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Synthesis and Stereochemistry of Some New Trispiro-1,3-dioxanes with Axial and Helical Chirality

Ion Grosu[1,*], **Sorin Mager**[1], **Gerard Plé**[2], **Istvan Turos**[1], **Eugen Mesaros**[1], and **Iosefina Schirger**[1]

[1] Babes-Bolyai University, Organic Chemistry Department, RO-3400 Cluj-Napoca, România
[2] Université de Rouen et IRCOF, UPRES-A-6014, Faculté des Sciences de Rouen, F-6821 Mont Saint-Aignan, France

Summary. The stereoisomerism of some trispiro-1,3-dioxanes obtained from substituted cyclohexanones and pentaerithrytol is discussed considering the possible trispiro-6,9-*syn*-9,12-*syn*, trispiro-6,9-*syn*-9,12-*anti*, and trispiro-6,9-*anti*-9,12-*anti* structures of the spiro skeleton and the characteristic axial and helical chirality of spiranes with six-membered rings. The influence of the presence of chiral carbon atoms and of the peculiar conformational behaviour of the molecules on the stereoisomerism of the these compounds is elucidated.

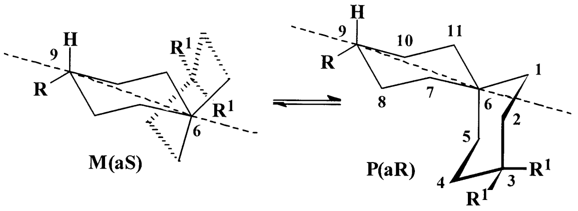
Keywords. Trispiro-1,3-dioxanes; *Syn* and *anti* structures; Conformational analysis; Axial and helical chirality; NMR studies.

Synthese und Stereochemie einiger neuer Trispiro-1,3-dioxane mit axialer und helikaler Chiralität

Zusammenfassung. Die Stereoisomerie einiger aus substituierten Cyclohexanonen und Pentaerythritol hergestellter Trispiro-1,3-dioxane wird im Hinblick auf die möglichen Trispiro-6,9-*syn*-9-12-*syn*-, Trispiro-6,9-*syn*-9,12-*anti*- und Trispiro-6,9-*anti*-9,12-Strukturen des Spiranskeletts und die charakteristische axiale und helikale Chiralität von Spiranen mit sechsgliedrigen Ringen diskutiert. Der Einfluß von chiralen Kohlenstoffatomen und des speziellen konformativen Verhaltens auf die Stereoisomerie dieser Verbindungen wird rationalisiert.

Introduction

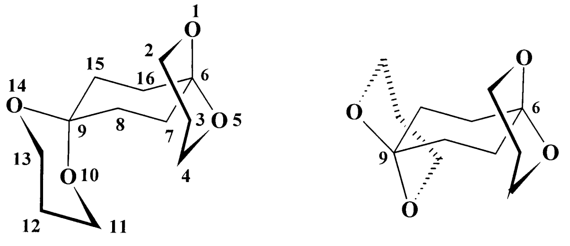
The stereochemistry of some spiro, dispiro, and trispiro-1,3-dioxanes has been previously reported [1–5], and the disymmetry of spiranes with six-membered rings has been explained on the basis of peculiar cases of axial and helical chirality. Spiranes with six-membered rings exhibit helical chirality; the helix with *P* or *M* configuration is repeated after each fourth six-membered ring. These spiro compounds display axial chirality even if different substituents exist only at one of the extremities of the molecule (Scheme 1).



Scheme 1

In spiro[5.5]undecanes (or heterocyclic analogs) with semiflexible structures, the C_6–C_9 axis is a chiral element, the reference groups being H and *R* at C_9 and the whole disubstituted ring at C_9 (in front or behind the chiral axis).

The stereochemistry of some dispiro-1,3-dioxanes [1] was studied considering the possible dispiro-6,9-*syn* and dispiro-6,9-*anti* dispositions of the spiro skeleton (Scheme 2).



