Considerations on the stereoselective synthesis of dibrominated spiro-1,3-dioxanes. Synthesis and stereochemistry of monobrominated precursors

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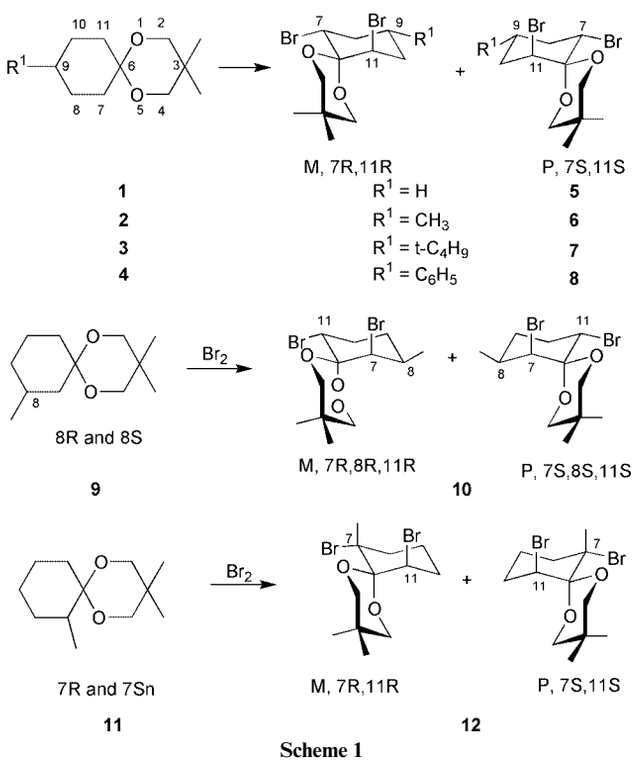
The synthesis and stereochemistry of monobrominated spiro-1,3-dioxanes, involved as precursors in the diastereoselective synthesis of dibrominated 1,5-dioxaspiro[5.5]undecane derivatives bearing substituents in positions 7, 8 or 9, are reported. The structural aspects are investigated by means of NMR methods and by the molecular structure of two compounds established by single-crystal X-ray diffractometry. The data are used to determine the routes followed by the bromination reactions of spiro-1,3-dioxanes and the asymmetric induction involved in the stereoselectivity of the process.

Introduction

Studies[1–3] on the synthesis of dibrominated spiranes exhibiting the 1,5-dioxaspiro[5.5]undecane skeleton revealed the high regio- and diastereoselectivity of the process. The reaction performed on spiro-1,3-dioxanes **1**–**4**, **9** and **11** under similar conditions to those used in the reaction with bromine of some 1,3-dioxolane derivatives[4–9] gave a single diastereoisomer (showing the bromine atoms *trans*) of the 7,11-dibrominated derivatives **5**–**8**, **10** and **12**[2] (Scheme 1).



Scheme 1

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It has been considered of interest to obtain the monobrominated precursors of these compounds, to determine their structure and to establish the mechanism of the diastereoselectivity for the preparation of dibromospiro-1,3-dioxanes.

Results and discussion

New monobrominated spiro-1,3-dioxanes (Scheme 2; compounds **13**–**15**, **17**) were obtained by the bromination reaction (ratio spirane : bromine = 1 : 1) of 9-, 8- or 7-substituted 1,5-dioxaspiro[5.5]undecane derivatives (**4**, **9**, **11** and **16**). The pure monobrominated compounds were separated from the crude product (containing also dibrominated and starting spiranes) by preparative chromatographic methods or by selective crystallization.

