# Synthesis and stereochemistry of new tetraspiro-1,3-dioxanes

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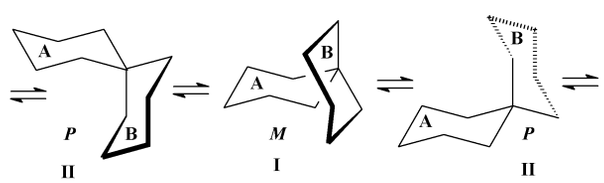
The synthesis and the stereochemistry of new tetraspiro-1,3-dioxanes are reported. The configuration of isomers is discussed considering the helical chirality of spiranes with six-membered rings. The X-ray structures of three compounds exhibiting different configurations and conformations of the polyspiro skeleton are described. The flexible or anancomeric behaviour of the rings of the spiro skeleton is investigated by conformational analysis and dynamic NMR.

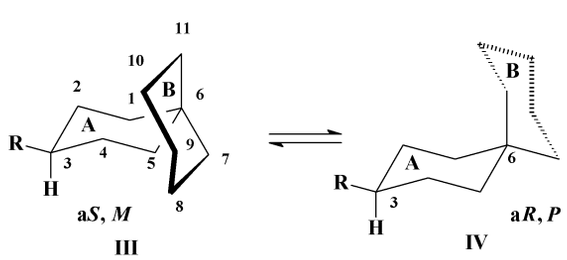
## Introduction

Our investigations[1–5] of the stereochemistry of some spiro-, dispiro- and trispiro-1,3-dioxanes revealed the helical chirality of the spiranes with six-membered rings. The helix exhibiting *P* or *M* configuration can show repeat spatial orientation after each fourth six-membered ring. The spiro[5.5]undecane **1**, considered as parent skeleton for the spiranes with six-membered rings, is flexible, the flipping of the rings (A and B, Scheme 1) resulting into an enantiomeric inversion [**I** (*M*) ⇌ **II** (*P*)].



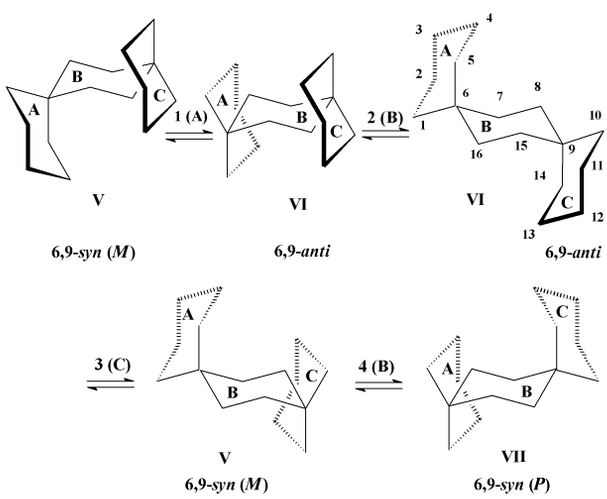

**Scheme 1**

A 3-substituted spiro[5.5]undecane or its analogous heterocycles[1,2] exhibit a semiflexible structure (Scheme 2); the substituted ring (A) is anancomeric, while the unsubstituted one is flexible (B). The flipping of ring B results in an enantiomeric inversion, both axial ($C^6$–$C^9$ as chiral axis†) and helical chiralities of the spirane being inverted [**III** (a*S*, *M*) ⇌ **IV**(a*R*, *P*)].




**Scheme 2**

† The reference groups are R and H at $C^3$ and the ring B (which can be in front or behind the chiral axis) at $C^6$.




**Scheme 3**

The marginal rings (A and C, Scheme 3) in dispiro-[5.2.5.2]hexadecane **2** (or in analogous heterocycles) show '*syn*' [$C^1C^5C^6$ ($C^9C^{10}C^{14}$) on the same side of the best plane of the middle ring B, structures **V** and **VII**] or '*anti*' (on opposite sides, structure **VI**) dispositions, the helix being conserved in the '*syn*' isomers or cancelled in the '*anti*' one.

A comparison of the configuration problems of dispirane **2** with those of [10]helicene is interesting. [10]Helicene can be considered as being obtained by the merging of two hexahelicene units. The chirality of [10]helicene can be deduced from the configurations of the jointed units.[6,7] Two units with identical configuration generate *P* or *M* [10]helicene, while the joining of units with different configurations leads to a symmetric structure (exhibiting an inversion centre). Similarly, the dispirane **2** is built up by the merging of two monospiro units (rings AB and BC) and the chirality of the dispirane is determined by the configurations of the two monospiro entities. If the two units (rings AB and BC) exhibit the same configuration the helix is continued in the whole structure (*P* and *M* '*syn*' isomer) and if they show opposite configurations the chirality of the system is cancelled ('*anti*' isomer; Table 1).

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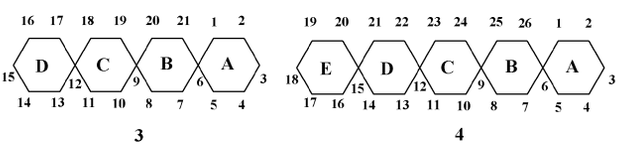
**Table 1** Possible stereoisomers of spiro compounds with six-membered-rings[a]

| Isomer | Orientation of the rings | AB | BC | CD | DE | Helix |
|---|---|---|---|---|---|---|
| **I** | | *M* | | | | *M* |
| **II** | | *P* | | | | *P* |
| **V** | 6,9-*syn* | *M* | *M* | | | *M* |
| **VI** | 6,9-*anti* | *P*(*M*) | *M*(*P*) | | | |
| **VII** | 6,9-*syn* | *P* | *P* | | | *P* |
| **VIII** | 6,9-*syn*-9,12-*syn* | *M* | *M* | *M* | | *M* |
| **IX** | 6,9-*syn*-9,12-*syn* | *P* | *P* | *P* | | *P* |
| **X** | 6,9-*syn*-9,12-*anti* | *P* | *P* | *M* | | *P* |
| **XI** | 6,9-*syn*-9,12-*anti* | *M* | *M* | *P* | | *M* |
| **XII** | 6,9-*anti*-9,12-*anti* | *P* | *M* | *P* | | *P* |
| **XIII** | 6,9-*anti*-9,12-*anti* | *M* | *P* | *M* | | *M* |
| **XIV** | 6,9-*syn*-9,12-*syn*-12,15-*syn* | *P* | *P* | *P* | *P* | *P* |
| **XV** | 6,9-*syn*-9,12-*syn*-12,15-*syn* | *M* | *M* | *M* | *M* | *M* |
| **XVI** | 6,9-*syn*-9,12-*syn*-12,15-*anti* | *P* | *P* | *P* | *M* | *P* |
| **XVII** | 6,9-*anti*-9,12-*syn*-12,15-*syn* | *P* | *M* | *M* | *M* | *M* |
| **XVIII** | 6,9-*anti*-9,12-*syn*-12,15-*anti* | *M* | *P* | *P* | *M* | *P* |
| **XIX** | 6,9-*anti*-9,12-*syn*-12,15-*anti* | *P* | *M* | *M* | *P* | *M* |
| **XX** | 6,9-*syn*-9,12-*anti*-12,15-*anti* | *P* | *P* | *M* | *P* | *P* |
| **XXI** | 6,9-*syn*-9,12-*anti*-12,15-*anti* | *M* | *M* | *P* | *M* | *M* |
| **XXII** | 6,9-*syn*-9,12-*anti*-12,15-*syn* | *M*(*P*) | *M*(*P*) | *P*(*M*) | *P*(*M*) | |
| **XXIII** | 6,9-*anti*-9,12-*anti*-12,15-*anti* | *M*(*P*) | *P*(*M*) | *M*(*P*) | *P*(*M*) | |

