Conformational analysis of some spiro and polyspiro 1,3-dioxane compounds with axial and helical chirality

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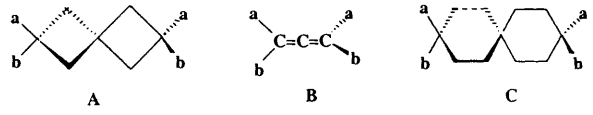
Some spiro and trispiro 1,3-dioxane compounds are discussed in terms of their axial and the helical chirality (all rings are six-membered). The influence of conformation on the number of isomers and on their interrelationship has been followed by means of high resolution and dynamic NMR experiments using the diastereotopicity of the proton and carbon atoms. Interconversions between configurational isomers (presenting three chiral elements) without the breaking of bonds are reported.

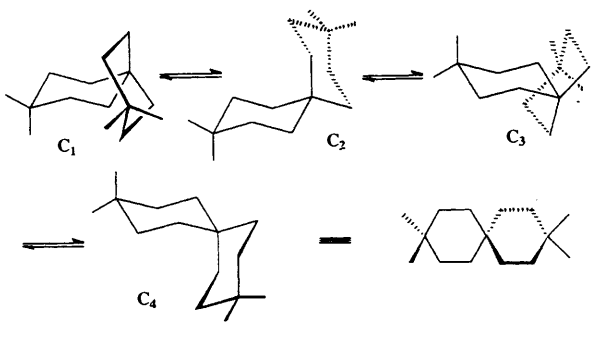
Introduction

The chirality of the spiro compounds with planar rings (Scheme 1, **A**) is usually discussed as a common example of axial chirality.[1] The condition to be fulfilled is, as in the case of the allenes (Scheme 1, **B**), the presence of different geminal groups at both extremities of the system. The dissymmetry of the structure is due to the geometry of the spiro joint resulting in the disposal of the substituents in orthogonal plans.



Scheme 1

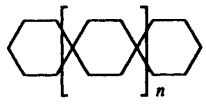
In early works,[2] the chirality of the compounds with a spiro[5.5]undecanic skeleton (Scheme 1, **C**) was not considered to be different to the general case of the axial chirality on the basis of the assumption that the rapid flipping of the cycles leads to an average structure with planar six-membered rings (Scheme 2). In this case, as well as in the case of the allenes (**B**) or the planar spiro systems (**A**), the compounds bearing identical substituents (a = b) at one or at both extremities of the spiro skeleton, *e.g.* the unsubstituted spiro[5.5]undecane (**C**, a = b = H), were considered as achiral.



Scheme 2

Later, Dodziuk[3] analysing (by means of the Dreiding models) the chirality of the frozen structure of spiro[5.5]undecane observed its chirality and the possibility of obtaining an enantiomeric structure (Scheme 2: conformer C_1 is identical with C_3, but it is enantiomeric with C_2 which is identical with C_4). At room temperature the fast flippings of the rings results in an enantiomeric interconversion and the chirality of the compound cannot be observed. This author considered the chirality of the spiro[5.5]undecane as a new example of a compound with a centre of chirality of the type $C_{a,a,a,a}$, *i.e.* a carbon atom (the spiro one) bearing four formally identical substituents, as was also observed in other examples described in the literature.[4,5] The stereochemistry of the polyspiro compounds with six-membered rings was discussed by taking into account a number of chiral centres (of the type $C_{a,a,a,a}$), identical with the number of the spiro joints. The chirality of the spiro compounds with six-membered rings was considered not to be included in the usual classification of chiral elements by Cahn, Ingold and Prelog (CIP)[6] or in the modified classification introduced by Prelog and Helmchen.[7] As a result, another classification of the chiral elements has been proposed.[8]

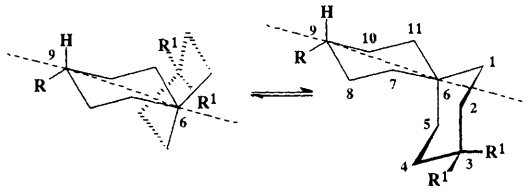
Recently, our investigations[9] on the structure of the spiranic compounds of the type



has revealed the helical disposal of the six-membered rings in a similar way to the helicity reported for helicenes, proteins or the very close example of the spiro compounds with five-membered rings (cyclopentylpentahelixane).[10] A detailed analysis by means of Dreiding models pointed out that the helix model (*P* or *M* configuration) can turn identically with itself after every fourth six-membered ring.

The parent compound spiro[5.5]undecane exhibits helical chirality (the helix begins to be built), but at room temperature the flipping of the rings (Scheme 2) leads to the enantiomeric interconversion of the *P* (conformations C_2, C_4) and of the *M* (conformations C_1,C_3) configurations.

In the case of the compounds bearing one substituent (or two different ones) at one extremity and two identical groups at the other extremity of the spiro[5.5]undecane skeleton the axial chirality can be also considered (Scheme 3). Such compounds exhibit a semi-mobile structure with an anancomeric mono-



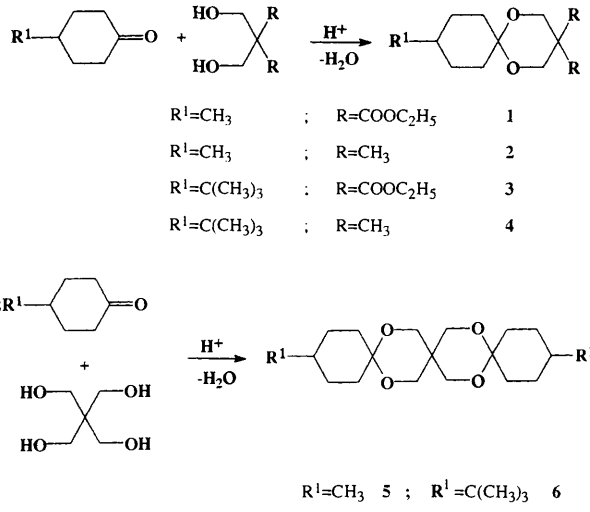
Scheme 3

substituted ring (R is a 'holding group') and a flipping disubstituted (or unsubstituted) one. The axis C(6)–C(9) can be considered as a chiral axis, the reference groups being R and H at C(9) and the whole disubstituted ring (which can be on the left or right side of the chiral axis) at C(6).

