3,7-Dioxa-1-azabicyclo[3.3.0]octanes Substituted at the C-5 Position − From Local to Global Stereochemistry

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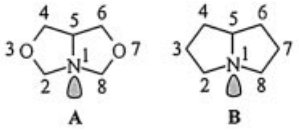
Dedicated to Professor Sorin Mager on the occasion of his 73rd birthday

Keywords: Chirality / Conformation analysis / Diastereoselectivity / Hyperconjugation / Molecular modeling

Multiple approaches are described for the elucidation of the stereochemistry in solution (high-resolution NMR spectroscopy) and in the solid state (X-ray diffractometry) that are based on ab initio calculations (level RHF/6-31G*) of some representative 3,7-dioxa-1-azabicyclo[3.3.0]octanes. The results are presented in terms of conformational analysis, anomeric effects, chelating properties and aggregation phenomena. The significance of these findings with respect to diastereoselective synthesis is discussed.

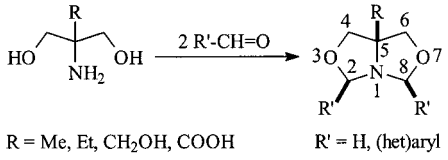
1. Introduction

The 3,7-dioxa-1-azabicyclo[3.3.0]octane heterocyclic saturated system **A** (Scheme 1), which is a synthetically readily available analogue of the core alkaloid pyrrolizidine, 1-azabicyclo[3.3.0]octane **B**, has been known for more than half a century because of the extensive use of its various (poly)-substituted derivatives.[1]



Scheme 1

The C-5-substituted (and, optionally, C-2- and C-8-substituted) structures of type **A** are of particular interest for applications in, for example, fertilisers, plasticisers, biocides and pesticides, mainly because of the simplicity of their synthesis: direct cyclocondensation between 2-substituted 2-amino-1,3-propanediols (the so called "serinols") and carbonyl compounds (Scheme 2).[2−11]



Scheme 2

Nevertheless, the stereochemistry of this class of compounds remained obscure for more than 20 years after the synthesis of its basic skeleton in 1945 (Scheme 2: R = R′ = H).[1] Upon the gradual evolution of NMR spectroscopy, early main stereochemical approaches focused on the magnitude of $^{n}J_{H,H}$ coupling in the X−C*H*$_2$ and X−*CH*$_2$−Y motifs (X, Y = −N<, −NH−, −P<, −O−, −S−), including the $^{2}J_{H,H}$ coupling in the aminalic sequence >N−*CH*$_2$−O− of the title compounds.[12−17] No connection was made in the 1970s to the stereoelectronic requirements, particularly the anomeric effect.[18,19] The first, but unsuccessful, attempt to provide evidence for the mobility of 5-substituted structures of types **A** and **B** (Scheme 1) by means of dynamic ^{1}H NMR spectroscopy was reported by Crabb in 1973.[16]

Our later developments in the field, starting from ab initio calculations, successive NOE difference experiments and NMR spectroscopy at low temperature, established

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some essential features to consider when analysing the stereochemistry of these systems:[20,21]

(i) The absence of the pyramidal inversion of the bridged nitrogen atom, together with the *cis* relationship between its lone pair and the ligand at C-5, results in a stable *cis*-fused double 1,3-oxazolidine system

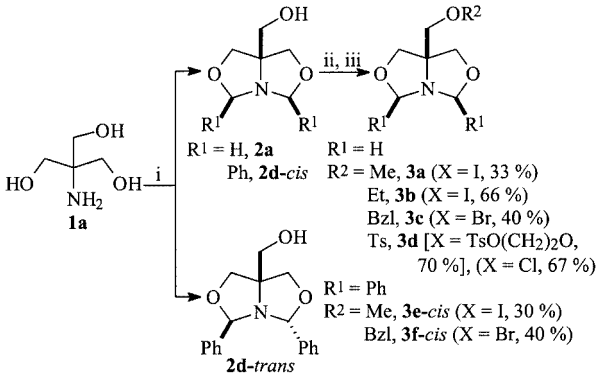
(ii) The flipping of the bicyclic skeleton

(iii) The conformation and configuration (poly)chirality

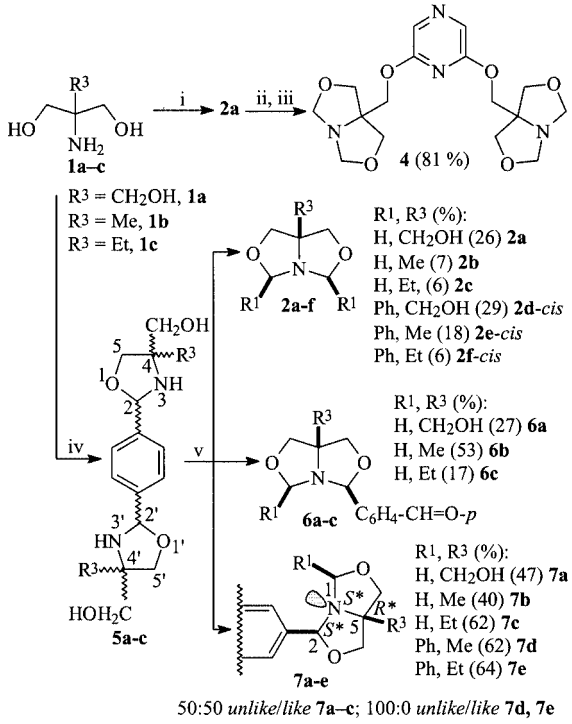
(iv) The all-*cis* linkage at C-2, C-4(-6), C-5 and C-8 (with respect to the lone pair of the bridged nitrogen atom) of the substituents, following, under thermodynamic control, a dominantly diastereoselective double ring closure (Scheme 2) (the lone pair of the bridged nitrogen atom is considered the fiducial substituent: *r*;[22] exceptions are known if both the C-2 and C-8 ligands are *p*-nitrophenyl or 4-pyridyl: the steric relationship between these ligands is dominantly *trans*[21])

To the best of our knowledge, the structure of the dioxaazabicyclooctane skeleton in the solid state has received little attention. Only two X-ray crystallographically determined structures have been reported so far: one in 1973 (the copper salt of 3,7-dioxa-*r*-1-azabicyclo[3.3.0]octane-*c*-5-carboxylic acid; Scheme 2: R = COOH, R′ = H)[22,23] and, more recently (2000), *c*-5-(hydroxymethyl)-*c*-2,*c*-8-diphenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]octane (Scheme 2: R = CH_2OH, R′ = Ph).[24] It is worth noting the importance of a cross-*endo*-anomeric effect described in the latter publication and the claim that it is responsible for the overall geometry of the molecular skeleton.

