Synthesis and stereochemistry of some new brominated spiro 1,3-dioxanes

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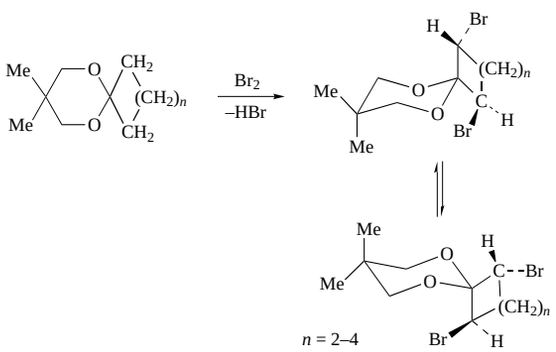
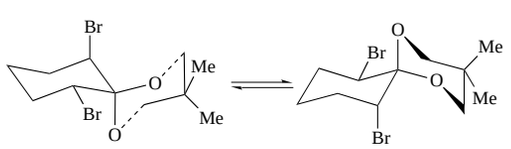
New dibrominated spiro 1,3-dioxanes have been obtained by a regio- and diastereo-selective reaction between six-membered ring spiro compounds and bromine. Studies on the stereochemistry of these brominated compounds, exhibiting a 1,5-dioxaspiro[5.5]undecane skeleton, were carried out by NMR methods in solution and by the solid-state molecular structure of four compounds established by single-crystal X-ray diffractometry. The diasteroselectivity of the bromination was explained by the asymmetric induction of chiral carbon atoms and the chiral spiro skeleton.

In previous work[1] the high regio- and diastereo-selectivity of the bromination of some flexible spiro 1,3-dioxane compounds was reported (Scheme 1).



Scheme 1

Studies on the stereochemistry of these compounds, by means of NMR spectroscopy, showed that only the (±)-isomers depicted (identical configurations for the chiral carbon atoms)† were obtained. In these diastereoisomers the bromine atoms exhibit a *trans* disposition. The spiro dibrominated compounds display flipping structures, the symmetrically substituted 1,3-dioxane ring being involved in a conformational equilibrium (Scheme 1). The compound exhibiting a 1,5-dioxaspiro[5.5]-undecane skeleton ($n = 3$) shows a flexible cyclohexane ring, too. In this case a complex conformational equilibrium has to be considered (Scheme 2).



Scheme 2

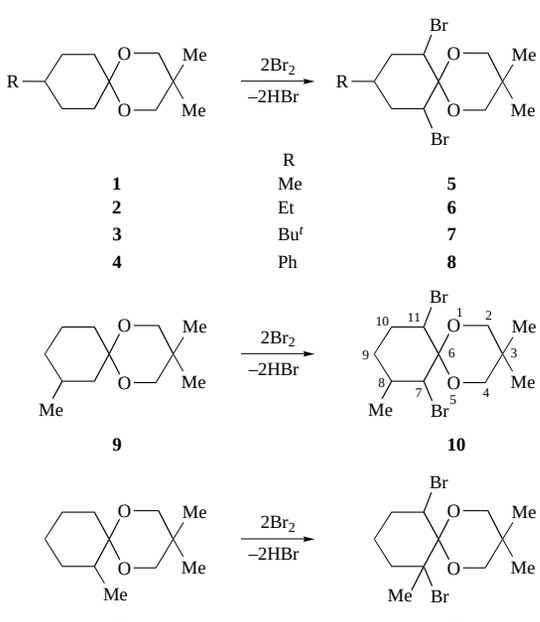
† Eliel[2] proposed denoting this diastereoisomer by the symbols *RS*,*RS* instead of + and −.

On the other hand, studies[3,4] of the stereochemistry of other spiro compounds with six-membered rings showed that they have both axial and helical chirality.

It was considered of interest to extend our previous study[1] on the flexible brominated spiro compounds to the bromination of spiro compounds exhibiting semiflexible or anomeric structures, in order to analyse the influences of the chirality of the spiro skeleton on the diastereoselectivity of the reaction.

Results and discussion

New dibrominated compounds have been obtained by the reaction between spiro compounds with six-membered rings and bromine (Scheme 3).



Scheme 3

Table 1 Composition (molar percents) of the crude products from bromination of compounds **1**–**4**, **9** and **11**

Brominated compounds	Bromination of spiro compounds					
	1	**2**	**3**	**4**	**9**	**11**
(%) 7-Br, 11-Br	~100	~96	~94	~80	~100	~100
(%) 7-Br, 7-Br, 11-Br	—	~4	~6	~20	—	—

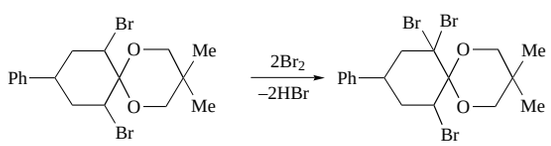
Table 2 Values of coupling constants (*J*/Hz, C_6D_6 solutions) of the protons of the 7- and 11-positions for compounds **5**–**8**, **10** and **12**

Compound	Equatorial proton		Axial proton	
	eq.-ax.	eq.-eq.	ax.-eq.	ax.-ax.
5*	3.0	3.0	4.6	12.8
6	3.3	3.3	4.8	12.5
7	3.2	3.2	4.9	12.5
8	3.2	3.2	4.9	12.2
10	—	3.0	4.7	12.7
12	4.0	4.0	—	—

* In the spectrum run in C_6D_6 the signals of the 7- and 11-protons overlapped, the coupling constants were measured for the spectrum obtained in $C_6D_5NO_2$.

The bromination is regio- and diastereo-selective and in the crude product mixtures only the 7,11-dibrominated compounds were identified. In addition, the bromination of compounds **2**–**4** resulted in small amounts of 7,7,11-tribrominated compounds as side-products. The tribrominated compounds were identified on the basis of mass and NMR spectral evidence determined with the product mixtures. The ratios between the dibrominated and tribrominated compounds were established from the ^{1}H NMR data (Table 1).

The tribrominated compound **13** was isolated by flash chromatography, using CH_2Cl_2 and hexane (1:4) as a side-product in the synthesis of compound **8** (Scheme 4).