Bromination of 9-substituted spiro[5.5]undecane derivatives

The investigations were carried out with compound **4** ($R^1 = C_6H_5$). Two monobrominated isomers (Scheme 2) showing the bromine atom at position 7 in equatorial (*cis*) or axial orientation (*trans*) were identified in the crude product (ratio *trans* : *cis* = 64 : 36). The major isomer exhibited the bromine atom in the axial orientation despite the positive *A*-value for the bromine atom on a cyclohexane ring ($A_{Br} = 0.48$–0.64).[10] The experimental ratio of isomers was close to that determined (axial : equatorial = 60 : 40) considering the calculated difference of energy between the axial and equatorial brominated isomers ($\Delta H^\circ = 0.91$ kcal mol^{-1},‡ PC Spartan Plus program, PM3 level). The mechanism of the reaction involves the participation of HBr and the formation of cation **I** and enol ether **II** (Scheme 3), which in reaction with bromine gave the *cis* and *trans* isomers of **13**. The formation of the enol ether **III**, involving the carbon atom which is bearing the bromine atom, determined the equilibrium of *cis* and *trans* isomers. It is considered that the reaction proceeds under thermodynamic control and that the ratio of isomers is given by the difference between their energies.

‡ 1 cal = 4.184 J.

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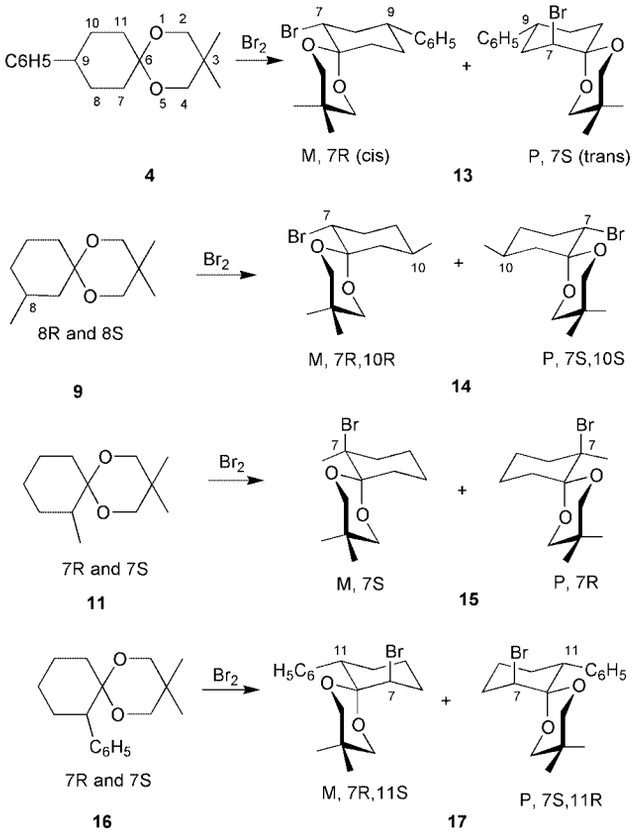
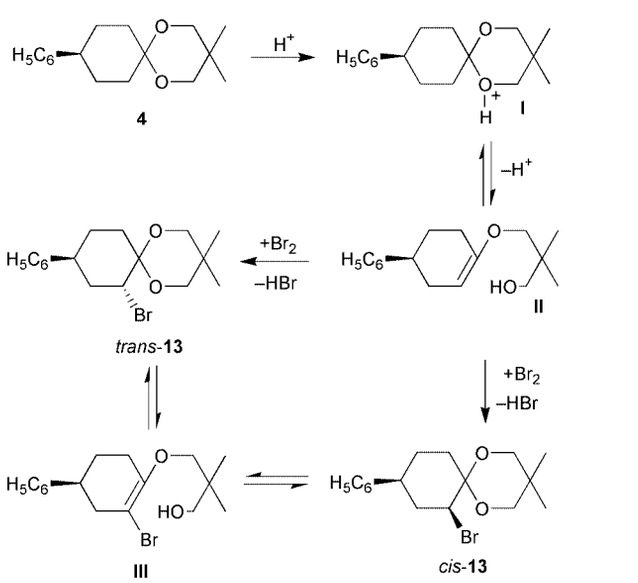
Table 1 NMR data (δ, C_6D_6) of compounds **13**–**15** and **17**