In the present work, we dedicated our investigations to a deeper re-examination of the stereochemistry of a range of different representatives of the title compounds in the gas phase (molecular modeling), in solution (NMR spectroscopy) and in the solid state (X-ray diffractometry) in connection with their (un)expectedly revealed chelating abilities through the effects of hydrogen bonds, chiral shift reagents and non-bonding interactions in aggregates. Thus, the four previous findings listed above [(i)−(iv)] now require a reassessment to define what is hereafter called *local stereochemistry*; that is, more complex structures were mandatory to a *global stereochemistry* approach.



Scheme 3. i: 2 equiv. R^1−CH=O, toluene, *p*TsOH, Dean−Stark, reflux; ii: 1.05 equiv. KH, THF, 40 °C, 1.5 h.; iii: 1.05−1.10 equiv. R^2X, THF, 40 °C to room temp., 12−24 h



Scheme 4. i: R^3 = CH_2OH, 2 equiv. CH_2=O;[21] ii: 1.05 equiv. KH, THF, 40 °C, 1.5 h; iii: 0.48 equiv. 2,6-dichloropyrazine, THF, 60 °C to room temp., 24 h; iv: 0.5 equiv. terephthalaldehyde;[26] v: 2 equiv. R^1−CH=O, toluene, *p*TsOH, Dean−Stark, reflux

2. Results and Discussion

2.1. Synthesis

For the present study, the selected target compounds were "monomeric" (Scheme 3: **2a**−**d**, **3a**−**f**) and "dimeric" structures (Scheme 4: **4**, **7a**−**e**). The interest raised by each compound or series is briefly outlined in this section.

The known compound **2a** exhibits chelating aptitude, which we anticipated from molecular modeling studies (detailed in Section 2.2.2.), but it behaved differently in solution (dynamic ^{1}H NMR spectroscopy) than in the solid state (X-ray diffractometry) as we discuss in Sections 2.3.1. and 2.4., respectively). Next, the diastereoisomers **2d**-*cis* and **2d**-*trans* were obtained under thermodynamic control in a 4.90:1 ratio as deduced by a ^{1}H NMR spectrum of the crude material (90% global yield; ΔG = −5.10 kJ/mol *cis* vs. *trans*); they were separated by simple fractional crystallisation. The stereochemistry and chelating properties of **2d**-*cis* (discussed in Sections 2.2.2. and 2.3.1.) are different from those of **2a**, but are in good agreement with its X-ray structure.[24] In turn, we succeeded in obtaining the X-ray structure of the other diastereoisomer, **2d**-*trans* (discussed in Section 2.4.), that provided a plausible explanation forits lower thermodynamic stability relative to **2d**-*cis*.

The molecular modeling of the methyl ethers derived from **2a** and **2d**-*cis* (presented in Section 2.2.2.) urged us to

synthesise these types of structures via their corresponding potassium alkoxides by treating them with potassium hydride in a near-stoichiometric ratio in THF (Scheme 3: **3a**−**d**, **3e**, **3f**-*cis*).

The same protocol yielded the 2,6-disubstituted pyrazine **4** (Scheme 4). As revealed to us by its X-ray crystallographically determined structure (depicted in Section 2.4.), only a certain *global stereochemistry* of this "dimer" (built on a specific chiral frozen conformation of each dioxaazabicyclooctane unit's *local stereochemistry*) allowed any possible stereoselective supramolecular interactions.

Finally, the versatile double ring−chain tautomerism manifested by the double oxazolidines **5a**−**c**,[25] which resulted from the condensation between the serinols **1a**−**c** and terephthalaldehyde, recently reported by us,[26] was exploited in the synthesis. Reaction of the mixture of epimers of **5a**−**c** with a slight excess of formaldehyde or benzaldehyde gave a separable mixture of three series of compounds (conversions mentioned in Scheme 4): the desired **7a**−**e**, the partial transaminalisation products **6a**−**c** (in reaction with formaldehyde only) and the known, total-transaminalisation compounds **2a**−**c** and **2d**−**f**-*cis*. The cyclocondensation between **5a** and benzaldehyde resulted in the almost complete decomposition of the reaction mixture, although **2d**-*cis* was isolated in low yield.

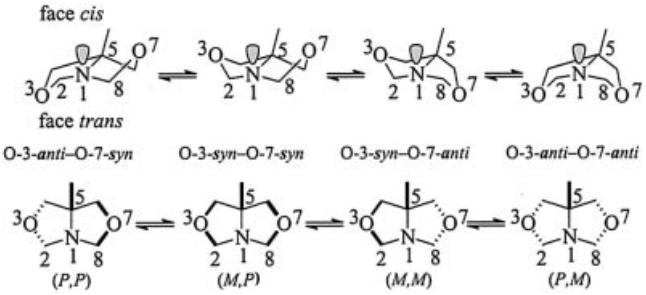
The stereochemistry of each of the new chiral compounds **6a**−**c** was, as expected, all-*cis*, and easily solved by successive NOE difference and NOESY experiments. The results indicated that this side reaction is completely diastereoselective.

In contrast, the target series **7a**−**e**, established as having all-*cis* *local stereochemistry*, raised the problem, both in solution and in the solid state, of the *global stereochemistry*. Indeed, the "dimerisation" at C-2 could link the two chiral bicyclic units possessing identical (*like* global stereochemistry) or opposite configurations (*unlike* global stereochemistry) at N-1, C-2 and C-5. Thus, despite the increased sensitivity of ^{1}H NMR detection at 600 MHz, only one complete set of signals was displayed, which is consistent with the envisaged constitutions **7a**−**e** as crude material and after isolation by flash column chromatography [however, at 600 MHz, only compound **7b** displays two singlets of equal intensity, located at $\delta = 1.369$ and 1.372 ppm, which we assign to the two different environments (*like* and *unlike*) for the methyl groups]. Moreover, because current NMR spectroscopy methods cannot distinguish between this type of *like*/*unlike* diastereoisomerism, we applied Eu(hfc)$_3$ as a chiral shift reagent (CSR). The conclusions of this analysis are discussed in Section 2.3.2. For the present discussion, only compound **7c** is mentioned because it provided crystals appropriate for X-ray diffractometry (described in Section 2.4.); as shown by its solid-state structure, it is the *like* (1*S**,1′*S**,2*S**,2′*S**,5*R**,5′*R**) diastereoisomer. Obviously, the results of the solid-state structure determination should not be extrapolated to either the solution or solid-state structures of **7a**−**e**. Therefore, in Scheme 4 we made the choice of limiting representation of these compounds as "half molecules".