8 **13**

Scheme 4

Dibrominated compounds **5**–**8**, **10** and **12** were obtained as single diastereoisomers displaying the bromine atoms in a *trans* disposition. In this isomer the two chiral carbon atoms have identical configurations (7*RS*,11*RS*). The *trans* disposition of the bromine atoms in compounds **5**–**8** was inferred from NMR results, using the values of the coupling constants (Table 2) of the 7- and 11-protons (at the same positions as the bromine atoms); one is equatorial and the other axial. The ^{1}H NMR spectra show a well-resolved doublet of doublets for the axial proton (let us consider it in position 7) and a triplet for the equatorial proton (position 11) resulting from overlapping of a doublet of doublets. The magnitude of the coupling constants (*J* 12.2–13.0 Hz and *J*′ 4.6–4.9 Hz) for the axial proton are characteristic[5] in six-membered rings for the coupling between vicinal axial–axial ($J_{ax.,ax.}$) and vicinal axial–equatorial ($J_{ax.,eq.}$) protons, respectively. The signal corresponding to the equatorial proton shows coupling constants with close values ($J \approx J'$ 3.0–3.3 Hz), in the normal range for the coupling between vicinal axial–equatorial ($J_{ax.,eq.}$) and vicinal equatorial-equatorial ($J_{eq.,eq.}$) protons. As an example, the spectrum of compound **7** shows a well-resolved doublet of doublets (δ 4.72 ppm) for the axial proton at position 7 and an overlapping doublet of doublets (δ 4.78 ppm) for the equatorial proton at position 11 [Fig. 1(*a*)].

Table 3 Values of bond lengths determined for compounds **7**, **10**, **12** and **13**

Bond	Compound			
	7	**10**	**12**	**13**
C(7)–Br	1.958(6)	1.976(7)	1.982(8)	1.976(9)
C(11)–Br	1.953(7)	1.943(9)	1.965(6)	1.956(6)
O(1)–C(2)	1.447(9)	1.431(7)	1.448(8)	1.436(8)
C(2)–C(3)	1.504(10)	1.533(12)	1.515(9)	1.509(9)
C(4)–O(5)	1.443(9)	1.424(8)	1.446(7)	1.460(8)
O(1)–C(6)	1.390(7)	1.429(8)	1.406(8)	1.416(9)
C(3)–C(4)	1.535(9)	1.521(11)	1.522(10)	1.507(12)
O(5)–C(6)	1.406(7)	1.400(9)	1.412(7)	1.420(7)
C(6)–C(7)	1.533(10)	1.552(11)	1.544(9)	1.508(9)
C(6)–C(11)	1.551(8)	1.522(10)	1.550(11)	1.552(12)
C(7)–C(8)	1.521(9)	1.545(11)	1.505(10)	1.529(12)
C(10)–C(11)	1.526(9)	1.512(13)	1.514(10)	1.532(12)
C(8)–C(9)	1.531(9)	1.520(11)	1.503(14)	1.543(12)
C(9)–C(10)	1.520(10)	1.533(13)	1.523(11)	1.524(10)
C(7)–X*	—	—	1.593(9)	1.939(7)

* X = Me for compound **12** and axial bromine atom for compound **13**. Standard bond lengths[6] for C–C, C–O and C–Br are: 1.53, 1.43 and 1.94 Å.

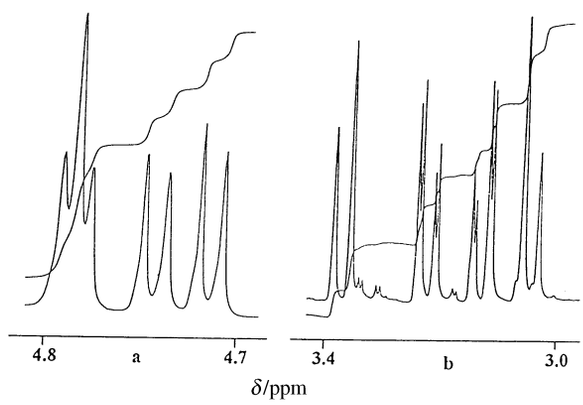


Fig. 1 ^{1}H NMR spectrum of compound **7** (details)

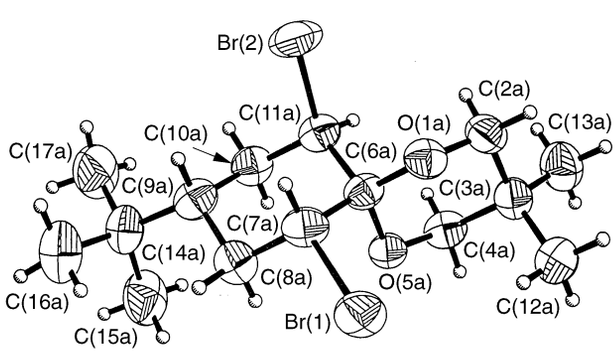


Fig. 2 X-Ray structure of compound **7**

The molecular structure of compound **7**, established by single-crystal X-ray diffractometry (Fig. 2), shows axial and equatorial orientations for the two bromine atoms and chair conformations for both the cyclohexane and the 1,3-dioxane rings. The bond lengths, bond angles and torsion angles (Tables 3, 4 and 5) for compound **7** are in the range reported for such rings.[5–7]

Compound **10** was obtained as a single diastereoisomer bearing an 8-methyl group and an 11-bromine atom in equatorial orientations, the 7-bromine atom being axial. For this disposition of the bromine atoms and the methyl group two enantiomers are possible, *i.e.* 7*R*,8*R*,11*R* and 7*S*,8*S*,11*S*, respectively. The ^{1}H NMR spectrum of compound **10** shows an observable doublet of doublets (δ 4.66 ppm, $J_{ax.,ax.}$ 12.7 Hz, $J_{ax.,eq.}$ 4.7 Hz) for the axial proton at the 11-position and an

Table 4 Values of bond angles determined for compounds **7**, **10**, **12** and **13**