	^{1}H							^{13}C		
Compound	2-e	4-e	$\Delta\delta$	2-a	4-a	$\Delta\delta$	3-Me(a)	3-Me(b)	2	4	$\Delta\delta$
13-*cis*	3.26	3.29	0.03	3.41	3.24	0.17	1.38	0.33	69.93	69.72	0.21
13-*trans*	3.23	3.15	0.08	3.34	3.11	0.23	0.84	0.53	70.04	69.12	0.92
14	3.24	3.24	0.00	3.44	3.27	0.17	1.37	0.33	70.05	70.02	0.03
15	3.21	3.13	0.08	3.43	3.24	0.19	1.14	0.31	70.07	69.59	0.48
17	2.98	2.97	0.01	3.32	3.01	0.31	0.44	0.14	70.04	69.92	0.12



Scheme 2



Scheme 3

The two isomers were separated by preparative TLC and their structures deduced from NMR investigations and by the molecular structure of the *cis*-isomer established in a single crystal by X-ray diffractometry. The ORTEP diagram (Fig. 1) shows the chair conformation of both six-membered rings. The selected bond lengths, bond angles and torsion angles are in the usual range.[11,12] The phenyl group exhibits a bisectional orientation, the angle between the plane of the aromatic ring ($C^{12}C^{13}C^{14}C^{15}C^{16}C^{17}$) and the plane described by the lengths of the spiro carbon atom with the two oxygen atoms of the heterocycle ($O^1C^6O^5$) being close to 0° (3.7°). Both isomers exhibit anancomeric[13] structures and show in their NMR spectra different signals for the equatorial and axial protons of the rings and for the protons and carbon atoms of the axial and equatorial similar groups located in the heterocycle (Table 1). The axial or equatorial position of the bromine atoms was determined using the values of the coupling constants of the protons at position 7. In the *cis*-isomer this proton is axial and it exhibits a well separated doublet of doublets ($\delta = 3.94$; $J = 12.7$, $J' = 4.2$ Hz; a large coupling constant between vicinal axial protons and a small one for the vicinal axial–equatorial coupling constant), whereas in the *trans* isomer this proton is equatorial and its signal is an overlapped doublet of doublets ($\delta = 4.64$) with two close and small coupling constants ($J = 5.4$, $J' = 3.0$ Hz; characteristic values for the coupling between vicinal equatorial–axial and equatorial–equatorial protons).

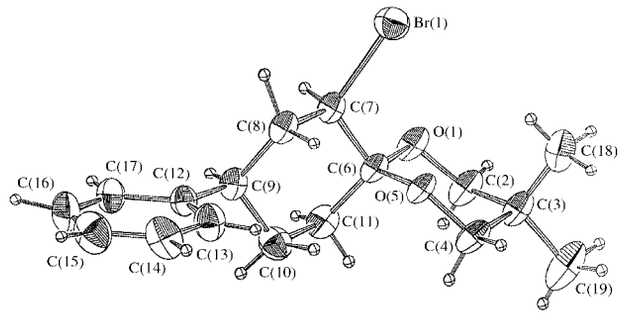


Fig. 1 ORTEP diagram of *cis*-isomer of compound **13**.

The reaction with bromine of both isomers of **13** gives compound **8** (7*R*,11*R*,7*S*,11*S* isomer).

Bromination of 8-substituted spiro[5.5]undecane derivatives

The bromination reaction of racemic 3,3,8-trimethyl-1,5-dioxaspiro[5.5]undecane (ratio spirane : bromine = 1 : 1) led to the single monobrominated derivative **14** (TLC and NMR analysis) displaying the bromine atom on the opposite side to the methyl substituent of the cyclohexane ring (positions 7 and 10). The high regioselectivity of the process is correlated with a high stereoselectivity, only the *trans* isomer being obtained. The structure of this compound has been deduced from NMR investigations.

