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Synthesis and Stereochemistry of Some 1,3-Oxazolidine Systems Based on TRIS (α,α,α-trimethylolaminomethane) and Related Aminopolyols Skeleton. Part 2: 1-Aza-3,7-dioxabicyclo[3.3.0]octanes

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Abstract—The reaction of TRIS with equivalent amounts of two carbonyl compounds is shown to afford, diastereoselectively, the title compounds. The results are discussed as a synthetic strategy and the stereochemistry is supported by theoretical calculations and high resolution NMR data.

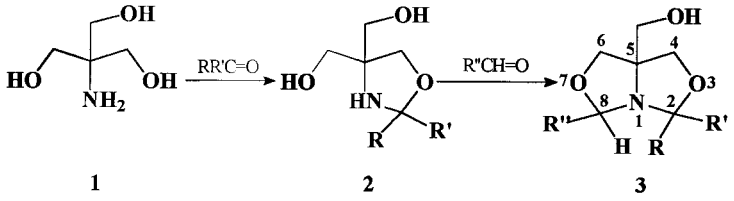
Introduction

TRIS® (α,α,α-trimethylolaminomethane) **1** is a very well-known β-aminopolyol[1,2] possessing four nucleophilic groups. Consequently, it was considered as both a suitable and versatile substrate for cyclocondensations with appropriate carbonyl compounds to give five-membered saturated heterocycles[3–6] (1,3-oxazolidines, **2**) or fused structures {1-aza-3,7-dioxabicyclo[3.3.0]octanes, **3**} (Scheme 1).

The latter were reported as the main products of the reaction between (substituted)-2-amino-1,3-propandiols and 2 equiv. of an aldehyde.[7] It was also established that this cyclocondensation occurs via 2-substituted oxazolidines **2** as non-isolable intermediates.

Depending on the substituents (R′≡R″, R=H) a very large series of substituted 1-aza-3,7-dioxa bicyclo[3.3.0]octanes were obtained, according to the chemistry depicted above. The method was also considered useful for (temporary) cancellation of –OH and $-NH_2$ nucleophilicity or a posteriori regioselective ring cleavage with certain nucleophiles.[5] In this context, special attention was paid to compounds **3** starting from TRIS (α,α,α-trimethylolaminomethane) because they exhibited extensive applications as plasticizers, biocides[8–14] etc. Accordingly, they are the object of a great number of patents.[15,16] The different synthetic approaches led us to assume the same strategy: double-ring closure using two equivalents of the same aldehyde, (optionally) followed by functionalisation of the C-5 hydroxymethyl group.

The common feature was the use of the same carbonyl partner (usually an aldehyde) in both steps of the synthesis. However, in the 1980s, Barbulescu et al.[16] claimed the synthesis of some 1-aza-5-hydroxymethyl-3,7-dioxabicyclo[3.3.0]octanes bearing different ligands at C-2 and C-8 [e.g. R″=H, *p*-CH_3O–C_6H_4–; R, R′=–$(CH_2)_5$–; Scheme 1].



1 **2** **3**

Scheme 1.

Keywords: asymmetry; diastereoselection; oxazolidines; stereochemistry.
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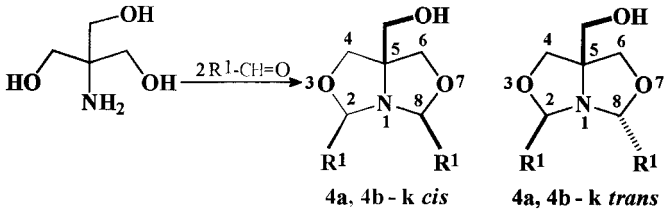


Scheme 2. R^1 = H (**4a**); Ph (**4b**); *p*–O_2N–C_6H_4 (**4c**); *o*-O_2N–C_6H_4– (**4d**); Bz (**4e**) Ph_3C–CH_2– (**4f**); 2-Py (**4g**); 3-Py (**4h**); 4-Py (**4i**); 2-Furyl (**4j**); 3-Thienyl (**4k**).

Subsequent treatment of asymmetrically C-2,8-disubstituted compounds **3** with aryl or alkyl isocyanates yielded carbamates with pesticide activity.[16] The structures were published only in patents and no structural assignment was made. In turn, our literature search led us to assume that the above idea was, in fact, inspired from Crabb's earlier study.[17] Thus, starting from 2-amino-2-methyl-1,3-propanediol (the methyl analogue of TRIS), some asymmetrically C-2,8-disubstituted 1-aza-5-methyl-3,7-dioxabicyclo[3.3.0]octanes were prepared in order to study their stereochemistry by means of ^{1}H NMR geminal coupling. The asymmetry was only tentatively assigned with no quantitative data (yields and diastereoselectivity). To the best of our knowledge, the above results have never been reported by another author and the synthetic proposal depicted in Scheme 1 ($R \neq R' \neq R''$) has been neglected so far. There are very few papers dedicated to stereochemical assignments and conformational analysis of compounds **3** since the practical aim of building their skeleton (similar to hexahydropyrolizine) obscured their chirality and diastereoisomerism.[17–19] Thus, the scope of our paper is focused on both synthesis and stereochemistry of the title compounds.

Results and Discussion

Synthesis

Depending on the substitution at C-2 and C-8, the synthesis of two major types of compounds **3** was explored; since the synthetic strategy was different, their preparation will be discussed separately.

1-Aza-3,7-dioxabicyclo[3.3.0]octanes bearing at C-2 and C-8 homomorphic ligands as the (hetero)aryl group. Eleven cases of cyclocondensation to prepare 2,8-substituted-1-aza-5-hydroxymethyl-3,7-dioxabicyclo[3.3.0]octanes have been investigated, starting from TRIS, following the classical method, previously developed by Senkus,[3,15] Pierce,[4–6] Bergmann,[7] Vanelle[9,12] and Crabb[17] (Scheme 2). Compounds **4d–k** are new ones and yields are not optimised. The representative results are summarised in Table 1.

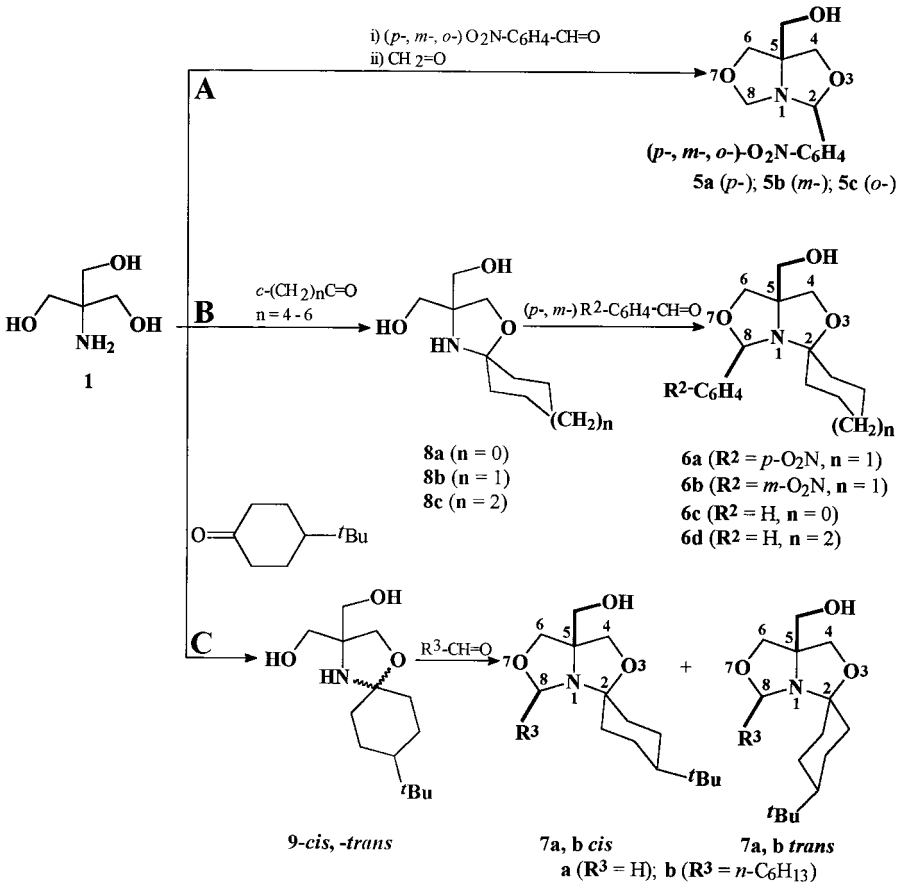
All reactions were performed under thermodynamic control (TLC monitoring) and quenched when the ratio between the (expected) diastereomers (Scheme 2) seemed to remain unchanged and TRIS was detected in small traces only. The substituted 1-aza-3,7-dioxabicyclo[3.3.0]octane ring system is sensitive to hydrolysis in acidic media[20] and this behaviour was also encountered in compounds **4**. Therefore, the simplest method, in order to isolate crystalline products, had to be used (e.g. one single solvent, one crystallisation) to afford the *first crystalline crop* (f.c.c., see Table 1) which was examined by NMR. If non crystallisable oils were isolated (compounds **4e**, **j**), flash column chromatography was performed. This last option is risky since, during the work-up, the crude reaction mixtures partially decomposed on silica gel to afford TRIS and the corresponding aldehyde; in turn, isolated compounds are stable on storage. The reaction solvent (benzene or toluene) was selected taking into account the sensitivity to heating of the aldehyde;[12] nevertheless, for compounds **4h**, **j** and **k**, this crucial lability affected the yields.

The diastereoselectivity ratios were calculated from high resolution (400 MHz) ^{1}H NMR spectra by choosing as

Table 1. Quantitative and qualitative results of the synthesis of the compounds **4**

Compd	R^1	Solvent	Time (h)	Yield[a] (%)	Mp (°C)	Diastereoselectivity as (%) *cis* vs. *trans*	Isolation
4a	H	Toluene	6	80	58–59	–	f.c.c.[b]
4b	Ph	Toluene	16	90	71–78	87:13	f.c.c
4c	*p*-O_2N–C_6H_4–	Toluene	8	91	182–184	0:100	f.c.c.
4d	*o*-O_2N–C_6H_4–	Toluene	6	77	148–149	78:22	f.c.c.
4e	Bz	Benzene	7	52[c]	113–114	95:5	Flash. column.
4f	Ph_3C–CH_2–	Benzene	20	85	112–113	95:5	f.c.c
4g	2-Py	Benzene	6	93	89–90	100:0	f.c.c
4h	3-Py	Toluene	16	20	95–100	93:7	f.c.c
4i	4-Py	Benzene	12	65	122–136	25:75	f.c.c
4j	2-Furyl	Benzene	5	17[c]	Oil	67:33	Flash. column.
4k	3-Thienyl	Benzene	6	37	105–106	96:4	f.c.c

[a] Calculated with respect to both diastereomers (where formed, see discussion and Scheme 2).
[b] First crystalline crop (f.c.c.), see discussion.
[c] Calculated after flash column chromatography.



Scheme 3.

reference the very well separated benzyl H-2 and H-8 protons (isochronous in *cis* forms but anisochronous in *trans* forms; for the use of *cis* and *trans* descriptors,[22,23] see the Stereochemistry section); discrimination between diastereomers has been fully accomplished by successive NOE-difference experiments.

Table 2. Quantitative and qualitative results in the synthesis of compounds **5–7**

Compound	Yield (%)[a]	Diastereoselectivity *cis* vs. *trans* (%)[b]	Mp (°C)	Isolation
5a	77	100:0	84–85	f.c.c.
5b	62	100:0	Oil	Flash column.
5c	65	100:0	Oil	Flash column.
6a	52	100:0	96–97	f.c.c.
6b	65	100:0	Oil	Flash column.
6c	54	97:3	Oil	Flash column.
6d	54	78:22	Oil	Flash column.
7a	78	94:6	138–139	f.c.c.
7b	55	100:0	oil	Flash column.

[a] For compounds **5a–c**, calculated starting directly from TRIS (one-pot synthesis); for the rest of the series, yields are calculated starting from the corresponding spirooxazolidines **8**, **9** with respect to both diastereomers (where formed) (Scheme 3).

[b] For the compounds **5**, **6** *cis* descriptor refers to *all cis* orientation: the aromatic ligand, the lone pair at N-1 and CH_2OH group placed on the same side of the molecule; if *trans*, the C-2 or C-8 ligand is placed on the opposite side. For the compounds **7**, *cis* and *trans* descriptors refer to ^{t}Bu and oxazolidine O-3 as reference. All ratios are calculated from ^{1}H NMR spectra by choosing protons H-2 and H-8 as 'reference signals'.

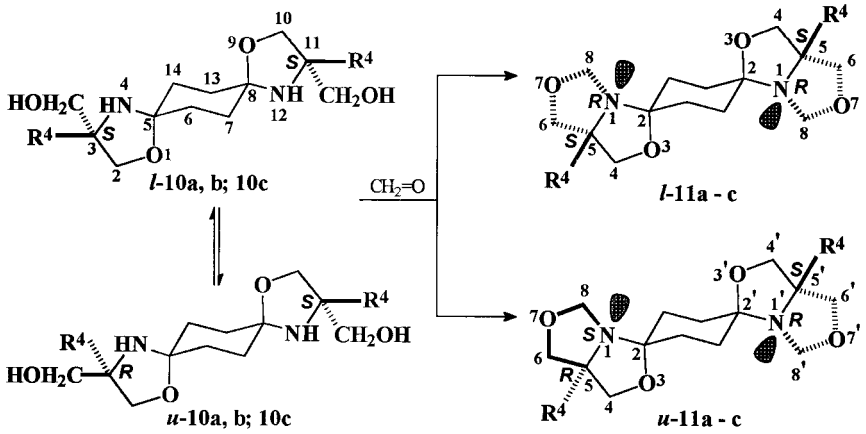
One can observe the dominant preference towards *cis* diastereomers (except compounds **4c** and **i**) which is in complete agreement with the theoretical calculations. However, in our hands, compound **4c** exhibited just one diastereomer, in contradiction with Vanelle et al.'s assignments[9] in 1985 but in agreement with the same authors[12] in 1990. The mp is, however, different.