	Compound			
Bond angles	**7**	**10**	**12**	**13**
Br–C(7)–C(6)	109.7(4)	109.3(4)	107.4(5)	112.6(4)
Br–C(7)–C(8)	109.3(4)	111.3(5)	108.3(5)	109.4(5)
Br–C(11)–C(6)	110.3(4)	111.4(5)	113.8(5)	114.4(5)
Br–C(11)–C(10)	111.9(5)	110.0(6)	111.1(5)	111.2(5)
C(2)–O(1)–C(6)	113.5(5)	114.1(5)	113.9(5)	114.5(6)
C(2)–C(3)–C(4)	107.1(5)	105.8(6)	105.8(6)	108.1(6)
C(3)–C(4)–O(5)	110.9(5)	112.1(6)	112.3(6)	111.6(6)
O(1)–C(6)–O(5)	112.8(5)	111.7(5)	112.2(5)	111.6(5)
O(1)–C(2)–C(3)	110.9(5)	112.1(6)	111.8(5)	112.6(5)
C(4)–O(5)–C(6)	114.4(5)	114.6(5)	116.0(4)	117.3(5)
C(7)–C(6)–C(11)	107.2(5)	109.8(6)	112.2(6)	113.8(6)
C(6)–C(7)–C(8)	113.1(5)	112.2(6)	111.4(6)	113.0(7)
C(6)–C(11)–C(10)	112.5(5)	112.5(7)	112.8(6)	112.1(6)
C(7)–C(8)–C(9)	110.3(5)	110.8(6)	113.2(6)	111.3(6)
C(9)–C(10)–C(11)	112.7(5)	111.1(8)	112.1(7)	113.2(7)
C(8)–C(9)–C(10)	108.9(6)	112.2(7)	110.7(7)	109.0(6)
C(6)–C(7)–X*	—	—	112.5(5)	109.0(5)
Br–C(7)–X	—	—	105.1(5)	105.5(4)
C(8)–C(7)–X	—	—	111.8(6)	106.9(5)

* X = Me for compound **12** and axial bromine atom for compound **13**.

Table 5 Values of torsion angles determined for compounds **7**, **10**, **12** and **13**

	Compound			
Angles	**7**	**10**	**12**	**13**
C(2)–O(1)–C(6)–O(5)	54.6	52.6	51.9	50.6
C(6)–O(1)–C(2)–C(3)	57.3	54.7	57.7	55.9
O(1)–C(2)–C(3)–C(4)	55.1	53.2	55.5	53.8
C(2)–C(3)–C(4)–O(5)	53.6	53.8	52.3	49.5
C(3)–C(4)–O(5)–C(6)	53.7	56.6	51.7	49.4
C(4)–O(5)–C(6)–O(1)	53.2	53.4	49.4	48.1
C(6)–C(7)–C(8)–C(9)	60.4	53.7	54.8	55.0
C(7)–C(8)–C(9)–C(10)	57.3	53.6	57.6	58.4
C(8)–C(9)–C(10)–C(11)	56.0	55.0	55.4	57.2
C(6)–C(11)–C(10)–C(9)	56.1	56.4	51.7	51.0
C(7)–C(6)–C(11)–C(10)	53.7	55.9	48.7	45.8
C(8)–C(7)–C(6)–C(11)	56.7	54.3	49.4	48.3

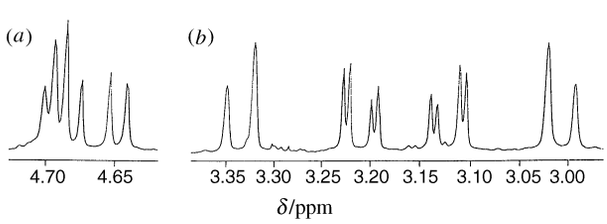


Fig. 3 ^{1}H NMR spectrum of compound **10** (details)

overlapping doublet of doublets (a triplet, $\delta = 4.69$ ppm) with very closely similar values for the coupling constants ($J \approx J' \approx 3$ Hz) for the equatorial proton at the 7-position [Fig. 3(*a*)]. The equatorial proton (position 7) is coupled with the axial proton at the 8-position and exhibits long-range coupling with the equatorial proton of the 9-position (W disposition of the $H_{eq.}$–C^7–C^8–C^9–$H_{eq.}$ skeleton). Long-range coupling was observed in the 2D homonuclear COSY spectrum and was also confirmed by decoupling experiments.

The X-ray structure of compound **10** (Fig. 4) shows the axial orientation of the 7-bromine atom and equatorial orientations for the 8-methyl group and of the 11-bromine atom. Both six-membered rings display chair conformations, with normal values for the molecular parameters of the rings (Tables 3, 4 and 5).

An X-ray study on compound **12** (Fig. 5) shows an interesting molecular structure corresponding to a *trans* disposition of the bromine atoms (the 11-bromine atom is axial and the 7-bromine atom is equatorial).

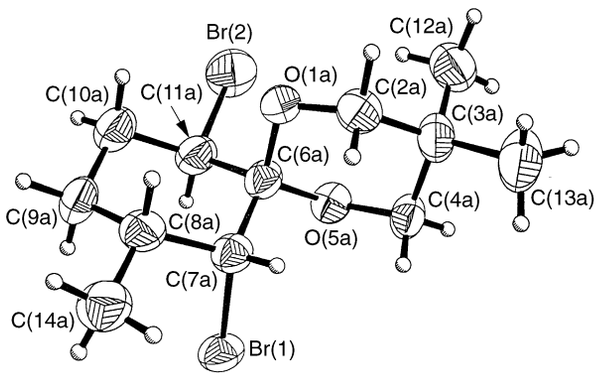


Fig. 4 X-Ray structure of compound **10**

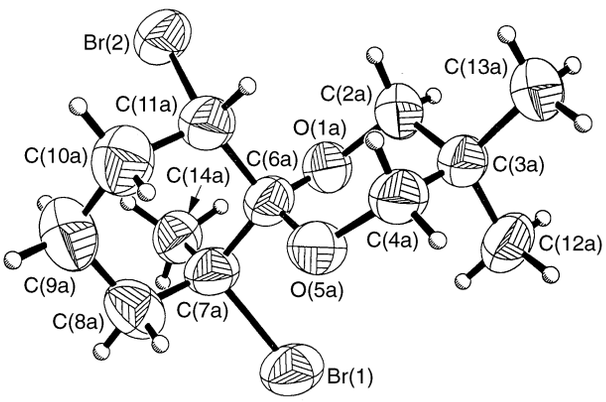


Fig. 5 X-Ray structure of compound **12**

The 7-methyl group is forced into an axial orientation. For this arrangement of the substituents on the cyclohexane ring two structures with opposite configurations of the chiral elements are possible, *i.e.* 7*R*,11*R* and 7*S*,11*S*, respectively. Although the rings exhibit chair conformations, close to the spiro carbon atom, their flattening can be observed.

The interactions between the two axial groups result in modifications of the torsion angles (Table 5). The magnitude of the torsion angles C_7–C_6–C_{11}–C_{10} and C_8–C_7–C_6–C_{11}, smaller than usual,[5,7] results in a non-parallel orientation of the bonds C_7–$Me_{ax.}$ and C_{11}–$Br_{ax.}$. An angle of *ca.* 25° between these bonds has been measured. The bond length of the axial methyl group (Table 3, C_7–Me, 1.593 Å) is also longer than usual. The distortion of the cyclohexane and 1,3-dioxane rings due to the two axial groups is also suggested by the increased values of the endocyclic bond angles at the spiro carbon atom (Table 4).