Compound **14** exhibits an anancomeric structure. The 1,3-dioxane ring is rendered anancomeric by the equatorial bromine atom at position 7. The conformational equilibrium involving the flipping of the 1,3-dioxane ring is shifted towards the conformer exhibiting the heterocycle on the opposite side to the equatorial bromine atom (*e.g.*, for the 7*R*,10*R* isomer the spiro skeleton with ***M*** configuration is preferred, Scheme 4). The NMR spectrum of compound **14** exhibited different

signals for the equatorial and axial protons of the diastereotopic positions 2 and 4, as well as for the protons and carbon atoms of the axial and equatorial methyl groups at position 3 (Table 1). The equatorial position of the bromine atom was deduced from the values of the coupling constants of the proton in the same position (C-7). This proton (with axial orientation) exhibits a doublet of doublets ($\delta = 3.88$; $J = 12.8$, $J' = 4.5$ Hz).

The mechanism involves the obtaining of enol ethers **V** and **VI** (Scheme 5). The calculations (PM3) show a higher stability (≈3.6 kcal mol^{-1}) for enol ether **VI**. The reaction of this enol ether with bromine can give the *cis* and *trans* isomers of **14**. These isomers are in equilibrium *via* enol ether **VII**. It is believed that the reaction proceeds under thermodynamic control and that the obtainment of the *trans*-isomer is due to the higher stability of this compound over its *cis*-isomer. The reaction of the *trans*-**14** with bromine led to the formation of the dibrominated spiro-1,3-dioxane **10** (7*R*,8*R*,11*R*, 7*S*,8*S*,11*S* isomer).

Bromination of 7-substituted spiro[5.5]undecane derivatives

The reaction of **11** with bromine (1 : 1) gave the isomer of **15** exhibiting the methyl group in an equatorial orientation. This structure of the compound has been observed both in the solid state and in solution. The ORTEP diagram (Fig. 2) shows chair conformations for both rings, and bond and/or angle measurements revealed modifications of bond angles and lengths at the spiro carbon atom and to the disubstituted carbon atom of the cyclohexane ring. The NMR investigations showed the anancomeric behaviour of both rings (Table 1).

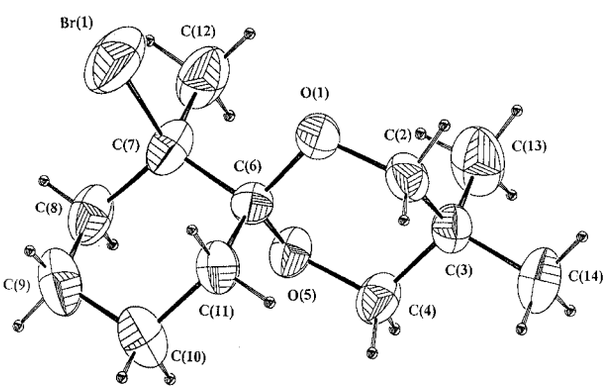
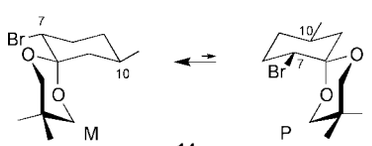


Fig. 2 ORTEP diagram of compound **15**.



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Scheme 4

The reaction of **16** with bromine (1 : 1) proceeded to the *trans* isomer of compound **17** (Scheme 2) as shown by NMR data. The axial proton at position 11 exhibited a well separated doublet of doublets ($\delta = 3.54$; $J = 13.1$, $J' = 3.9$ Hz), whereas the doublet of doublets ($\delta = 4.83$) corresponding to the equatorial proton of position 7 is overlapped into a triplet (two small and close coupling constants; $J = J' = 3.2$ Hz). Both rings are anancomeric and the NMR spectra show different signals for similar axial and equatorial groups (Table 1).