6,9-dispiro-*syn*

6,9-dispiro-*anti*

Scheme 2

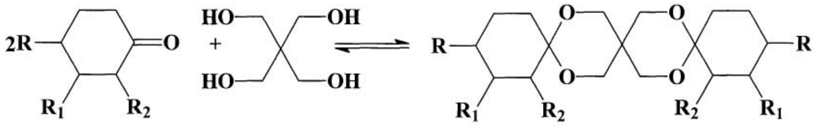
The dispiro-6,9-*syn* structure shows the rings A and C on the same side of the best plan (bisectional plane: $C^6O^1O^5C^9O^{10}O^{14}$) of ring B, whereas the dispiro-6,9-*anti* structure exhibits the rings A and C on opposite sides of this plane.

It was considered to be of interest to study trispiranes with six-membered rings by the investigation of some new compounds (obtained from 2-, 3-, and 4-substituted cyclohexanones) displaying semiflexible or anancomeric structures and to continue with the *syn* and *anti* stereoisomerism of spiro compounds with six-membered rings.

Results and Discussion

New trispiro-1,3-dioxanes have been obtained by the acetalization of some substituted cyclohexanones with pentaerithritol (Scheme 3).

The investigated trispiro skeleton (7,11,18,21-tetraoxatrispiro[5.2.2.5.2.2]henicosane) can display its rings in *syn* or in *anti* position as previously shown for dispiro-1,3-dioxane compounds. According to Ref. [1], three arrangements of the investigated trispiro skeleton are possible: trispiro-6,9-*syn*-9,12-*syn*, trispiro-6,9-*syn*-9,12-*anti*, and trispiro-6,9-*anti*-9,12-*anti* (Scheme 4). The relative dispositions of rings A and C (the bisectional plane of ring B is considered as best plane) are suggested by the orientations of the bonds C^8–O^7 and C^{13}–C^{14}, whereas the



$R = C_2H_5, R_1 = R_2 = H$	**1**
$R = C_6H_5, R_1 = R_2 = H$	**2**
$R = R_2 = H, R_1 = CH_3$	**3**[1]
$R = R_1 = H, R_2 = CH_3$	**4**

[1]The enantiomerically pure ketone (*R* configuration) has been used in the synthesis

Scheme 3

relative dispositions of rings B and D (the bisectional plane of ring C is considered as best plane) are revealed by the orientations of bonds C^1–C^2 and C^{10}–O^{11} (indicated by arrows).

In these arrangements, the helicity of the system is more or less conserved. We propose to take groups of two rings (AB, BC and CD, Scheme 4, Table 1) and to consider the configuration of the helix for each of these groups[1].

Investigations of molecular models revealed that the helix is continued by all rings only in the trispiro 6,9-*syn*-9,12-*syn* disposition of the spirane (Table 1). In the other cases, two groups of rings show one orientation, and the third one exhibits a different configuration of the helix (the disymmetry of the system is conserved). In the unsubstituted trispiro skeleton six arrangements are possible, the conformational equilibria involving all these structures. These structures are pairs of conformational enantiomers.

The 3,15-disubstituted-7,11,18,21-tetraoxatrispiro[5.2.2.5.2.2]henicosane derivatives showing equatorial substituents form six stereoisomers [2, 3] which can be determined in correlation with the *syn* and *anti* dispositions of the rings (Table 1) and with the helical chirality of the spirane and the configurations of the two chiral axes C_3–C_6 and C_{12}–C_{15}.