1-Aza-3,7-dioxabicyclo[3.3.0]octanes bearing different ligands at C-2 and C-8. The synthesis of two types of target compounds have been investigated, depending on the number of azadioxabicyclooctane units involved in the final structure. Since the common structural feature of both types of compounds is different substitution at C-2 and C-8, the successive use of two different carbonyl partners in reaction with TRIS was attempted.

Compounds possessing different ligands at C-2 and C-8 in a single azadioxabicyclooctane unit. In Scheme 3 the synthetic strategy and compounds are illustrated; Table 2 summarises the qualitative and quantitative results.

All structures **5–7** have not been previously reported.

The basic strategy of our approach has consisted in the use of an appropriate pair of carbonyl compounds and deciding which one should be the first reactant. Thus, nitrobenzaldehydes and formaldehyde (compounds **5**) have been found to be a good pair of this type (Scheme 3, Route A): the first ring closure, to afford a 2-nitrophenyl-1,3-oxazolidine



Scheme 4. 10a, **11a** (R^4=Me); **10b**, **11b** (R^4=Et); **10c**, **11c** (R^4=–CH_2OH).

Table 3. Quantitative and qualitative results in the synthesis of compounds **11a–c**

Compound	Solvent	Mp (°C)	Yield (%)[a]	Diastereoselectivity *unlike* vs. *like* (%)[b]
11a	Benzene	150–151 and 194–195	31	50:50
11b	Benzene	148–149	33	90:10
11c	Toluene	181–182	70	50:50

[a] Calculated with respect to both diastereomers.
[b] Calculated based on GC–MS data.

(equimolar ratio TRIS/nitrobenzaldehyde), has been selective enough for a one-pot synthesis.[12] Consequently, these intermediates have not even been isolated. The next cyclocondensation occurred with complete diastereoselectivity (only $1R^*,2R^*,5S^*$-diastereomers have been formed). In turn, if formaldehyde has been chosen as the first reactant (equimolar ratio TRIS/formaldehyde), any selectivity disappeared since, after the first step, only unreacted TRIS and its corresponding trivial bicyclo derivative with formaldehyde (**4a**, Scheme 2) were detected in the crude reaction mixture. The option to use the less reactive carbonyl in the first step of the synthesis was then confirmed by the preparation of compounds **6**. Based on our previously reported data concerning the complete selectivity of the reaction of TRIS with simple C_{5-7} monocyclanones (to yield the spirooxazolidines **8**) we used them for the first ring-closure.[24,25] Next, depending on the different stability against transketalisation of these intermediates, the aryl aldehydes that yielded the best results are shown in Scheme 3 (Route B) and Table 2.

Thus, in the case of compounds **6a**, **b** the second cyclocondensation occurred simply by using an equimolar ratio of spirane **8b**: *para*- or *meta*-nitrobenzaldehyde. No reaction took place with *ortho*-nitrobenzaldehyde, presumably due to the steric hindrance in the final structure. The side product, normally expected and identified in the crude reaction mixture, was, in both cases, the corresponding C-2,8-di(nitrophenyl)bicyclo derivative formed by the replacement of cyclohexanone by a nitrobenzaldehyde (side reaction, similar to the well-known transketalisation). Since the latter product became dominant for spiranes **8a**, **c**, less reactive benzaldehyde was used. Even so, a 3–4:1 molar ratio of spirane **8a**, **c**: benzaldehyde has to be used to obtain pertinent results.

In this context, we have also examined the role (if any) of mobility of the alicycle moiety (Scheme 3, Route C). Preparation of compounds **7** exhibited unexpected results. Spirane **9** (as a mixture of *cis* and *trans* diastereomers), possessing the cyclohexane ring rigid, underwent no reaction with any of the (nitro)benzaldehydes. Only formaldehyde gave the mixture of diastereomers **7a** *cis–trans*, but in a different ratio (**7a** *cis* vs. *trans* 94:6) than in the starting spirane[25] (**9**, *cis* vs. *trans* 75:25). Therefore, since six carbon atoms (tied together in an aromatic ring or alicyclic fragment) could not be inserted in spirane **9**, we have attempted the insertion of an *n*-aliphatic six membered chain (reaction with *n*-heptanal, Scheme 3, Route C); thus, we have successfully accessed compound **7b** with full diastereoselectivity (*cis* orientation of the spirane fragment and *cis* orientation of *n*-hexyl and hydroxymethyl groups). Other stereochemical details of this synthesis will be discussed later on.

Finally, we point out that the same synthetic methodology as for compounds **4** was used but the influence of the solvent was more obvious: on increasing the temperature in toluene, the transketalisation process became significant. As in the series **4**, all compounds discussed here have partially decomposed on flash column chromatography (see yields in Table 2).

Compounds possessing different ligands at C-2 and C-8 in two azadioxabicyclooctane units tied together in a single structure. We imagined two distinct pathways to link together two azadioxabicyclooctane units: (a) Linkage as a dispirane structure (Scheme 4): this type of linkage has been realised starting from dispiranes **10a–c** in reaction with formaldehyde (stoichiometric molar ratio). The results are listed in Table 3.

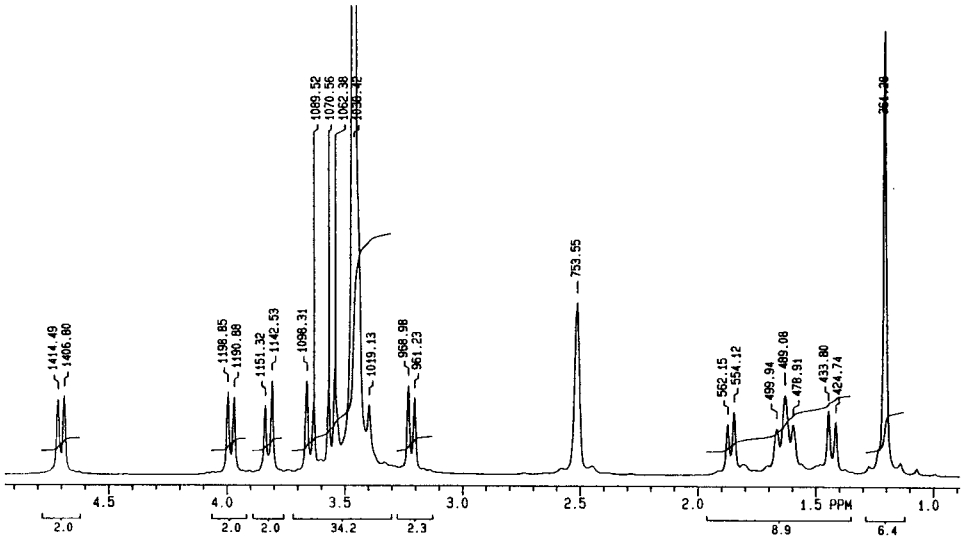


Figure 1. ^{1}H NMR spectrum of the compound **11a** (*l*-form); solvent DMSO-d_6, 300 MHz; from downfield to upfiled (δ, ppm): 4.70 (d, H-8*t*); 3.99 (d, H-8*c*); 3.82 (d, H-6*t*); 3.65 (d, H-6*c*); 3.55 (d, H-4*t*); 3.22 (d, H-4*c*); 1.86 (d); 1.65 (d); 1.61 (d); 1.44 (d); 1.21 (s, 2×–CH_3).

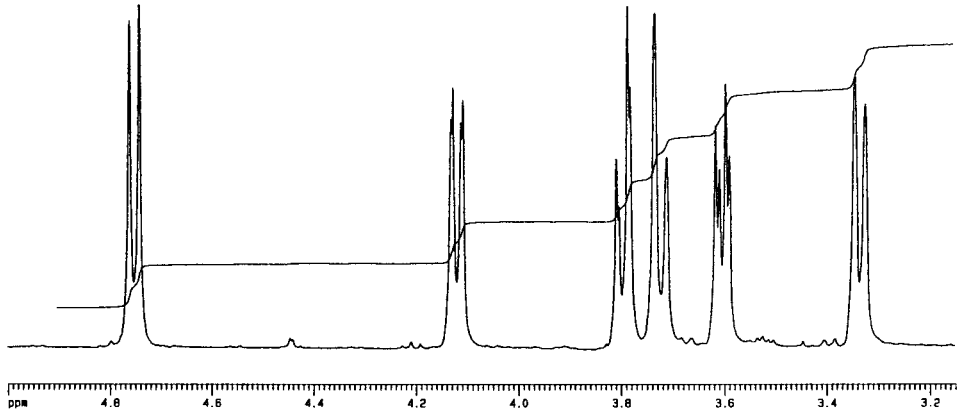
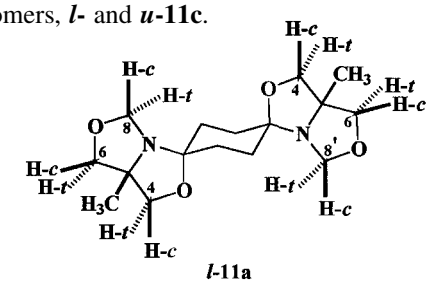
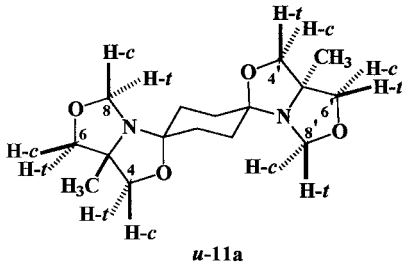


Figure 2. ^{1}H NMR spectrum of the compound **11a** (both *l*- and *u*-forms); solvent $CDCl_3$, 400 MHz; from downfield to upfield (δ, ppm): 4.75 (d, H-8*t*, -8′*t*); 4.12 (d, H-8*c*, -8′*c*); 3.79 and 3.78 (d, H-6*t*, -6′*t*); 3.72(d, H-6*c*, -6′*c*); 3.61 and 3.60 (d, H-4*t*, -4′*t*); 3.33 (d, H-4*c*, -4′*c*).

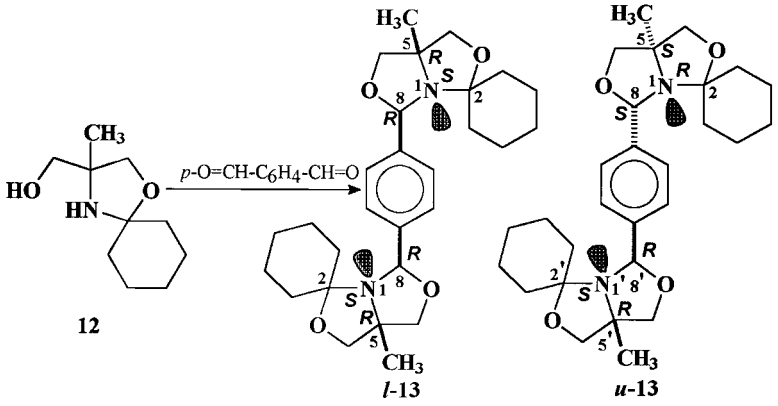
Data from Table 3 should be compared with our previous results regarding the epimerisation in non-protic solvents of the starting dispiranes **10** (ring–ring tautomerism[25]); in these conditions, they are, in fact, mixtures of diastereomers: a racemic form (***l-like***, 3*S**,11*S**) and a *meso* form (***u-unlike***, 3*R**,11*S**)[16] (Scheme 4). Obviously, this intrinsic behaviour was recognised by examining the diastereoselective ratios between possible reaction products, **11**. Thus, dispiranes **10a**, **b** as *u*-forms (***u*-10a**, **b**) gave the corresponding ***u*-11a**, **b**, as dispiranes **10a**, **b** (*l*-forms, ***l*-10a**, **b**) gave ***l*-11a**, **b** (in these last cases, in Scheme 4 only one enantiomer is depicted). Although dispirane **10c** has no chiral centre, its hydroxymethyl groups are diastereotopic, hence the structure obtained was expected to be a possible mixture of diastereomers, ***l*-** and ***u*-11c**.





In terms of diastereoselectivity, compounds **11** should be similar but the results showed then to be different (Table 3). Thus, the small yields (**11a**, **b**) could be motivated by the occurrence of transketalisation which becomes, in these cases, the dominant process. The same was not true for compound **11c** (see yield).

Diastereoselectivities have been found to be different too. Inspection of Dreiding models led us to assume that the steric differences between *l*- and *u*-diastereomers **11** are insignificant, in agreement with ratios depicted in Table 3 (compounds **11a**, **c**). Compound **11b** has revealed the



Scheme 5.

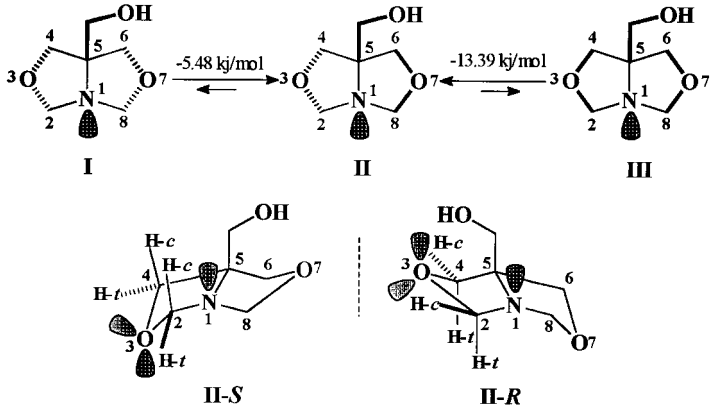
presence of a single form, preliminarily assigned as ***u*-11b** (see further discussion); only the QC NMR-spectrum allowed the detection of another minor diastereomer meanwhile in the ^{1}H NMR-spectrum all peaks were overlapped.