[a] The *syn* or *anti* disposition of rings A and C with reference to ring B in dispirane **2** can be deduced from the value of the dihedral angle $C^1C^2C^4C^5$/$C^{10}C^{11}C^{13}C^{14}$. If the value of this dihedral angle is close to zero, the rings A and C are *anti* and if the value of this angle is close to 90° the *syn* disposition of rings A and C must be taken into account. The *syn* or *anti* orientations of the rings of the tetraspirane **4** can be deduced similarly from the values of the angles $C^1C^2C^4C^5/C^{10}C^{11}C^{23}C^{24}$; $C^7C^8C^{25}C^{26}/C^{13}C^{14}C^{21}C^{22}$ and $C^{16}C^{17}C^{19}C^{20}/C^{10}C^{11}C^{23}C^{24}$.

The flipping (steps 1 and 3, Scheme 3) of marginal rings (A or C) changes the configuration of one of the two monospiro constituent units and transforms '*syn*' into '*anti*' isomers and *vice versa*, while the flipping of the middle ring B (steps 2 and 4) changes the configuration of both constituent units and results in a homomeric equilibrium (step 2) in the '*anti*' isomer and in an enantiomeric inversion (step 4) in the '*syn*' ones. The parent trispirane **3** or tetraspirane **4** (Scheme 4) or their analogous heterocycles can be built up from three or four monospiro units respectively, giving five or possibly six, or ten isomers, respectively (Table 1).




**3** **4**

**Scheme 4**

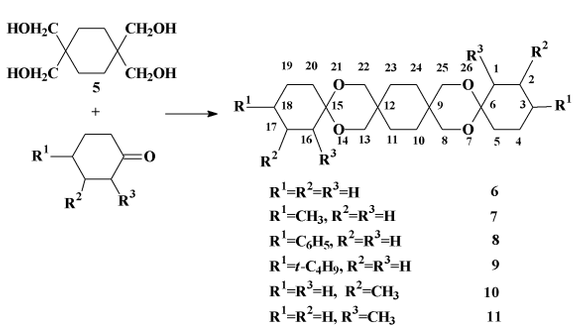
All the possible isomers of trispirane **3** are chiral, whereas the polyspiro skeleton in tetraspirane **4** exhibits two isomers with higher symmetry (both showing an inversion centre). The configuration problems of polyspiranes, as are those of polyhelicenes (formed by multiply joined hexahelicene units or linked [*n*]helicenes[8]), are correlated with the odd or even number of spiro joined structural units. It is to be observed that when odd numbers of spiro-units are joined (or odd numbers of hexahelicene units form the polyhelicene) all the possible structures of the polyspiranes (polyhelicenes) are chiral, whereas the polyspiranes with even numbers of spiro units (or polyhelicenes with even numbers of hexahelicene units) exhibit achiral isomers (with centre of inversion).

Few data concerning the solid-state molecular structure of polyspiranes exhibiting six-membered rings (dispiranes,[9] trispiranes[10–12] and tetraspiranes[13]) have been reported. In all data reported until now the polyspiranes display rings of different sizes. To our knowledge no X-ray diffractometry data for tetraspiranes exhibiting only six-membered rings have yet been reported.

Considering the complexity of configurational and conformational problems in the stereochemistry of spiranes with six-membered rings it has been considered of interest to continue structural studies on the stereochemistry of polyspiranes and to perform synthesis and NMR and X-ray investigations of some new tetraspiro-1, 3-dioxanes.

## Results and discussion

New tetraspiro compounds **6**–**11** were obtained by the condensation of 1,1,4,4-tetrakis(hydroxymethyl)cyclohexane **5** with several (substituted) cyclohexanones (Scheme 5 ‡). Compound **6** exhibits flexible structure, the flipping of cyclohexane or 1,3-dioxane rings determines the equilibration of all possible isomers (ten isomers, as for **4**, six of them being diastereoisomers, Table 1). The $^1$H NMR spectrum of **6** recorded at rt is quite simple (Table 2), the protons of the 1,3-dioxane rings, rendered equivalent by the flexibility of the molecule, exhibiting one singlet at $\delta$ 3.55. The spectrum run at low temperature (223 K in $CD_2Cl_2$, this temperature barrier is dictated by the low solubility of the compound in all usual NMR solvents) shows for the protons of the heterocycles a broad band between $\delta$ 3.25–3.75. The shape of this signal (band) denotes the proximity of coalescence and the incurrent imminent freezing of the flipping of the rings.




**Scheme 5**

The molecular structure of **6** (ORTEP diagrams, Fig. 1) established in the solid state by X-ray diffractometry shows chair conformations for both the cyclohexane and 1,3-dioxane rings.

‡ The optically pure 3(*R*)-methylcyclohexanone was used.

The crystal contains two kinds of molecules corresponding to the centrosymmetric structures 6,9-*anti*-9,12-*anti*-12,15-*anti* and 6,9-*syn*-9,12-*anti*-12,15-*syn*. The structures were best solved for a 1 : 1 ratio between the two conformers. The disposition of the rings was deduced from the calculated values of the reference dihedral angles (Table 3).

Compounds **7**–**11** exhibit semiflexible structures. In **7**–**9** rings A and E are anancomeric and rings B, C and D are flipping. The structural modifications of the spiro skeleton produced by the flipping of the middle part of the molecules are summarised in Table 4.