2.2. The Stereochemistry Determined by Conformational Analysis

2.2.1. The Conformation Chirality

The 3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl skeleton is heterofacial; all of its (hetero)atoms are prostereogenic centres.[27,28] The importance of this fact should be related to some of our earlier considerations on the conformational chirality exhibited by the molecular skeleton itself (Scheme 5).[21]



Scheme 5

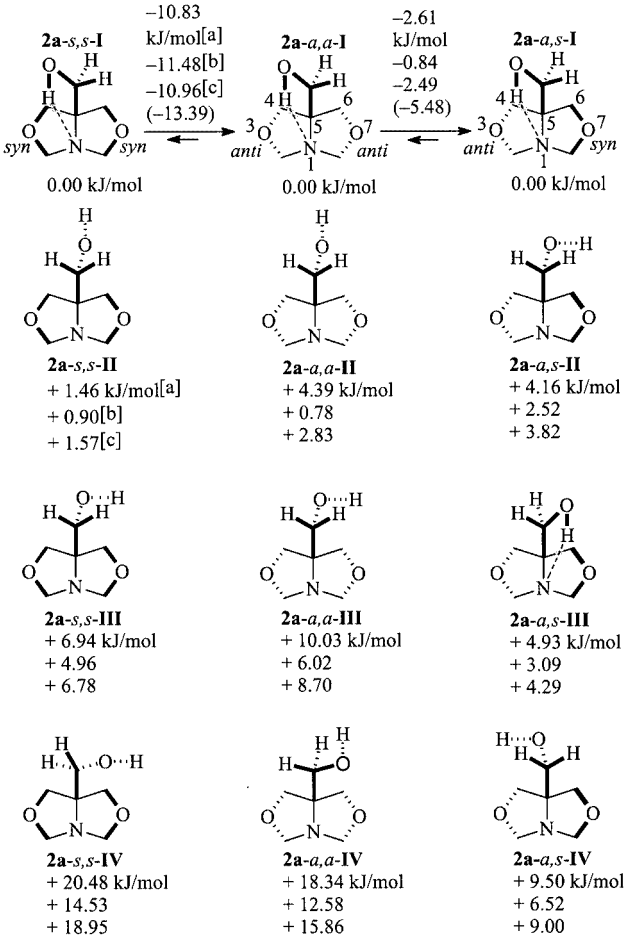
Hence, four different stereoisomers can be observed that are differentiated by the sense of the puckering in the two oxazolidine rings, which is seen as *syn* or *anti* O-3/O-7 envelope conformers. These assignments (apparently restrictive, e.g., rotation about the C−O−C bonds only) are based on previous X-ray crystallographically determined frozen conformations[23,24] and our earlier calculations (level RHF/6-21G*).[21] The *cis* ligands, i.e., the lone pair at N-1 and/or the ligand at C-5, were chosen as references for the descriptors *syn* and *anti*. Furthermore, by applying the helicity rule to the torsion angles of the O-3−C-2−N-1−C-5 and O-7−C-8−N-1−C-5 bonds, the enantiomeric conformers O-3-*anti*−O-7-*syn* and O-3-*syn*−O-7-*anti* are easily recognisable as having the opposite configurations (*M*,*M*) and (*P*,*P*), respectively.[22a,27] If this analysis is valid, the conformers O-3-*syn*−O-7-*syn* and O-3-*anti*−O-7-*anti* are, mutatis mutandis, diastereoisomeric *meso* forms: (*M*,*P*) and (*P*,*M*).

On the basis of this knowledge, we continued an enlarged set of ab initio calculations of the possible rotamers derived from some of the prepared compounds (Scheme 3).

2.2.2. Conformational Analysis Based on Ab Initio RHF/6-31G* Molecular Orbital Calculations of the Compounds 2a, 2d, 3a and 3e

In the case of the 5-(hydroxymethyl) derivative **2a**, three skeleton conformers were found to be representative of internal five-membered chelates (Scheme 6): **2a**-*s*,*s*-**I**, **2a**-*a*,*a*-**I** and **2a**-*a*,*s*-**I**. These descriptors are the parent terms of three different series of rotamers **I**−**IV** discriminated by the orientation of the hydroxymethyl group and are designated as *in* or *out*. Only for **2a** did we examine two solvation

models (DMSO and toluene; PCM Model, see Exp. Sect., General).

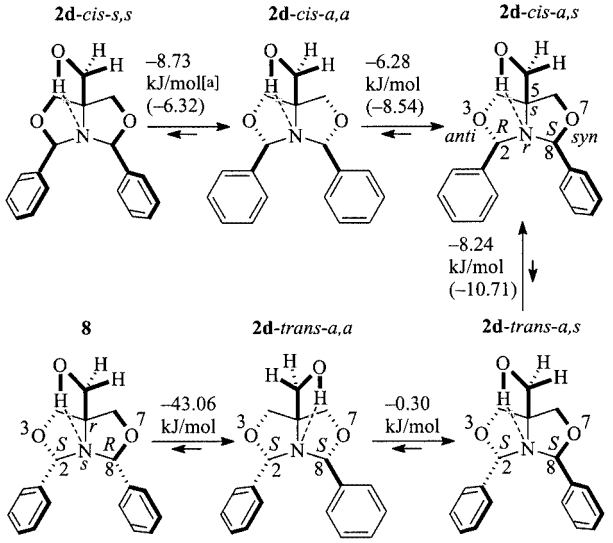


Scheme 6. [a] ΔE values in vacuo and in the gas phase; [b] in DMSO; [c] in toluene; (in parentheses): ΔE values obtained by neglecting the orientation of the hydroxymethyl group[21]

To be more explicit, only the difference between the total energy of each rotamer belonging to the same series (**2a**-*s,s*, **2a**-*a,a* or **2a**-*a,s*) and the parent conformer **I** (the reference, arbitrarily considered 0.00 kJ/mol) is depicted as vertical increasing ΔE values. Similarly, only the total energy differences between the parent skeleton conformers (**2a**-*s,s*-**I**, **2a**-*a,a*-**I** and **2a**-*a,s*-**I**) are listed (ΔE values, horizontally).

The most stable was the chiral rotamer **2a**-*a,s*-**I** in which the oxygen atom in the C-5 hydroxymethyl group was oriented to develop stereoselectively an intramolecular hydrogen bond with the pseudo-axial lone pair of electrons of the bridged nitrogen atom. This assignment was credible because a similar hydrogen bond was less stable in rotamer **2a**-*a,s*-**III**. The calculated interatomic N···H−O distances ranged between 2.400 and 2.600 Å. In all the series **2a**-*a,s*, we found no rotamer possessing the *N*-1−*C*-5−CH_2OH motif in an almost coplanar arrangement. Such a type of rotamer was minor even in the **2a**-*a,a* series (e.g., ΔE = +25.55 kJ/mol in DMSO; not depicted in Scheme 6). The presence of the intramolecular hydrogen bond seems to reduce the differences between the total energy of the most stable skeleton conformers: **2a**-*s,s*-**I** > **2a**-*a,a*-**I** > **2a**-*a,s*-**I**. The conformational equilibrium between **2a**-*a,a*-**I** and **2a**-*a,s*-**I** (*meso* vs. chiral) was influenced the most. The solvation model revealed, however, that the difference between the *in* and *out* rotamers (**I** vs. **II**) is minor in DMSO for all three of the series.