The axial orientation of the 11-bromine atom is confirmed by the values of the coupling constants (Table 2) measured for the proton at the same position (overlapped doublet of doublets giving a triplet, with small and close values of the coupling constants $J = J'$ 4.0 Hz).

The NMR spectrum of the tribrominated compound **13** shows an anomeric structure. The 11-bromine atom has again an axial orientation. The proton on the same carbon atom (position 11) displays in the ^{1}H NMR spectrum a doublet of doublets with small values for the coupling constants (J 4.1; J' 2.6 Hz).

The X-ray structure (Fig. 6) of the compound shows the chair conformation for both cyclohexane and 1,3-dioxane rings. The two bulky groups (bromine atoms) in axial positions lead to modifications of the standard geometry of the chair conformations. Significant changes of the torsion angles (resulting in flattened rings) should be noted (Table 5). The axial bonds of

Table 6 NMR data (δ, C_6D_6) of compounds **5**–**8**, **10** and **12** (+ and − isomers)

	^{1}H			^{13}C							
Comp.	2eq.	4eq.	$\Delta\delta$	2ax.	4ax.	$\Delta\delta$	3-Me(ax.)	3-Me(eq.)	2	4	$\Delta\delta$
5	3.20	3.11	0.09	3.31	2.98	0.33	1.28	0.24	64.86	63.71	1.15
6	3.22	3.15	0.07	3.36	3.05	0.31	1.29	0.28	70.43	69.33	1.10
7	3.22	3.12	0.10	3.37	3.04	0.33	1.29	0.25	64.93	63.84	1.09
8	3.49	3.42	0.07	3.63	3.60	0.03	1.30	0.23	70.49	69.31	1.18
10	3.21	3.12	0.09	3.33	3.00	0.33	1.29	0.26	70.43	69.37	1.06
12	3.25	3.18	0.07	3.60	3.28	0.32	1.29	0.30	71.26	69.74	1.52

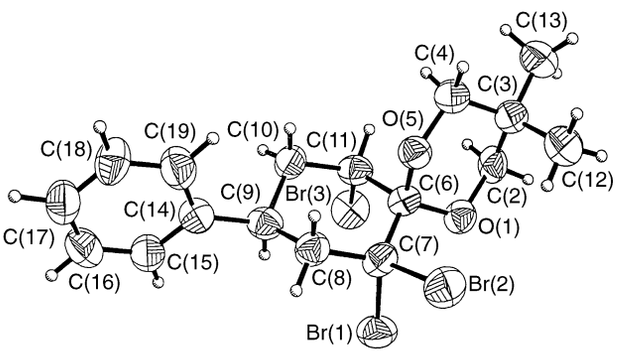
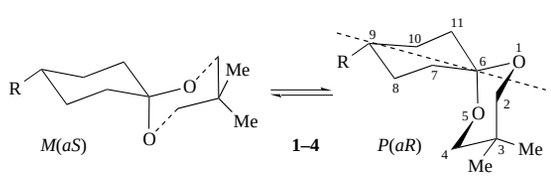


Fig. 6 X-Ray structure of compound **13**

the carbon atoms of the 7- and 11-positions (C_7–$Br_{ax.}$ and C_{11}–$Br_{ax.}$) are not parallel and show an angle of about 28°. The hindrance due to the presence of the two axial bromine atoms induces modifications of bond lengths and bond angles of the spiro carbon atom (C-6), as well as of those of the atoms connected to this one (Tables 3 and 4). The third bromine atom in compound **13** is directed stereoselectively to an axial position during the course of the reaction. Analysis of Dreiding models shows a considerably higher hindrance of the spiro skeleton if two bromine atoms occupy equatorial positions at the same time (at C-7 and C-11).

Stereochemistry of compounds having a 'holding group' in the 9-position

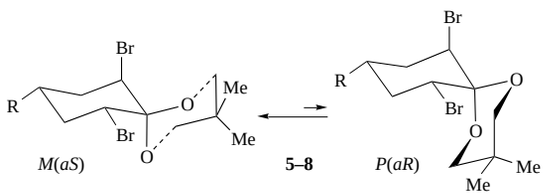
Compounds **5**–**8** show significantly different stereochemistry compared to the starting unbrominated spiro compounds **1**–**4**. Compounds **1**–**4** have a semi-flexible structure[3,4,8] with an anomeric unsymmetrical substituted six-membered ring (R is a 'holding group') and a flipping symmetrical substituted one (Scheme 5).



Scheme 5

Compounds **1**–**4** exhibit typical axial and helical chirality observed for spiro compounds with six-membered rings. The flipping of the 1,3-dioxane ring inverts both axial and helical chiralities, resulting in an enantiomeric interconversion, $M(aS) \rightleftharpoons P(aR)$.

In compounds **5**–**8** both rings are anomeric. The characteristic conformational equilibrium (*e.g.* for the isomer 7*R*,11*R*: A ⇌ B, Scheme 6) for the flipping of the symmetrical substituted 1,3-dioxane ring is shifted towards the conformer **A**, displaying the heterocycle on the opposite side of the equatorial bromine atom. In this conformation (**A**) the interactions between the equatorial bromine atom (position 7) and the 1,3-



Scheme 6

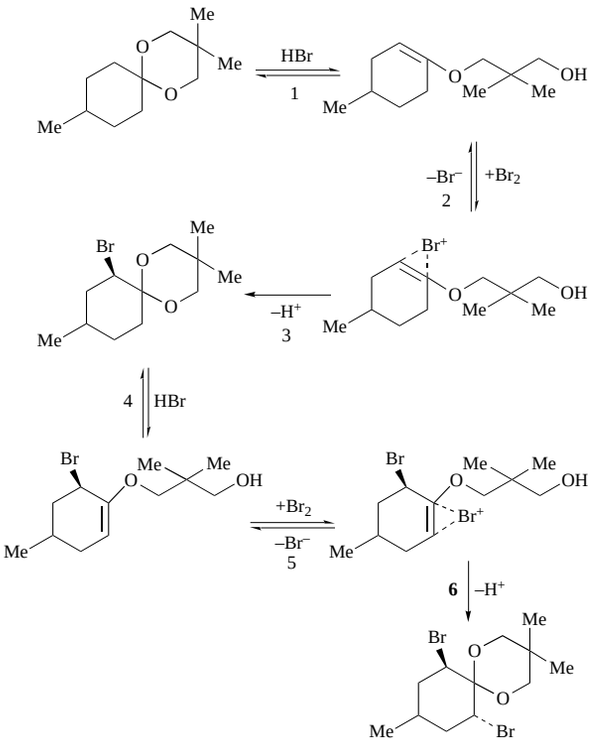
dioxane ring are significantly smaller than in the other conformer. This behaviour brings about the rigidity in the heterocycle, in spite of its symmetrical substitution.