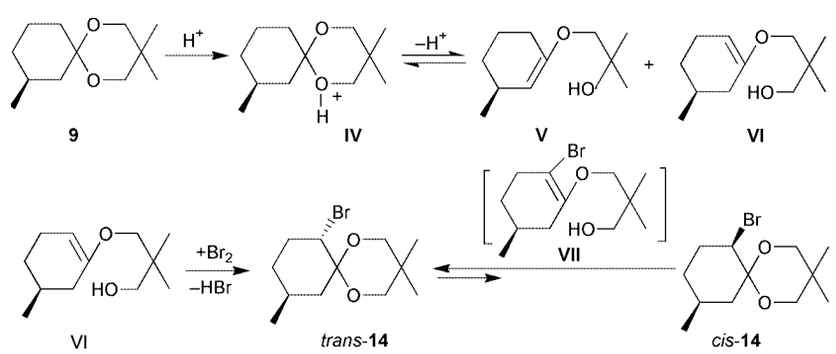
The reaction involves the formation of oxonium ion **VIII** and enol ethers **IX** and **X** (Scheme 6). Despite the supposed higher stability of enol ether **IX** for both substituents (Me and Ph) the regio- and stereoselectivity of the processes are very different. In the reaction of compound **11** the bromine atom is connected to the tertiary carbon atom, suggesting the participation, in the second step of the reaction, of the more stable enol ether **IX**. The considerably more stable conformation showing the methyl group with higher *A*-value (1.74 kcal mol^{-1}) in the equatorial position is adopted. Surprisingly, the reaction of **16** does not produce the benzylic brominated derivative, and the 7-bromo, 11-phenyl derivative **17** was instead isolated. In this case the participation in the second step of the process of enol ether **X** has been taken into account. The highly stereoselective formation of *trans*-isomer (equatorial phenyl group and axial bromine atom) is due to the high energy of the *cis*-isomer (the spirane exhibiting bulky substituents at both positions 7 and 11 in equatorial positions is highly unstable due to the interactions of the equatorial substituent with the heterocycle as shown for similar conformations in Scheme 4). The reaction of **15** with bromine proceeded with formation of dibrominated spirane **12**, whereas the reaction of **17** with bromine does not lead to the corresponding 7,11-dibrominated derivative. Moreover, all attempts to obtain the dibrominated spirane in the reaction of **16** with bromine (ratio 1 : 2) under all usual conditions (CCl_4, diethyl ether, CH_2Cl_2; with or without $CaCO_3$) failed.

Conclusions

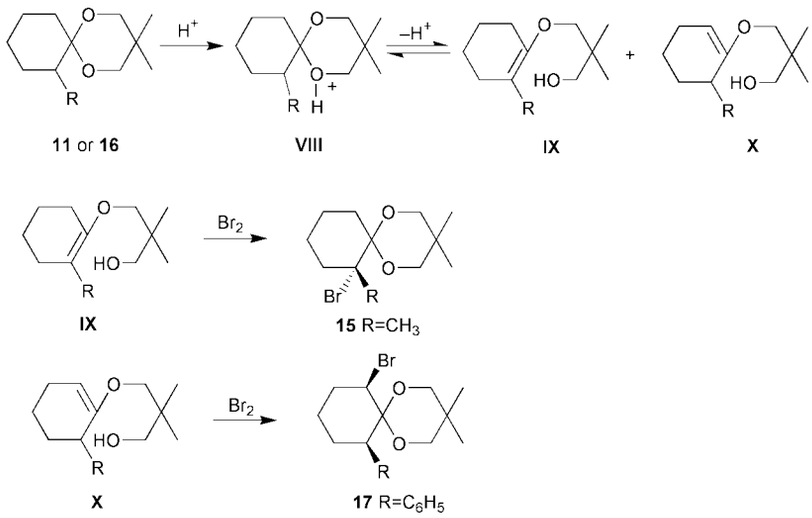
The structure of the monobrominated derivatives obtained in the reaction of 7-, 8- and 9-substituted 1,5-dioxaspiro[5.5]-undecane with bromine (1 : 1) has been established by NMR investigations and by the molecular structures observed by single-crystal X-ray diffractometry. The reaction of 7- and 8-substituted spiranes proved to be of high regio- and diastereoselectivity. The reaction of the separated monobrominated compounds with bromine led to the *trans*-isomer of 7,11-dibrominated spiro derivatives, confirming the proposed pathways of the reaction.