By linking two phenyl groups at positions 2 and 8, the calculations for optimal geometry provided the two series of **2d**-*cis* and **2d**-*trans* stereoisomers as *in* rotamers (Scheme 7).



Scheme 7. [a] ΔE values taking into account the orientation of the hydroxymethyl group; (in round parentheses): ΔE values obtained by neglecting the orientation of the hydroxymethyl group[21]

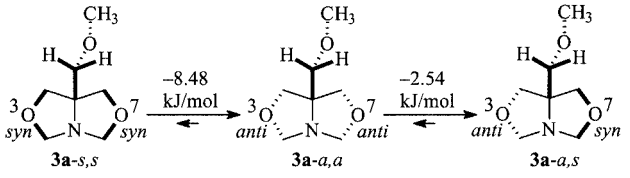
Their configurational chirality was described by us previously[21] and it is repeated simply in Scheme 7; only the descriptors *cis* and *trans* are used to discriminate the relative diastereoisomerism of the substituents at C-2 and C-8. Their *trans* disposition is chiral (depicted throughout as one enantiomer), whereas the *cis* one is a mediated *meso* form (possessing also the pseudoasymmetric centres N-1 and C-5). We have previously calculated the most stable skeleton conformation of **2d**-*cis* as O-*anti*−O-*syn* (RHF6/21-G*)[21] as a term of a three-component equilibrium between **2d**-*cis*-*s,s*, **2d**-*cis*-*a,a* and **2d**-*cis*-*a,s*. This finding agrees with the flexibility of the skeleton supported by our ^{1}H NMR spectroscopic data and the X-ray structure determined independently soon after by Pavia.[24]

The present enlarged calculations provide evidence, besides the *in* disposition of the hydroxymethyl group, for the same O-3/O-7 oriented flexibility (Scheme 7), but in correlation with the predilection for a certain phenyl rotamer: bisectional or orthogonal. This preference appears somehow to come into conflict with the development of an intramolecular hydrogen bond, since the calculated N···H−O distances were 2.434 Å in the least stable **2d**-*cis*-*s,s*, 2.513 Å in **2d**-*cis*-*a,a* and 2.756 Å in the most stable stereoisomer, **2d**-*cis*-*a,s*. No similar interaction could be assigned to any

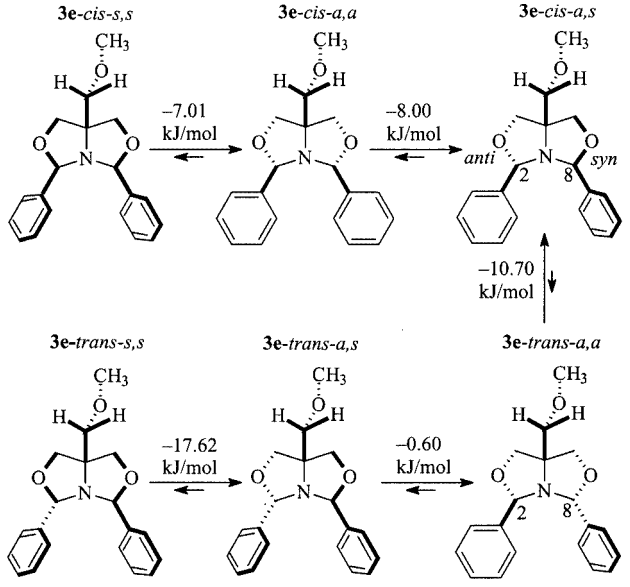
O-*syn* system (e.g., a bifurcated hydrogen bond: the O−H···O-*syn* distance was 3.037 Å in **2d**-*cis*-*s*,*s*).

An expected difference was calculated ($\Delta E = -8.24$ kJ/mol) between the most stable configurational diastereoisomers **2d**-*cis*-*a*,*s* and **2d**-*trans*-*a*,*s*. Surprisingly, the value is very similar to the ΔE values found between the conformational diastereoisomers in the *cis* series. In the *trans* series, only two conformers were relevant: **2d**-*trans*-*a*,*s* and **2d**-*trans*-*a*,*a* (Scheme 7); they have a negligible difference between their total energy, which means that, in the *trans* series, the preferred geometry of the bicyclic skeleton is unpredictable. In total agreement with the experimental data, we found that a diastereoisomer of type **8** is strongly disfavoured; indeed, in this class, only once did we pertinently confirm such a type of *r*-1−*t*-2−*c*-5−*t*-8 linkage.[26]

We extended our calculations to the *O*-methyl analogues **3a**, **3e**-*cis* and **3e**-*trans*. Although, as normally expected, only *out* rotamers were revealed in all three cases, the results exhibited some stimulating differences (Schemes 8 and 9).



Scheme 8



Scheme 9

For compound **3a** (Scheme 8), the ΔE values involving the same most stable skeleton conformers (*s*,*s*, *a*,*a* and *a*,*s*) are similar to those depicted in Scheme 6; the shifting of the equilibrium between *a*,*s* and *a*,*a* (chiral vs. *meso*) was not influenced. In turn, upon *O*-methylation, the equilibrium between *s*,*s* and *a*,*s*, which also involves only one oxazolidine ring inversion, was shifted less towards the most stable conformer *a*,*s* in **3a** than in the **2a** series: $\Delta E = -11.02$ kJ/mol vs. 13.73 kJ/mol; **3a** might be predicted to be a "more flipping" structure than its starting hydroxymethyl derivative **2a**. Similar remarks apply to the diphenyl derivatives **3e**-*cis* and -*trans* (Scheme 9).

In comparison with the series **2d**, the ΔE value of the most stable stereoisomers belonging to each *cis* or *trans* series (**2d**-*cis*-*a*,*s* vs. **2d**-*trans*-*a*,*s* and **3e**-*cis*-*a*,*s* vs. **3e**-*trans*-*a*,*s*) was slightly shifted towards the *cis* series: $\Delta E = -8.24$ vs. 10.70 kJ/mol; by neglecting the orientation of the hydroxymethyl group in series **2d** (Scheme 7), however, there is no difference between the shifting of the above type of equilibria. The flexibility of the basic skeleton in conformers **3e**-*cis* appears more favoured by more comparable ΔE values in each equilibrium.