Compounds **5**–**8** are obtained as racemic (7*R*,11*R*,*M*,*aS* and 7*S*,11*S*,*P*,*aR*).

These results were inferred from the NMR spectra (Table 6), analysis of Dreiding models and X-ray structure determinations. The NMR spectra exhibit different signals for the axial and equatorial protons of the 1,3-dioxane ring and for the protons and carbon atoms of the axial and equatorial methyl groups located at C-3. The chiral elements induce the diastereotopicity of the 2- and 4-positions. The NMR spectra display different signals for the protons and carbon atoms of these positions. The pattern of the spectrum [*e.g.* compound **7**, Fig. 1(*b*)] shows for the protons of the 1,3-dioxane ring four signals, two doublets corresponding to the axial and equatorial protons of position 2 ($\delta_{2ax.}$ 3.37; $\delta_{2eq.}$ 3.22 ppm) and two doublets belonging to those of the 4-position ($\delta_{4ax.}$ 3.04; $\delta_{4eq.}$ 3.12 ppm). The signals associated with the equatorial protons exhibit a further splitting due to the long-range coupling possible as a consequence of the W disposition of the bonds $H_{eq.}$–C^2–C^3–C^4–$H_{eq.}$. The long-range coupling constants (compounds **5**–**8**) have usual values ($2.2 < {}^4J_{2eq.,4eq.} < 2.7$ Hz) close to those reported in the lierature.[5] The values of the diastereotopicities (Table 6) of protons ($\Delta\delta_{2eq.,4eq.}$ 0.07–0.10; $\Delta\delta_{2ax.,4ax.}$ 0.03–0.33 ppm) and carbon atoms ($\Delta\delta_{2-4}$ 1.09–1.15 ppm) are similar to those observed for other chiral 1,3-dioxane compounds.[1,3,4,8–10] The close values of the chemical shifts for the axial and for the equatorial protons of the 1,3-dioxane ring are correlated with the deshielding of the axial protons by 'steric compression' of the group of atoms belonging to the axial position 7 (or 11) of the heterocycle.

Despite earlier opinions[1,11] in which a radical mechanism was suggested for the bromination of 1,3-dioxanes, our work employing similar techniques to those used in studying the bromination mechanism of some 1,3-dioxolanes,[12–18] suggests instead an HBr-catalysed mechanism (HBr produced by autocatlysis in the reaction) with an enol ether as an intermediate. The following general mechanism for the spiro 1,3-dioxanes **1**–**4** is, therefore, proposed (Scheme 7).

The bromination of compounds **1**–**4** involves asymmetric induction of the first created chiral centre. Initially a bromine atom is attached at either the 7- or 11-position to display different prochiralities and generating a chiral centre with either an *R* or *S* configuration. In the second step of the bromination the bromine atom is substituted into the opposite side of the cyclohexane ring to generate a new chiral centre that



Scheme 7

exhibits the same configuration as the first created chiral carbon atom.

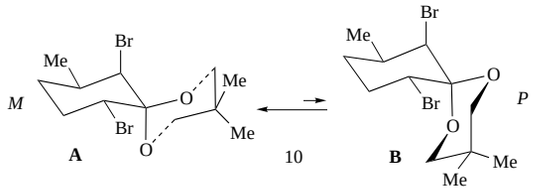
The stereochemistry of the compounds having a 'holding group' in the 7- and 8-positions

The spiro compound **9** (used in the synthesis of compound **10**) was obtained as a racemate (by the acetalization of racemic 3-methylcyclohexanone). The dibrominated compound **10** was obtained as one diastereoisomer (also racemic). All the chiral elements have a well-defined configuration (corresponding to a *trans* disposition of the bromine atoms: axial in the 7-position and equatorial in the 11-position). The correlation between the configuration of the initial chiral carbon atom (position 8) and the configurations of the newly introduced chiral centres (7 and 11) has to be taken into account. Thus, the bromination of the spiro compound displaying a chiral carbon atom with an *R* configuration leads to the isomer of the dibrominated compound **10** having *R* configurations for all the chiral carbon atoms (7*R*,8*R*,11*R*) and *M* for the helical chirality. The reaction of the *S* isomer of compound **9** leads to the dibrominated compound exhibiting chiral centres with only *S* configurations (7*S*,8*S*,11*S*) and *P* helicity.

The conformational behaviour of compound **10** is different to that observed for the starting 1,3-dioxane **9** (semi-flexible structure similar to that observed for compounds **1**–**4**, Scheme 5).

Compound **10** has an anomeric structure, with the conformational equilibrium characteristic of the flipping of the symmetrically substituted 1,3-dioxane ring being shifted towards the conformation that has the equatorial bromine atom on the opposite side to the heterocycle (*e.g.* for the isomer 7*R*,8*R*,11*R*: conformation A, Scheme 8). The spiro skeleton has *M* configuration in this isomer.

The anomeric structure of the compound is inferred from the results of the NMR studies. The ^{1}H NMR spectrum pattern for the protons of the 1,3-dioxane ring [Fig. 3(*b*)] is similar to that recorded for compounds **5**–**8** (Table 6, Fig. 1). Two AB systems for the diastereotopic axial ($\delta_{2ax.}$ 3.33; $\delta_{4ax.}$ 3.00 ppm) and diastereotopic equatorial protons ($\delta_{2eq.}$ 3.21; $\delta_{4eq.}$ 3.12 ppm) of the 2- and 4-positions have been recorded. The signals

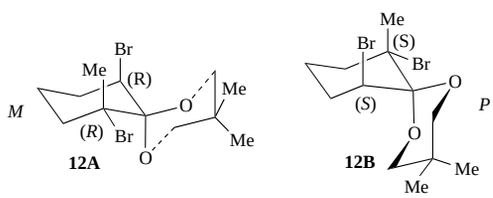


Scheme 8

corresponding to the equatorial protons display a further splitting due to the characteristic long-range coupling between the equatorial protons of the 2- and 4-positions ($^4J_{2eq.,4eq.}$ 2.6 Hz). The mechanism of the reaction is similar to that proposed for the bromination of compounds **1**–**4**.