Compounds **1** and **2** show semiflexible structures (Scheme 4) displaying anancomeric marginal cyclohexane rings (A and D) and a flexible heterocyclic middle part (rings B and C). The flipping of the 1,3-dioxane rings in compounds **1** and **2** equilibrates the possible structures of the diastereoisomers (**I** $\rightleftharpoons$ **II** $\rightleftharpoons$ **III** and **I′** $\rightleftharpoons$ **II′** $\rightleftharpoons$ **III′**) associated with the three chiral elements of the molecules (two axes and one helix, Table 1), affording a unique average structure; transformation of the helix from *M* to *P* configuration. (trispiro-6,9-*syn*-9,12-*syn* structures) however, demands the skeleton of the trispiro compound to be rebuilt. The NMR spectra of these compounds are quite simple showing one set of signals corre-

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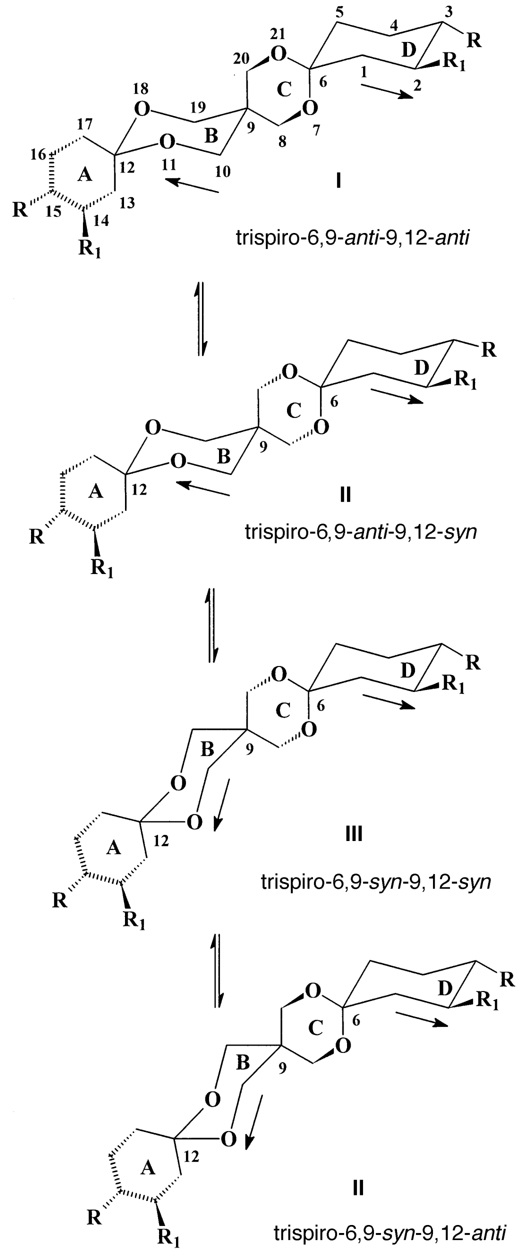
[1] Similar situations have been shown and studied for some [10] helicenes [6] when fragments with different configurations of the helix are connected.



I

trispiro-6,9-*anti*-9,12-*anti*

II

trispiro-6,9-*anti*-9,12-*syn*

III

trispiro-6,9-*syn*-9,12-*syn*

II

trispiro-6,9-*syn*-9,12-*anti*

Scheme 4

sponding to an average structure of the three possible diastereoisomers with unique signals at mean values of the chemical shifts for the axial and equatorial positions of the protons of the heterocycles, but exhibiting different signals for the diastereotopic positions 8 [19] and 10 [20]. Thus, the ^{1}H NMR spectrum of compound **1** exhibits two singlets (Fig. 1a; $\delta_{8(19)} = 3.55$ ppm, $\delta_{10(20)} = 3.63$ ppm) for the protons of the heterocycles, the value of the diastereotopicity ($\Delta\delta = 0.08$ ppm) being in the normal range.