Compounds **7**–**9** exhibit two separable diastereoisomers. The flipping of the rings (B, C and D, Scheme 6) in the major diastereoisomer $D_1$ leads to an equilibrium between structures XIV, XV, XIX, XX, XXIII and XXIV (Table 1). In the other isomer ($D_2$) the equilibria are running among the structures XVI, XVII, XX and XXI (Scheme 7). To convert one of the structures of $D_1$ into one of the structures of $D_2$ it is necessary to break bonds and to remake bonds. *Per contra* the possible enantiomers (XIV, XV; XVIII, XIX for $D_1$ and XVI, XVII; XX, XXI for $D_2$) are equilibrated by the flipping of the rings. This situation is different in the case of trispiro-1,3-dioxanes with semiflexible structures when the flipping of the middle part of the molecule is bringing in conformational equilibrium the possible diastereoisomers, but the enantiomers of the compounds are separable.[2,5] The case of tetraspiranes with semiflexible structure is similar with that of dispiro-1,3-dioxanes[3] that exhibit separable diastereoisomers and conformationally equilibrated enantiomers. The ratio between the two diastereoisomers of **7**–**9** is about $D_1 : D_2 = 4 : 1$ (estimated from NMR

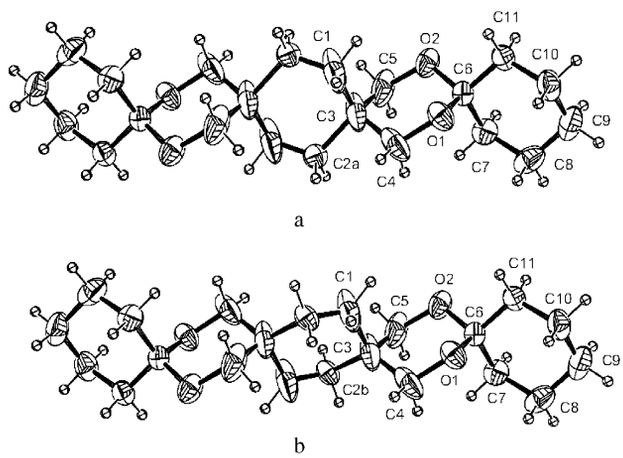
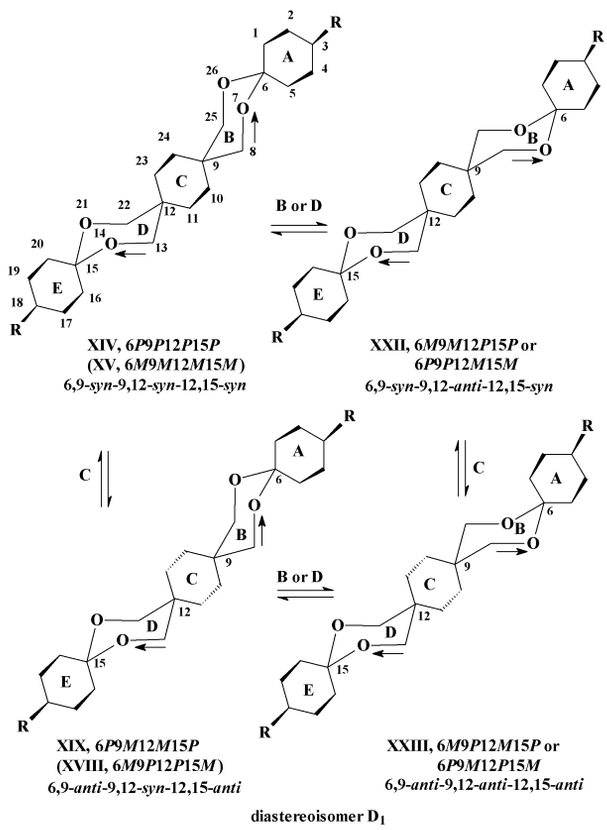



**Fig. 1** ORTEP diagrams for **6** (a: 6,9-*anti*-9,12-*anti*-12,15-*anti*; b: 6,9-*syn*-9,12-*anti*-12,15-*syn* isomers).

**Table 2** NMR data ($CD_2Cl_2$, $\delta$/ppm) of compounds **6**–**11**

| | $^1$H | | $^{13}$C |
|---|---|---|---|
| Compound | 8,22/13,25 | 10,11,23,24 | 8,22/13,25 |
| **6** | 3.55 | 1.38 | 67.67 |
| **7** ($D_1$, $D_2$) | 3.52/3.57 | 1.38 | 67.88/67.75 |
| **8** $D_1$ | 3.60/3.64 | 1.43 | 67.54/68.01[a] |
| **8** $D_2$ | 3.61/3.62 | 1.41 | 67.69/67.88[a] |
| **9** ($D_1$, $D_2$) | 3.53/3.57 | 1.38 | 67.93/67.72 |
| **10** ($D_1$, $D_2$) | 3.52/3.58 | 1.36, 1.40 | 67.75 |
| **11** $D_5$ | 3.51, 3.67/3.53, 3.54 | 1.20, 1.55 | 67.55/67.69 |

[a] Spectra taken in $CDCl_3$.




**Scheme 6**

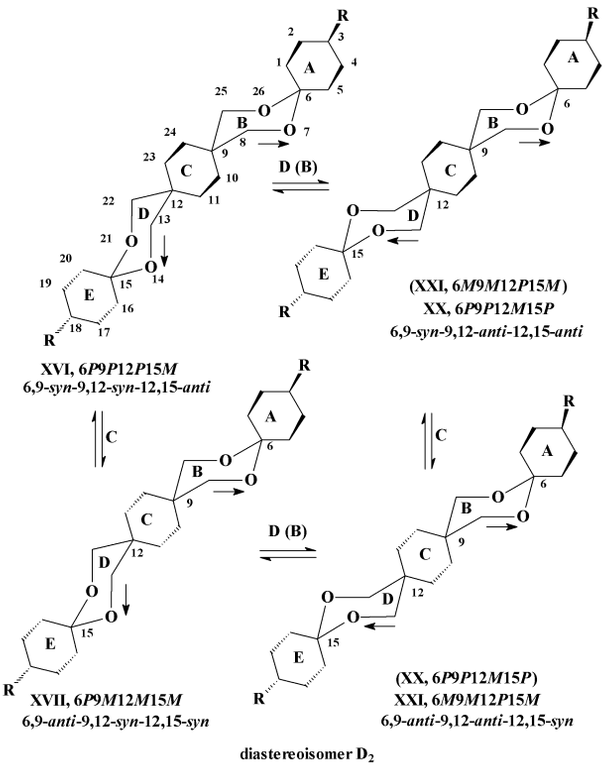
**Table 3** Values of the reference dihedral angles in the molecular structures of **6**, **8** and **11**

| | | Measured dihedral angles(°)[a] | | |
|---|---|---|---|---|
| Compound | Structure of the spiro skeleton | $C^1C^2C^4C^5/C^{10}C^{11}C^{23}C^{24}$ | $O^7C^8C^{25}O^{26}/C^{13}O^{14}O^{21}C^{22}$ | $C^{10}C^{11}C^{23}C^{24}/C^{16}C^{17}C^{19}C^{20}$ |
| **6** (a) | 6,9-*anti*-9,12-*anti*-12,15-*anti* | 26.7 | 0.0 | 26.7 |
| **6** (b) | 6,9-*syn*-9,12-*anti*-12,15-*syn* | 71.4 | 0.0 | 71.4 |
| **8** ($D_2$) | 6,9-*anti*-9,12-*anti*-12,15-*syn* | 7.9 | 1.4 | 82.6 |
| **11** ($D_5$) | 6,9-*anti*-9,12-*anti*-12,15-*anti* | 8.6 | 0.0 | 8.6 |

[a] The numbering of Scheme 5 is used. Dihedral angles done to 0° denote *anti* dispositions, whereas values close 90° denote *syn* orientations.