As a conclusion, we propose here an alternative possibility to Dodziuk's theory by discussing the chirality of spiro compounds with six-membered rings in terms of helical and axial chirality using the CIP classification of chiral elements.

Results and discussion

The configurational and conformational features of the stereochemistry of spiro and polyspiro compounds with six-membered rings were investigated in a series of saturated heterocyclic compounds with 1,3-dioxane rings obtained from some 4-alkylcyclohexanones (Scheme 4).



Scheme 4

The diesters **1**, **3** and **7** were transformed into the monoacids **8**–**10** and the corresponding methyl esters **11**–**13** (Scheme 5).

Spiro compounds with a semimobile structure

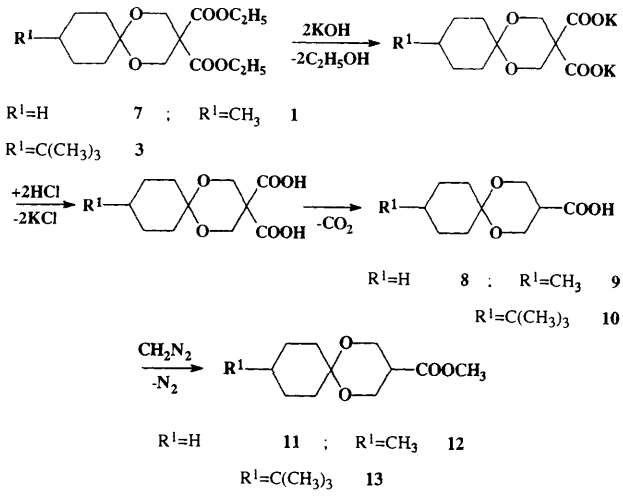
Compounds **1**–**4**, **8** and **11** display at room temperature semimobile structures (Scheme 6; a flipping unsubstituted or symmetrically substituted six-membered ring and an anancomeric unsymmetrically substituted one).

These compounds exhibit at the same time axial and helical chirality. The flipping of the rings inverts both helicity and axial chirality. The equilibria shown in Scheme 6 respresent enantiomeric interconversions of the type

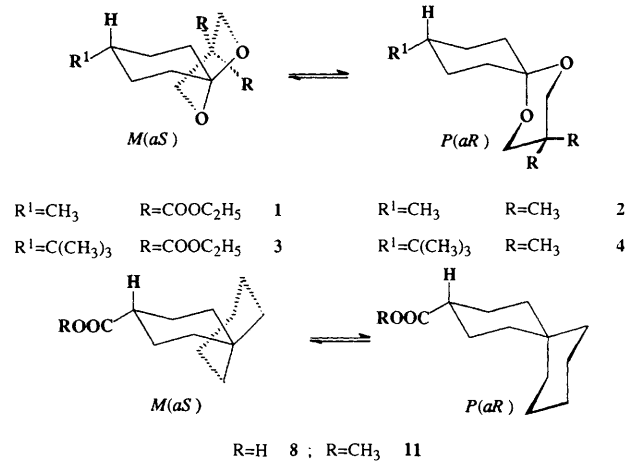
$$M(aS) \rightleftharpoons P(aR)$$

The chirality of the compounds can be observed in the NMR spectra by means of the diastereotopicity of the protons and of the carbon atoms.

The ^1H and ^{13}C NMR spectra show for the protons and for



Scheme 5



Scheme 6 Note: the symbols *aR* and *aS* are proposed by Eliel instead of the symbols *R* and *S* in the case of the axial chirality [1]

the carbon atoms of the diasterotopic positions 2 and 4 (compounds **1**–**4**) different signals (Table 1). As a result of the flexibility of the 1,3-dioxane ring, in the ^1H NMR spectra, mean values of the chemical shifts corresponding to the axial and to the equatorial positions are obtained. The flipping of the 1,3-dioxane ring renders isochronous and enantiotopic the protons and the carbon atoms of positions 7 and 11 and of positions 8 and 10, respectively (a fact easily observed using Dreiding models). Thus, in the NMR spectra unique signals for the equatorial protons, for the axial protons and for the carbon atoms of these positions are recorded.

Compounds **8** and **11** exhibit a semimobile structure, too. The 1,3-dioxane ring is anancomeric and the cyclohexane one is flipping. The carboxy or the methoxycarbonyl group prefers the equatorial position.

As in the case of spiranes **1**–**4**, the flipping of the flexible ring brings the protons and the carbon atoms of the anancomeric ring (positions 2 and 4) into the same average environment. The ^1H NMR spectra display for the protons located at C(2) and C(4) only one doublet of doublets for the equatorial position and another doublet of doublets for the axial one. The ^{13}C NMR spectra of these compounds (**8** and **11**) show only one signal for the methylenic carbon atoms of the 1,3-dioxane ring (Table 2).

On the other hand for the carbon atoms of the diastereotopic positions 7 and 11 and 8 and 10, respectively, different signals are obtained. The diastereotopicity of the carbon atoms is evaluated as: $\Delta\delta_{C(7)-C(11)} = 2.85$ and $\Delta\delta_{C(8)-C(10)} = 3.28$ ppm

for compound **8**, and as $\Delta\delta_{C(7)-C(11)}$ = 4.27 and $\Delta\delta_{C(8)-C(10)}$ = 3.29 ppm for compound **11**.

Compounds **1–4**, **8** and **11** were also investigated by means of variable temperature ^{1}H NMR experiments (from 20 to −110 °C).