Compound **12** was obtained as one diastereoisomer starting from the racemic spiro compound **11** (obtained by acetalization of racemic 2-methylcyclohexanone). The configurations of the chiral elements are well defined (7*R*,11*R*,*M* and 7*S*,11*S*,*P*; Scheme 9). Compound **12**, as well as the initial unbrominated spiro compound **11**, shows an anomeric structure.

The ^{1}H NMR spectrum of compound **12** (Table 6) exhibits for the protons of the heterocycle a close pattern to that recorded for compounds **5**–**8** and **10**. In compound **11** the 7-methyl group shows an equatorial orientation, while in compound **12** this group displays an axial orientation (established by an X-ray structure determination and NOE experiments). The spiro skeleton adopts a structure (**A**) showing an *M* configuration for the helix if the chiral centres have *R* configurations (Scheme 9) and a structure (**B**) corresponding to the *P*



Scheme 9

configuration of the helix if the chiral carbon atoms exhibit *S* configurations. The bromination is carried out in a similar way to that shown for the reaction of compounds **1**–**4**.

Conclusions

The bromination of some spiro 1,3-dioxanes showed high diastereoselectivity. The dibrominated compounds obtained have the bromine atoms in a *trans* disposition. The configuration of the first created chiral centre (or of the pre-existent chiral centre) influences the configurations of the next chiral centres introduced in the molecule by the brominations. All the dibrominated compounds investigated exhibited anomeric structures. The chirality of the molecules induces the diastereotopicity of protons and carbon atoms, that could be observed in the NMR spectra.

Experimental

^{1}H and ^{13}C NMR spectra were recorded at room temperature, using C_6D_6 as solvent, in 5 mm tubes, on a Bruker AM 400 (compounds **5**, **7**, **10**) or Varian VXR-300S* (compounds **6**, **8**, **12** and **13**) Fourier transform NMR spectrometer equipped with a dual ^{13}C-^{1}H (multinuclear)* head operating at 400 (300)* MHz for protons and 100 (75.4)* MHz for carbon atoms. *J* Values are recorded in Hz. Mps were measured with a Fisher Johns melting-point apparatus and are uncorrected. Microanalyses were performed in the microanalytical laboratory of the 'Institute of Chemical and Pharmaceutical Research' in

Table 7 Parameters of the crystallographic determinations for compounds **7**, **10**, **12** and **13**

	Compound **7**	Compound **10**	Compound **12**	Compound **13**
Colour/shape	Colourless/prism	Colourless/plates	Colourless/prism	Colourless/prism
Crystal dimensions (mm)	0.42 × 0.32 × 0.26	0.58 × 0.52 × 0.12	0.58 × 0.36 × 0.20	0.32 × 0.18 × 0.12
Crystal system/space group	Monoclinic/$P2_1/c$	Monoclinic/$P2_1/c$	Triclinic/$P\bar{1}$	Monoclinic/$P2_1/c$
a/Å	12.495(2)	15.279(2)	7.036(2)	9.609(2)
b/Å	24.794(2)	9.676(2)	10.921(3)	18.045(4)
c/Å	11.543(2)	19.673(2)	19.338(5)	11.374(2)
α/°			91.18(2)	
β/°	102.46(2)	101.99(2)	95.91(2)	112.29(3)
γ/°			104.96(2)	
Cell volume (Å^3)	3491.8(3)	2845.0(8)	1426.2(7)	1824.8(9)
Formula units	8	8	4	4
D_{calc}/Mg m^{-3}	1.515	1.663	1.658	1.809
μ_{calc}/mm^{-1}	5.859	7.114	7.096	8.231
2θ Scan range (°/ω scan)				
Width (°)	3 to 110/0.86	3 to 110/1.0	3 to 105/1.2	3 to 105/1.2
Reflns. collected/unique reflns.	4646[a]/4387	3733[a]/3574	3591[b]/3257	2222[b]/2073
Observed[c]/parameters	3786/344	3123/290	2814/290	1750/200
Isotropic extinction[d]				
Parameter χ	0.000 98(17)	0.0006(2)	0.0234(14)	0.0062(6)
R, wR[e]	4.64/7.01	5.52/8.13	5.19/7.72	4.40/6.86
Residuals (e Å^{-3})	−0.56/0.79	−0.74/1.32	−0.58/0.48	−0.52/0.75

[a] Collected on a Siemens P4/PC Diffractometer equipped with graphite monochromated CuKα radiation. [b] Collected on a Nicolet P3/F Diffractometer equipped with Ni-filtered CuKα radiation. [c] $F_o \geqslant 4\sigma(F_o)$. [d] $F_c^* = F_c[1 + 0.002\chi F_c^2/\sin(2\theta)]^{-1/4}$. [e] $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR = [\Sigma w||F_o| - F_c|^2/\Sigma w|F_o|^2]^{1/2}$ where $w^{-1} = \sigma^2(F_o) + 0.0008F_o^2$.

Cluj-Napoca, Roumania. High resolution mass-spectrometry determinations of molecular weight were made on a JEOL SX-102 apparatus. The experimental conditions of the X-ray structure determinations for compounds **7**, **10**, **12** and **13** are given in Table 7.

Intensity data were measured in ω scan mode at variable scan speed; two octants for monoclinic crystals (hkl and $hk\bar{l}$) and half of the sphere for the triclinic crystals (h, $\pm k$, $\pm l$). Collected data were corrected for Lp effects and face-indexed numerical absorbtion corrections were applied. The structures were solved by direct methods using the SIR92 program[19] and refined by a full matrix least-squares procedure using the SHELXTL program.[20] In the final cycles of refinement all non-hydrogen atoms were treated anisotropically while hydrogen atoms were included as fixed contributors at idealized positions. Reliability indexes are calculated for observed reflexions. All the investigated crystals were racemates.‡

The synthesis and stereochemistry of the starting compounds **1**–**4**, **9** and **11** have already been reported.[3,4,8]

New compounds 5–8, 10 and 12: general procedure

The spiro 1,3-dioxane (0.1 mol) and dry diethyl ether (100 ml) (or dichloromethane) were introduced into a four-necked flask equipped with a reflux condenser, a mechanical stirring system, a thermometer and a dropping funnel. Bromine (0.2 mol) was added dropwise to this stirred mixture cooled in an ice-bath at 0–5 °C, the ensuing reaction being monitored initially by the fading of the solution colour. After the addition of the bromine, the ice-bath was removed and the stirring was continued for 1 h, the contents in the flask being allowed slowly to reach room temperature (20–25 °C). The mixture was evaporated *in vacuo* and the residue was recrystallized from ethanol. Compounds **8** and **13** were separated by flash chromatography (eluent: hexane–dichloromethane, 4:1). A column (50 cm × 2.4 cm) filled up with silica gel 70–230 mesh was charged with crude product (0.2 g) and then eluted (1.5 l of eluent; 30 ml min^{-1}) 30 ml samples then being collected. Pure dibrominated (0.078 g) and pure tribrominated (0.046 g) compounds were separated; compound **13** R_F 0.71 and compound **8** R_F 0.61.