Next, very difficult problems are raised from the separation of diastereomers. Different TLC eluents were unable to resolve the two compounds. Therefore, in the case of compounds **11b**, **c** their isolation as *l*+*u* mixture was the only option. Even so, the NMR spectra (400 MHz) were complicated by overlapping peaks (mainly in ^{1}H NMR spectra). The best analytical separation was encountered in ^{13}C NMR spectra. Compound **11a** has been a helpful exception. From Scheme 4 it is easy to observe that ***l*-11a** possesses a molecular dipole moment, meanwhile ***u*-11a** is a non-polar molecule because of its symmetry. This structural characteristic has been useful (unfortunately only in this case) in NMR studies. Thus, in deuterated solvents, pure ***l*-11a** could be selectively (but not completely) extracted from the *l*+*u* mixture, with DMSO-d_6. Its ^{1}H NMR spectrum is depicted in Fig. 1. {In order to simplify further discussion labelling of positions was made according to the basic 1-aza-3,7-dioxabicyclo[3.3.0]octane ring system; since the ligand at C-5 has the permanent *cis* orientation with the lone pair at N-1 (*cis* fused rings), protons are designed as ***c*** (*cis*) and ***t*** (*trans*) with respect to C-5 ligand.} In turn, the NMR spectra of the remaining mixture ***u*-** and ***l*-11a** was explored in $CDCl_3$ (Fig. 2). It must be emphasised that the positions 4–4′, 6–6′ and 8–8′ are isochronous in each *l*- or *u*-diastereomer and the single way to discriminate them is the splitting in the cyclohexane region: in *l*-form (Fig. 1) two distinct and separate AX-systems are revealed (8 peaks), in agreement with inspection of Dreiding models. In *u*-form the expected splitting is much more complicated (an AA′XX′-system, 32 peaks).

The method of selective extraction could not be extended to the rest of the compounds; the NMR spectra of **11b** were performed in $CDCl_3$ (suggesting a non-polar structure, ***u*-11b**, completely insoluble in DMSO-d_6). The single solvent with acceptable solubility for **11c** was CD_3OD (both *l*- and *u*-diastereomers, as a mixture).

(b) Linkage through a 1,4-phenylene unit (Scheme 5): this type of cyclocondensation is promising from a diastereoselectivity point of view.

We have postulated that a double condensation of a spirane of type **8** with a dialdehyde (e.g. terephtaldicarboxyaldehyde) should also obey the same rule of diastereoselectivity as in the series **4b–k**, **5** and **6** (Scheme 5). The reaction required unexpectedly strong conditions (up to 150°C) and the absence of any solvent. None of the spirane of type **8** was appropriate for this purpose, but the spirane **12** (e.g. for spiranes **8a**, **c** transketalisation was the major process, meanwhile **8b** required more than 200°C, when the dialdehyde sublimed). Although the yield was very small (about 2.5%) the reaction was very clean and diastereoselective. From Scheme 5 one can identify the same two possibilities concerning the global topicity: a *like*-pair ***l*-13** (racemic) and



Scheme 6.

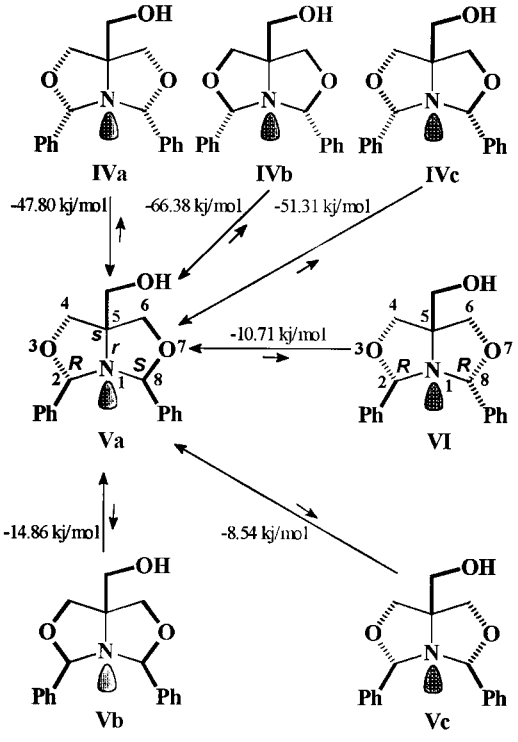
an *unlike*-structure ***u*-13** (*meso* form). The ^{1}H NMR spectrum has shown unambiguously that the compound obtained was ***u*-13** (e.g. just one singlet, located at 7.46 ppm, for all four aromatic protons).

Stereochemistry

Stereochemistry of the basic skeleton as issued from the RHF/6-21G* molecular orbital calculation. Since we found few literature stereochemical data in the field,[17–21] we started our analysis by a preliminary examination of the results of RHF/6-21G* molecular orbital calculation (with full geometry optimisation) in the case of compounds **4a**, **b**. These results, as differences between total energies of the possible involved stereoisomers, are illustrated in Schemes 6 and 7.

The common structural feature found is that the C-5 hydroxymethyl group and the lone-pair at N-1 are always placed on the same side of the molecular plane (C-2, -4, -6, -8) (*cis* fused structure); hence, the pairs of bonds N-1-C-2 vs. C-5-C-4 and N-1-C-8 vs. C-5-C-6 are nearly eclipsed (indeed, in this class, the N-1–C-5 bond can be a stereogenic axis, as we previously reported[20]). No pyramidal inversion at N-1 could be a priori assigned and the NMR evidence is in complete agreement with this configurational stability. We note here, anyhow, the similar empirical assignments, previously reported by Crabb et al.[17] for the 5-Me analogue of TRIS.

II has been found to be the most stable calculated conformation which is chiral; that is, the plane N-1–C-5–CH_2– is a symmetry plane for the conformers **I** and **III** but a chirality plane for **II**. Obviously, the ΔE difference between total energy of conformers **I** and **II** suggests a diastereomeric interconversion between them and an enantiomeric one, **II*R*–II*S***. The flipping of the parent compound **4a** was confirmed by its ^{1}H NMR spectra (Fig. 3) performed successively at low temperature.



Scheme 7.

Toluene-d_8 was the only appropriate solvent for this exploration. The coalescence was found at about −60°C but, unfortunately, the frozen conformation **II** could not be exhibited [as a double anisoschronism between the C-4–C-6 and C-2–C-8 positions, diastereotopic in **II*S*(*R*)** environment] since, at −70°C, 4a completely crystallised from the NMR solvent.

Compound **4b** exhibited a similar behaviour (Scheme 7): its configurational and conformational equilibria are shifted towards **Va** and supported by the diastereoselectivity ratios listed in Table 1.

One must observe that **Va** is more stable than its conformational diastereomers **Vb**, **c** but the ΔE values suggest again the flipping of the molecule if Ph and hydroxymethyl groups are placed on the same side of the molecule (all *cis*). The ^{1}H NMR spectra, performed at low temperature, are comparable to those of **4a** (Scheme 8, Fig. 4) but the conformational chirality of the frozen conformer **Va** (chirality plane N-1–C-5–CH_2–, just one enantiomer is depicted) remained obscure again. In turn, at room temperature, positions C-4–C-6 and C-2–C-8 have been found isochronous since the chirality plane becomes a symmetry one.

Therefore, in order to simplify further discussion, the diastereomers of type **V** are hereafter considered as a single averaged *meso* form ($1r^*,2R^*,5s^*,8S^*$) and the descriptor *cis* will be used to emphasise only that all three ligands (linked to C-2, -5 and -8) are placed on the same side of the molecule. These assignments were entirely supported by NOE-difference experiments (see later, Table 4).

From a synthetic point of view, the diastereomers of type **VI** (Scheme 4) had a minor occurrence, except compounds **4c**, **i** (Table 1); this might demonstrate the reasonable limits of our calculations. Indeed, we have no pertinent explanation for this reverse diastereoselectivity, other than the rejection between the two identically oriented dipole-moments promoted by a strong withdrawing group (–NO_2 and –N=) placed *para* to the benzyl carbon (indeed, for the analogue nitro derivative of **4j**, Vanelle et al.[12] reported only the *trans* form).

The correct location of heterocyclic protons was more complicated since **VI** is a stable chiral form (Scheme 9), and rigid from a conformational point of view, as shown from the calculations.

Since all compounds described in this paper have been isolated as racemates, the diastereomers **VI** will be hereafter designed only as *trans* forms ($2R^*,8R^*$) (one ligand is placed on the opposite face of the medium plane of the molecule). About the diastereomers of type **VI**, two final remarks should also be mentioned.

(a) The ΔE=−10.71 kJ/mol between the configurational diasteromers *cis*-(**Va**) and *trans*-(**VI**) is unexpectedly

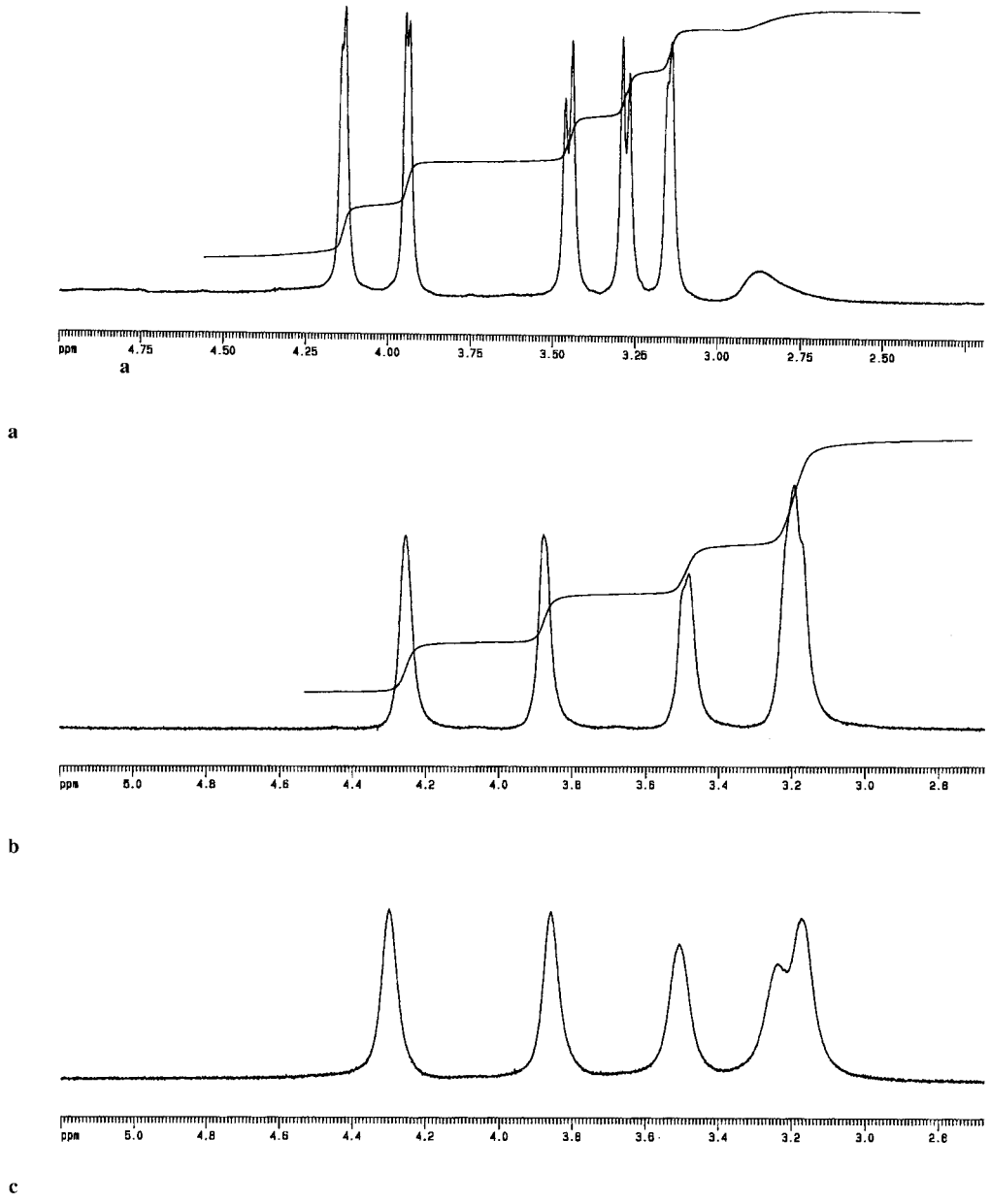
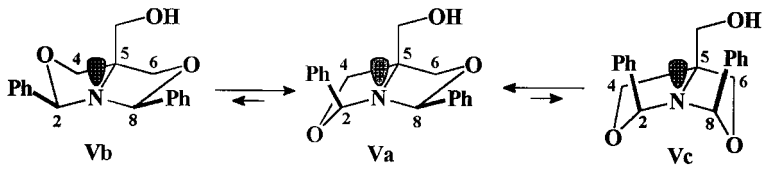


Figure 3. ^{1}H NMR spectra performed at low temperature for the compound **4a** (A—0°C; B—−40°C; C—−60°C); solvent toluene-d_8, 400 MHz.

small (even smaller than ΔE=−14.85 kJ/mol between the conformational diastereomers **Va**, **b**) (Scheme 4); thus, we believe that the equilibrium **Va**–**Vb** is normally completely shifted to **Va** (the remaining conformational equilibrium is **Va**–**Vc**). Anyhow, as previously pointed out, all syntheses were performed under thermodynamic control, to yield, where effective, a mixture of diastereomers **V**+**VI**. Therefore, extrapolation mutatis–mutandis of ΔE— values from the equilibrium **Va**–**VI** to the entire series **4** should be hazardous.