The flipping of the 1,3-dioxane ring in compounds **1–4** is frozen at low temperature, and as a result, the ^{1}H NMR spectra exhibit different signals for the axial and for the equatorial protons of this ring. In the case of compound **2** the protons of the diastereotopic positions 2 and 4 show two well resolved AB systems (Fig. 1).

Compound **4** has been investigated by Greenberg[11] in a dynamic ^{1}H NMR experiment (60 MHz) using the shape of the signals corresponding to the C(3) geminal methyl groups. The coalescence was observed at T_C = 185.2 K and the free energy of activation was calculated as $\Delta G^{\ddagger}$ = 8.9 ± 0.2 kcal mol^{-1},† in agreement with the free energy of activation values found in the case of 2,2-disubstituted-1,3-dioxanes.[12]

At low temperature the flipping of the cyclohexane ring in compounds **8** and **11** is frozen. Unfortunately, the ^{1}H NMR spectra at low temperature (Fig. 2) exhibit overlaps of the signals and are too complex to be resolved. Thus, the recording of different signals for the axial and for the equatorial protons as well as for the diastereotopic positions can be deduced only by the multiplication of the number of peaks comparatively with the spectra run at room temperature.

Spiro compounds with two anancomeric rings

The acids **9** and **10** and the esters **12** and **13** (Scheme 5) have anancomeric structure, both cyclohexane and 1,3-dioxane rings bear 'holding groups' [alkyl or acid (esteric) groups].

The analysis of the possible isomers made taking into account the existence of three chirality elements [two axes, C(3)–C(6) and C(6)–C(9), having *aR* or *aS* configurations and a helix with *P* or *M* configuration] reveals eight possible isomers (Table 3). Conformational analysis of these isomers shows that the investigated compounds prefer to exist as a pair of enantiomers (I and V) with both substituents (positions 3 and 9) in equatorial orientation.

The diastereotopicity of the positions 2 and 4 of the 1,3-dioxane ring and of the positions 7 and 11, as well as of the positions 8 and 10, of the cyclohexane ring is observed in the NMR spectra, different signals for the protons and for the carbon atoms of these positions being recorded (Table 4 and Table 5).

Because of the anancomericity of both rings, different signals for the axial and for the equatorial protons are also observed (Table 4). Thus, in the ^{1}H NMR spectrum of compound **13**, a complex system of signals for the axial and equatorial protons of diastereotopic positions 2 and 4 are recorded (Fig. 3). The pattern contains two doublets of doublets for the more deshielded axial protons ($J_{2(4)ax,2(4)eq}$ = 11.5; $J_{2(4)ax,3ax}$ = 8.5 Hz) and another two doublets of doublets ($J_{2(4)eq,3ax}$ = 4.9 Hz, $J_{2(4)ax,2(4)eq}$ = 11.5 Hz) for the equatorial protons. A further splitting of the signals as a result of the W-disposal of the bonds H_{eq}–C^2–C^3–C^4–H_{eq} (^4J = 1.4 Hz) was also observed.

The axial protons of the 1,3-dioxane ring are the more deshielded ones as a consequence of the 'steric compression' exerted by the axial α-CH_2 group of the cyclohexane ring.

The diastereotopicity is evaluated as 0.06–0.09 ppm for the equatorial protons ($\Delta\delta_{H^{2eq}-H^{4eq}}$) and as 0.11–0.12 ppm for the

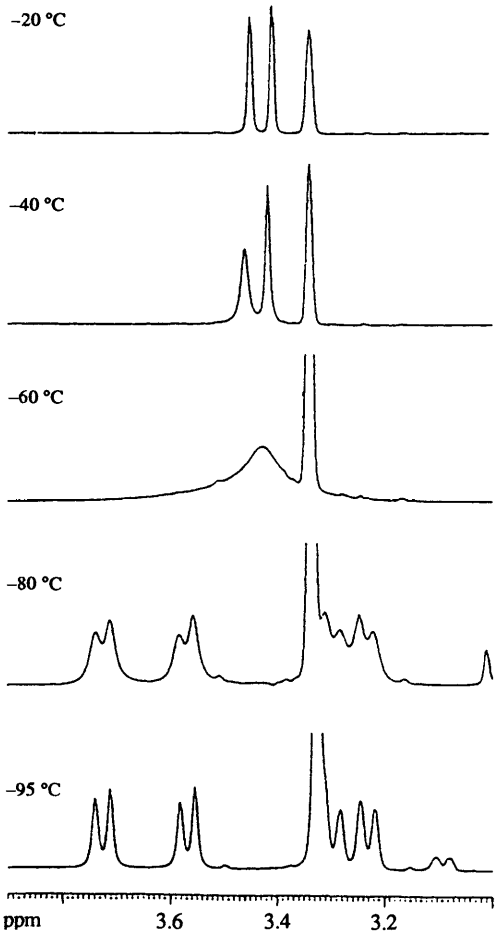


Fig. 1 Results of the variable temperature ^{1}H NMR experiment for compound **2**. Note: the signal of 3.26 ppm is a solvent line [$(C_2D_5)_2O$].

† 1 cal = 4.184 J.

Table 1 Chemical shift values (δ) of diastereotopic protons and carbon atoms of compound **1–4**[a]

	^{1}H			^{13}C		
Compd.	C(2)	C(4)	$\Delta\delta_{2-4}$	C(2)	C(4)	$\Delta\delta_{2-4}$
1	4.59	4.51	0.08	62.18	62.10	0.08
2	3.40	3.32	0.08	69.87	69.72	0.15
3	4.57	4.47	0.10	62.32	62.18	0.14
4	3.50	3.44	0.06	70.00	69.72	0.28

[a] In C_6D_6 solution.

Table 2 ^{1}H and ^{13}C NMR (δ and J/Hz) data of compounds **8** and **11**[a]

	^{1}H					^{13}C
Compound	$\delta_{2,4eq}$	$\delta_{2,4ax}$	$J_{2(4)ax-2(4)eq}$	$J_{2(4)ax-5ax}$	$J_{2(4)eq-5eq}$	C(2),C(4)
8	3.80	3.99	11.9	7.5	4.8	58.95
11	3.90	4.05	12.0	8.7	5.0	59.73

[a] In C_6D_6 solution.