Table 1. Possible structures of the trispiranes in correlation with the dispositions of the six-membered rings and the configurations of chiral elements

	Orientations of the rings	Helicity			Axes[1]		Centres[2]	
		AB	BC	CD	C_6–C_9	C_{12}–C_{15}	C_2	C_{13}
I	6,9-*anti*-9,12-*anti*	*P*	*M*	*P*	*aR*	*aR*	*S*	*S*
I′	6,9-*anti*-9,12-*anti*	*M*	*P*	*M*	*aS*	*aS*	*R*	*R*
II	6,9-*anti*-9,12-*syn*	*M*	*P*	*P*	*aS*	*aR*	*R*	*S*
II′	6,9-*anti*-9,12-*syn*	*P*	*M*	*M*	*aR*	*aS*	*S*	*R*
III	6,9-*syn*-9,12-*syn*	*M*	*M*	*M*	*aS*	*aS*	*R*	*R*
III′	6,9-*syn*-9,12-*syn*	*P*	*P*	*P*	*aR*	*aR*	*S*	*S*

[1] Compounds **1** and **2**; [2]Compound **4**

Similarly to compounds **1** and **2**, the trispirane **3** (obtained from enantiomeric pure ketone) exhibits a semiflexible structure (as do the monospiranes obtained from 3-methyl-cyclohexanone [7, 8]), the heterocyclic middle part being flexible and the marginal cyclohexane rings showing anancomeric structures. The NMR spectra of this compound exhibit unique signals for the axial and equatorial positions of the protons of the 1,3-dioxane rings (mean values of the chemical shifts). Despite of the flipping of the rings, however, the magnetic environments are different for all eight protons of the heterocycles (they are rendered diastereotopic by the chirality of the molecule), and different signals are recorded for all of them. Four AB systems (Fig. 1b; peaks 1, 2, 3, 4 (*m*), 3, 4, 6, 9 (*n*), 4, 5, 7, 10, (*o*), and 8, 11, 12, 13 (*p*)) associated with the protons of positions 8, 10, 19, and 20 could be identified in the ^{1}H NMR spectrum of compound **3** (*m*: $\delta = 3.516$, $\delta' = 3.564$ ppm; *n*: $\delta = 3.564$, $\delta' = 3.645$ ppm; $\delta = 3.596$, $\delta' = 3.658$ ppm; *p*: $\delta = 3.667$, $\delta' = 3.717$ ppm). The differences of the chemical shifts measured for geminal protons ($\Delta\delta = 0.048$–0.081 ppm) are considerably smaller than those between axial and equatorial protons for anancomeric 1,3-dioxane derivatives of pentaerithrytol ($\Delta\delta = 0.30$–1.50 ppm) [4, 9].

Compound **4** exhibits an anancomeric structure, all rings of the spiro compound being rigid. As has been observed with some monospiro compounds obtained from 2-substituted cyclohexanones, the equatorial substituent located close to the spiro carbon atom determines a shift of the conformational equilibrium associated with the flipping of the heterocycle towards the substituent [7, 8]. As a consequence, the configuration of the chiral carbon atom bearing the substituent induces the configuration of the spiro skeleton (Scheme 5). The *R* configuration of the chiral carbon atom shifts the flipping equilibrium of the heterocycle towards the *M* configuration of the helix (the *S* configurated chiral carbon atom determines a *P* configuration of the helix).

The trispirane **4**, obtained from racemic 2-methyl-cyclohexanone, exists as three diastereoisomers with anancomeric structures with equatorial substituents. These diastereoisomers display specific helicities in correlation with the configurations of the chiral carbon atoms of the included molecules of ketone (Table 1, Scheme 6). Two of these diastereoisomers (**I**(**I′**) and **III**(**III′**)) possess