(b) The total energy of diastereomer **VI** was calculated starting from the already defined **IVc** and **Va** (Scheme 7) by a priori placing the two Ph-groups in *trans* one against the other. Although both pathways afforded the same unique geometry (Schemes 8 and 9), this was only partially supported by NMR data (see further).



Scheme 8.

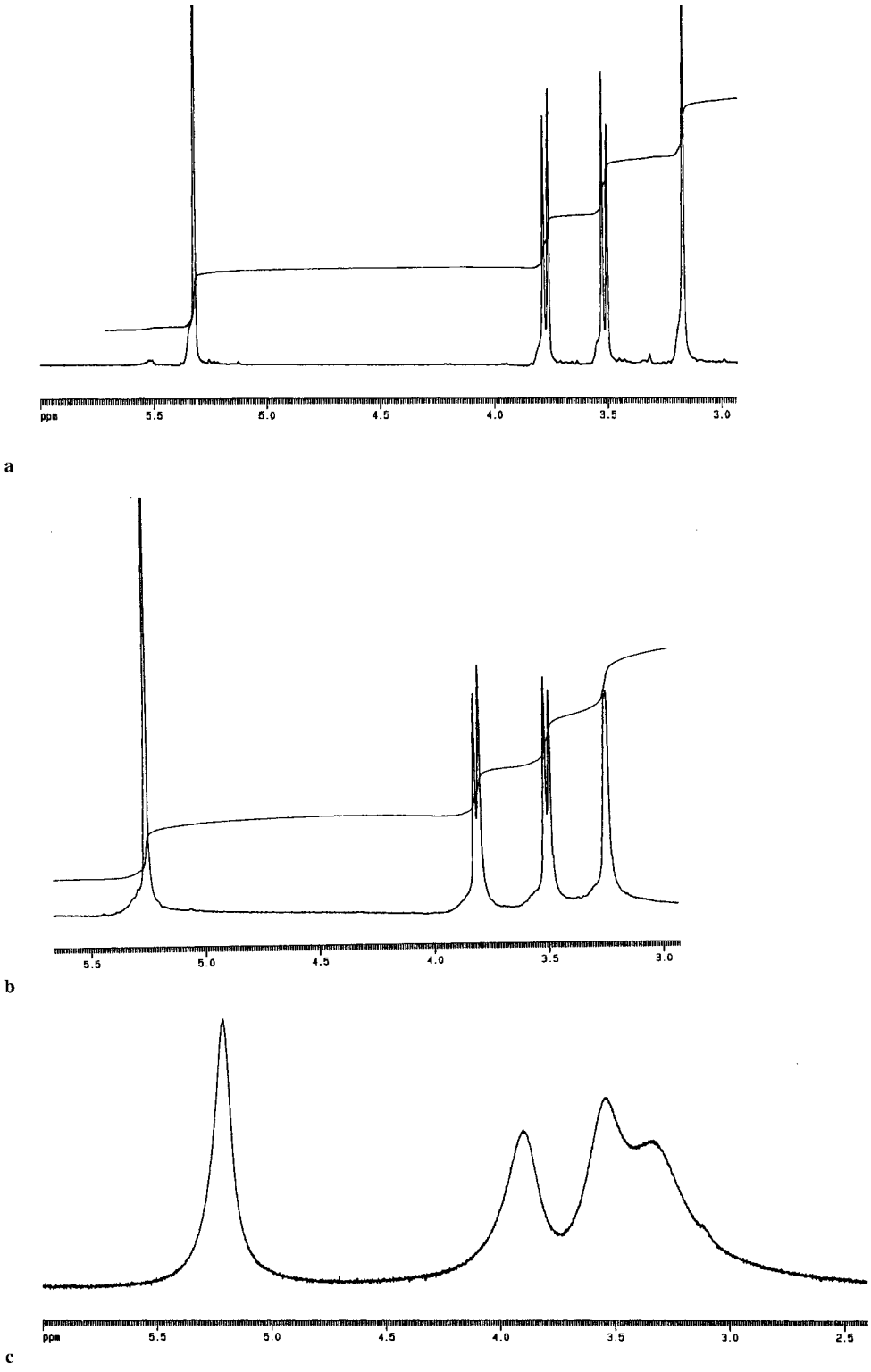
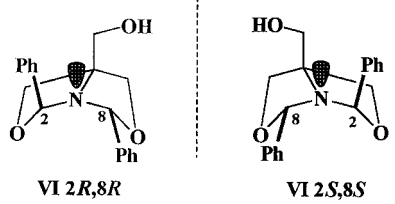


Figure 4. ^{1}H NMR spectra performed at low temperature for the compound **4b** (A—0°C; B—−40°C; C—−60°C); solvent toluene-d_8, 400 MHz.



VI 2*R*,8*R* VI 2*S*,8*S*

Scheme 9.

Stereochemical assignments based on high resolution NMR data. The above considerations were then explored by means of high resolution NMR. The results are listed in Tables 4–6. For unitary discussion, the permanent substituent $-CH_2OH$ located at C-5 is considered as reference in all structures and protons are labelled as ***c*** (*cis*) and ***t***

Table 4. Relevant ^{1}H NMR data (δ, ppm and J, Hz) for the compound **4a** and *cis* diastereomers **4b**, **4d–k** (**bold**, signals irradiated in NOE-difference experiments; *italics*, signals where NOE-difference was observed)

No.	R[1]	Solvent	H-2c (H-8c)	H-2t (H-8t)	H-4c (H-6c)	H-4t (H-6t)	$-CH_2-$ (C-5)	$-OH$
4a	H	DMSO-d_6	*4.26(d) J*=5.5	4.39(d) *J*=5.5	*3.66(d) J*=8.6[b]	3.71(d) *J*=8.6	**3.43(d)** *J*=5.4**a**	*4.89(t) J*=5.4
		Toluene-d_8	3.94(d) *J*=4.4	4.14(d) *J*=4.4	3.28(d) *J*=8.5	3.45(d) *J*=8.5	3.15(d) *J*=4.7	2.87(tc)
4b	Ph	DMSO-d_6	–	**5.58(s)**	3.93(d) *J*=8.8	*3.82(d) J*=8.8	3.33(t) *J*=5.1	4.90(t) *J*=5.1
		Toluene-d_8	–	5.32(s)	3.77(d) *J*=8.7	3.52(d) *J*=8.7	3.17(s)	–
4d	*o*-$O_2N-C_6H_4-$	DMSO-d_6	–	6.39(s)	*3.71(d) J*=8.9	3.88(d) *J*=8.9	**3.25(d)** *J*=5.0	*4.99(t) J*=5.0
4e	Bz	DMSO-d_6	–	6.28(s)	*4.12(d) J*=8.6	4.02(d) *J*=8.6	**3.40(d)** *J*=5.3	*4.87(t) J*=5.3
4f	Ph_3C-CH_2-	DMSO-d_6	–	*3.50(d) J*=6.9	*3.17(d) J*=8.9	**3.80*(d)*** *J*=8.9	3.57(d) *J*=3.0	5.02(tc)[a]
		C_6D_6	–	4.09(d) *J*=7.1	2.97(d) *J*=8.9	3.57(d) *J*=8.9	3.34(s)	1.48(bs)
4g	2-Py	DMSO-d_6	–	5.64(s)	*4.10(d) J*=8.6	3.84(d) *J*=8.6	**3.47(d)** *J*=5.0	*5.16(d) J*=5.0
4h	3-Py	DMSO-d_6	–	5.74(s)	*3.93(d) J*=9.0	3.86(d) *J*=9.0	**3.33(d)** *J*=5.3	*5.01(d) J*=5.3
4i	4-Py	DMSO-d_6	–	5.73(s)	–[b]	–[b]	3.26(d) *J*=4.0	4.97(t) *J*=4.0
4j	2-Furyl	DMSO-d_6	–	**5.69(s)**	3.94(d) *J*=8.8	*3.77(d) J*=8.8	3.49(d) *J*=5.5	5.00(t) *J*=5.5
4k	3-Thienyl	DMSO-d_6	–	5.60(s)	3.89(d) *J*=8.7	3.76(d) *J*=8.7	3.36(d) *J*=5.3	4.91(d) *J*=5.3

[b] Overlapped signals.
[a] (tc) triplet at coalescence.

(*trans*) indices according to the hydroxymethyl group position.

The parent compound **4a** has a different stereochemistry than all the other terms of the series **4–7**. Thus, all *cis* protons H-2*c*, H-8*c* and H-4*c*, H-6*c* are more shielded than the corresponding *trans* ones despite their *cis* arrangement with respect to the lone pair at N-1. Examination of the conformational equilibrium depicted in Scheme 6 and the *gauche* interactions with the lone-pairs at N-1 and O-3(7) show that protons H-*c* are successively placed *gauche* with both lone pairs at O-3(7) in a conformation in which their position is equatorial, hence NOE-difference is not observed (Table 4, Scheme 2). NOE-difference was normally expected when the positions of H-2*c*, -8*c* and H-4*c*, -6*c* were axial but the deshielding *gauche* arrangement is now valid for H-2*t*, -8*t* and H-4*t*, -6*t* (placed in equatorial position, less accessible to NOE detection).

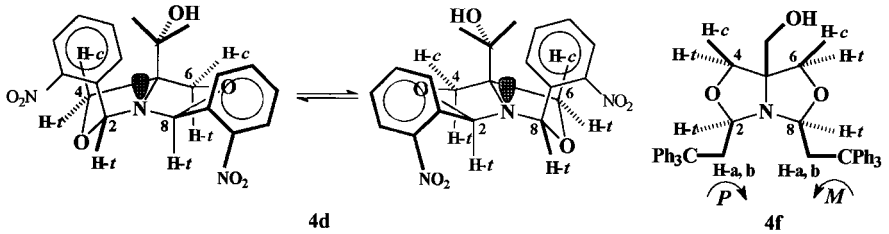
Insertion of two (hetero)aryl groups at C-2 and C-8. For the *cis* diastereomers **4b**, **d–k** the following aspects are worth mentioning (Table 4, Scheme 2):

- NOE-difference experiments have demonstrated that protons H-4*c*, 6*c* are constantly more deshielded than H-4*t*, -6*t* ones, in agreement with the *cis* position of the two C-2, -8 (hetero)aromatic rings, and with their plausible preference for a bisectonal rotamer (exposure to the deshielding zone).
- Compound **4d** should be seen as an exception since δ-values (discriminated by NOE-difference experiments) have indicated the shielding of H-4*c*, -6*c* protons vs. H-4*t*, -6*t*. This fact may be correlated with the proposed orthogonal positions (preferred rotamer) of *o*-nitrophenyl fragments (which imposes restrictions of their free rotation) and the flexibility of the basic molecular skeleton (Scheme 10).

Thus, protons *cis* located (when axial) are, this time, placed successively in the shielding zone of the aromatic ring.

Furthermore, exciting results also arose from analysis of compound **4f** in connection with the same hindrance of free rotation at C-2 and C-8. The ^{1}H NMR spectra performed in DMSO-d_6 and C_6D_6 revealed a strong geminal anisochronism of the α-position vs. triphenylmethyl group: $\Delta\delta$H-a, -b=0.44 ppm (DMSO-d_6) and 0.50 ppm (C_6D_6) (Scheme 10, Figs. 5 and 6). In turn, the two α-methylene groups are isochronous, as the positions H-4*c* vs. H-6*c* and H-4*t* vs. H-6*t*.

The single explanation found is, in our opinion, the helical arrangement of the six (3+3) phenyl groups, required by their linkage in a structure of type **4** (we mention that the



Scheme 10.

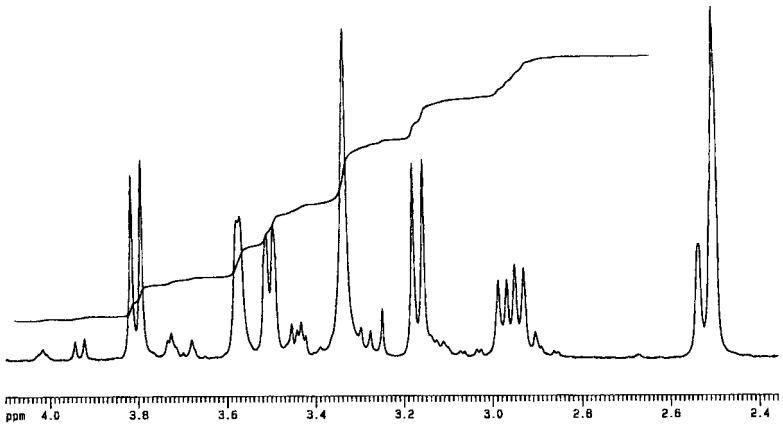


Figure 5. ^{1}H NMR spectrum of the compound **4f**; solvent DMSO-d_6, 400 MHz; from downfield to upfield (δ, ppm):3.80 (d, H-4, -6*t*); 3.57 (d, –CH_2OH); 3.50 (d, H-2, -8*t*); 3.17 (d, H-4, -6*c*); 2.96 (dd, H-a, -b); 2.52 (d, H-b, -a).

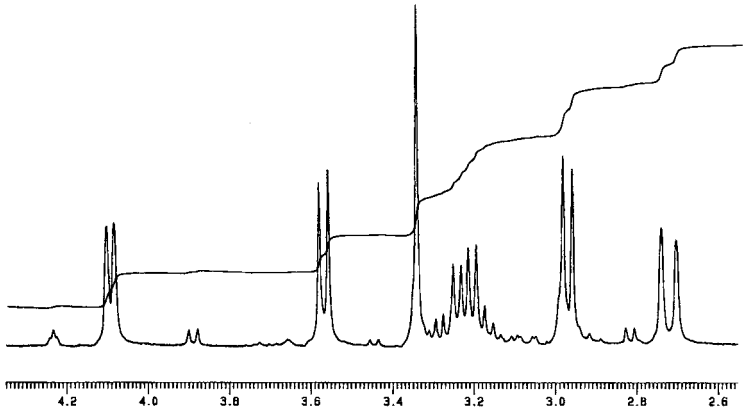


Figure 6. ^{1}H NMR spectrum of the compound **4f**; solvent C_6D_6, 400 MHz; from downfield to upfield (δ, ppm): 4.09 (d, H-2, -8*t*); 3.57 (d, H-4, -6*t*); 3.34 (s, –CH_2OH); 3.22 (dd, H-a, -b); 2.97 (d, H-4, -6*c*), 2.72 (d, H-b, -a).