**Table 4** Structural modifications produced by the flipping of rings B, C and D in **7**–**9**

| Flipping ring | Spiro units with modified configuration (at carbon atom) | Rings with modified *syn* or *anti* disposition (at carbon atoms) |
|---|---|---|
| B | AB (6) and BC (9) | B and D (9,12) |
| C | BC (9) and CD (12) | A and C (6,9), C and E (12,15) |
| D | CD (12) and DE (15) | B and D (9,12) |




**Scheme 7**

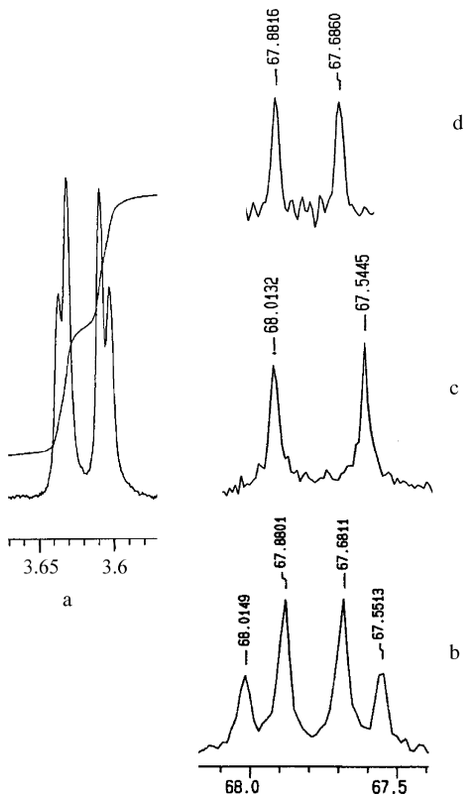



**Fig. 2** NMR spectra (fragments) of **8** (a: $^{1}$H NMR, mixture of $D_1$ and $D_2$, b: $^{13}$C NMR, mixture of $D_1$ and $D_2$, c: $^{13}$C NMR of $D_1$, d: $^{13}$C NMR of $D_2$).

spectra). The magnetic environments of the similar protons and similar carbon atoms in the two diastereoisomers ($D_1$ and $D_2$) are very close and in the NMR spectra of the mixture of diastereoisomers the majority of the signals are not separated. However, for the protons and carbon atoms of the heterocycles (positions 8, 13, 22, 25) very close, but separated signals, are observed. As an example, the $^{1}$H NMR spectrum of **8** exhibits for the protons of each diastereotopic position of the heterocycles two very close signals ($\delta_{8,22}$ 3.60 and 3.61, $\delta_{13,25}$ 3.64 and 3.62 ppm, Fig. 2a). The $^{13}$C NMR spectrum also exhibits two sets of signals for the carbon atoms of these positions ($\delta_{C8,22}$ 67.54 and 67.69, $\delta_{C13,25}$ 68.01 and 67.88, Fig. 2b). The two diastereoisomers of **8** have been separated by flash chromatography (dichloromethane–diethyl ether 5 : 1). The NMR spectra of the separated isomers showed unique sets of signals (*e.g.*, for the carbon atoms of positions 8, 22 and 13, 25 respectively, Fig. 2c and 2d).

The molecular structure of the minor isomer ($D_2$) of **8** was investigated by X-ray diffractometry. The ORTEP diagram (Fig. 3) shows the preference in the solid state for the polyspiro skeleton for the 6,9-*anti*-9,12-*anti*-12,15-*syn* structure (Table 3). The orientation of the phenyl groups (at positions 3 and 18) is intermediary (dihedral angles $\alpha = O^{26}C^{6}O^{7}/C^{27}–C^{32} = 68.1°$ and $\beta = O^{14}C^{15}O^{21}/C^{33}–C^{38} = 65.7°$) between those observed in the typical bisectional ($\alpha$, $\beta = 0°$) and orthogonal ($\alpha$, $\beta = 90°$) rotamers.[14]

The variable-temperature NMR experiments run with **7**–**9** showed [at low temperatures (*e.g.*, for **9** the coalescence is close to 213 K, Fig. 4)] the freezing of the flipping of rings B, C and D. The low-temperature spectra of these compounds are very complex, due on the one hand to the six possible diastereoisomers and on the other hand to the different axial and equatorial positions of the protons of the rings and they are not solved. These spectra exhibit for the protons of the heterocycles (instead of the two singlets recorded at *rt*) four or five groups of large signals between $\delta$3 and 4. These modifications of the spectra prove the freezing of the flipping of the middle part of the tetraspirane.

The stereochemistry of **10** [2*R*,17*R* isomer, pure 3(*R*)-methylcyclohexanone was used as starting material] is similar to

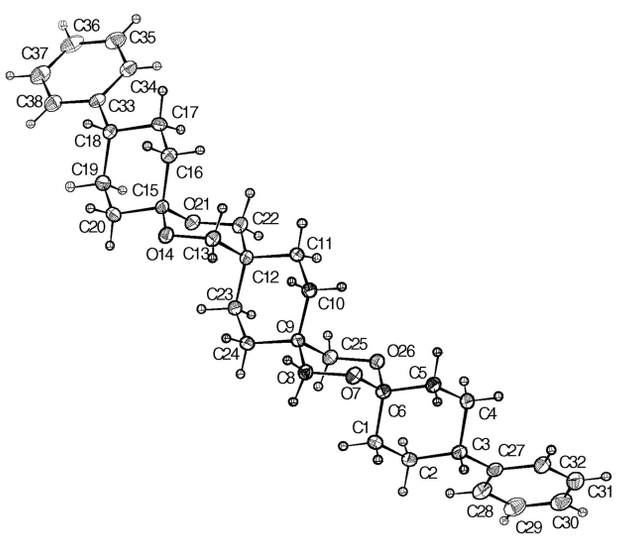



**Fig. 3** ORTEP diagram of **8** ($D_2$).

that of **7**–**9**. The marginal rings (A and E) are anancomeric while the middle part of the spirane is flipping. The conformational behaviour of the compound is deduced from the NMR spectra run at rt (Table 2) and at low temperature (similar modifications with those observed for **7**–**9** are recorded).