Minor changes in stability were found in series **3e**-*trans* relative to **2d**-*trans*: conformer **3e**-*trans*-*a*,*a* was the one that exhibited a negligible stability, this time in relation to **3e**-*trans*-*a*,*s* (see also Scheme 7). A **3e**-*trans*-*s*,*s* geometry is the most disfavoured, presumably because one of the phenyl rings is placed in both axial and bisectional orientations.

Before taking into account the validity of our calculation above, an estimation can be made a priori as follows:

(i) In all cases, the oxazolidine ring inversion took place about the C−O−C bonds because only O-3(-7) envelope conformers were revealed

(ii) Of the three possible skeleton diastereoisomeric conformers (*a*,*a*, *a*,*s* and *s*,*s*), the latter is disfavoured; for the C-5-monosubstituted compounds, the global flexibility involves an enantiomeric inversion that can be described as *a*,*s* → *a*,*a* → *s*,*a* (one oxazolidine ring inversion, Scheme 5); the ΔE values between the chiral *a*,*s* and *meso* *a*,*a* conformations is too small to predict a preferred frozen structure

In the case of the C-2/C-8 diphenyl derivatives, the conformational behaviour of the bicyclic skeleton is influenced by:

(i) The *cis* or *trans* linkage of the aromatic rings: the *trans* diastereoisomers flip more

(ii) The preferred rotamer (orthogonal or bisectional); the global bicyclic ring inversion, however, is of the same type as that for non-substituted C-2/C-8 analogues *a*,*a*, *a*,*s* and *s*,*s* (Schemes 7 and 9)

An intramolecular five-membered chelate (*in* rotamers) developed by a C-5-(hydroxymethyl) group or the presence of a methoxymethyl group (*out* rotamers) promoted a general decrease of the differences between the stabilities of the significant skeleton conformers.

2.3. NMR Spectroscopic Assignments

2.3.1. Conformation Analysis Based on NMR Spectroscopy

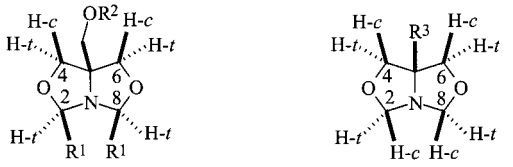
We have recently reported a satisfactory agreement between calculations and the results of ^{1}H NMR spectra recorded in [D$_8$]toluene at low temperature for compounds **2a** and **2d**-*cis*: the anticipated mobility of the bicyclic skeleton was evidenced by general coalescence phenomena at about 203 K for **2a** and 213 K for **2d**-*cis*.[21] Unfortunately, they crystallised from the solvent below coalescence, which, thus, prevents us from developing this investigation any further.

In the present work, the examination was enlarged to consider more selected examples: the relevant ^{1}H NMR spectroscopic data collected in Table 1 show, wherever possible, the dependence of their appearance on the solvent, temperature and the influence of the aromatic solvent-induced shift (ASIS) phenomena.[29,30]

We proceed by considering the assumption that the coalescence found earlier for compounds **2a** and **2d**-*cis* in [D_8]toluene depicts, in fact, a slow skeletal motion of their *in* rotamers or, at least, a shifted conformational equilibrium in which they were the dominant species (Schemes 6 and 7). If this assumption is valid, one has to consider the data listed in Table 1 as describing, besides the skeletal flipping, different populations of rotamers of **2a** and **2d**-*cis* (*in* vs. *out*) depending on the chelating properties of the solvent used to obtain the NMR spectra. Thus, in [D_6]DMSO, both **2a** (as predicted in Scheme 6) and **2d**-*cis* were assigned instead as *out* rotamers because the hydroxy proton clearly displays a partially overlapped doublet of doublets with a typical $^3J_{H,H}$ value of 5.0−5.5 Hz in a narrow domain from δ = 4.89 to 5.16 ppm.

Hence, we tested compound **2a** by variable-temperature ^{1}H NMR spectroscopy in [D_4]MeOD; we expected **2a** also to be chelated in this solvent, involving, besides all het-

Table 1. Relevant chemical shifts (as δ values, ppm) and geminal anisochrony (absolute Δδ values in ppm) in the ^{1}H NMR spectra of compounds **2a**−**c**, **2d**-*cis*, **3a**, **3c**, **3e**-*cis* and **3f**-*cis*



R1 = H, **2a** Ph, **2d**-*cis* R2 = H

R1 = H R2 = Me, **3a** Bzl, **3c**

R1 = Ph R2 = Me, **3e**-*cis* Bzl, **3f**-*cis*

R3 = Me, **2b**; Et, **2c**

No.	Solvent	*T* [K][a]	2-H, 8-H-*c*[b]	2-H, 8-H-*t*[b]	Δδ	4-H, 6-H-*c*	4-H, 6-H-*t*	Δδ
2a	[D_8]toluene	298	3.94	4.14[c]	0.20	3.28	3.45[c]	0.17
		203	4.34	4.34	0.00	3.54	3.80	0.26
	$CDCl_3$	298	4.40	4.45	0.05	3.73	3.77	0.04
	[D_6]DMSO	298	4.26	4.39	0.13	3.66	3.71	0.05
	[D_4]MeOD	328	4.41	4.43	0.02	3.76	3.81	0.05
		200	4.39	4.45	0.06	3.78	3.80	0.02
2b	$CDCl_3$	298	4.33	4.33	0.00	3.40	3.68	0.28
	C_6D_6	298	4.21	4.31	0.10	3.21	3.49	0.28
			4.18[d]	*4.28*	0.10	*3.21*	*3.50*	0.29
2c	$CDCl_3$	298	4.30	4.32	0.02	3.51	3.64	0.13
	C_6D_6	298	4.20	4.29	0.09	3.35	3.46	0.11
2d-*cis*	[D_8]toluene	298	−	5.32	−	3.77[e]	3.52[e]	0.25
		213	−	5.21	−	3.88	3.56	0.32
	[D_6]DMSO	298	−	5.58	−	3.93	3.82	0.11
	[D_4]MeOD	328	−	5.57	−	4.07	3.89	0.18
		180	−	5.51	−	3.96	3.88	0.08
3a	[D_8]toluene	298	4.07	4.26	0.19	3.59	3.66	0.07
		193	4.00	4.28	0.28	3.67	3.73	0.06
	$CDCl_3$	298	4.38	4.42	0.04	3.75	3.75	0.00
3c	[D_8]toluene	298	4.07	4.24	0.17	3.60	3.69	0.09
		193	4.00	4.23	0.23	3.69	3.74	0.05
	$CDCl_3$	298	4.40	4.44	0.04	3.80	3.80	0.00
3e-*cis*	[D_8]toluene	298	−	5.39	−	4.03	3.74	0.29
		183	−	5.30	−	4.17	3.81	0.36
	$CDCl_3$	298	−	5.47	−	3.96	3.80	0.16
3f-*cis*	[D_8]toluene	298	−	5.40	−	4.05	3.74	0.31
		183	−	5.30	−	4.18	3.77	0.41
	$CDCl_3$	298	−	5.46	−	3.98	3.82	0.16