Table 5. Relevant ^{1}H NMR data (δ, ppm and *J*, Hz) for the *trans* diastereomers **4b–e**, **h–k** (**bold** shows signals irradiated in NOE-difference experiments; *italics* shows signals where NOE-difference was observed)

No.	R^1	H-2*t*	H-8*c*	H-4*c*	H-4*t*	H-6*c*	H-6*t*	–CH_2– (C-5)	–O*H*
4b	Ph	5.10(s)	5.51(s)	4.07(d) *J*=8.8	3.82(d) *J*=8.8	3.76(d) *J*=8.8	4.09(d) *J*=8.8	3.65(s)	–[a]
4c	*p*-O_2N–C_6H_4–	5.10(s)	*5.65(s)*	*4.12(d)* *J*=8.8	3.86(d) *J*=8.8	*3.85(d)* *J*=8.7	4.13(d) *J*=8.7	**3.66(d)** *J*=5.4	*5.15(m)* *J*=5.2 10.7
4d	*o*-O_2N–C_6H_4–	5.56(s)	6.07(s)	3.92(d) *J*=8.8	3.85(d) *J*=8.8	3.68(d) *J*=8.8	4.11(d) *J*=8.8	3.65(d) *J*=5.1	5.17(m) *J*=5.1
4e	Bz	5.25(s)	5.90(s)	–[a]	–[a]	–[a]	–[a]	–[a]	–[a]
4h	3-Py	5.11(s)	5.56(s)	4.11(d) *J*=8.7	3.81(d) *J*=8.7	3.80(d) *J*=8.9	4.20(d) *J*=8.9	–[a]	–[a]
4i	4-Py	5.02(s)	*5.54(s)*	*4.03(d)* *J*=8.9	3.85(d) *J*=8.9	*3.82(d)* *J*=8.8	4.09(d) *J*=8.8	**3.63(d)** *J*=3.9[a]	*5.14(tc)*[b]
4j	2-Furyl	5.40(s)	5.47(s)	3.94(d) *J*=8.6	3.85(d) *J*=8.6	3.79(d) *J*=8.7	4.01(d) *J*=8.7	3.59(d) *J*=5.4	5.09(t) *J*=5.4
4k	3-Thienyl	5.26(s)	5.51(s)	–[a]	–[a]	–[a]	–[a]	–[a]	–[a]

[a] Overlapped signals.
[b] (tc): triplet at coalescence.

starting aldehyde exhibited no diastereotopicity of the same –CH_2– fragment but the expected doublet H-a, -b at 3.35 ppm, *J*=2.4 Hz). Thus, the two helix have an opposite sense (*M*+*P*) and the entire molecule is built as a *meso* form (the small peaks in Figs. 5 and 6 are assigned to *P*+*P* or *M*+*M* diastereomer).

For the *trans* compounds **4b–e**, **h–k**, definite discriminations from NMR point of view (Table 5, Scheme 2) were more difficult to ascertain because of the overlapping of signals in positions 4 and 6 (diastereotopic) or due to the very small differences of δ-values between *cis* and *trans* diastereomers.

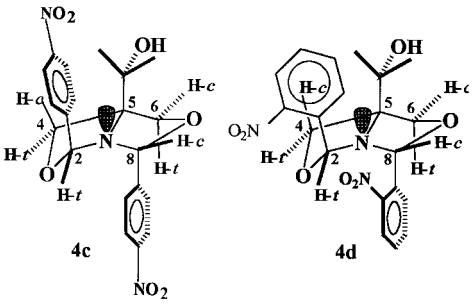
Therefore, since the compounds **4c** and **i** gave about the same results in NOE-difference experiments, the following extrapolations have been made for the entire series *trans* **4**.

- The deshielding promoted by the aromatic substituents, decreasing as H-6*t*≈H-4*c*>H-4*t*≈H-6*c*, is again motivated by the same preference for the bisectonal rotamers.
- $\Delta\delta$-values H-6*t*, -4*c* (the most deshielded protons) from

Table 6. Relevant ^{1}H NMR data (δ, ppm and J, Hz) of the compounds **5**–**7**, **11**, 1**3** (in **bold**, signals irradiated in NOE-difference experiments; in *italics*, signals where the NOE-difference was observed)

No.	H-2*t*	H-4*c*	H-4*t*	H-6*c*	H-6*t*	H-8*c*	H-8*t*	Others
5a (DMSO-d_6)	**5.36** (s)[a]	4.15 (d, 8.6)	*3.70* (d, 8.6)	*3.55* (d, 8.8)	**3.87** (d, 8.8)	4.16 (d, 6.7)	*4.62* (d, 6.7)	–CH_2OH 3.51 and 3.43 (dd, 5.3, 10.7)
5b (DMSO-d_6)	**5.38** (s)	4.17 (d, 8.7)	*3.71* (d, 8.7)	3.55 (d, 8.8)	3.88 (d, 8.8)	4.16 (d, 6.8)	*4.63* (d, 6.8)	–CH_2OH 3.52 and 3.45 (dd, 5.2, 10.8)
5c (DMSO-d_6)	**5.92** (s)	3.83 (d, 8.8)	*3.65* (d, 8.8)	3.80 (d, 8.8)	3.82 (d, 8.8)	4.26 (d, 6.2)	*4.64* (d, 6.2)	–CH_2OH 3.38 and 3.24 (dq, 4.0, 4.5, 10.6)
6a (DMSO-d_6)	–	*3.85* (d, 8.7)	3.76 (d, 8.7)	*3.87* (d, 8.8)	*3.64* (d, 8.8)	–	**5.93** (s)	–CH_2OH **3.35** and **3.17** (dq, 5.1, 5.6, 10.6)
6b (DMSO-d_6)	–	3.87 (d, 8.8)	3.76 (d, 8.8)	3.87 (d, 8.4)	*3.65* (d, 8.4)	–	**5.94** (s)	–CH_2OH 3.38 and 3.20 (dq, 4.7, 5.1, 10.3)
6c (DMSO-d_6)[b]	–	3.74 (d, 8.6)	3.57 overl.	4.16 (d, 8.6)	*3.57* (d, 8.6)	–	**5.43** (s)	–CH_2OH 3.53 and 3.45 (dd, 5.3, 10.4)
6d (DMSO-d_6)[b]	–	3.84 (d, 9.0)	3.68 (d, 9.0)	3.88 (d, 8.5)	*3.57* (d, 8.5)	–	**5.71** (s)	–CH_2OH 3.40 and 3.26 (dd, 5.3, 10.4)
7a-*cis* (DMSO-d_6)[b]	–	*3.84* (d, 8.9)	**3.72** (d, 8.9)	3.49 (d, 8.3)	*3.55* (d, 8.3)	3.94 (d, 7.6)	4.70 (d, 7.6)	–CH_2OH 3.45 and 3.39 (dd, 2.8, 10.6)
7b-*cis* (DMSO-d_6)	–	3.92 (d, 8.7)	3.59 (d, 8.7)	3.56 (d, 9.0)	3.73 (d, 9.0)	–	4.84 (t, 5.3)	–CH_2OH 3.41 and 3.30 (m)
***l*-, *u*-11a** ($CDCl_3$)	–	3.33 and 3.33 (d, 7.9)	3.60 and 3.61 (d, 7.9)	3.72 and 3.72 (d, 9.0)	3.78 and 3.79 (d, 9.0)	and 4.12 (d, 7.8)	4.75 and 4.75 (d, 7.8)	–CH_3 1.28 (s)
***l*-11a** (DMSO-d_6)	–	*3.22* (d, 7.9)	3.55 (d, 7.9)	*3.65* (d, 8.9)	3.82 (d, 8.9)	*3.99* (d, 7.8)	**4.70** (d, 7.8)	–CH_3 **1.21**(s)
***u*-11b** ($CDCl_3$)	–	3.43 (d, 7.9)	3.59 (d, 7.9)	3.74 (d, 8.9)	3.83 (d, 8.9)	4.05 (d, 7.7)	4.73 (d, 7.7)	–CH_2CH_3 1.62 and 1.64 (dd, 7.3, 14.2) –CH_2CH_3 0.90 (m, 7.4)
***l*-, *u*-11c** (CD_3OD)	–	3.57 (d, 8.5)	3.62 (d, 8.5)	3.77 (d, 9.1)	3.96 (d, 9.1)	4.03 (d, 7.7)	4.73 (d, 7.7)	–CH_2OH 3.51 (m)
***u*-13** (DMSO-d_6)	–	*3.58* (d, 8.8)	*3.60* (d, 8.8)	*3.58* (d, 8.8)	*3.78* (d, 8.8)	–	**5.78**(s)	–CH_3 **1.18** (s) H(arom.) 7.46 (s)

[a] **s**: singlet; **d**, doublet; **t**, triplet; **dd**, doublet of doublets; **dq**, doublet of quartets.
[b] See NMR data for the minor *trans* diastereomer in Experimental.



Scheme 11.

one hand and $\Delta\delta$-values H-4*t*,-6*c* (the most shielded protons) on the other hand, are surprisingly small (less than 0.1 ppm) and have suggested very similar environments between these positions. As an example (compound **4c**, Scheme 11), we assumed, for *trans* **4** series, a different geometry than predicted by the calculations (Scheme 9): in this type of *cis* fused structure, rigid from conformational point of view, the two oxazolidine rings are fused as a double envelope–envelope skeleton possessing a *trans* disposal of heterocyclic oxygens. Both aromatic rings (bisectonal rotamers) and protons H-4*c*, -6*t* have an axial position, in agreement with the deshielding observed.

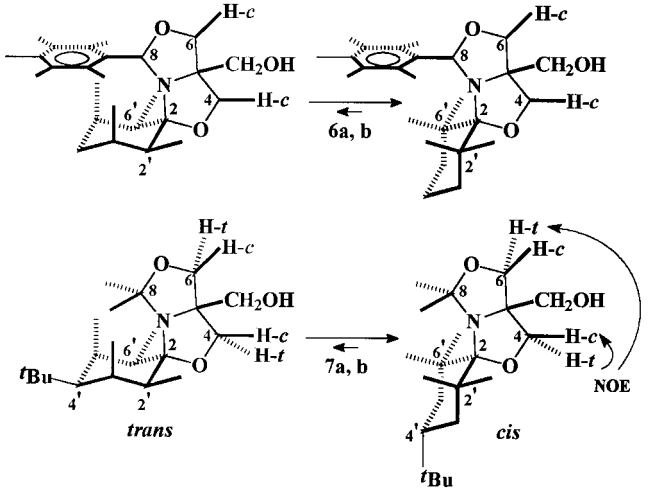
Manipulation of Dreiding models has confirmed that this orientation best allows the free rotation of the aromatic moieties. Then, as a consequence of the proposed geometry of the bicycle-skeleton (Scheme 11), protons H-4*t*, -6*c* are equatorial but H-4*t* is closer to the aromatic fragment (linked to C-8) than H-6*c*. All these steric assignments have been supported by three pieces of NMR evidence.

(a) The diastereotopicity $\Delta\delta$H-4*c*, -4*t* (0.07–0.30 ppm) is constantly smaller than $\Delta\delta$H-6*t*, -6*c* (0.22–0.43 ppm) because protons H-4 are, by their disposal, more influenced by the aromatic vicinity than H-6.
(b) NOE-difference experiment (Table 5, compound **4c**) (irradiation of the methylene C-5 group) showed unambiguously a stronger enhancement at H-4*c* (axial) than H-6*c* (equatorial).
(c) The protons H-8*c* are constantly more deshielded than H-2*t* (see Table 3).

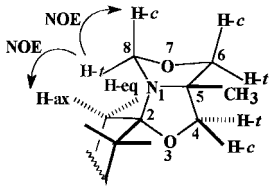
As in the *cis* series, the analog *trans*-di(*o*-nitro)derivative **4d** was once more an extreme case since it exhibited the smallest diastereotopicity at C-4 (0.07 ppm) but the greatest one at C-6 (0.43 ppm). Inspection of Dreiding models (Scheme 11, compound **4d**) have indicated that the *o*-nitrophenyl group linked to C-8 (placed *trans* vs. the C-5 hydroxymethyl group) encounters serious restriction of its rotation and a bisectonal position of this ligand is consistent with the deshielding observed. In turn, the same group, but placed *cis* (linked to C-2) is, for the same reason, very likely in an orthogonal position and the C-4 methylene is more shielded.

- Surprisingly, although the *trans* diastereomers are intrinsic chiral forms, no diastereotopicity has been detected concerning the C-5 methylene group; in turn, the conformation of $-CH_2OH-$group (for entire series **4**, at least in DMSO-d_6) should consist with the hydroxyl proton oriented *out* of the molecule, in order to develop the well-known chelate with the solvent (see the shape of the –O*H* signal and its corresponding $J_{vicinal}$ values). Consequently, C-5 methylene protons are oriented *in*, closer to the deshielding C-2 and C-8 substituents (a different stereochemistry than previously reported, if a freely rotating Me-group is linked to C-5, Crabb et al.[17]). In $CDCl_3$ this diastereotopicity was clearly exhibited by some of the compounds *trans* **4** (if soluble); the broad singlet detected and assigned to –O*H* suggests an intramolecular hydrogen bond with the N-1 lone pair (oriented *in*); consequently, the adjacent methylene is supposed to be oriented *out*.
- All geminal couplings are consistent with the proposed structures but their magnitude has revealed no remarkable dependence regarding the substituents at C-2, -8 as previously noticed for other trisubstituted 1-aza-3,7-dioxabicylo[3.3.0]octanes.[17–21]

Insertion of two different ligands at C-2 and C-8 (Table 6, Schemes 3–5). In the series **5**, **6** one can observe the same influence of the aromatic ring, linked to positions C-2 or C-8 as in the *cis* series **4b–k**: the *cis* arrangement between aryl and $-CH_2OH$ groups has promoted the deshielding of



Scheme 12.



