) 1.27–1.48 (36H, overlapped peaks, 1-H_2, 5-H_2, 22-H_2, 26-H_2; 2-H_2, 4-H_2, 23-H_2, 25-H_2; 3-H_2, 24-H_2; 11-H_2, 16-H_2, 30-H_2, 33-H_2; 13-H_2, 14-H_2, 31-H_2, 32-H_2), 1.80 (4H, m, 10-*H*H′, 17-*H*H′, 29-*H*H′, 34-*H*H′), 1.84 (4H, m, 10-H*H*′, 17-H*H*′, 29-H*H*′, 34-H*H*′), 2.65 (4H, s, 7-H_2, 20-H_2) and 3.46 (4H, s, 27-H_2, 36-H_2).

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