[a] At room temperature; if variable temperature was used, only the initial and final values are given. Spectra were recorded for each variation of Δ*T* = 10 K. [b] Labelled *c* (*cis*) or *t* (*trans*) according to their *cis* or *trans* disposition with respect to the C-5 substituent and the lone pair of the bridged nitrogen atom. [c] The deshielding of *trans* vs. *cis* protons was established by us previously by means of NOE difference experiments. [d] *Italicised*: Crabb's δ values (1973):[16] no change in the ^{1}H NMR spectrum of this compound was observed between −85 and +110 °C. [e] For the C-2,C-8-*cis*-diaryl-disubstituted compounds, as a general rule, the shielding of *trans* vs. *cis* protons was established by us previously by means of successive NOE difference experiments.[21] Exceptions are also known.[26]

eroatoms, the *out* rotamer. The comparative appearance of the spectra ([D_8]toluene vs. [D_4]MeOD) is presented in Figure 1 and 2A−D. The coalescence of the signals of the aliphatic methylene protons C-4(-6) occurred at about 260 K: from an AB system (328 K, $\Delta\delta/^2J_{H,H}$ = 1.95, $^2J_{H,H}$ = 9.0 Hz, Figure 2B) to a singlet (260 K, A_2 system, Figure 2C) and finally to a new partially overlapped doublet of doublets (200 K, AB system $\Delta\delta/^2J_{H,H}$ = 1.02, $^2J_{H,H}$ = 9.2 Hz, Figure 2D). We detected no such process for the aminalic methylene O−CH_2−N units, which are present as the other "internal clock".[22] The accuracy of this determination was confirmed on the 400-MHz time scale by estimating the rate constant at coalescence k_c [s^{-1}] [Equation (1)] and the free enthalpy of activation $\Delta G^{\ddagger}$ [J/mol] of the oxazolidine ring inversion in **2a**, which we consider as a first-order reaction from *a,a* to *a,s* [Scheme 6, Equation (2), Eyring equation].[31]

$$k_c = 2.22\,(\Delta\nu^2 + 6J^2)^{0.5}\ [s^{-1}] \quad (1)$$

$$\Delta G^{\ddagger} = 19.14\,T_c\,(10.32 + \log T_c/k_c)\ [J/mol] \quad (2)$$

The following values were used: $\Delta\nu$ = 9.2 Hz, $^2J_{H,H}$ = 9.2 Hz (at 200 K) and T_c = 260 K. These values give k_c = 54 s^{-1} [Equation (1)]; since **2a** is a double oxazolidine system, the real value of k_c should be twice the observed value, that is, k_c = 108 s^{-1}. According to Equation (2), $\Delta G^{\ddagger}$ = 53.252 kJ/mol (12.72 kcal/mol).

One may conclude that **2a** was flipping faster in [D_8]toluene (*in* rotamer, Scheme 6) than in [D_4]MeOD as the *out* rotamer. On the other hand, the behaviour of **2a** in [D_4]MeOD in the aliphatic part of the spectrum (Figure 2) was normal because, in any alternative conformation, the geminal protons 4-(6-)H-*c*/4-(6-)H-*t* are diastereotopic (Schemes 5 and 6). Therefore, we believe that the conformational evolution of **2a** in solution occurs towards a symmetrical structure of the *meso*-type form **2a**-*a*,*a*-**II** (Schemes 5 and 6). The X-ray crystallographically determined structure fully confirmed this frozen conformation to be the *local stereochemistry* (see the discussion in Section 2.4.).

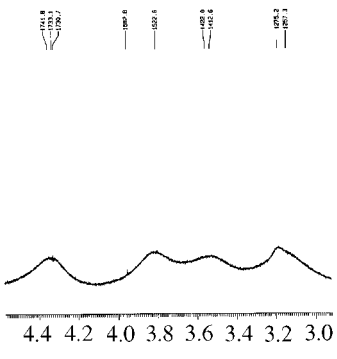


Figure 1. ^{1}H NMR spectrum of compound **2a** in [D_8]toluene at the coalescence temperature (203 K, 400 MHz)

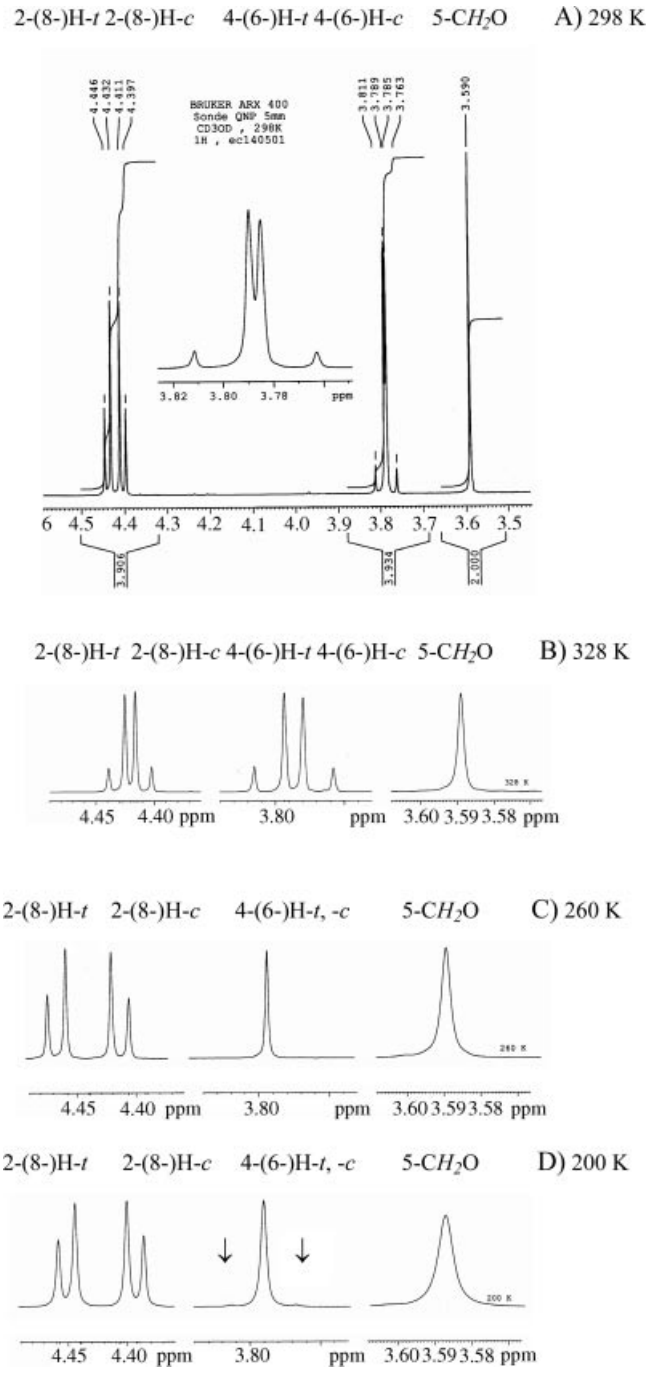


Figure 2. ^{1}H NMR spectra of compound **2a** in [D_4]MeOD (400 MHz)

In turn, for **2d**-*cis* (Table 1), no coalescence was reached in [D_4]MeOD; instead, we observed only a decrease in the geminal anisochrony of the aliphatic methylene protons, from δ = 0.18 to 0.08 ppm (similar to **2a**), which suggests a much greater difference in flexibility in comparison to **2a**, and even with respect to [D_8]toluene.