The synthesis of **11** was performed using the racemic ketone. A mixture of *like* and *unlike* isomers was obtained. The equatorial methyl groups at positions 1 and 16 determine, besides the anancomericity of rings A and E, the anancomericity of neighbouring rings **B** and **D**, too (Scheme 8).[4] Both *like* and *unlike* isomers exhibit semiflexible structures: the middle ring C is flipping, while the other rings (A, B, D, E) are anancomeric. The configuration of the chiral centres determines the configuration of the neighbouring spiro units (AB and DE). A chiral centre exhibiting *R* configuration is correlated with an *M*

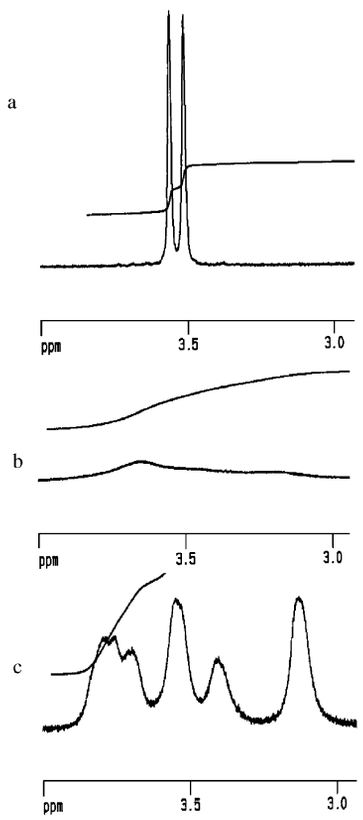
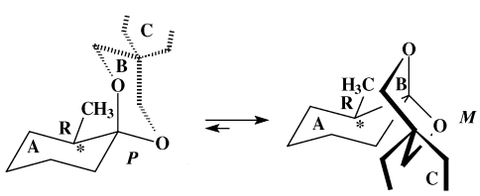


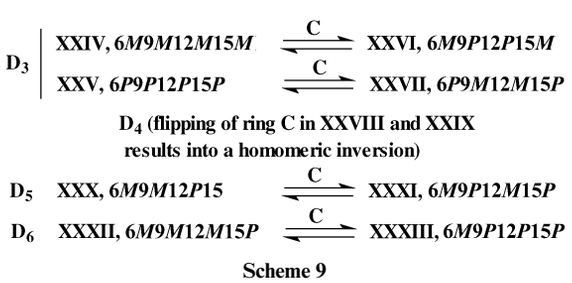

**Fig. 4** Variable-temperature NMR spectra (fragments) of **9** (a: 273 K, b: 213 K, c: 193 K).




**Scheme 8**

configuration of the close spiro unit and the *S* configuration of the chiral centre involves the *P* configuration of the neighbouring spiro unit (Scheme 8).

Two separable diastereoisomers for the *like* isomer ($D_3$, $D_4$; Table 5, Scheme 9) and two other ones for the *unlike* structure




**Scheme 9**

($D_5$, $D_6$) are possible. In the synthesis of **11** (yield 62%) the diastereoisomer $D_5$ (of the *unlike* compound) is the main product (about 70%) and it was separated by crystallisation.

The structure of this compound was assumed by the molecular structure determined by X-ray diffractometry and from NMR spectra (Fig. 5 and 6). The ORTEP diagram and the calculated reference angles (Table 3) show the centrosymmetric 6,9-*anti*-9,12-*anti*-12,15-*anti* structure in the solid state of the isolated isomer. The $^1$H NMR spectrum of **11** run at rt is not similar to those of compounds **7**–**10**, different signals being

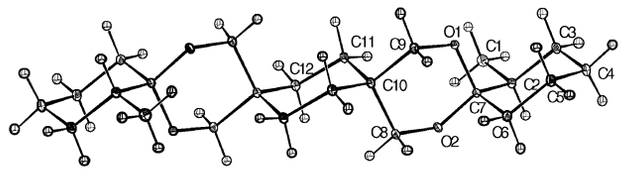



**Fig. 5** ORTEP diagram of **11** ($D_5$).

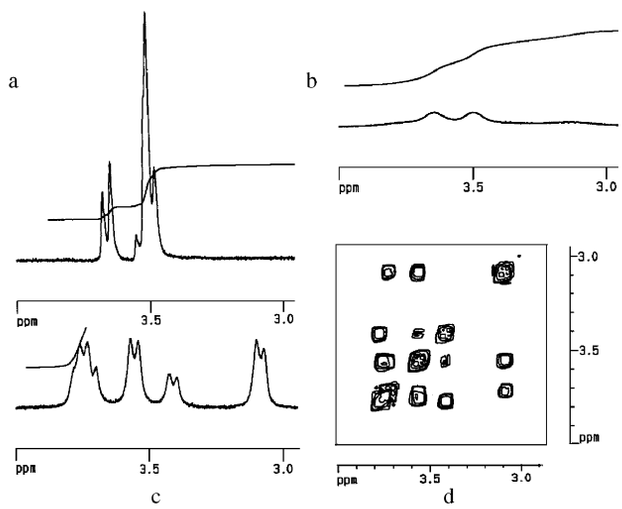



**Fig. 6** Variable-temperature NMR spectra (fragments) of **11** (a: 273 K, b: 223 K, c: 203 K, d: COSY spectrum at 203 K).

obtained for the axial and equatorial protons of the heterocycles (Table 2, Fig. 6).

The flipping of ring C determines the recording (at rt) of signals belonging to average magnetic environments and the measured differences of chemical shifts between the axial and equatorial protons of the heterocycles are smaller than usual.[14] In the low-temperature spectrum (203 K, coalescence at 223 K, Fig. 6) the protons of the heterocycles exhibit two sets of signal with close intensities. These signals belong to the two frozen structures of $D_5$ [6,9-*anti*-9,12-*anti*-12,15-*anti* (**XXXI**) and 6,9-*syn*-9,12-*anti*-12,15-*syn* (**XXX**)]. The theoretically eight doublets are overlapped into four signals. As can be deduced from the intensities of the signals and from the COSY spectrum (Fig. 6d) in the more deshielded signal ($\delta$ 3.73), there are three overlapping doublets, while the signals at $\delta$ 3.57 and $\delta$ 3.09 are both obtained by the overlapping of two doublets. The supplementary coupling between the signals at $\delta$ 3.57 and at $\delta$ 3.41 (observed in the COSY spectrum) is probably due to the characteristic long-range coupling between the equatorial protons at positions 4 and 6 of the 1,3-dioxane ring.

### Conclusions

The stereochemistry of spiranes with six-membered rings is discussed considering the helical chirality and the *syn* and *anti* isomerism of the compounds of this type. Comparison of the stereochemistry of polyspiranes, polyhelicenes and cumulenes reveals the differences between the compounds with odd and even numbers of building blocks. The flexibility of the rings is assumed from variable-temperature NMR experiments, and the different arrangements of the six-membered rings in the solid state are analysed in the first molecular structures obtained for compounds of this type.