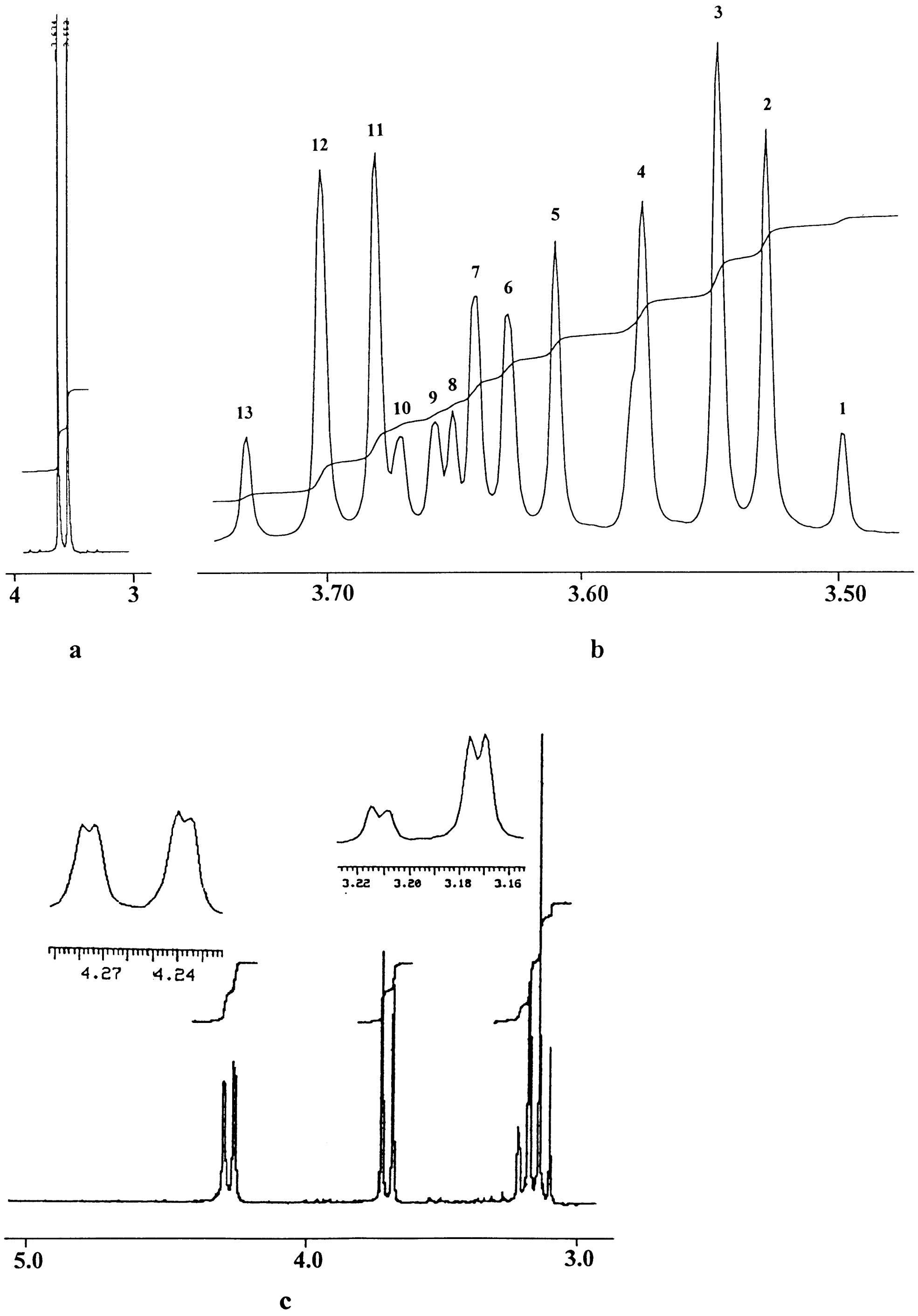
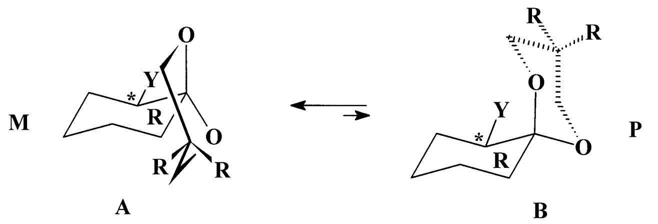
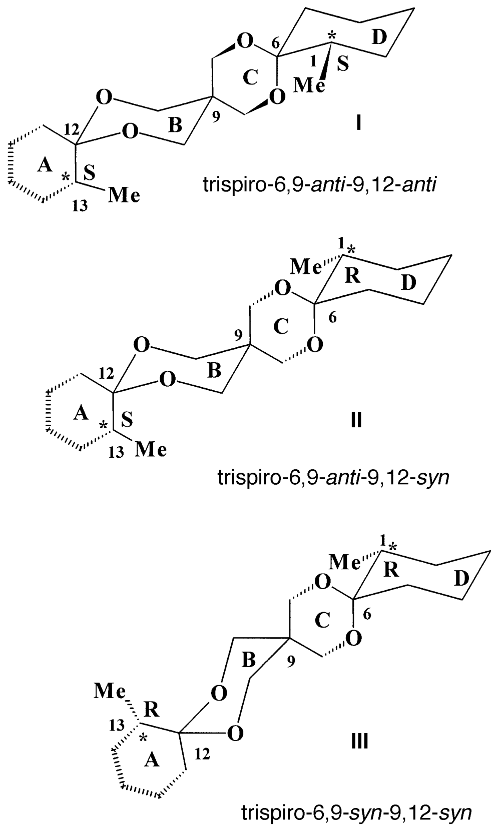