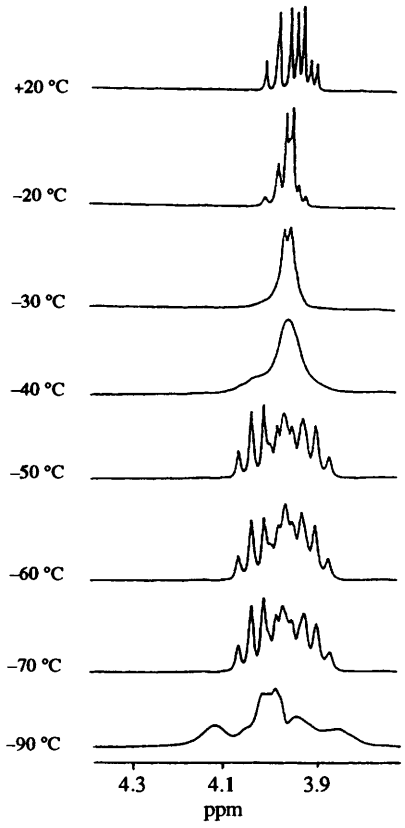


Fig. 2 Results of the variable temperature ^1H NMR experiment for compound **8**. Note: the solubility of the compound is very small under −70 °C: the signal of 3.26 ppm is a solvent line [$(C_2D_5)_2O$].

Table 3 Possible configurational isomers of compounds **9**, **10**, **12** and **13**

	Configuration			Orientation of the substituents	
Isomer	axis C^3–C^6	axis C^6–C^9	Helix	C^3	C^9
I	*aS*	*aS*	*M*	eq.	eq.
II	*aR*	*aS*	*M*	ax.	eq.
III	*aS*	*aR*	*M*	eq.	ax.
IV	*aR*	*aR*	*M*	ax.	ax.
V	*aR*	*aR*	*P*	eq.	eq.
VI	*aS*	*aR*	*P*	ax.	eq.
VII	*aR*	*aS*	*P*	eq.	ax.
VIII	*aS*	*aS*	*P*	ax.	ax.

axial ($\Delta\delta_{H^{2ax}-H^{4ax}}$) ones. The calculated diastereotopicity of the carbon atoms is 0.14–0.22 ppm for positions 2 and 4 ($\Delta\delta_{C(2)-C(4)}$) and 2.59–5.05 or 0.12–0.23 ppm for the carbon atoms of the positions 7 and 11 ($\Delta\delta_{C(7)-C(11)}$) or 8 and 10 ($\Delta\delta_{C(8)-(10)}$), respectively.

Trispiro compounds

Trispiro compounds **5** and **6** with the 7,11,18,21-tetraoxa-trispiro[5.2.2.5.2.2]henicosane skeleton also exhibit a semi-mobile structure (Scheme 7).

These compounds contain a flipping 1,3-dioxane middle part (B, C), and marginal anancomeric cyclohexane rings (A, D) bearing equatorial alkyl groups at the positions 3 and 15.

A combined study by molecular model observations and by NMR spectroscopy revealed that compound **5** and **6** display axial chirality [axes of chirality C(3)–C(6) and C(12)–C(15)] and the characteristic helical chirality for spiro compounds

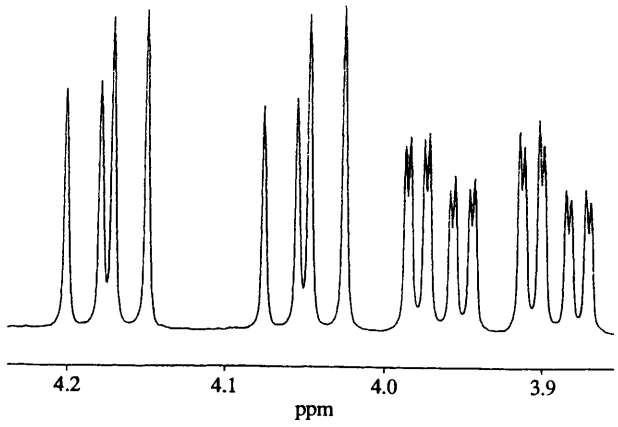


Fig. 3 ^1H NMR spectrum of compound **10** (fragment)

Table 4 ^1H NMR data (C_6D_6) of acids **9**, **10** and esters **12**, **13**[a]

	δ					
Compd.	2ax	4ax	$\Delta_{2ax-4ax}$	2eq	4eq	$\Delta_{2eq-4eq}$
9	4.05	3.94	0.11	3.85	3.77	0.08
10	4.12	4.00	0.12	3.94	3.88	0.06
12	4.08	3.97	0.11	3.87	3.78	0.09
13	4.17	4.05	0.12	3.96	3.89	0.07

[a] Correlation between the signals of the AB systems is deduced from the 2D Homonuclear COSY spectra.

with six-membered rings, due to the whole structure of the molecules.

The NMR spectra show different signals for the protons and for the carbon atoms of the diastereotopic positions 8(19) and 10(20) [^1H (singlets): 3.20 and 3.28 ppm; ^{13}C: 63.37 and 63.53 ppm for **5**; ^1H (singlets): 3.22 and 3.31 ppm; ^{13}C: 63.45 and 63.68 ppm for **6**]. The diastereotopicity of the protons and of the carbon atoms is 0.08 ppm < $\Delta\delta_{H^{8(19)}-H^{10(20)}}$ < 0.09 ppm and 0.15 ppm < $\Delta\delta_{C(8)(19)-C(10)(20)}$ < 0.23 ppm, respectively.