## Experimental

### General remarks

$^1$H and $^{13}$C NMR spectra were recorded at room temperature using $CD_2Cl_2$ ($CDCl_3$) as solvent in 5 mm tubes on a Bruker AM 400 (Varian Gemini 300) NMR spectrometer equipped

**Table 5** Possible stereoisomers of **11**

| Isomer | Type | Configuration at $C^1$ and $C^{16}$ | Configuration of spiro units | | | | Arrangements of the polyspiro skeleton |
|---|---|---|---|---|---|---|---|
| | | | AB (6) | BC (9) | CD (12) | DE (15) | |
| **XXIV** | *like* | 1*R*16*R* | *M* | *M* | *M* | *M* | 6,9-*syn*-9,12-*syn*-12,15-*syn* |
| **XXV** | *like* | 1*S*16*S* | *P* | *P* | *P* | *P* | 6,9-*syn*-9,12-*syn*-12,15-*syn* |
| **XXVI** | *like* | 1*R*16*R* | *M* | *P* | *P* | *M* | 6,9-*anti*-9,12-*syn*-12,15-*anti* |
| **XXVII** | *like* | 1*S*16*S* | *P* | *M* | *M* | *P* | 6,9-*anti*-9,12-*syn*-12,15-*anti* |
| **XXVIII** | *like* | 1*R*16*R* | *M* | *P* | *M* | *M* | 6,9-*anti*-9,12-*anti*-12,15-*syn* |
| **XXIX** | *like* | 1*S*16*S* | *P* | *M* | *P* | *P* | 6,9-*anti*-9,12-*anti*-12,15-*syn* |
| **XXX** | *unlike* | 1*R*16*S* | *M* | *M* | *P* | *P* | 6,9-*syn*-9,12-*anti*-12,15-*syn* |
| **XXXI** | *unlike* | 1*R*16*S* | *M* | *P* | *M* | *P* | 6,9-*anti*-9,12-*anti*-12,15-*anti* |
| **XXXII** | *unlike* | 1*R*16*S* | *M* | *M* | *M* | *P* | 6,9-*syn*-9,12-*syn*-12,15-*anti* |
| **XXXIII** | *unlike* | 1*R*16*S* | *M* | *P* | *P* | *P* | 6,9-*anti*-9,12-*syn*-12,15-*syn* |

with a dual $^{13}C$–$^{1}H$ (multinuclear) head operating at 400 (300) MHz for protons and 100 (75) MHz for carbon atoms. Mps were measured with an APOTEC melting-point apparatus and are uncorrected. Elemental analyses were obtained at the University of Medicine and Pharmaceutics, Cluj-Napoca. Their results agreed favourably 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.

### General procedure for the synthesis of compounds

To a solution of 5 mmol of 1,1,4,4-tetrakis(hydroxymethyl)-cyclohexane in 20 ml of toluene and 2 ml of DMSO were added 11 mmol of the corresponding cyclohexanone and 0.05 g of toluene-*p*-sulfonic acid. The mixture was refluxed and the resultant water from the reaction was removed using a Dean–Stark trap. When the theoretical quantity of water had separated, and after cooling to room temperature, the catalyst was neutralised (under stirring) with $CH_3COONa$ powder in excess (0.05 g). The reaction mixture was washed twice with 20 ml of water. The organic layer was dried ($Na_2SO_4$), then toluene was removed and the spiro compounds were purified by crystallisation from acetone.

**7,14,21,26-Tetraoxatetraspiro[5.2.2.2.5.2.2.2]hexacosane (6).** *White crystals*, mp 186–187 °C, 55% yield [Found: C, 72.61; H, 10.23. $C_{22}H_{36}O_4$ (364.26) requires C, 72.49; H, 9.95%]; $\delta_H$(400 MHz; $CD_2Cl_2$) 1.38 (8H, s, 10-$H_2$, 11-$H_2$, 23-$H_2$, 24-$H_2$), 1.38 (4H, m, 3-$H_2$, 18-$H_2$), 1.48 (8H, m, 2-$H_2$, 4-$H_2$, 17-$H_2$, 19-$H_2$), 1.69 (8H, m, 1-$H_2$, 5-$H_2$, 16-$H_2$, 20-$H_2$), 3.55 (8H, s, 8-$H_2$, 13-$H_2$, 22-$H_2$, 25-$H_2$); $\delta_C$(100 MHz; $CD_2Cl_2$) 22.98 (C-3, C-18), 26.14 (C-9, C-12), 26.6 (C-10, C-11, C-23, C-24), 32.92, 32.99 (C-2, C-4, C-17, C-19; C-1, C-5, C-16, C-20), 67.67 (C-8, C-13, C-22, C-25), 98.44 (C-6, C-15).

**3,18-Dimethyl-7,14,21,26-tetraoxatetraspiro[5.2.2.2.5.2.2.2]-hexacosane (7).** *White crystals*, mp 190–192 °C, 61% yield, $D_1$ + $D_2$ [Found: C, 73.18; H, 10.09. $C_{24}H_{40}O_4$ (392.29) requires C, 73.43; H, 10.27%]; $\delta_H$(400 MHz; $CD_2Cl_2$) 0.88 (6H, d, 3-$CH_3$, 18-$CH_3$, $^3J$ 6.5 Hz), 1.11 [4H, dq (overlapped dddd), 2-$H_{ax}$, 4-$H_{ax}$, 17-$H_{ax}$, 19-$H_{ax}$, $^2J = {}^3J' = {}^3J''$ = 13.2 Hz, $^3J$ 3.0 Hz], 1.29 [4H, dt (overlapped ddd), 1-$H_{ax}$, 5-$H_{ax}$, 16-$H_{ax}$, 20-$H_{ax}$, $^2J = {}^3J'$ = 13.2 Hz, $^3J$ 3.9 Hz], 1.38 (8H, s, 10-$H_2$, 11-$H_2$, 23-$H_2$, 24-$H_2$), 1.39 [2H, m (overlapped with the peak at $\delta$ 1.38), 3-H, 18-H], 1.53 (4H, m, 2-$H_{eq}$, 4-$H_{eq}$, 17-$H_{eq}$, 19-$H_{eq}$), 2.14 (4H, m, 1-$H_{eq}$, 5-$H_{eq}$, 16-$H_{eq}$, 20-$H_{eq}$), 3.52 (4H, s, 8-$H_2$, 22-$H_2$), 3.57 (4H, s, 13-$H_2$, 25-$H_2$); $\delta_C$(100 MHz; $CD_2Cl_2$) 21.86 (3-$CH_3$, 18-$CH_3$), 26.59 (C-10, C-11, C-23, C-24), 31.27 (C-3, C-18), 32.31 (C-2, C-4, C-17, C-19), 32.37 (C-1, C-5, C-16, C-20), 32.99 (C-9, C-12), 67.75 (C-13, C-25), 67.88 (C-8, C-22), 99.43 (C-6, C-15).

**3,8-Diphenyl-7,14,21,26-tetraoxatetraspiro[5.2.2.2.5.2.2.2]hexacosane (8).** *White crystals*, $D_1$ + $D_2$, subjected to column chromatography (dichloromethane–diethyl ether 5 : 1, $\Delta R_f$ = 0.07, isomer $D_1$ with $R_f$ = 0.64 and isomer $D_2$ with $R_f$ = 0.57), 62% yield [Found: C, 78.96; H, 8.65. $C_{34}H_{44}O_4$ (516.32) requires C, 79.03; H, 8.58%].