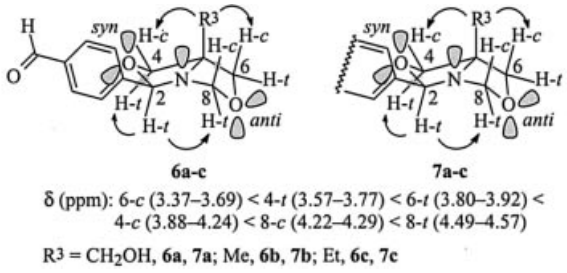
Rather poor solubility of compounds **2d**-*trans* and **3d** in [D_8]toluene and $CDCl_3$ made them unsuitable for dynamic NMR spectroscopy experiments at low temperature.

To solve this trivial problem, we prepared the simple *O*-methyl and *O*-benzyl ethers **3a**, **3c**, **3e**-*cis* and **3f**-*cis*. In agreement with the molecular modeling, we detected no coalescence in the ^{1}H NMR spectra recorded at low temperature in [D_8]toluene (Table 1); instead, we observed only changes assigned to selective ASIS interactions that are due to the heterofacial character of each molecule.

From a comparative examination of our data (Table 1), we see that when a more chelating ([D_4]MeOD, [D_6]DMSO) or only polar ($CDCl_3$) solvent was used, the geminal anisochrony[12−17] strongly decreased (even cancelled in compounds **3a** and **3c**), but the expected greater Δδ values remain in the N−CH_2−O sequence (compounds **2a**, **3a** and **3c**) than in its aliphatic counterparts. This observation also applies for the methylene C-4(-6) units in the 2,8-diphenyl derivatives **2d**-*cis*, **3e**-*cis* and **3f**-*cis*.

By cancelling the polarity of the substituent at C-5 (compounds **2b**, **2c**), a very small or even no geminal anisochrony was displayed by the aminalic methylene protons relative to the aliphatic ones: the Δδ values (H-*c* vs. H-*t*) for the latter were more sensitive to C-5 substitution (Me or Et) than to ASIS phenomena. In our opinion, these last two examples suggest that exploring the conformational mobility in this class of compounds by dynamic NMR spectroscopy is more appropriate when a polar substituent is linked at C-5.

Finally, the stereochemistry of the side compounds **6a**−**c** (Scheme 4) was also in agreement with our theoretical findings (Scheme 10; see also Schemes 7 and 9).

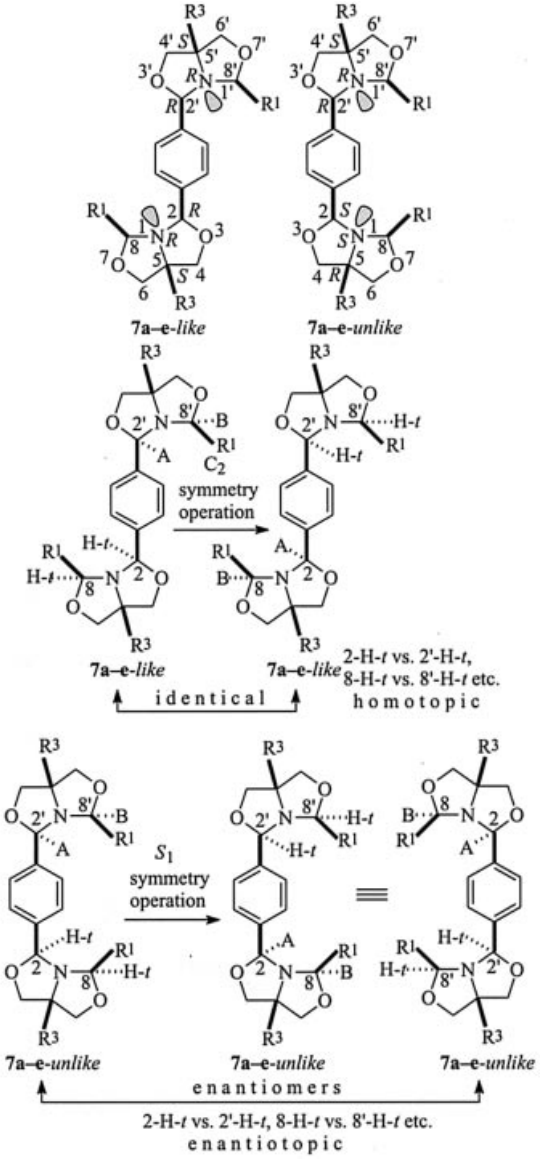


Scheme 10

Besides the all-*cis* diastereoisomerism, the order of deshielding of heterocyclic protons, determined by NOE experiments, could be explained only by the preferred O-3-*syn*−O-7-*anti* chiral conformation of the bicyclic skeleton together with the pseudoequatorial orientation of the aromatic ring as a bisectional rotamer. In comparison with **6a**−**c**, we observed no differentiation regarding this *local stereochemistry* of the "dimeric" forms **7a**−**c** (entirely supported by the X-ray crystal structure of **7c**).

2.3.2. Assignment by NMR Spectroscopy of the Global Stereochemistry of Compounds 7a−e[22,28,31]

The dilemma of determining the *global stereochemistry* of compounds **7a**−**e** was made clear only under chiral conditions, i.e., by using enantiomerically pure Eu(hfc)$_3$ {europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]} as a chiral shift reagent (CSR). The rationalisation, provided by high-resolution ^{1}H NMR spectra, was based on a preliminary configurational analysis of compounds **7a**−**e**, as a result of the steric relationships that arise from the substitution test (Scheme 11) and their expected interactions with the CSR [Equations (3)−(5)].