Experimental

^{1}H and ^{13}C spectra were recorded at room temperature using C_6D_6 as solvent in 5 mm tubes on a Bruker AM 400 (Varian Gemini 300) NMR spectrometer equipped with a dual ^{13}C–^{1}H (multinuclear) head operating at 400 (300) MHz for protons and 100 (75) MHz for carbon atoms. *J*-Values are in Hz. Mps



Scheme 5



Scheme 6

were measured with an Electrothermal melting-point apparatus and are uncorrected. The experimental conditions for the X-ray structure determinations of compounds **15** and *cis*-**13** and details of the refinements are given in Table 2. The data for compound **15** were collected on a CAD4 Nonius automatic diffractometer equipped with graphite-monochromatized MoKα radiation. The cell parameters are obtained by fitting a set of 25 high-θ reflections. After Lorenz and polarization corrections[14] and analytical absorption correction the structure was solved with SIR-97.[15] After anisotropic refinement, all the hydrogen atoms were found with a Fourier Difference; Calc. $w = 1/[\sigma^2(F_o^2) + (0.0491P)^2 + 1.0094P]$ where $P = (F_o^2 + 2F_c^2)/3$.

The data for compound **13** (*cis*-isomer) were collected on a CAD4 Enraf-Nonius automatic diffractometer with graphite-monochromatized MoKα radiation. The cell parameters were obtained by fitting a set of 25 high-θ reflections. After Lorenz and polarization correction (empirical absorption correction: 0.753–1.372) the structure was solved with SIR-92 which revealed the non-hydrogen atoms of the structure.[16] The whole structure was refined by full-matrix least-square techniques ($w = 1/\sigma(F_o^2) = [\sigma^2(I) + (0.04F_o^2)^2]^{-1/2}$).§

Table 2 Parameters of the crystallographic determinations for compounds **15** and *cis*-**13**

Parameter	**15**	*cis*-**13**
Chemical formula	$C_{12}H_{21}BrO_2$	$C_{17}H_{23}BrO_2$
Formula mass	277.20	339.28
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
μ(MoKα)/cm^{-1}	31.04	25.289
Final R	0.0431	0.042
R_w	0.1037	0.039
Unit-cell dimensions		
a/Å	12.232(2)	12.698(2)
b/Å	9.1020(10)	9.275(4)
c/Å	12.322(9)	14.006(2)
α/°	90	90
β/°	106.32(3)	102.88(1)
γ/°	90	90
Unit-cell volume/Å^3	1316.6(10)	1608(1)
Temperature of data collection/K	293	294
Z	4	4
Reflections measured	2862	3582
Reflections observed	2742	2296
R(int)	0.0209	0.017

New compounds 13–15 and 17; general procedure

The spiro-1,3-dioxane (0.1 mol) and dry dichloromethane (or diethyl ether) (100 ml) were introduced into a three-necked flask equipped with a reflux condenser, a thermometer and a dropping funnel. Bromine (0.1 mol) was added dropwise, under magnetic stirring, to this mixture cooled in an ice-bath at 0–5 °C, the ensuing reaction being monitored initially by the fading of the solution's color. 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 crystallized from ethanol. It was observed that compound **15** decomposes when heated above 45 °C. Compounds *cis*-**13** and *trans*-**13** were separated by preparative TLC (developing system: heptane–chloroform = 2 : 1).

7-Bromo-3,3-dimethyl-9-phenyl-1,5-dioxaspiro[5.5]undecane 13. Yield 59%; white crystals, mp 80–85 °C. Separated into *cis* and *trans* isomers by PLC (Merck 2 mm plates).