*Isomer $D_1$.* White crystals, mp 243 °C; $\delta_H$(400 MHz; $CD_2Cl_2$) 1.43 (8H, s, 10-$H_2$, 11-$H_2$, 23-$H_2$, 24-$H_2$), 1.45 (4H, m, overlapped with the peak at $\delta$ 1.43, 2-$H_{ax}$, 4-$H_{ax}$, 17-$H_{ax}$, 19-$H_{ax}$), 1.63–1.72 (8H, overlapped peaks, 1-$H_{ax}$, 5-$H_{ax}$, 16-$H_{ax}$, 20-$H_{ax}$, 2-$H_{eq}$, 4-$H_{eq}$, 17-$H_{eq}$, 19-$H_{eq}$), 2.25 (4H, m, 1-$H_{eq}$, 5-$H_{eq}$, 16-$H_{eq}$, 20-$H_{eq}$), 2.54 (2H, m, 3-H, 18-H), 3.60 (4H, s, 8-$H_2$, 22-$H_2$), 3.64 (4H, s, 13-$H_2$, 25-$H_2$), 7.15–7.29 (10H, overlapped peaks, Ar: H); $\delta_C$(75 MHz; $CDCl_3$) 26.36 (C-10, C-11, C-23, C-24), 31.17 (C-2, C-4, C-17, C-19), 32.81 (C-9, C-12), 33.54 (C-1, C-5, C-16, C-20), 43.96 (C-3, C-18), 67.54 (C-8, C-22), 68.01 (C-13, C-25), 97.91 (C-6, C-15), 126.11, 126.93, 128.40 (tertiary aromatic carbon atoms), 146.67 (quaternary aromatic carbon atom).

*Isomer $D_2$.* White crystals, mp 190–191 °C; $\delta_H$(400 MHz; $CD_2Cl_2$) 1.41 (8H, s, 10-$H_2$, 11-$H_2$, 23-$H_2$, 24-$H_2$), 1.42 (4H, m, overlapped with the peak at $\delta$ 1.41, 2-$H_{ax}$, 4-$H_{ax}$, 17-$H_{ax}$, 19-$H_{ax}$), 1.57–1.73 (8H, overlapped peaks, 1-$H_{ax}$, 5-$H_{ax}$, 16-$H_{ax}$, 20-$H_{ax}$, 2-$H_{eq}$, 4-$H_{eq}$, 17-$H_{eq}$, 19-$H_{eq}$), 2.33 (4H, m, 1-$H_{eq}$, 5-$H_{eq}$, 16-$H_{eq}$, 20-$H_{eq}$), 2.53 (2H, m, 3-H, 18-H), 3.61 (4H, s, 8-$H_2$, 22-$H_2$), 3.62 (4H, s, 13-$H_2$, 25-$H_2$), 7.14–7.29 (10H, overlapped peaks, aromatic H); $\delta_C$(75 MHz; $CDCl_3$) 26.37 (C-10, C-11, C-23, C-24), 30.19 (C-2, C-4, C-17, C-19), 32.55 (C-1, C-5, C-16, C-20), 32.81 (C-9, C-12), 43.97 (C-3, C-18), 67.69 (C-8, C-22), 67.88 (C-13, C-25), 97.21 (C-6, C-15), 126.12, 126.93, 128.40 (tertiary aromatic carbon atoms), 146.67 (quaternary aromatic carbon atom).

**3,18-Di-*tert*-butyl-7,14,21,26-tetraoxatetraspiro[5.2.2.2.5.2.2.2]hexacosane (9).** *White crystals*, mp 241–242 °C, 47% yield, $D_1$ + $D_2$ [Found: C, 75.79; H, 10.68. $C_{30}H_{52}O_4$ (476.39) requires C, 75.58; H, 10.99%]; $\delta_H$(400 MHz; $CD_2Cl_2$) 0.84 [18H, s, 3-C($CH_3$)$_3$, 18-C($CH_3$)$_3$], 1.02 (2H, m, 3-H, 18-H), 1.11 (4H, m, 2-$H_{ax}$, 4-$H_{ax}$, 17-$H_{ax}$, 19-$H_{ax}$), 1.19 (4H, m, 1-$H_{ax}$, 5-$H_{ax}$, 16-$H_{ax}$, 20-$H_{ax}$), 1.38 (8H, s, 10-$H_2$, 11-$H_2$, 23-$H_2$, 24-$H_2$), 1.60 (4H, m, 2-$H_{eq}$, 4-$H_{eq}$, 17-$H_{eq}$, 19-$H_{eq}$), 2.24 (4H, m, 1-$H_{eq}$, 5-$H_{eq}$, 16-$H_{eq}$, 20-$H_{eq}$), 3.53 (4H, s, 8-$H_2$, 22-$H_2$), 3.57 (4H, s, 13-$H_2$, 25-$H_2$); $\delta_C$(100 MHz; $CD_2Cl_2$) 23.67 (C-10, C-11, C-23, C-24), 26.52 (C-2, C-4, C-17, C-19), 27.72 [C($C$H$_3$)$_3$], 32.35 [$C$(CH$_3$)$_3$], 32.48 (C-9, C-12), 32.97 (C-1, C-5, C-16, C-20), 48.07 (C-3, C-18), 67.72 (C-13, C-25), 67.93 (C-8, C-22), 98.34 (C-6, C-15).

**2,17-Dimethyl-7,14,21,26-tetraoxatetraspiro[5.2.2.2.5.2.2.2]-hexacosane (10).** *White crystals*, mp 172–173 °C, 51% yield, $D_1$ + $D_2$ [Found: C, 73.3; H, 10.37. $C_{24}H_{40}O_4$ (392.29) requires C 73.4; H 10.1%]; $\delta_H$(400 MHz; $CD_2Cl_2$) 0.83 (2H, m, 3-$H_{ax}$, 18-$H_{ax}$), 0.88 (6H, d, 2-$CH_3$, 17-$CH_3$, $^3J$ 6.5 Hz), 0.89 [2H, t (overlapped dd), 1-$H_{ax}$, 16-$H_{ax}$, $^2J = {}^3J$ = 12.6 Hz], 1.11 [2H, dt (overlapped ddd), 5-$H_{ax}$, 20-$H_{ax}$, $^2J = {}^3J'$ = 13.2 Hz, $^3J$ 4.2 Hz), 1.36 (4H, s, 10-$H_2$, 11-$H_2$), 1.38 (2H, m, 4-$H_{ax}$, 19-$H_{ax}$), 1.40 (4H, s, 23-$H_2$, 24-$H_2$), 1.56 [6H, m (overlapped peaks), 2-H, 17-H, 3-$H_{eq}$, 4-$H_{eq}$, 18-$H_{eq}$, 19-$H_{eq}$], 2.14 (2H, m, 1-$H_{eq}$, 16-$H_{eq}$),