Fig. 1. Partial ^{1}H NMR spectra of compounds **1** (a), **3** (b), and **4** (c, details for the signals of the equatorial protons).



Scheme 5



Scheme 6

chiral carbon atoms with identical configurations (corresponding to the trispiro-6,9-*syn*-9,12-*syn* and trispiro-6,9-*anti*-9,12-*anti* structures of the spiro skeleton); the third one (**II**(**III′**)) exhibits different configurations of the chiral carbon atoms (trispiro-6,9-*syn*-9,12-*anti*).

NMR investigations of the products obtained in the synthesis of compound **4** (starting from racemic ketones) show a mixture of isomers in the raw product, their characteristic peaks being overlapped.

A small amount of the main diastereoisomer of compound **4** has been separated as a pure product by several crystallization from ethanol. The NMR spectra of this diastereoisomer show unique sets of signals for the protons and for the carbon atoms of the two heterocycles and one signal for the methyl groups of positions 1 and 13. Molecular model considerations pointed out that only in the diastereomers **I**(**I′**) and **III**(**III′**) the two methyl groups as well as the positions 8 with 19 and 10 with 20 are homotopic. The pattern of the ^{1}H NMR spectrum with respect to the protons of the heterocycles (Fig. 1c) of this isolated diastereoisomer is very close to that observed for anancomeric derivatives of 2,4,8,10-tetraoxaspiro[5.5]undecane [4, 9]. The spectrum exhibits two AB systems for the protons of the heterocycles, one belonging to the equatorial and axial protons ($\delta_{eq} = 4.26$ ppm and $\delta_{ax} = 3.70$ ppm) of positions 10, and 20, whereas the other one is associated with the equatorial and axial protons ($\delta_{eq} = 3.19$ ppm and $\delta_{ax} = 3.12$ ppm) of positions 8 and 19. The signals corresponding to the equatorial protons show a further splitting due to the characteristic long-range coupling ($J = 1.8$ Hz) between the diastereotopic equatorial protons due to the W arrangement of the bonds H_{eq}-$C_{8(19)}$-C_9-$C_{20(10)}$-H_{eq}. The differences of the chemical shifts are in the normal range for axial and equatorial protons and are considerably higher than those recorded for the diastereotopic protons of compound **3**.

Conclusions

The stereoisomerism of trispiro compounds with six-membered rings can be discussed considering the trispiro-6,9-*syn*-9,12-*syn*, trispiro-6,9-*syn*-9,12-*anti* and trispiro-6,9-*anti*-9,12-*anti* structures of the spiro skeleton. The conformational behaviour of the 1,3-dioxanic middle part of the investigated compounds is correlated with the positions of the substituents located in the cyclohexane rings. If these substituents are close to the spiro carbon atoms (positions 1 and 13), they induce anancomericity of the heterocycles; if these substituents are further away (positions 2, 14 or 3, 15), the 1,3-dioxane rings are flexible.