NMR analyses at variable temperature (from 20 to −110 °C) were performed in deuteriated diethyl ether. The two singlets observed at room temperature (^1H NMR: $\delta_{8(19)}$ = 3.64 and $\delta_{10(20)}$ = 3.68 ppm for compound **5** and $\delta_{8(19)}$ = 3.65 and $\delta_{10(20)}$ = 3.70 ppm for compound **6**) for the diastereotopic protons of the 1,3-dioxane rings, are transformed in the low temperature recorded spectra (T < −90 °C) into four unresolved groups of signals located between 3.2 and 4.3 ppm (Fig. 4), in agreement with the differentiated equatorial and axial positions of the frozen 1,3-dioxane rings.

On the other hand, it is worthwhile to mention the influence of the Eu chiral chelate, $Eu(TFC)_3$ in $CDCl_3$ solution, which is not able to separate the signals of the enantiomers, but allows the observation of the diastereotopicity for the geminal protons located at C(8)(19) and C(10)(20) respectively. In the spectrum of compound **5** the influence is more significant and the initial singlets (δ_1 = 3.66 and δ_2 = 3.73 ppm) are transformed into two shifted AB systems, the most shielded one, being well resolved (δ_{1a} = 4.00 ppm; δ_{1b} = 4.07 ppm and J = 12.0 Hz).

The possible stereoisomers of the compounds **5** and **6** are given in Table 6.

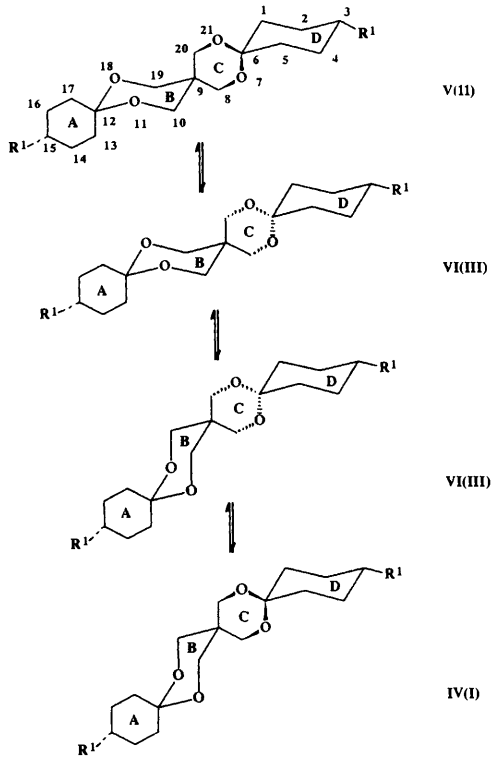
The flipping of the dioxane rings (Scheme 7) induces the interconversions of the isomers as shown in the following equilibria sequences.

Helix *M* Helix *P*

$$I \rightleftharpoons III \rightleftharpoons II \quad IV \rightleftharpoons VI \rightleftharpoons V$$

Table 5 ^{13}C NMR data (C_6D_6) of acids **10**, **11** and esters **12**, **13**

Compd.	δ C-2	C-4	C-7	C-11	C-8	C-10
9	59.19	59.05	33.35	30.67	30.67	30.51
10	59.25	59.07	33.86	31.25	23.22	23.09
12	59.57	59.42	34.69	30.73	30.58	29.35
13	59.68	59.46	35.16	30.11	23.25	23.13



Scheme 7

These equilibria are unusual, because they involve the interconversion between diastereoisomers having three chiral elements, without any bond breaking.

At room temperature, the product is isolated as a racemic mixture because the change of the helical chirality is possible only if the whole molecule is rebuilt, once formed, the helix preserves its initial structure (*P* or *M* configuration).

Experimental

General

NMR spectra were obtained on a Bruker AM 400 spectrometer (with an Aspect 3000 calculator) operating at 400 MHz for protons and 100 MHz for carbon atoms. No Me_4Si was added; the chemical shifts were measured against the solvent line.

Mps were determined with an Electrothermal apparatus and are uncorrected. Microanalyses were performed in the microanalytical laboratory of the 'Institute of Chemical and Pharmaceutical Research' in Cluj-Napoca, Romania.

The synthesis of compounds **4**,[11] **6**[13] and **7**[14] have been reported previously.

Compounds 1–3 and 5. General procedure

Equimolecular (0.1 mol) amounts of 1,3-diol and ketone with catalytic quantities of toluene-*p*-sulfonic acid (0.1 g) were dissolved in 200 cm^3 of benzene. The mixture was refluxed and the water was removed using a Dean–Stark trap (for compound **5** the ratio between pentaerythritol and 4-methylcyclohexanone was 1:2 and due to the low solubility of the pentaerythritol in benzene, vigorous stirring was necessary). When 80% (theoretical) of the water was separated, after cooling at room temperature, the catalyst was neutralized (under stirring 0.5 h) with excess CH_3CO_2Na powder (0.2 g). The mixture was washed twice with 100 cm^3 water. After drying (Na_2SO_4) the benzene was removed and the 1,3-dioxane compound was purified by crystallization from ethanol or by vacuum distillation (1–2 mmHg).