Scheme 13.

positions H-4*c* vs. H-4*t* (**5a**–**c**) or H-6*c* vs. H-6*t* (**6a**–**d**). In turn, in the adjacent oxazolidine ring (compounds **5**) positions 6*c* are shielded vs. 6*t* as in the parent compound **4a**; that is, if no ligand is attached to C-8, no preferred rotamer can be predicted because of the free rotation of the C-2 nitrophenyl fragment.

If a C_{4-6} alicyclic system has been attached at C-2 as a spirane moiety (series **6**), we note a combined effect that makes protons H-*c* more deshielded than *trans* ones in both oxazolidine rings. That is, the steric hindrance promoted by the alicyclic fragment to the less free rotation of the aromatic ring makes the differences between *cis* environments (defined as $\Delta\delta$H-4*c*, -6*c*) unexpectedly small [signals (nearly)overlapped (**6a**, **b**, **d**)]. On the other hand, it is expected that, at least for the spirocyclohexyl fragment (compounds **6a**, **b**), its conformational equilibrium is almost completely shifted towards the conformer in which the N-1 ligand is placed in an equatorial position (Schemes 12 and 13).

In this context, significant details are provided by the analysis of compounds **7**. Since the alicycle fragment is now an authentic ananchomeric structure, its stereochemistry could be revealed more easily by means of NOE-difference experiments. Thus, compound **7a** (bearing no bulky ligand at C-8) has been isolated as a mixture of *cis*–*trans* diastereomers (Table 6) (O-3 and 4′-*t*-Bu group as reference) and the major *cis* diastereomer also possesses the N-1 ligand in equatorial position (Scheme 12). If an *n*-hexyl fragment has been linked to C-8 the diastereoselectivity become complete. The NOE-difference experiment performed on H-4*t* (Table 6, compound **7a-*cis***) has shown no enhancements on the alicyclic region, but the expected ones at H-4*c* and H-6*t*, to confirm the above assignments.

As the parent compound **4a**, the dispirane compounds **11** (Scheme 4) have exhibited the shielding of heterocyclic *cis* protons (H-4*c*, -6*c*, -8*c*) vs. *trans* (H-4*t*, -6*t*, -8*t*). Their analysis confirmed the ananchomericity of the cyclohexane fragment and the *trans* diequatorial disposal of the aminic (N-1, N-1′) ligands by successive NOE-difference experiments. They made possible not only discrimination between *cis* and *trans* positions of the basic azadioxabicyclooctane system but also revealed a single enhancement in the cyclohexane moiety, assigned to axial position, closer to H-8*t* (**11a**, Scheme 13).

If flipping, the cyclohexane fragment had exhibited two different enhancements; moreover, in complete agreement with two *trans* diaxial oxygen atoms is the deshielding of axial positions with respect to equatorial ones in the alicycle (see also Fig. 1).

Conclusion

1-Aza-3,7-dioxa-2,5,8-trisubstituted-bicyclo[3.3.0]octanes are formed in the reaction of TRIS (α,α,α-trimethylolaminomethane) with two equivalents of aldehyde and *all-cis* disposal of the three ligands is the dominant diastereoselectivity; in this case, they are flipping structures, at r.t. The NMR values are strongly influenced by the preferred rotamer, depending on the (hetero)aromatic ligand linked to C-2(8). Structures bearing different substituents at C-2 and C-8 are also readily available from TRIS and some of its analogues but for the moment, only as racemic mixtures. Induction of a chiral centre in one of the oxazolidine rings, with good diastereoselectivity, does not require the previous existence of a stereodirecting substituent on the other ring. Two azadiozabicyclooctane units can be linked together as a dispiranic structure but diastereoselectivity is poor. Linkage as disubstituted 1,4-phenylene unit is much more promising from this point of view, as shown from our preliminary data.

Experimental

Mass spectra were recorded on ATI UNICAM Automass System 2 by electronic impact at 70 eV. All reactions were monitored by TLC on MERCK silica gel, by using benzene/methanol 3:1 or benzene/acetone 3:1 v/v as eluent (double visualisation: I_2 bath and UV where appropriate). Other eluents used will be further mentioned. RHF/6-21G* molecular orbital calculations were performed by using Spartan 5.0 package of programs; Spartan version 5.0, Wavefunction, Inc. 18401 Von Karman Avenue, Suite 370, Irvine, CA 92612, USA.

See preceding paper for other experimental protocols.

Typical procedure for preparing compounds 4

TRIS (1.50–3.00 g), as 0.25–0.5 M benzene or toluene solution (1–5 mol% *p*-TsOH as catalyst) and a slight excess (2–5%) of the stoichiometric amount of the aldehyde were refluxed in a Dean–Stark trap with continuous removal of water until the starting materials were detected by TLC in small traces only.

The work-up of the reaction mixture followed one of the following routes.

- A—If the desired compound was soluble in aromatic solvent, the solution was decanted from the unreacted TRIS, neutralised with solid Na_2CO_3 and concentrated in vacuo. The residue was crystallised from an appropriate solvent to yield the first crystalline crop (see Table 1).
- B—If the desired compound was insoluble in aromatic solvent, the reaction mixture was concentrated in vacuo and the residue was crystallised from an appropriate solvent to yield the crude product. The unreacted TRIS was then removed by washing at 0°C with a minimum amount of cold methanol, to yield the first crystalline crop.
- C—If none of the above methods was suitable, the reaction mixture was concentrated in vacuo and the residue was taken with dichloromethane; the unreacted TRIS was

filtered off and the solution was neutralised with solid Na_2CO_3. After filtering, the solution was evaporated in vacuo to afford the crude product, which was purified by flash column chromatography. Diastereomeric mixtures (compounds **4e**, **j**) were isolated as a single fraction.

Compound yield (%), method of isolation, mp (solvent), elemental analysis and NMR data (if not collected in Table 4–6 or Figures) are listed below. Compound **4a** was prepared according to literature.[4]

r*-1-Aza-*c*-5-hydroxymethyl-3,7-dioxa-*c*-2-*c*-8-diphenylbicyclo[3.3.0]octane (87%), 4b-*cis* and *r*-1-aza-*c*-5-hydroxymethyl-3,7-dioxa-*c*-2-*t*-8-diphenylbicyclo[3.3.0]octane (13%), 4b-*trans*.** White crystalline powder; 90; A; 71–78(Et_2O); Anal. Calcd for $C_{18}H_{19}NO_3$: C 72.70%, H 6.44%, N 4.71%. Found: C 72.50%, H 6.50%, N 5.00%. **4b-*cis ^{13}C NMR (δ, ppm, 75 MHz, DMSO-d_6): 140.3 (2C), 128.2 (4C), 128.1 (4C), 126.9 (2C), 96.3 (2C, C-2, C-8), 74.3 (1C, C-5), 72.7 (2C, C-4, -6), 66.0 (1C, $-CH_2OH$); **4b-*trans*** ^{13}C NMR (δ, ppm, 75 MHz, DMSO-d_6, only distinct peaks are mentioned): 93.4 and 92.2 (2C, C-2, –C-8), 74.3 and 74.1 (2C, C-4, -6), 72.7 (1C, C-5), 65.2 (1C, $-CH_2OH$). Pure diastereomer ***r*-1-aza-*c*-5-hydroxymethyl-3,7-dioxa-*c*-2-*c*-8-diphenylbicyclo[3.3.0]octane 4b-*cis*** white crystalline powder; –; A; 95–96(Et_2O) (lit.[5]: 93–95) was isolated from the mixture by washing the crude reaction mixture with excess of ether.

***r*-1-Aza-*c*-5-hydroxymethyl-*c*-2-*t*-8-di(4-nitrophenyl)-3,7-dioxabicyclo[3.3.0]octane, 4c-*trans*.** Yellowish crystalline powder; 91; **A**; 182–184(Et_2O) (lit: 235–237[9,12]). Anal. Calcd for $C_{18}H_{17}N_3O_7$: C 55.81%, H 4.42%, N 10.85%. Found: C 56.00%, H 4.37%, N 11.15%. ^{13}C NMR (δ, ppm, 75 MHz, DMSO-d_6): 147.3 (1C), 147.2 (1C), 141.5 (2C), 128.6 (2C), 128.3 (2C), 123.1 (2C), 122.6 (2C), 92.0 and 91.1 (2C, C-2, -8), 74.4 and 74.3 (2C, C-4, -6), 72.5 (1C, C-5), 64.7 (1C, $-CH_2OH$).

r*-1-Aza-*c*-5-hydroxymethyl-*c*-2-*c*-8-di(2-nitrophenyl)-3,7-dioxabicyclo[3.3.0]octane (78%), 4d-*cis and ***r*-1-aza-*c*-5-hydroxymethyl-*c*-2-*t*-8-di(2-nitrophenyl)-3,7-dioxabicyclo-[3.3.0]octane (22%), 4d-*trans*.** Yellowish crystalline powder; 77; A; 148–149(Et_2O). Anal. Calcd for $C_{18}H_{17}N_3O_7$: C 55.81%, H 4.42%, N 10.85%. Found: C 56.09%, H 4.77%, N 10.45%. **4d-*cis*** ^{13}C NMR (δ, ppm, 75 MHz, DMSO-d_6): 148.8 (2C), 134.1 (2C), 132.6 (2C), 129.6 (2C), 128.7 (2C), 124.4 (2C), 94.6 (2C, C-2, -8), 74.4 (1C, C-5), 72.9 (2C, C-4, -6), 64.8 (1C, $-CH_2OH$). **4d-*trans*** ^{13}C NMR (δ, ppm, 75 MHz, DMSO-d_6, only distinct peaks are mentioned): 148.2 (1C), 147.0 (1C), 133.7 (1C), 133.2 (1C), 1304 (1C), 1298 (1C), 128.4 (1C), 128.0 (1C), 124.6 (1C), 123.6 (1C), 89.1 and 87.3 (2C, C-2, -8), 74.4 (1C, C-5), 73.9 and 72.2 (2C, C-4, -6), 64.3 (1C, $-CH_2OH$).

r*-1-Aza-*c*-2-*c*-8-dibenzoyl-*c*-5-hydroxymethyl-3,7-dioxabicyclo[3.3.0]octane (95%), 4e-*cis and ***r*-1-aza-*c*-2-*t*-8-dibenzoyl-*c*-5-hydroxymethyl-3,7-dioxabicyclo[3.3.0]octane (5%), 4e-*trans*.** White crystalline powder; 52; C (eluent toluene/acetone 3:1 v/v); 113–114(pentane). Anal. Calcd for $C_{20}H_{19}NO_5$: C 67.97%, H 5.42%, N 3.96%. Found: C 67.75%, H 5.80%, N 3.90%. **4e-*cis*** ^{13}C NMR (δ, ppm, 100 MHz, DMSO-d_6): 194.9 (2C, >C═O), 134.6, (2C), 133.4 (2C), 128.8 (4C), 128.5 (4C), 95.4 (2C, C-2, -8), 74.8 (2C, C-4, -6), 74.0 (1C, –C-5), 65.1 (1C, $-CH_2OH$).

r*-1-Aza-*c*-5-hydroxymethyl-3,7-dioxa-*c*-2-c-8-di(2,2,2-triphenylethyl)-bicyclo[3.3.0]octane (95%), 4f-*cis*.** White crystalline powder; 85; B; 112–113(heptane). Anal. Calcd for $C_{46}H_{43}NO_3$: C 83.98%, H 6.58%, N 2.13%. Found: C 83.90%, H 6.33%, N 2.30%. **4f-*cis ^{13}C NMR (δ, ppm, 100 MHz, DMSO-d_6): 147.4 (6C), 129.7 (12C), 129.6 (12C), 126.0 (6C), 95.6 (2C, C-2, -8), 73.0 (2C, C-4, -6), 71.9 (1C, C-5), 65.9 (1C, $-CH_2OH$), 56.5 (2C, $-CPh_3$), 46.9 (2C, $-CH_2-$).