**Table 6** Crystal data and data-collection information for **6**, **8** and **11**

| Compound | **6** | **8** | **11** |
|---|---|---|---|
| Empirical formula | $C_{22}H_{36}O_4$ | $C_{34}H_{44}O_4$ | $C_{24}H_{40}O_4$ |
| Formula weight | 364.51 | 516.69 | 392.56 |
| Temperature/K | 293 | 293 | 293 |
| Wavelength (Å) | 0.710 69 | 0.710 69 | 0.710 69 |
| Crystal system | Monoclinic | Monoclinic | Triclinic |
| Space group | *C*2/*c* | *Ia* | *P*-1 |
| Unit-cell dimension | | | |
| *a*/Å | 22.773(9) | 6.0770(10) | 7.1914(2) |
| *b*/Å | 6.899(4) | 83.01(2) | 7.6935(3) |
| *c*/Å | 13.080(2) | 6.2190(10) | 10.8709(5) |
| *α*/° | 90 | 90 | 97.588(2) |
| *β*/° | 103.47(2) | 117.140(10) | 100.393(2) |
| *γ*/° | 90 | 90 | 112.749(3) |
| *V*/Å$^3$ | 1998.4(14) | 2791.6(9) | 531.89(4) |
| *Z* | 4 | 4 | 1 |
| $D_{calc}$ (g cm$^{-3}$) | 1.212 | 1.229 | 1.226 |
| $2\theta_{max}$/° | 54 | 54 | 60 |
| Absorption coefficient (mm$^{-1}$) | 0.081 | 0.079 | 0.081 |
| *F*(000) | 800 | 1120 | 216 |
| Crystal size (mm) | 0.42 × 0.32 × 0.30 | 0.40 × 0.32 × 0.24 | 0.22 × 0.18 × 0.15 |
| *θ*-range for data collection/° | 1.84–26.99 | 1.47–26.96 | 2.94–27.49 |
| Reflections collected | 2277 | 6626 | 2398 |
| Independent reflections | 2176 [$R_{int}$ = 0.0078] | 3325 [$R_{int}$ = 0.0301] | 2398 [$R_{int}$ = 0.0000] |
| Refinement method | Full-matrix least-squares in $F^2$ | Full-matrix least-squares in $F^2$ | Full-matrix least-squares in $F^2$ |
| Data/restraints/parameters | 2176/0/119 | 3325/2/344 | 2398/0/128 |
| Goodness-of-fit on $F^2$ | 1.054 | 1.015 | 1.056 |
| Final *R*-indices [$F^2 > 2\sigma(F^2)$] | $R_1$ = 0.0961, $wR_2$ = 0.2645 | $R_1$ = 0.0853, $wR_2$ = 0.0875 | $R_1$ = 0.0415, $wR_2$ = 0.1074 |
| *R*-indices (all data) | $R_1$ = 0.1780, $wR_2$ = 0.3172 | $R_1$ = 0.0781, $wR_2$ = 0.0996 | $R_1$ = 0.0498, $wR_2$ = 0.1138 |
| Largest difference peak and hole (e Å$^{-3}$) | 0.533 and −0.531 | 0.140 and −0.129 | 0.306 and −0.233 |

2.19 (2H, m, 5-$H_{eq}$, 20-$H_{eq}$), 3.52 (4H, s, 8-$H_2$, 22-$H_2$), 3.58 (4H, s, 13-$H_2$, 25-$H_2$); $\delta_C$(100 MHz; $CD_2Cl_2$) 22.36 (2-$CH_3$, 17-$CH_3$), 22.48 (C-3, C-18), 26.54 (C-10, C-11), 26.58 (C-23, C-24), 29.30 (C-2, C-17), 32.15 (C-4, C-19), 32.97 (C-9, C-12), 34.85 (C-5, C-20), 41.46 (C-1, C-16), 67.75 (C-8, C-13, C-22, C-25), 98.95 (C-6, C-15).

**1,16-Dimethyl-7,14,21,26-tetraoxatetraspiro[5.2.2.2.5.2.2.2]-hexacosane (11).** *White crystals*, mp 194–195 °C, 43.4% yield in $D_5$ [Found: C, 73.15; H, 10.39; $C_{24}H_{40}O_4$ (392.29) requires C, 73.4; H, 10.1%]; $\delta_H$(400 MHz; $CD_2Cl_2$) 0.93 (6H, d, 1-$H_3$, 16-$H_3$, $^3J$ 6.7 Hz), 1.07 (2H, m, 5-$H_{ax}$, 20-$H_{ax}$), 1.20 (4H, m, 10-$H_2$, 23-$H_2$), 1.43 [6H, m (overlapped peaks), 2-$H_{ax}$, 3-$H_{ax}$, 4-$H_{ax}$, 17-$H_{ax}$, 18-$H_{ax}$, 19-$H_{ax}$], 1.55 [10H, m (overlapped peaks), 2-$H_{eq}$, 3-$H_{eq}$, 4-$H_{eq}$, 17-$H_{eq}$, 18-$H_{eq}$, 19-$H_{eq}$, 11-$H_2$, 24-$H_2$], 1.66 (2H, m, 1-H, 16-H), 2.5 (2H, m, 5-$H_{eq}$, 20-$H_{eq}$), 3.51 (2 H, d, 8-$H_{ax}$, 22-$H_{ax}$, $^2J$ 11.7 Hz), 3.53 (2H, d, 13-$H_{ax}$, 25-$H_{ax}$), 3.54 (2H, d, 13-$H_{eq}$, 25-$H_{eq}$), 3.67 (2 H, d, 8-$H_{eq}$, 22-$H_{eq}$, $^2J$ 11.7 Hz); $\delta_C$(100 MHz; $CD_2Cl_2$) 14.20 (1-$CH_3$, 16-$CH_3$), 23.14 (C-3, C-18), 25.21 (C-9, C-12), 25.83 (C-4, C-19), 27.26 (C-11, C-24), 27.66 (C-10, C-23), 31.30 (C-2, C-17), 32.76 (C-5, C-20), 40.15 (C-1, C-16), 67.55 (C-8, C-22), 67.69 (C-13, C-25), 99.63 (C-6, C-15).

### X-Ray crystallographic study §

Crystal data and data-collection information are summarised in Table 6. The samples were studied on a Nonius CAD4 automatic diffractometer (**6**, **8**)[15] (Nonius Kappa CCD[16] for **11**) with graphite-monochromatised Mo-Kα radiation. The cell parameters were obtained by fitting a set of 25 high-theta reflections (respectively with Denzo and Scalepack techniques[17] with 10 frames). The structures were solved with SIR-97[18] which revealed the non-hydrogen atoms of the compound. After anisotropic refinement a Fourier difference revealed many hydrogen atoms. The whole structure was refined with SHELXL97[19] by the full-matrix least-square techniques.

Atomic scattering factors were from International Tables for X-ray Crystallography[20]. ORTEP views were realised with PLATON98[21] and ORTEP-3 for Windows[22]. All calculations were performed on a Pentium NT Server computer.

§ CCDC reference number(s) 160708–160710. See http://www.rsc.org/suppdata/p1/b1/b104604g/ for crystallographic files in .cif or other electronic format.

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