7,11-Dibromo-3,3,9-trimethyl-1,5-dioxaspiro[5.5]undecane 5. Yield 61%; white crystals, mp 146–147 °C [Found: C, 40.29; H, 5.49; Br, 45.04; M(HRMS), 355.9814. $C_{12}H_{20}Br_2O_2$ requires C, 40.48; H, 5.66; Br, 44.88%; M(HRMS), 355.9810]; $\delta_H(C_6D_6)$ 0.24 [s, 3 H, 3-CH_3(eq.)], 0.60 (d, 3 H, J 5.8, 9-CH_3), 1.28 [s, 3 H, 3-CH_3(ax.)], 1.44–1.90 (overlapped peaks, 5 H, C-8–10), 2.98 (d, 1 H, J 11.5, 4-ax.), 3.11 (dd, 1 H, J 11.5, 2.7, 4-eq.), 3.20 (dd, 1 H, J 11.5, 2.7, 2-eq.), 3.31 (d, 1 H, J 11.5, 2-ax.) and 4.60–4.70 (m, overlapping peaks, 2 H, 7-ax., 11-eq.); $\delta_C(C_6D_6)$ 14.98 (9-CH_3), 16.32 [3-CH_3(eq.)], 17.85 [3-CH_3(ax.)], 23.02 (C-9), 23.90 (C-3), 33.31 (C-8), 36.77 (C-10), 42.15 (C-7), 48.26 (C-11), 63.71 (C-4), 64.86 (C-2) and 90.18 (C-6); $\delta_H(C_6D_5NO_2)$ 4.56 (dd, 1 H, J 12.8, 4.6, 7-ax.) and 5.28 (t from overlapping dd, 1 H, $J = J'$ 3, 11-eq.).

7,11-Dibromo-9-ethyl-3,3-dimethyl-1,5-dioxaspiro[5.5]-undecane 6. Yield 65%; white crystals, mp 116–117 °C [Found: C, 41.96; H, 5.88; Br, 43.33; M(HRMS), 369.9971. $C_{13}H_{22}Br_2O_2$ requires C, 42.19; H, 5.99; Br, 43.18%; M(HRMS), 369.9966]; $\delta_H(C_6D_6)$ 0.28 [s, 3 H, 3-CH_3(eq.)], 0.67 (t, 3 H, J 7.3, 9-CH_2CH_3), 1.00 [two overlapping ddq, 2 H, 9-$CH(H')CH_3$] 1.29 [s, 3 H, 3-CH_3(ax.)], 1.40–2.05 (overlapping peaks, 5 H, C-8–10), 3.05 (d, 1 H, J 11.3, 4-ax.), 3.15 (dd, 1 H, J 1.3, 2.6, 4-eq.), 3.22 (dd, 1 H, J 11.4, 2.6, 2-eq.), 3.36 (d, 1 H, J 11.4, 2-ax.), 4.66 (dd, 1 H, J 12.5, 4.8, 7-ax.) and 4.73 (t from overlapping dd, 1 H, $J = J'$ 3.3, 11-eq.); $\delta_C(C_6D_6)$ 11.28 (9-CH_2CH_3), 21.78 [3-CH_3(eq.)], 23.33 [3-CH_3(ax.)], 28.25 (9-CH_2CH_3), 29.43 (C-3), 35.08 (C-8), 36.82 (C-10), 40.10 (C-9), 47.78 (C-7), 54.06 (C-11), 69.33 (C-4), 70.43 (C-2) and 95.93 (C-6).

7,11-Dibromo-9-*tert*-butyl-3,3-dimethyl-1,5-dioxaspiro-[5.5]undecane 7. Yield 68%; white crystals, mp 143–144 °C [Found: C, 46.49; H, 6.71; Br, 38.95; M(HRMS), 397.0193. $C_{16}H_{28}Br_2O_2$ requires C, 46.62; H, 6.85; Br, 38.77% M(HRMS), 397.0201]; $\delta_H(C_6D_6)$ 0.25 [s, 3 H, 3-CH_3(eq.)], 0.68 [s, 9 H, 9-C(CH_3)$_3$], 1.29 [s, 3 H, 3-CH_3(ax.)], 1.50–2.15 (overlapping peaks, 5 H, C-8–10), 3.04 (d, 1 H, J 11.4, 4-ax.), 3.12 (dd, 1 H, J 11.4, 2.6, 4-eq.), 3.22 (dd, 1 H, J 11.6, 2.6, 2-eq.), 3.37 (d, 1 H, J 11.6, 2-ax.), 4.72 (dd, 1 H, J 12.5, 4.9, 7-ax.) and 4.78 (t from overlapping dd, 1 H, $J = J'$ 3.2, 11-eq.); $\delta_C(C_6D_6)$ 15.92 [3-CH_3(eq.)], 17.54 [3-CH_3(ax.)], 22.07 [9-C(CH_3)$_3$], 23.92 (C-3), 25.96 [9-C(CH_3)$_3$], 26.62 (C-8), 30.13 (C-10), 37.82 (C-9),

‡ Full crystallographic results for the compounds studied have been deposited with the Cambridge Crystallographic Data Centre. They are available on request when a full bibliographic reference should be given together with the reference no. CCDC 207/80. For details, see Instructions for Authors (1997), *J. Chem. Soc., Perkin Trans. 1*, 1997, Issue 1.

42.86 (C-7), 48.14 (C-11), 63.84 (C-4), 64.93 (C-2) and 90.16 (C-6).