***r*-1-Aza-*c*-5-hydroxymethyl-3,7-dioxa-*c*-2-*c*-8-di(2-pyridin-1yl)-bicyclo[3.3.0]octane, 4g-*cis*.** Yellowish crystalline powder; 93; B; 89–90(Et_2O); Anal. Calcd for $C_{16}H_{17}N_3O_3$: C 64.20%, H 5.72%, N 14.04%. Found: C 63.95%, H 6.04%, N 13.98%. ^{13}C NMR (δ, ppm, 75 MHz, DMSO-d_6): 159.1 (2C), 148.7 (2C), 136.8 (2C), 123.3 (2C), 121.0 (2C), 97.8 (2C, C-2, -8), 74.8 (1C, C-5), 72.2 (2C, C-4, -6), 65.3 (1C, $-CH_2OH$).

r*-1-Aza-*c*-5-hydroxymethyl-3,7-dioxa-*c*-2-*c*-8-di(3-pyridin-1yl)-bicyclo[3.3.0]octane (93%), 4h-*cis* and *r*-1-aza-*c*-5-hydroxymethyl-3,7-dioxa-*c*-2-*t*-8-di(3-pyridin-1yl)-bicyclo[3.3.0]octane (7%), 4h-*trans*.** Yellowish crystalline powder; 20; B; 95–100 (Et_2O+ligroine); Anal. Calcd for $C_{16}H_{17}N_3O_3$: C 64.20%, H 5.72%, N 14.04%. Found: C 64.44%, H 6.02%, N 14.33%. **4h-*cis ^{13}C NMR (δ, ppm, 75 MHz, DMSO-d_6): 149.5 (2C), 148.4 (2C), 135.5 (2C), 134.8 (2C), 123.4 (2C), 94.5 (2C, C-2, -8), 74.6 (1C, C-5), 72.5 (2C, C-4, -6), 65.5 (1C, $-CH_2OH$).

r*-1-Aza-*c*-5-hydroxymethyl-3,7-dioxa-*c*-2-*c*-8-di(4-pyridin-1yl)-bicyclo[3.3.0]octane (25%), 4i-*cis* and *r*-1-aza-*c*-5-hydroxymethyl-3,7-dioxa-*c*-2-*t*-8-di(4-pyridin-1yl)-bicyclo[3.3.0]octane (75%), 4i-*trans*.** White crystalline powder; 65; B; 122–136(Et_2O); Anal. Calcd for $C_{16}H_{17}N_3O_3$: C 64.20%, H 5.72%, N 14.04%. Found: C 64.51%, H 5.49%, N 14.40%. **4i-*cis ^{13}C NMR (δ, ppm, 75 MHz, DMSO-d_6, only distinct peaks are mentioned): 149.7 (2C), 149.0 (4C), 121.7 (4C), 95.1 (2C, C-2, -8), 72.6 (2C, C-4, -6), 65.4 (1C, $-CH_2OH$); **4i-*trans*** ^{13}C NMR (δ, ppm, 75 MHz, DMSO-d_6): 149.5 (2C), 149.2 (2C), 148.5 (1C), 143.0 (1C), 121.8 (2C), 121.7 92C), 91.8 and 90.8 (2C, C-2, -8), 74.1 and 72.5 (2C, C-4, -6), 72.6 (1C, C-5), 64.5 (1C, $-CH_2OH$).

r*-1-Aza-*c*-2-*c*-8-di(2-furyl)-*c*-5-hydroxymethyl-3,7-dioxabicyclo[3.3.0]octane (67%), 4j-*cis* and *r*-1-aza-*c*-2-*t*-8-di-(2-furyl)-*c*-5-hydroxymethyl-3,7-dioxabicyclo[3.3.0]-octane (33%), 4j-*trans*.** Yellowish oil; 17; C (eluent toluene/AcOEt 1:1 v/v). Anal. Calcd for $C_{14}H_{15}NO_5$: C 60.64%, H 5.45%, N 5.05%. Found: C 61.01%, H 5.49%, N 4.98%. **4j-*cis ^{13}C NMR (δ, ppm, 100 MHz, DMSO-d_6): 153.0 (2C), 110.0 (4C), 108.3 (2C), 91.4 (2C, C-2, -8), 73.9 (1C, C-5), 72.1 (2C, C-4, -6), 65.5 (1C, $-CH_2OH$). **4j-*trans*** ^{13}C NMR (δ, ppm, 100 MHz, DMSO-d_6 only distinct peaks are mentioned): 152.7 (1C), 148.2 (1C), 110.3 (1C), 110.1 (1C), 109.9 (1C), 107.9 (1C), 88.4 and 86.5 (2C, C-2, -8), 73.6 and 72.3 (2C, C-4, -6), 73.5 (1C, C-5), 64.7 (1C, $-CH_2OH$).

r*-1-Aza-*c*-5-hydroxymethyl-3,7-dioxa-*c*-2-*c*-8-di(3-thienyl)-bicyclo[3.3.0]octane (96%), 4k-*cis* and *r*-1-aza-*c*-5-hydroxymethyl-3,7-dioxa-*c*-2-*t*-8-di(3-thienyl)-bicyclo-[3.3.0]octane (4%), 4k-*trans*.** White crystalline powder; 37; B; 105–106(Et_2O+pentane). Anal. Calcd for $C_{14}H_{15}NO_3S_2$: C 54.35%, H 4.88%, N 4.53%; S 20.72%%. Found: C 54.50%, H 4.45%, N 4.66%, S 21.11%. **4k-*cis ^{13}C NMR (δ, ppm, 100 MHz, DMSO-d_6): 142.6 (2C), 126.6 (4C), 123.5 (2C), 93.4 (2C, C-2, -8), 74.1 (1C, C-5), 72.5 (2C, C-4, -6), 66.0 (1C, $-CH_2OH$).

Typical procedure for the synthesis of compounds 5

TRIS (2.50 g, 0.02 mol) and the corresponding nitrobenzaldehyde (3.1 g, 0.02 mol) in benzene (50 mL, *p*-TsOH as catalyst) were refluxed in a Dean–Stark trap with vigorous stirring and continuous removal of water. After 10 h TLC monitoring (eluent benzene/acetone 4:1/I_2 bath) indicated the unreacted TRIS only in small traces. Paraformaldehyde (0.6 g, 0.02 mol) was then added to the reaction mixture which was refluxed with removal of water for additional 1.5 h. After cooling at room temperature, solid Na_2CO_3 (0.5 g) was added with stirring, then filtered. The benzene was removed under vacuum to yield the crude reaction mixture which was crystallised from an appropriate solvent (**5a**) or purified by flash chromatography on silica gel (**5b**, **c**).

Compounds, yields (%), mp (°C), elemental analysis and NMR data (if not collected in Table 6) are listed below. Synthesis of the compounds **8** and **9** was described elsewhere.[25]

(1*R,2*R**,5*S**)-1-Aza-5-hydroxymethyl-2-(4-nitrophenyl)-3,7-dioxabicyclo[3.3.0]octane, 5a.** Yellowish powder; 77; 84–85(Et_2O). Anal. Calcd for $C_{12}H_{14}N_2O$: C 54.13%, H 5.30%, N 10.52%. Found: C 54.25%, H 4.98%, N 10.55%. ^{13}C NMR (DMSO-d_6, 75 MHz, δ, ppm): 147.8 (1C), 147.0 (1C), 128.5 (2C), 123.3 (2C), 96.6 (1C, C-8), 84.4 (1C, C-2), 74.1 and 72.4 (2C, C-4, -6), 73.8 (C-5), 64.8 (1C, $-CH_2OH$).

(1*R,2*R**,5*S**)-1-Aza-5-hydroxymethyl-2-(3-nitrophenyl)-3,7-dioxabicyclo[3.3.0]octane, 5b.** Yellowish oil (benzene/acetone 4:1 v/v); 62. Anal. Calcd for $C_{12}H_{14}N_2O_5$: C 54.13%, H 5.30%, N 10.52%. Found: C 54.39%, H 5.51%, N 10.46%. ^{13}C NMR (DMSO-d_6, 75 MHz, δ, ppm): 148.3.7 (1C), 141.9 (1C), 133.5 (1C), 129.6 (1C), 123.9 (1C), 122.3 (1C), 97.5 (1C, C-2), 85.1 (1C, C-8), 74.6 and 72.0 (2C, C-4, -6), 74.2 (1C, C-5), 65.0 (1C, $-CH_2OH$).

(1*R,2*R**,5*S**)-1-Aza-5-hydroxymethyl-2-(2-nitrophenyl)-3,7-dioxabicyclo[3.3.0]octane, 5c.** Yellow oil (benzene/acetone 4:1 v/v); 65. Anal. Calcd for $C_{12}H_{14}N_2O_5$: C 54.13%, H 5.30%, N 10.52%. Found: C 53.90%, H 5.55%, N 10.22%. ^{13}C NMR (DMSO-d_6, 75 MHz, δ, ppm): 149.2 (1C), 134.3 (1C), 132.6 (1C), 129.5 (1C), 128.6 (1C), 124.0 (1C), 94.1 (1C, C-2), 86.6 (1C, C-8), 73.6 and 73.3 (3C, C-4, -5, -6), 64.8 (1C, $-CH_2OH$).

Typical procedure for the synthesis of compounds 6

The corresponding spirane **8**, (0.01 mol) in anhydrous benzene (50 mL, *p*-TsOH as catalyst) was brought to reflux in a Dean–Stark trap with vigorous stirring. The corresponding aldehyde (0.01 mol for **8b** but 0.033–0.025 mol for **8a**, **c**) was then added very slowly (2–3 h) as 10% benzene solution. The reaction mixture was then kept under reflux with continuous removal of water (about 12 h) until the starting material was detected in small traces only (TLC monitoring, eluent benzene/acetone 4:1 v/v for **6a**, **b**, pentane/AcOEt 2.5:1 v/v for **6c**, **d**/I_2 bath). In the case of compounds **6c**, **d** the unreacted spirane **8a**, **c** was removed by hot filtering the reaction material. After cooling at room temperature, solid Na_2CO_3 (0.5 g) was added with stirring for additional 0.5 h, then filtered off. The benzene filtrate was removed under vacuum to yield the crude reaction mixture that was crystallised from an appropriate solvent (**6a**) or purified by flash chromatography on silica gel (**6b**–**d**).

Compounds, yields (%), mp (°C), elemental analysis and NMR data (if not collected in Table 6) are listed below.

(1*S,8*R**,5*R**)-1-Aza-5-hydroxymethyl-8-(4-nitrophenyl)-3,7-dioxa-2-spirocyclohexyl-bicyclo[3.3.0]octane, 6a.** White crystalline powder; 52; 96-7(toluene/ligroine 1:1). Anal. Calcd for $C_{17}H_{22}N_2O_5$: C 61.07%, H 6.63%, N 8.38%. Found: C 60.95%, H 6.91%, N 8.00%. ^{13}C NMR (DMSO-d_6, 75 MHz, δ, ppm): 149.2 (1C), 147.2 (1C), 128.2 (2C), 123.2 (2C), 96.6 (1C, C-8), 89.8 (1C, C-2), 73.9 (1C, C-5), 73.2 and 69.9 (2C, C-6, -4), 66.5 (1C, $-CH_2OH$), 36.9 (1C), 31.6 (1C), 24.7 (1C), 23.1 (1C), 23.0 (1C).

(1*S,8*R**,5*R**)-1-Aza-5-hydroxymethyl-8-(3-nitrophenyl)-3,7-dioxa-2-spirocyclohexyl-bicyclo[3.3.0]octane, 6b.** Yellow oil (benzene/acetone 4:1 v/v); 65. Anal. Calcd for $C_{17}H_{22}N_2O_5$: C 61.07%, H 6.63%, N 8.38%. Found: C 61.31%, H 6.99%, N 8.44%. ^{13}C NMR (DMSO-d_6, 75 MHz, δ, ppm): 147.7 (1C), 133.7 (1C), 129.8 (1C), 122.9 (1C), 121.5 (1C), 96.6 (1C, C-2), 89.6 (1C, C-8), 73.9 (1C, C-5), 73.2 and 69.9 (2C, C-4, -6), 66.6 (1C, $-CH_2OH$), 36.9 (1C), 31.6 (1C), 24.8 (1C), 23.1 (1C), 22.9 (1C).

(1*S,8*R**,5*R**)-1-Aza-5-hydroxymethyl-3,7-dioxa-8-phenyl-2-spirocyclopentyl-bicyclo[3.3.0]octane (97%), 6c.** Yellow oil (pentane/AcOEt 2.5:1 v/v); 54. Anal. Calcd for $C_{16}H_{21}NO_3$: C 69.79%, H 7.69%, N 5.09%. Found: C 70.09%, H 7.51%, N 4.80%. ^{13}C NMR (DMSO-d_6, 100 MHz, δ, ppm): 145.8 (1C), 133.4 (2C), 133.1 (2C), 132.6 (1C), 110.6 (1C, C-2), 98.8 (1C, C-8), 79.2 and 74.6 (2C, C-4, -6), 78.9 (1C, C-5), 71.4 (1C, $-CH_2OH$), 41.9 (1C), 36.8 (1C), 27.4 (1C), 26.9 (1C). During the isolation by flash chromatography of this compound, its *trans* diastereomer (phenyl and hydroxymethyl groups as references) was also isolated, as the first fraction: **(1*S**,8*S**,5*R**)-1-Aza-5-hydroxymethyl-3,7-dioxa-8-phenyl-2-spirocyclopentyl-bicyclo-[3.3.0]octane** (3%), yellow oil; Anal. Calcd for $C_{16}H_{21}NO$: C 69.79%, H 7.69%, N 5.09%. Found: C 70.15%, H 7.88%, N 5.25%. ^1H NMR (DMSO-d_6, 400 MHz, δ, ppm and *J*, Hz): 7.50–7.22 (5H, m); 5.58 (1H, s, H-8); 4.90 (1H, t, 5.3, $-OH$); 3.94 (1H, d, 8.8, H-6); 3.82 (1H, d, 8.8, H-6); 3.81 (1H, d, 8.5, H-4); 3.80 (1H, d, 8.5, H-4); 3.45 (2H, m, $-CH_2OH$); 2.00–1.39 (8H, m); ^{13}C NMR (DMSO-d_6, 100 MHz, δ, ppm): 145.3 (1C), 133.4 (2C), 133.1 (2C), 132.9 (1C), 110.0 (1C, C-2), 101.3 (1C, C-8), 77.7 and 74.2 (2C, C-4, -6), 70.6 (1C, C-5), 67.1 (1C, $-CH_2OH$).