7-Bromo-3,3-dimethyl-9-phenyl-1,5-dioxaspiro[5.5]undecane *cis*-13. Ratio 36%, white crystals, mp 84–85 °C; R_f 0.24 (Found: C, 60.25; H, 6.96; Br, 23.43. $C_{17}H_{23}BrO_2$ requires C, 60.18; H, 6.84; Br, 23.55%); $\delta_H(C_6D_6)$ 0.33 [3H, s, 3-CH_3(eq.)], 1.38 [3 H, s, 3-CH_3(ax.)], 0.89–2.28 (5H, overlapping peaks, 8-H^{eq}, 10- and 11-H_2), 2.44–2.58 (2H, overlapping peaks, 8-H^{ax}, 9-H^{ax}), 3.24 (1H, d, J 11.7, 4-H^{ax}), 3.26 (1H, dd, J 11.4 and 2.4, 2-H^{eq}), 3.29 (1H, dd, J 11.7 and 2.4, 4-H^{eq}), 3.41 (1H, d, J 11.4, 2-H^{ax}), 3.94 (1H, dd, J 12.7 and 4.2, 7-H^{ax}), 6.87–7.22 (5H, overlapping peaks, 9-C_6H_5); $\delta_C(C_6D_6)$ 21.55 [3-CH_3(eq.)], 23.12 [3-CH_3-(ax.)], 26.59 (C-10), 29.44 (C-8), 29.65 (C-3), 41.50 (C-11), 45.15 (C-9), 57.42 (C-7), 69.72 (C-4), 69.93 (C-2), 126.36, 126.75, 128.42 (tertiary aromatic C), 144.7 (quaternary aromatic C).

7-Bromo-3,3-dimethyl-9-phenyl-1,5-dioxaspiro[5.5]undecane *trans*-13. Ratio 64%; white crystals, mp 87–88 °C; R_f 0.32 (Found: C, 60.29; H, 6.77; Br, 23.59%); $\delta_H(C_6D_6)$ 0.53 [3H, s, 3-CH_3(eq.)], 0.84 [3H, s, 3-CH_3(ax.)], 1.61 (1H, m, 10-H^{eq}), 1.86 (1H, dddd, $J = J' = J'' = 12.95$, $J''' = 3.76$, 10-H^{ax}), 1.97 (1H, ddd, J 13.75, 6.0 and 3.3, 11-H^{eq}), 2.1 (1H, m, 8-H^{eq}), 2.2–2.31 (3H, overlapping peaks, 8-H^{ax}, 9-H^{ax}, 11-H^{ax}), 3.11 (1H, d, J 11.4, 4-H^{ax}), 3.15 (1H, dd, J 11.4 and 1.4, 4-H^{eq}), 3.23 (1H, dd, J 11.5 and 1.4, 2-H^{eq}), 3.34 (1H, d, J 11.5, 2-H^{ax}), 4.64 (1H, dd, J 5.4 and 3.0, 7-H^{eq}), 7.0–7.2 (5H, m, overlapping peaks, 9-C_6H_5); $\delta_C(C_6D_6)$ 21.9 [3-CH_3(eq.)], 22.36 [3-CH_3(ax.)], 29.35 (C-10), 29.79 (C-8), 37.99 (C-9), 38.85 (C-11), 50.89 (C-7),

§ CCDC reference number 207/480. See http://www.rsc.org/suppdata/p1/b0/b004282j/ for crystallographic files in .cif format.

69.12 (C-4), 70.04 (C-2), 96.52 (C-6), 126.25, 128.45 (tertiary aromatic C), 145.38 (quaternary aromatic C).