7,11-Dibromo-3,3-dimethyl-9-phenyl-1,5-dioxaspiro[5.5]-undecane 8. Yield 48%; white crystals, mp 138–139 °C [Found: C, 48.97; H, 5.39; Br, 38.31; M(HRMS), 416.9890. $C_{17}H_{22}Br_2O_2$ requires C, 48.83; H, 5.30; Br, 38.22%; *M*(HRMS), 416.9888]; $\delta_H(C_6D_6)$ 0.23 [s, 3 H, 3-CH_3(eq.)], 1.30 [s, 3 H, 3-CH_3(ax.)], 2.08–2.40 (overlapping peaks, 4 H, C-8–10), 3.25 [tt, 1 H, *J* 11.8, 3.8, 8-H(ax.)], 3.42 [dd, 1 H, *J* 11.7, 2.6, 4-H(eq.)], 3.49 [dd, 1 H, *J* 11.8, 2.6, 2-H(eq.)], 3.60 [d, 1 H, *J* 11.7, 4-H(ax.)], 3.63 [d, 1 H, *J* 11.8, 2-H(ax.)], 4.63 (dd, 1 H, *J* 12.2, 4.9, 7-ax.), 5.15 [t (overlapping dd), 1 H, $J = J'$ 3.2, 11-eq.], 7.12–7.25 (overlapping peaks, 5 H, 9-C_6H_5); $\delta_C(C_6D_6)$ 21.73 [3-CH_3(eq.)], 23.30 [3-CH_3(ax.)], 29.43 (C-3), 38.32 (C-8), 39.79 (C-9), 41.07 (C-10), 47.69 (C-7), 53.53 (C-11), 69.31 (C-4), 70.49 (C-2), 95.54 (C-6), 126.39, 127.23, 128.30 (tertiary aromatic C) and 143.64 (quaternary aromatic C).

7,11-Dibromo-3,3,8-trimethyl-1,5-dioxaspiro[5.5]undecane 10. Yield 70%; white crystals, mp 110–111 °C [Found: C, 40.57; H, 5.79; Br, 44.71; M(HRMS), 355.9807. $C_{12}H_{20}Br_2O_2$, requires C, 40.48, H, 5.66; Br, 44.88%; *M*(HRMS), 355.9810]; $\delta_H(C_6D_6)$ 0.26 [s, 3 H, 3-CH_3(eq.)], 0.83 (d, 3 H, *J* 6.6, 8-C*H*$_3$), 0.95–1.00 (m, 1 H, 9-ax.) 1.29 [s, 3 H, 3-CH_3(ax.)], 1.25–1.30 (m, 1 H, 9-eq.) 1.66 (m, 1 H, 8-ax.), 1.90 (m, 1 H, 10-eq.), 2.15 (ddd, 1 H, *J* 4.1, 13.2, 13.0, 10-ax.), 3.00 (d, 1 H, *J* 11.6, 4-ax.), 3.12 (dd, 1 H, *J* 11.6, 2.6, 4-eq.), 3.21 (dd, 1 H, *J* 11.6, 2.6, 2-eq.), 3.33 (d, 1 H, *J* 11.6, 2-ax.), 4.66 (dd, 1 H, *J* 12.7, 4.7, 11-ax.) and 4.69 (t from overlapping dd, 1 H, *J* 3.1, 2.9, 7-eq.); $\delta_C(C_6D_6)$ 20.61 (8-CH_3), 21.80 [3-CH_3(eq.)], 23.37 [3-CH_3(ax.)], 29.41 (C-3), 29.70 (C-9), 33.04 (C-8), 33.57 (C-10), 54.00 (C-11), 57.50 (C-7), 69.37 (C-2), 70.43 (C-4) and 96.37 (C-6).

7,11-Dibromo-3,3,7-trimethyl-1,5-dioxaspiro[5.5]undecane 12. Yield 59%; white crystals, mp 92–93 °C [Found: C, 40.65; H, 5.79; Br, 45.03; M(HRMS), 355.9802. $C_{12}H_{20}Br_2O_2$ requires C, 40.48; H, 5.66; Br, 44.88%; *M*(HRMS), 355.9810]; $\delta_H(C_6D_6)$ 0.30 [s, 3 H, 3-CH_3(eq.)], 1.12 (m, 1 H, 9-ax.) 1.29 [s, 3 H, 3-CH_3(ax.)], 1.80–2.05 (overlapping peaks, 4 H, 8-eq., 9-eq., 10-ax., 10-eq.) 2.29 (s, 3 H, 7-CH_3), 2.40–2.45 (m, 1 H, 8-ax.), 3.18 (dd, 1 H, *J* 11.3, 2.3, 4-eq.), 3.25 (dd, 1 H, *J* 11.5, 2.3, 2-eq.), 3.28 (d, 1 H, *J* 11.3, 4-ax.), 3.60 (d, 1 H, *J* 11.5, 2-ax.) and 4.81 ppm (t from overlapping dd, 1 H, $J = J'$ 4, 11-eq.); $\delta_C(C_6D_6)$ 20.49 (C-9), 22.12 [3-CH_3(eq.)], 23.91 [3-CH_3(ax.)], 29.14 (C-3), 29.82 (C-8), 32.64 (C-10), 41.60 (C-11), 46.77 (7-CH_3), 69.74 (C-4), 71.26 (C-2), 73.51 (C-7) and 96.43 (C-6).

7,7,11-Tribromo-3,3-dimethyl-9-phenyl-1,5-dioxaspiro[5.5]-undecane 13. Yield 11%; white crystals, mp 147–148 °C [Found: C, 41.25; H, 4.40; Br 48.07; M(HRMS), 493.9098. $C_{17}H_{21}Br_3O_2$ requires C, 41.08; H, 4.26; Br, 48.23%; *M*(HRMS), 493.9091]; $\delta_H(C_6D_6$–$CDCl_3$, 1:1) 0.38 [s, 3 H, 3-CH_3(eq.)], 1.28 [s, 3 H, 3-CH_3(ax.)], 2.05–2.25 (overlapping peaks, 2 H, C-9,10), 2.82–3.05 (m, 2 H, C-8,10), 3.17 [d, 1 H, *J* 11.7, 4-H(ax.)] 3.33 [dd, 1 H, *J* 11.7, 2.3, 4-H(eq.)], 3.40 [dd, 1 H, *J* 11.7, 2.3, 2-H(eq.)], 3.53 [d, 1 H, *J* 11.7, 2-H(ax.)], 3.67 [tt, 1 H, *J* 11.8, 4.7, 8-H(ax.)], 4.80 [t (overlapping dd), 1 H, *J* 4.1, *J*′ 2.6, 11-H(eq.)] and 7.12–7.25 (overlapping peaks, 5 H, 9-C_6H_5); $\delta_C(C_6D_6)$ 21.77 [3-CH_3(eq.)], 23.67 [3-CH_3 (ax.)], 30.16 (C-3), 37.99 (C-9), 39.25 (C-10), 42.12 (C-8), 53.81 (C-11), 69.92 (C-4), 70.58 (C-7), 71.83 (C-2), 94.99 (C-6), 127.09, 127.37, 128.96 (tertiary aromatic C) and 142.69 (quaternary aromatic C).

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