1-Aza-5-hydroxymethyl-3,7-dioxa-8-phenyl-2-spirocycloheptyl-bicyclo[3.3.0]octane, 6d. yellow oil (pentane/AcOEt 2.5:1 v/v); 54. Anal. Calcd for $C_{18}H_{25}NO_3$: C 71.26%, H 8.31%, N 4.62%. Found: C 70.99%, H 8.51%, N 4.80%. **(1*S**, 8*R**,5*R**)**-diastereomer (78%, *cis*); ^{13}C NMR (DMSO-d_6, 100 MHz, δ, ppm): 146.4 (1C), 133.1 (2C), 132.1 (2C), 131.9 (1C), 105.5 (1C, C-2), 96.1 (1C, C-8), 79.0 (1C, C-5), 77.9 and 74.8 (2C, C-6, -4), 71.7 (1C, –*C*H$_2$OH), 44.0 (1C), 39.6 (1C), 33.9 (1C), 33.7 (1C), 27.2 (1C), 26.7 (1C). **(1*S**,8*S**,5*R**)**-Diastereomer (22%, *trans*); ^{1}H NMR (DMSO-d_6, 400 MHz, δ, ppm and *J*, Hz, only distinct signals are listed): 7.48–7.28 (5H, m); 5.58 (1H, s, H-8); 4.90 (1H, t, 5.4, –O*H*); 3.92 (1H, d, 8.8, H-6); 3.84 (1H, d, 9.0, H-6); 3.82 (1H, d, 8.9, H-4); 3.80 (1H, d, H-4); 3.45 (2H, m, –C*H*$_2$OH); 2.00–1.39 (8H, m). ^{13}C NMR (DMSO-d_6, 100 MHz, δ, ppm, only distinct signals are listed): 136.1 (1C), 133.0 (1C), 129.7 (1C), 101.3 (1C, C-8), 79.3 and 77.7 (2C, C-6, -4), 71.0 (1C, –*C*H$_2$OH). Both diastereomers were isolated as a single fraction.

Typical procedure for the synthesis of the compounds 7 and 11

(Di)spiranes **9**, **10** as 0.12 M benzene solution (for dispirane **10c**, as toluene suspension) were treated with the stoichiometric amount of the corresponding aldehyde (*p*-TsOH as catalyst) and refluxed in a Dean–Stark trap with stirring and continuous removal of water. After 8 h TLC monitoring indicated the starting materials in small traces. After neutralising at room temperature with solid Na_2CO_3 the reaction mixture was concentrated in vacuo to yield the crude product which was crystallised from an appropriate solvent (**7a**, **11**) or purified by flash chromatography (**7b**).

Compounds, yields (%), mp (°C, isolation), elemental analysis and NMR data (if not collected in Table 6) are listed below.

(1*S,5*R**)-1-Aza-5-hydroxymethyl-*r*-3-oxa-7-oxa-2-(*c*-4′-tertbutylspirocyclohexyl)-bicyclo[3.3.0]octane, 7a-*cis* and (1*S**,5*R**)-1-aza-5-hydroxymethyl-*r*-3-oxa-7-oxa-2-(*t*-4′-tertbutilspirocyclohexyl)-bicyclo[3.3.0]octane, 7a-*trans*.** White crystalline powder; 78; 138-9(pentane/Et$_2$O 4:1). Anal. Calcd for $C_{15}H_{27}NO_3$: C 66.88%, H 10.10%, N 5.20%. Found: C 67.00%, H 9.94%, N 4.95%. 7a-*cis* (94%) ^{13}C NMR (DMSO-d_6, 100 MHz, δ, ppm): 110.3 (1C, C-2), 96.5 (1C, C-8), 80.1 (1C, C-5), 72.9 and 70.8 (2C, C-6, -4), 65.5 (1C, –*C*H$_2$OH), 46.4 (1C, –*C*H<), 37.6 (1C), 32.0 (1C), 31.0 (1C), 27.5 (1C, –*C*H$_3$), 23.9 (1C), 23.7 (1C); 7a-*trans* (6%) ^{1}H NMR (DMSO-d_6, 400 MHz, δ, ppm and *J*, Hz, only distinct signals are listed): 4.70 (1H, d, 7.0, H-8*t*), 4.16 (1H, d, 7.0, H-8*c*), 3.82 (1H, d, 9.8, H-6*t*), 3.75 (1H, d, 9.8, H-6*c*), 3.66 (1H, d, 8.5, H-4*t*), 3.61 (1H, d, 8.5, H-4*c*).

(1*S,5*R**,8*R**)-1-Aza-8-*n*-hexyl-5-hydroxymethyl-*r*-3-oxa-7-oxa-2-(*c*-4′-tertbutilspirocyclohexyl)-bicyclo-[3.3.0]octane, 7b-*cis*.** Yellow oil (eluent toluene/acetone 3:1); 55. Anal. Calcd for $C_{21}H_{39}NO_3$: C 71.34%, H 11.12%, N 3.96%. Found: C 70.99%, H 10.94%, N 3.85%. **7b-*cis*** ^{13}C NMR (DMSO-d_6, 100 MHz, δ, ppm): 102.5 (1C, C-2), 95.9 (1C, C-8), 78.5 (1C, C-5), 76.9 and 74.3 (2C, C-6, -4), 72.1 (1C, –*C*H$_2$OH), 45.6 (1C, –*C*H<), 42.4 (1C), 41.8 (1C), 41.6 (1C), 41.3 (1C), 37.0 (1C), 36.7 (1C), 36.3 (1C), 32.4 (1C), 30.0 (1C), 29.0 (1C), 28.7 (1C), 19.0 (1C).

trans*-Di-{(1*R**,5*S**)-1-aza-5-methyl-3,7-dioxabicyclo-[3.3.0]octa-2-ylidene}-1,4-dispirocyclohexane, *l*-11a (50%) and *trans*-1-{(1*R**,5*S**)-1-aza-5-methyl-3,7-dioxabicyclo[3.3.0]octa-2-ylidene}-4-{(1′*S**,5′*R**)-1′-aza-5′-methyl-3′,7′-dioxabicyclo[3.3.0]octa-2′-ylidene}-dispirocyclohexane, *u*-11a** (50%); white crystalline powder; 31; 150-1 and 194-5(Et$_2$O, mixture *u*+*l* forms); 194-5 (DMSO, *l*-form). Anal. Calcd for $C_{16}H_{26}N_2O_4$: C 61.91%, H 8.44%, N 9.03%. Found: C 62.10%, H 8.11%, N 8.88%. ^{13}C NMR (DMSO-d_6, 100 MHz, δ, ppm) ***l*-11a**: 96.8 (2C, C-2), 80.3 (2C, C-8), 75.3 and 73.0 (4C, C-6, -4), 68.8 (2C, C-5), 34.4 (2C), 28.5 (2C), 23.6 (2C, 2×–*C*H$_3$). ^{13}C NMR (CDCl$_3$, 100 MHz, δ, ppm) ***l*-11a**+u*-11a**: 96.6 (4C, C-2, C-2′), 81.15 and 81.08 (4C, C-8, -8′), 76.12, 76.00, 73.82 and 73.76 (8C, C-6, -6′, -4, -4′), 69.3 (4C, C-5, -5′), 34.8 (2C), 34.4 (2C), 29.2 (2C), 29.0 (2C), 23.8 (4C, 4×–*C*H$_3$).

***trans*-1-{(1*R**,5*S**)-1-Aza-5-ethyl-3,7-dioxabicyclo[3.3.0]-octa-2-ylidene}-4-{(1′*S**,5′*R**)-1′-aza-5′-ethyl-3′,7′-dioxabicyclo[3.3.0]octa-2′-ylidene}-dispirocyclohexane, *u*-11b (90%) and *trans*-di-{(1*R**,5*S**)-1-aza-5-ethyl-3,7-dioxabicyclo[3.3.0]octa-2-ylidene}-1,4-dispirocyclohexane, *l*-11b** (10%); white crystalline powder; 33; 148-9(Et$_2$O). Anal. Calcd for $C_{18}H_{30}N_2O_4$: C 63.88%, H 8.93%, N 8.28%. Found: C 64.05%, H 8.66%, N 8.55%. ^{13}C NMR (CDCl$_3$, 75 MHz, δ, ppm): ***u*-11b** (90%) 96.6 (2C, C-2, -2′), 81.3 (2C, C-8, -8′), 74.6 and 72.1 (4C, C-6, -6′, -4, -4′), 73.1 (2C, C-5, -5′), 34.4 (2C), 30.4 (2C), 28.8 (2C, 2×–*C*H$_2$CH$_3$), 8.9 (2C, 2×–*C*H$_3$). ^{13}C NMR (CDCl$_3$, 75 MHz, δ, ppm): ***l*-11b** (10%): 96.9 (2C, C-2, -2′), 82.0 (2C, C-8, -8′), 75.7 and 72.0 (4C, C-6,,-6′,-4, -4′), 74.5 (2C, C-5, -5′), 34.8 (2C), 30.4 (2C), 28.6 (2C, 2×–*C*H$_2$CH$_3$), 9.0 (2C, 2×–*C*H$_3$).

trans*-Di-{(1*R**,5*S**)-1-aza-5-hydroxymethyl-3,7-dioxabicyclo[3.3.0]octa-2-ylidene}-1,4-dispiro cyclohexane *l*-11c (50%) and *trans*-1-{(1*R**,5*S**)-1-aza-5-hydroxymethyl-3,7-dioxabicyclo[3.3.0]octa-2-ylidene}-4-{(1′*S**,5′*R**)-1′-aza-5′-hydroxymethyl-3′,7′-dioxabicyclo[3.3.0]octa-2′-ylidene}-dispirocyclohexane, *u*-11c** (50%); white crystalline powder; 70; 181-2(Et$_2$O). Anal. Calcd for $C_{16}H_{26}N_2O_6$: C 56.13%, H 7.65%, N 8.18%. Found: C 55.95%, H 8.00%, N 8.37%. ^{13}C NMR (CD$_3$OD, 100 MHz, δ, ppm) ***l*-11c**+u*-11c**: 100.5 (4C, C-2, -2′), 86.1 and 85.0 (4C, C-8, -8′), 77.3 and 72.1 (4C, C-5, -5′), 76.5, 74.6, 74.4 (8C, C-6, -6′, -4, 4′), 68.9 and 67.4 (4C, 4×–*C*H$_2$OH), 38.4 (2C), 38.0 (2C), 32.0 (2C), 31.7 (2C).

Preparation of the monospirane 12

To 2-amino-2-methylpropane-1,3-diol (7.50 g, 0.071 mol) in benzene (75 mL), cyclohexanone (8 mL, 7.6 g, 0.078 mol) and *p*-TsOH as catalyst were added. The reaction mixture was then refluxed in a Dean–Stark trap with continuous removal of water (about 12 h, TLC monitoring: benzene/methanol 3:1 v/v, I$_2$-bath). The reaction mixture, as a solution, was cooled at room temperature, neutralised with solid Na_2CO_3, filtered off and concentrated in vacuo to yield the crude product which was crystallised from excess of ligroine. The solid was collected, taken with the minimum amount of THF and the insoluble residue was filtered off.

The THF solution was then concentrated in vacuo to afford the product which was crystallised from ligroine (250 mL). Yield 9.4 g (71%).

4-Aza-3-hydroxymethyl-3-methyl-1-oxaspiro[4.5]decane, 12. Yellowish powder; mp 48–49°C (ligroine). Anal. Calcd for $C_{11}H_{21}NO_2$: C 66.29%, H 10.62%, N 7.03%. Found: C 66.47%, H 10.50%, N 7.09%. ^{1}H NMR (DMSO-d_6, 400 MHz, δ, ppm and J Hz): 4.73 (1H, bs, –O*H*), 3.66 (1H, d, –C*H*$_2$–, 8.0), 3.32 (1H, d, –C*H*$_2$–, 8.0), 3.25 (1H, d, –C*H*$_2$OH, 10.6), 3.14 (1H, d, –C*H*$_2$OH, 10.6), 2.40 (1H, bs, –N*H*–), 1.57–1.28 (10H, m), 1.08 (3H, s, –C*H*$_3$). ^{13}C NMR (DMSO-d_6, 100 MHz, δ, ppm): 95.1 (1C, C-5), 71.4 (1C, C-2), 67.1 (1C, C-3), 66.6 (1C, –*C*H$_2$OH), 37.9 (1C), 37.6 (1C), 24.9 (1C), 23.8 (1C, –*C*H$_3$), 23.6 (1C), 23.5 (1C).

Preparation of the compound 13

Finely powdered 4-aza-3-hydroxymethyl-3-methyl-1-oxaspiro[4.5]decane **12** (3.00 g, 0.0162 mol) was vigorously stirred and heated at 100°C to give a melted mass. Terephthaldicarboxyaldehyde (1.08 g, 0.0081 mol) was added as fine powder, portionwise and very slowly (within 1 h). The reaction mixture was then heated with stirring at 150°C, where it was kept for additional 5 h. At the end of this period, the reaction mixture became a red solid. It was left to cool at less than 80°C when it was taken up with toluene (50 mL). The reaction mixture was filtered off and the toluene solution was evaporated in vacuo to give the crude product as an oil. This oil was separated by flash chromatography (eluent toluene/acetone 2.5:1) to afford the desired product **13** as the first fraction (0.060 g). Next, elution with pure acetone yielded the unreacted starting material **12**.

1-{(1*S**,8*R**,5*R**)-1-Aza-5-methyl-3,7-dioxa-2-spirocyclohexyl-bicyclo[3.3.0]octane-8-yl}-4-{(1′*R**,8′*S**,5′*S**)-1′-aza-5′-methyl-3′,7′-dioxa-2′-spirocyclohexyl-bicyclo[3.3.0]octane-8′-yl}-benzene, *u*-13. Yield 2.5%; mp 235–7°C(Et$_2$O). Anal. Calcd for $C_{28}H_{40}N_2O_4$: C 71.76%, H 8.60%, N 5.98%. Found: C 71.95%, H 8.66%, N 6.11%. ^{13}C NMR (DMSO-d_6, 100 MHz, δ, ppm): 140.9 (2C), 127.2 (2C), 96.4 (2C, C-2, -2′), 91.7 (2C, C-8, -8′), 75.9 and 71.7 (4C, C-4, -4′, -6, -6′), 69.3 (2C, C-5, -5′), 38.6 (2C), 31.6 (2C), 27.5 (2C), 24.5 (2C, 2×–*C*H$_3$), 22.7 (2C), 22.5 (2C).

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