Experimental

General

NMR spectra have been run on a Bruker AM 400 (Varian) spectrometer operating at 400 (300) MHz for protons and 100 (75) MHz for carbon atoms. No Me_4Si was added; the chemical shifts were referenced to the solvent resonance. Melting points were measured with an Electrothermal melting point apparatus and are uncorrected.

Compounds **1–4**, general procedure

Stoichiometric amounts of pentaerithritol and carbonyl compounds (0.1 mol) with catalytic amounts of *p*-toluenesulfonic acid (0.1 g) were dissolved in 200 ml benzene. The mixture was refluxed, and the liberated water was removed using a *Dean-Stark* trap. When 80% of the theoretical amount of water was separated, the catalyst was neutralized after cooling to room temperature (0.2 g CH_3COONa, stirring for 0.5 h). The reaction mixture was washed twice with 100 ml water. After drying (Na_2SO_4), the benzene was removed, and the 1,3-dioxane spiranes were purified by crystallization from ethanol.

3,15-Diethyl-7,11,18,21-tetraoxatrispiro[5.2.2.5.2.2]henicosane (**1**)

Yield: 81%; m.p.: 123–124°C; $C_{21}H_{36}O_4$ (352.51); calc.: 71.55 C, 10.29 H; found: 71.72 C, 10.40 H; ^{1}H NMR: $\delta = 0.85$ (t, 6H, $J = 6.5$ Hz, 3,15-CH_2-CH_3), 1.03 (m, 2H, 3,15-H_{ax}), 1.19 (q, 4H, $J = 6.5$ Hz, 3,15-CH_2-CH_3), 1.20–1.30 (overlapped peaks, 8H, 1,2,4,5,13,14,16,17-H_{ax}), 1.50–1.55 (overlapped peaks, 4H, 2,4,14,16-H_{eq}), 2.15–2.20 (overlapped peaks, 4H, 1,5,13,17-H_{eq}), 3.55 (s, 4H, 8, 19-H), 3.63 (s, 4H, 10,20-H) ppm; ^{13}C NMR: $\delta =$ 11.90 (3,15-CH_2-CH_3), 28.51, 28.79 ($C^{2,4,14,16}$), 29.20 (3,15-CH_2-CH_3), 31.19, 32.12 ($C^{1,5,13,17}$), 32.97 (C^9), 38.98 ($C^{3,15}$), 63.50 ($C^{8,19}$), 63.66 ($C^{10,20}$), 98.82 ($C^{6,12}$) ppm.

3,15-Diphenyl-7,11,18,21-tetraoxatrispiro[5.2.2.5.2.2]henicosane (**2**)

Yield: 75%; m.p.: 170–171°C; $C_{29}H_{36}O_4$ (448.60); calc.: 77.65 C, 8.09 H; found: 77.49 C, 8.24 H; ^{1}H NMR: $\delta = 1.37$ (tt, 4H, $J = 12.0$, $J' = 4.5$ Hz, 1,5,13,17-H_{ax}), 1.64–1.88 (overlapped peaks, 8H, 2,4,14,16-$H_{ax,eq}$), 2.23 (d, 4H, $J = 12.0$ Hz, 1,5,13,17-H_{eq}), 2.37 (tt, 2H, $J = 12.0$, $J' = 3.6$ Hz, 3,15-H_{ax}), 3.57 (s, 4H, 8,19-H), 3.64 (s, 4H, 10,20-H), 7.06–7.22 (overlapped peaks, 10H, aromatic) ppm; ^{13}C NMR: $\delta = 30.55$ (C^9), 32.74 ($C^{2,4,14,16}$), 32.93 ($C^{1,5,13,17}$), 44.29 ($C^{3,15}$), 63.57 ($C^{8,19}$), 63.67 ($C^{10,20}$), 98.22 ($C^{6,12}$), 126.39, 127.19, 128.70 (tertiary aromatic carbon atoms), 147.01 (quaternary aromatic carbon atom) ppm.