Table 6 The configurational stereoisomers of the compound **5**, **6**

Isomer	Configuration axis C^3–C^6	axis C^{12}–C^{15}	Helix	Enantiomer with
I	*aR*	*aR*	*P*	V
II	*aS*	*aS*	*P*	IV
III	*aR*(*aS*)	*aS*(*aR*)	*P*	VI
IV	*aR*	*aR*	*M*	II
V	*aS*	*aS*	*M*	I
VI	*aS*(*aR*)	*aR*(*aS*)	*M*	III

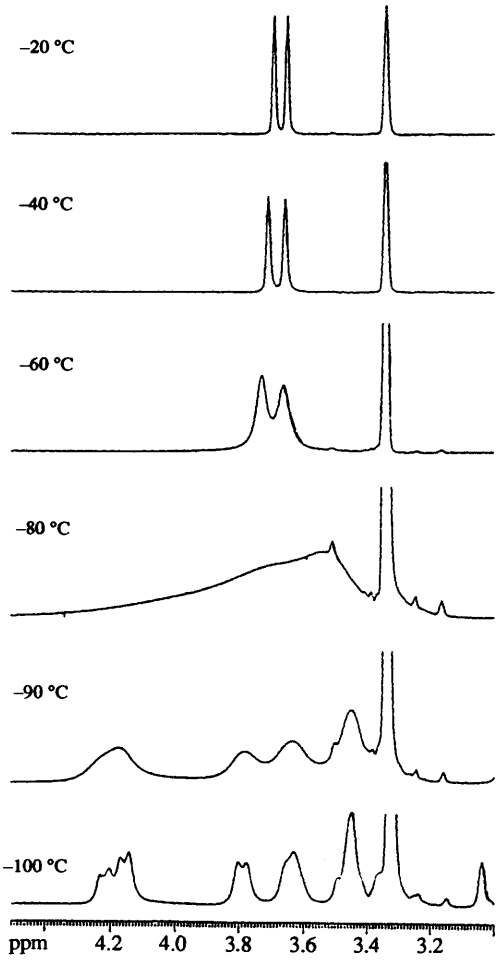


Fig. 4 Results of the variable temperature ^1H NMR experiment for compound **6**. Note: the signal of 3.26 ppm is a solvent line [$(C_2D_5)_2O$].

Acids 8–10. General procedure

The corresponding diesters (**1**, **3** and **7**) were saponified using a 10% ethanolic KOH (100% excess) and the reaction mixture was heated to reflux for 2 h. The resulting potassium salt was

filtered, then washed with dry ethanol and acetone. The salt was dissolved in a small amount of water and a volume 20 times larger of diethyl ether was added. A concentrated HCl solution was then added dropwise at 0–5 °C, under stirring until pH = 2 was reached. After, separation the organic phase was dried and the ether was removed (*in vacuo*; $T < 30$ °C). The diacid obtained was decarboxylated without purification, by heating (1 h at 90–95 °C) its pyridine solution (50 cm^3 pyridine per 1 g diacid). The pyridine was then removed *in vacuo* and the raw product was dissolved in 10% aqueous KOH (20% excess) and washed twice with 50 cm^3 diethyl ether. To the potassium salt solution a ten times larger volume of diethyl ether was added. After cooling (at 0–5 °C) a concentrated HCl solution was slowly added, under stirring, until pH = 2 was reached. The ether solution was separated and washed with a small amount of cold water. After drying, the ether was removed *in vacuo*. The acids were crystallized from hexane.

Methylic esters 11–13. General procedure

The corresponding acids **8–10** were reacted with CH_2N_2 under the usual conditions. The esters were crystallized from ethanol (**12** and **13**) or high vacuum distilled (**11**).

3,3-Bis(ethoxycarbonyl)-9-methyl-1,5-dioxaspiro[5.5]undecane 1

Colourless oil, bp 160–162 °C/2 mmHg, 19.4 (0.062 mol) yield 62% (Found: C, 60.9; H, 8.0. $C_{16}H_{26}O_6$ requires C, 61.1; H, 8.1%); $\delta_H(C_6D_6)$ 0.83 (3 H, d, *J* 6.5, 9-CH_3), 0.90 (6 H, t, *J* 7.1, 3-$CO_2CH_2CH_3$), 1.2–1.45 (7 H, overlapped peaks, $H_{ax}^{7,11}$, H^{8-10}), 2.23 (2 H, m, $H_{eq}^{7,11}$), 3.96 (4 H, q, *J* 7.1, 3-$CO_2CH_2CH_3$) and 4.51 (2 H, s, H^4) and 4.59 (2 H, s, H^2); $\delta_C(C_6D_6)$ 13.85 (3-$CO_2CH_2CH_3$) 21.75 (9-CH_3), 31.02 ($C^{8,10}$), 32.06 (C^9), 32.16 ($C^{7,11}$) 54.37 (C^3), 61.57 (3-$CO_2CH_2CH_3$), 62.10 (C^4), 62.18 (C^2), 98.56 (C^6) and 168.07 (5-$CO_2CH_2CH_3$).

3,3,9-Trimethyl-1,5-dioxaspiro[5.5]undecane 2

Colourless oil, bp 110–112 °C/2 mmHg, 14.05 g (0.071 mol), yield 71% (Found: C, 72.4; H, 11.0. $C_{12}H_{22}O_2$ requires C, 72.68; H, 11.18%); $\delta_H(C_6D_6)$ 0.82 (6 H, s, 3-CH_3), 0.90 (3 H, d, *J* 5.8, 9-CH_3), 1.30–1.55 (7 H, overlapped peaks, $H_{ax}^{7,11}$,H^{8-10}), 2.30 (2 H, m, 2 $H_{eq}^{7,11}$), 3.32 (2 H, s, H^4) and 3.40 (2 H, s, H^2); $\delta_C(C_6D_6)$ 21.96 (9-CH_3), 22.70 (3-CH_3), 30.07 (C^3), 31.20 ($C^{8,10}$), 32.34 (C^9), 32.42 ($C^{7,11}$), 69.72 (C^4), 69.87 (C^2) and 97.58 (C^6).