7-Bromo-3,3,10-trimethyl-1,5-dioxaspiro[5.5]undecane 14. Yield 63%; white crystals, mp 103–104 °C (Found: C, 52.13; H, 7.78; Br, 28.71. $C_{12}H_{21}BrO_2$ requires C, 51.99; H, 7.64; Br, 28.82%); $\delta_H(C_6D_6)$ 0.33 [3 H, s, 3-CH_3(eq.)], 0.50–0.52 (3 H, overlapping peaks, 9-H^{eq}, 10-H^{ax}, 11-H^{ax}), 0.66 [3 H, d, *J* 6.6, 10-CH_3(eq.)], 1.27 (1 H, m, 9-H^{ax}), 1.37 [3 H, s, 3-CH_3(ax.)], 2.00 (1 H, dd, *J* 11.6 and 3.3, 8-H^{eq}), 2.25 (1H, dd, *J* 12.9 and 4.06, 8-H^{ax}), 2.48 (1H, dt, *J* 13.7 and 3.0, 11-H^{eq}), 3.24 (2 H, d, *J* 11.04, 2-H^{eq}, 4-H^{eq}), 3.27 (1H, overlapping peaks, 4-H^{ax}), 3.44 (2 H, d, *J* 10.98, 2-H^{ax}), 3.88 (1H, dd, *J* 12.8 and 4.5, 7-H^{ax}); $\delta_C(C_6D_6)$ 21.64 [3-CH_3(eq.)], 21.95 [3-CH_3(ax.)], 23.49 (10-CH_3), 28.39 (C-9), 29.13 (C-3), 30.01 (C-11), 34.30 (C-8), 35.69 (C-10), 58.49 (C-7), 70.02 (C-2), 70.05 (C-4), 96.51 (C-6).

7-Bromo-3,3,7-trimethyl-1,5-dioxaspiro[5.5]undecane 15. Yield 55%; white crystals, mp 56–58 °C (Found: C, 51.87; H, 7.77; Br, 28.69%); $\delta_H(C_6D_6)$ 0.31 [3 H, s, 3-CH_3(eq.)], 1.14 [3 H, s, 3-CH_3(ax.)], 1.22–1.43 (3H, overlapping peaks, 9-H^{eq}, 10-H_2), 1.83–2.04 (5H, overlapping peaks, 8-H_2, 9-H^{ax}, 11-H_2), 2.08 (3 H, s, 7-CH_3), 3.13 (1 H, dd, *J* 11.2 and 2.6, 4-H^{eq}), 3.21 (1 H, dd, *J* 11.3 and 2.7, 2-H^{eq}), 3.24 (1 H, d, *J* 11.4, 4-H^{ax}), 3.43 (1 H, d, *J* 11.4, 2-H^{ax}); $\delta_C(C_6D_6)$ 21.38 [3-CH_3(eq.)], 21.66 (C-10), 22.33 (C-9), 22.78 (C-8), 23.07 [3-CH_3(ax.)], 27.96 (7-CH_3), 29.23 (C-3), 40.09 (C-11), 69.59 (C-4), 70.07 (C-2), 72.96 (C-7), 98.58 (C-6).

7-Bromo-3,3-dimethyl-11-phenyl-1,5-dioxaspiro[5.5]undecane 17. Yield 62%; white crystals, mp 94–95 °C (Found: C, 60.30; H, 6.77; Br, 23.67. $C_{17}H_{23}BrO_2$ requires C, 60.18; H, 6.84; Br, 23.55%); $\delta_H(C_6D_6)$ 0.14 [3H, s, 3-CH_3(eq.)], 0.44 [3H, s, 3-CH_3(ax.)], 0.92 (1H, m, 9-H^{eq}), 1.26–2.2 (5H, overlapping peaks, 8-H_2 9-H^{ax}, 10-H_2), 2.96–3.02 (3H, overlapping peaks, *J* 11.5 and 4.6, 4-H_2, 2-H^{eq}), 3.32 (1H, d, *J* 11.8, 2-H^{ax}), 3.54 (1H, dd, *J* 13.1 and 3.9, 11-H^{ax}), 4.83 (1H, t from overlapping dd, $J = J' = 3.2$, 7-H^{eq}), 7.2–7.54 (5H, overlapping peaks, 11-C_6H_5); $\delta_C(C_6D_6)$ 21.89 [3-CH_3(eq.)], 22.35 [3-CH_3(ax.)], 29.35 (C-9), 29.85 (C-10), 34.4 (C-3), 38.00 (C-11), 38.86 (C-8), 50.89 (C-7), 69.92 (C-4), 70.04 (C-2), 97.8 (C-6), 126.78, 127.93 (tertiary aromatic C), 141.5 (quaternary aromatic C).

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