2(R),14(R)-Dimethyl-7,11,18,21-tetraoxatrispiro[5.2.2.5.2.2]henicosane (**3**)

Yield: 73%; m.p.: 100–101°C; $[\alpha] = +6.5°$; $C_{19}H_{32}O_4$ (324.46); calc.: 70.33 C, 9.94 H; found: 70.51 C, 10.08 H; ^{1}H NMR: $\delta = 0.76$ (2H, ddd, $J = 12.0$, $J' = 6.4$, $J'' = 4.5$ Hz, 3,15-H_{eq}), 0.86 (6H, d, $J = 6.6$ Hz, 2,14-CH_3), 0.99 (2H, dt (overlapped ddd), $J = J' = 12.6$, $J'' = 8.5$ Hz, 1,13-H_{ax}), 1.16 (2H, m (overlapped ddd), 5,17-H_{ax}), 1.44–1.62 (6H, overlapped peaks, 3,15-H_{ax}, 4,16-H_{ax}, 4,16-H_{eq}), 1.74 (2H, m, 2,14-H_{ax}), 2.20 (4H, m (overlapped peaks), 1,5,13,17-H_{eq}), 3.516, 3.564 (2H, AB system (two doublets), $J = 11.7$ Hz, 8-H), 3.564, 3.645 (2H, AB system (two doublets), $J = 11.4$ Hz, 10-H), 3.596, 3.658 (2H, AB system (two doublets), $J = 11.5$, 19-H), 3.667, 3.717 (2H, AB system (two doublets), $J = 11.6$, 20-H) ppm; ^{13}C NMR: $\delta = 22.08$ (2C, 14-CH_3), 22.12 ($C^{3,15}$), 28.82 ($C^{2,14}$), 31.46, 31.82 ($C^{4,16}$), 32.63 (C^9), 34.48 ($C^{5,17}$), 41.04, 41.42 ($C^{1,13}$), 63.19 ($C^{8,10,19,20}$), 98.73 ($C^{6,12}$) ppm.

1,13-Dimethyl-7,11,18,21-tetraoxatrispiro[5.2.2.5.2.2]henicosane (**4**)

Yield: 59%; (mixture of diastereomers); isolated diastereomer **I**(**I′**) or **III**(**III′**): 30% after separation; m.p.: 94–95°C; $C_{19}H_{32}O_4$ (324.46); calc.: 70.33 C, 9.94 H; found: 70.11 C, 10.12 H; ^{1}H NMR: $\delta = 1.11$ (6H, d, $J = 6.6$ Hz, 1,13-CH_3), 1.00–1.30 (14H, overlapped peaks), 1.78 (2H, m, 1,13-H_{ax}), 2.23 (2H, m, 5,17-H_{eq}), 3.12 (2H, d, $J = 11.7$, 8,19-H_{ax}), 3.19 (2H, dd, $J = 11.7$, $J' = 1.8$ Hz, 8,19-H_{eq}), 3.70 (2H, d, $J = 11.7$, 10,20-H_{ax}), 4.26 (2H, dd, $J = 11.7$, $J' = 1.8$ Hz, 10,20-H_{eq}) ppm; ^{13}C NMR: $\delta = 11.64$ (13-CH_3), 28.51 ($C^{3,15}$), 29.10 ($C^{4,16}$), 31.91 ($C^{4,14}$), 32.12 ($C^{5,17}$), 32.97 (C^9), 38.70 ($C^{1,13}$), 63.21 and 63.37 ($C^{8,10,19,20}$), 98.82 ($C^{6,12}$) ppm.

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