3,3-Bis(ethoxycarbonyl)-9-*tert*-butyl-1,5-dioxaspiro[5.5]-undecane 3

White plates, mp 75 °C, 12.46 g (0.035 mol), yield 70% (Found: C, 63.85; H, 6.3. $C_{19}H_{32}O_6$ requires C, 64.02; H, 6.22%); $\delta_H(C_6D_6)$ 0.79 [9 H, s, 9-$C(CH_3)_3$], 0.86 (6 H, t, *J* 7.1, 3-$CO_2CH_2CH_3$), 1.24–1.27 (5 H, overlapped peaks, H^{8-10}), 1.43–1.45 (2 H, m, $H_{ax}^{7,11}$), 2.30–2.33 (2 H, m, $H_{eq}^{7,11}$), 3.93 (4 H, q, *J* 7.1, 3-$CO_2CH_2CH_3$), 4.47 (2 H, s, H^4) and 4.57 (2 H, s, H^2); $\delta_C(C_6D_6)$ 13.87 (3-$CO_2CH_2CH_3$), 23.58 ($C^{8,10}$), 27.72 [9-$C(CH_3)_3$], 32.25 [9-$C(CH_3)_3$], 32.78 ($C^{7,11}$), 47.73 (C^9), 54.46 (C^3), 61.59 (3-$CO_2CH_2CH_3$), 62.18 (C^4), 62.32 (C^2), 98.58 (C^6) and 168.14 (3-$CO_2CH_2CH_3$).

3,15-Dimethyl-7,11,18,21-tetraoxatrispiro[5.2.2.5.2.2]-henicosane 5

White plates, mp 88–89 °C, 10.04 g (0.031 mol), yield 62% (Found: C, 70.1; H, 9.75. $C_{19}H_{32}O_4$ requires C, 70.33; H, 9.94%); $\delta_H(C_6D_6)$ 0.86 (6 H, d, *J* 6.5, 3-CH_3, 15-CH_3), 1.10 (4 H, m, $H_{ax}^{2,4,14,16}$), 1.30 (4 H, m, $H_{eq}^{2,4,14,16}$), 1.37 (2 H, m, H^3,H^{15}), 1.52 (4 H, m, $H_{ax}^{1,5,13,17}$), 2.12 (4 H, m, $H_{eq}^{1,5,13,17}$), 3.66 (4 H, s, $H^{8,19}$) and 3.71 (4 H, s, $H^{10,20}$); $\delta_C(C_6D_6)$ 21.89 (3-CH_3, 15-CH_3), 31.11 ($C^{2,4,14,16}$), 32.18 ($C^{5,17}$), 32.23 ($C^{3,15}$), 32.28 ($C^{1,13}$), 32.81 (C^9), 63.37 ($C^{8,19}$), 63.52 ($C^{10,20}$) and 98.43 ($C^{6,12}$).

3-Carboxy-1,5-dioxaspiro[5.5]undecane 8

White plates, mp 104–105 °C, 14.8 g (0.037 mol), yield 74% (Found: C, 59.7; H, 8.1. $C_{10}H_{16}O_4$ requires C, 59.98; H, 8.05%); $\delta_H(C_6D_6)$ 1.26 (2 H, m, H^9), 1.41 (2 H, m, H^8), 1.51 (2 H, m, H^{10}), 1.68–1.73 (4 H, m, $H^{7,11}$), 2.39 (1 H, tt, *J* 7.6, 4.8, H_{ax}^3), 3.80 (2 H, dd, *J* 11.9, 4.8, $H_{eq}^{2,4}$) and 3.99 (2 H, dd, *J* 11.9, 7.6, $H_{ax}^{2,4}$); $\delta_C(C_6D_6)$ 22.27 (C^{10}), 22.41 (C^9), 25.55 (C^8), 31.01 (C^{11}), 33.87 (C^7), 39.98 (C^3), 58.95 ($C^{2,4}$), 97.90 (C^6) and 176.50 (3-CO_2H).

3-Carboxy-9-methyl-1,5-dioxaspiro[5.5]undecane 9

White plates, mp 86–87 °C, 10.91 g (0.051 mol), yield 51% (Found: C, 61.4; H, 8.6. $C_{11}H_{18}O_4$ requires C, 61.66; H, 8.46%); $\delta_H(C_6D_6)$ 0.85 (3 H, d, *J* 5.8, 9-CH_3), 1.11–1.33 (4 H, overlapped peaks, H_{ax}^{11}, $H_{eq}^{8,10}$ H^9), 1.37–1.46 (3 H, overlapped peaks, H_{ax}^7,$H_{eq}^{8,10}$), 2.10 (1 H, ddd, *J* 12.6, 6.1, 3.0, H_{eq}^7), 2.21 (1 H, ddd, *J* 12.6, 6.5, 3.3, H_{eq}^{11}), 2.41 (1 H, tt, *J* 7.7, 4.8, H_{ax}^3), 3.77 (1 H, ddd, *J* 11.7, 4.8, 0.8, H_{eq}^4), 3.85 (1 H, ddd, *J* 11.7, 4.8, 0.8, H_{eq}^2), 3.94 (1 H, dd, *J* 11.7, 7.7, H_{ax}^4) and 4.05 (1 H, dd, *J* 11.7, 7.7, H_{ax}^2); $\delta_C(C_6D_6)$, 21.47 (9-CH_3), 30.51 (C^{10}), 30.67 ($C^{8,11}$), 31.72 (C^9), 33.35 (C^7), 39.83 (C^3), 59.05 (C^4) and 59.19 (C^2).

3-Carboxy-9-*tert*-butyl-1,5-dioxaspiro[5.5]undecane 10

White plates, mp 153–154 °C, 8.96 g (0.035 mol), yield 70% (Found: C, 65.4; H, 9.6. $C_{14}H_{24}O_4$ requires C, 65.59; H, 9.43%); $\delta_H(C_6D_6)$ 0.85 [9 H, s, 9-$C(CH_3)_3$], 0.90–0.95 (1 H, m, H_{ax}^9), 1.14–1.29 (2 H, m, H_{ax}^{11},H_{ax}^{10}), 1.33–1.40 (2 H, overlapped peaks, H_{ax}^8,H_{eq}^8), 1.46–1.54 (2 H, overlapped peaks, H_{ax}^7,H_{eq}^{10}), 2.19–2.23 (1 H, m, H_{eq}^7), 2.34–2.36 (1 H, m, H_{eq}^{11}), 2.40 (1 H, tt, *J* 7.5, 4.6, H_{ax}^3), 3.78 (1 H, dd, *J* 11.6, 4.6, H_{eq}^4), 3.87 (1 H, dd, *J* 11.6, 4.6, H_{eq}^2), 3.97 (1 H, dd, *J* 11.6, 7.5, H_{ax}^4) and 4.08 (1 H, dd, *J* 11.6, 7.5, H_{ax}^2); $\delta_C(C_6D_6)$ 23.09 (C^{10}), 23.22 (C^8), 27.24 [9-$C(CH_3)_3$], 31.25 (C^{11}), 31.90 [9-$C(CH_3)_3$], 33.86 (C^7), 40.16 (C^3), 47.48 (C^9), 59.04 (C^4), 59.25 (C^2), 97.87 (C^6) and 176.95 (3-CO_2H).

3-Methyloxycarbonyl-1,5-dioxaspiro[5.5]undecane 11

Colourless oil, bp 126–128 °C/2 mmHg, 1.81 g (0.0085 mol), yield 68% (Found: C, 61.5; H, 8.6. $C_{11}H_{18}O_4$ requires C, 61.66; H, 8.46%); $\delta_H(C_6D_6)$ 1.28 (2 H, m, H^9), 1.40 (2 H, m, H^8), 1.55 (2 H, m, H^{10}), 1.70–1.75 (4 H, m, $H^{7,11}$), 2.57 (1 H, tt, *J* 8.7, 5.0, H_{ax}^3), 3.26 (3 H, s, 3-CO_2CH_3), 3.90 (2 H, dd, *J* 11.9, 5.0, $H_{eq}^{2,4}$) and 4.05 (2 H, dd, *J* 11.9, 8.7, $H_{ax}^{2,4}$); $\delta_C(C_6D_6)$ 22.69 (C^{10}), 22.84 (C^9), 25.98 (C^8), 30.28 (C^{11}), 35.54 (C^7), 40.58 (C^3), 51.20 (3-$COOCH_3$), 59.73 ($C^{2,4}$), 98.06 (C^6) and 170.96 (3-$COCH_3$).

3-Methoxycarbonyl-9-methyl-1,5-dioxaspiro[5.5]undecane 12

Solid, mp 43–44 °C, 2.85 g (0.0125 mol), yield 50% (Found: C, 63.3; H, 9.0. $C_{12}H_{20}O_4$ requires C, 63.13; H, 8.83%); $\delta_H(C_6D_6)$ 0.86 (3 H, d, *J* 6.1, 9-CH_3), 1.11–1.25 (3 H, overlapped peaks, H_{ax}^9,H_{ax}^{11},H_{ax}^8), 1.27–1.42 (2 H, overlapped peaks, H_{eq}^8,H_{ax}^{10}), 1.45–1.52 (2 H, overlapped peaks, H_{ax}^7,H_{eq}^{10}), 2.11 (1 H, ddd, *J* 12.9, 6.6, 3.1, H_{eq}^7), 2.31 (1 H, ddd, *J* 12.8, 6.4, 3.0, H_{eq}^{11}), 2.57 (1 H, tt, *J* 8.7, 5.0, H_{ax}^3), 3.25 (3 H, s, 3-CO_2CH_3), 3.88 (1 H, ddd, *J* 11.6, 5.0, 1.4, H_{eq}^4), 3.94 (1 H, ddd, *J* 11.6, 5.0, 1.4, H_{eq}^2), 4.00 (1 H, dd, *J* 11.6, 8.7, H_{ax}^4) and 4.12 (1 H, dd, *J* 11.6, 8.7, H_{ax}^2); $\delta_C(C_6D_6)$ 21.45 (9-CH_3), 29.35 (C^{10}), 30.58 (C^8), 30.73 (C^{11}), 31.78 (C^9), 34.69 (C^7), 40.18 (C^3), 50.82 (3-CO_2CH_3), 59.42 (C^4), 59.57 (C^2), 97.69 (C^6) and 170.57 (3-CO_2CH_3).

9-*tert*-Butyl-3-methoxycarbonyl-1,5-dioxaspiro[5.5]undecane 13

Solid, mp 74–75 °C, 2.43 g (0.009 mol), yield 72% (Found: C, 66.4; H, 9.8. $C_{15}H_{26}O_4$ requires C, 66.63; H, 9.69%); $\delta_H(C_6D_6)$ 0.85 [9 H, s, $C(CH_3)_3$], 0.87–0.95 (1 H, m, H_{ax}^9), 1.12–1.28 (2 H, overlapped peaks, H_{ax}^{11},H_{ax}^8), 1.37–1.56 (4 H,

overlapped peaks, H_{eq}^{8},H_{ax}^{7},H_{ax}^{10},H_{eq}^{10}), 2.25 (1 H, ddd, *J* 12.5, 5.8, 2.6, H_{eq}^{7}), 2.45 (1 H, ddd, *J* 12.5, 6.4, 3.2, H_{eq}^{11}), 2.55 (1 H, tt, *J* 8.5, 4.9, H_{ax}^{3}), 3.24 (3 H, s, 3-CO_2CH_3), 3.89 (1 H, ddd, *J* 11.5, 4.9, 1.2, H_{eq}^{4}), 3.96 (1 H, ddd, *J* 11.5, 4.9, 1.4, H_{eq}^{2}), 4.05 (1 H, dd, *J* 11.5, 8.5; H_{ax}^{4}) and 4.17 (1 H, dd, *J* 11.5, 8.5, H_{ax}^{2}); $\delta_C(C_6D_6)$ 23.13 (C^{10}), 23.25 (C^{8}), 27.31 [9-C(CH_3)$_3$], 30.11 (C^{11}), 31.90 [9-*C*(CH_3)$_3$], 35.16 (C^{7}), 40.16 (C^{3}), 47.53 (C^{9}), 50.78 (C-CO_2CH_3), 59.46 (C^{4}), 59.68 (C^{2}), 97.66 (C^{2}) and 170.60 (3-CO_2CH_3).

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