Scheme 11

K_3: (±)-**7a**−**e** *like* + Eu(hfc)$_3$ ⇄ [(+)-**7a**−**e** *like* Eu(hfc)$_3$] (3)

K_4: (±)-**7a**−**e** *like* + Eu(hfc)$_3$ ⇄ [(−)-**7a**−**e** *like* Eu(hfc)$_3$] (4)

K_5: **7a**−**e** *unlike* + Eu(hfc)$_3$ ⇄ [**7a**−**e** *unlike* Eu(hfc)$_3$] (5)

To simplify the analysis, the discussion below is restricted, from the isochronous nuclei 1−1′ → 8−8′, to the benzyl 2(′)-H-*t* (in **7a**−**e**) [and 8(′)-H-*t* in **7b**, **7c**] and 1,4-phenylene protons because their spectral appearance was the most convincing.

The latter protons, while anisogamous,[22] are isochronous because of free rotation of the benzene ring: one resonance, a singlet, appears in either the *like* or *unlike* form. Thus, upon complexation [Equations (3) and (4), Scheme 11], the internal homotopic 2(′)-H and 8(′)-H-*t* and external anisogamous 1,4-phenylene protons of **7a**−**e**-*like* remain as such, whereas the internal enantiotopic protons 2(′)-H and 8(′)-H-*t* of **7a**−**e**-*unlike* (Scheme 11) become externally diastereotopic as the 1,4-phenylene ones (AA′XX′ system).

The relevant NMR spectroscopic data of this experiment are collected in Table 2; the spectral evolutions of compounds **7a**, **7c** and **7d** are illustrated in Figure 3A−D.

One might conclude that in solution, compounds **7b** and **7c** exist as an equimolar mixture of the racemic and *meso* forms since the best separated signals — four singlets assigned to protons 2(′)-H-*t* — have almost equal intensity (Figure 3A,B). We trusted this result, assuming $K_3 = K_4 = K_5$ [Equations (3)−(5)], despite the fact that the anticipated aromatic AA′XX′ coupling pattern was overlapped.

Unpredictably, in the presence of Eu(hfc)$_3$, the diol **7a** displayed only two singlets for the benzylic protons, which is consistent with the presence of either the *like* or *unlike* form. The expected separation of the initial singlet of the 1,4-phenylene protons into two singlets [in (+)-**7a**-*like*/Eu(hfc)$_3$ and (−)-**7a**-*like*/Eu(hfc)$_3$] or an AA′XX′ system [in **7a**-*unlike*/Eu(hfc)$_3$] was not observed (Figure 3C). Nevertheless, the spectral appearance of the aromatic protons was very different from those of **7b** and **7c**. A comparative inspection of the Δδ values for the entire series **7a**−**e** indicates that the benzyl positions are the most sensitive to the lanthanide cation's vicinity. In the aromatic region, by far the maximum deshielding was exhibited by the diol **7a**: δ = +1.12 ppm (Table 2). As expected, the signals of the hydroxy protons were located at lowest field (broad singlet at δ ≈ 10.5 ppm); meanwhile, the resonance of one of each diastereotopic C-5−CH_2O methylene proton was identified as a broad singlet at δ = 6.82 ppm (see Figure 3C). We encountered no major integration problems arising from broadening line width of the discussed signals that arises according to equation $\delta\nu = \pi(\Delta\delta)^{-2}/2k$ (see Figure 3C: $X_{CSR} = 0.45$).[28b][28c] Therefore, we used a known relation [Equation (6)] to calculate the chemical shift of the phenylene protons of **7a** in the complex environments [Table 2, see also Equations (3)−(5)]; where $\delta_{obsd.}$ = successive observed weighted average chemical shifts of phenylene protons (ppm; Table 2); $\delta_{\mathbf{7a}}$ = chemical shift of phenylene protons in the absence of CSR (δ = 7.50 ppm); $X_{\mathbf{7a}}$ = successive molar fractions of free **7a** at equilibrium; $\delta_{Comp.}$ = chemical shift (ppm) of 1,4-phenylene protons in the complex environment and X_{CSR} = successive molar fractions of Eu(hfc)$_3$ for the considered equilibrium. We approximated $X_{CSR} = X_{Comp.}$; i.e., no free CSR was present at the equilibrium state and $K_3 = K_4$.

Table 2. Relevant ^{1}H NMR spectroscopic data [as chemical shifts (δ, ppm) and deshielding influence (Δδ, ppm)] of compounds **7a**−**e** in the presence of Eu(hfc)$_3$ (600 MHz, $CDCl_3$, 25 °C)

No.	X_{CSR}	2(′)-H-*t*	8(′)-H	1,4-Ph
7a	0.00	5.25	4.57(*t*); 4.26(*c*)	7.50
	0.12	5.454; 5.446	4.80; 4.79(*t*); 4.56; 4.54(*c*)	7.67
	0.30	5.98; 5.95	−	8.11
	0.45	6.61; 6.56	−	8.62
Δδ	−	+1.34[a]	−	+1.12
7b	0.00	5.28	4.56(*t*); 4.34(*c*)	7.53
	0.12	5.65; 5.64; 5.61; 5.60	5.09-5.05(*t*); 4.81-4.78(*c*)	7.664; 7.658[b]
	0.30	6.33; 6.30; 6.23; 6.20	−	7.890; 7.886; 7.870
	0.45	7.02; 6.98; 6.86; 6.81	−	8.13; 8.12; 8.11;8.09
Δδ	−	+1.64	−	+0.58
7c	0.00	5.24	4.53(*t*); 4.26(*c*)	7.53
	0.12	5.65; 5.64; 5.62; 5.61	4.53(*t*); 4.26(*c*)	7.665; 7.660
	0.30	6.12; 6.10; 6.04; 6.02	5.14-5.10(*t*)-4.79-4.77(*c*)	7.83; 7.82; 7.81
	0.45	6.76; 6.73; 6.63; 6.60	−	8.046; 8.043; 8.02
Δδ	−	+1.44	−	+0.51
7d	0.00	5.59; 5.58		7.56
	0.12	5.79; 5.79; 5.77; 5.76		7.63
	0.30	6.35; 6.35; 6.29; 6.25		7.85; 7.83: AA′XX′
	0.45	7.03; 7.03; 6.92; 6.84		8.10; 8.07: AA′XX′
Δδ	−	+1.37		+0.53
7e	0.00	5.57; 5.56		7.53
	0.13	5.94; 5.90		7.67
	0.30	6.72; 6.72; 6.61; 6.56		7.96; 7.94: AA′XX′
	0.45	7.43; 7.43; 7.40; 7.38		8.23; 8.18
Δδ	−	+1.85		+0.68

[a] The difference between the averaged maximum δ values ($X_{CSR} = 0.45$) and the initial value ($X_{CSR} = 0.00$).[b] In series **7a**−**c** only, if more than one value is given, they appeared as singlets (no typical $^3J_{H,H}$*ortho* coupling pattern could be assigned).

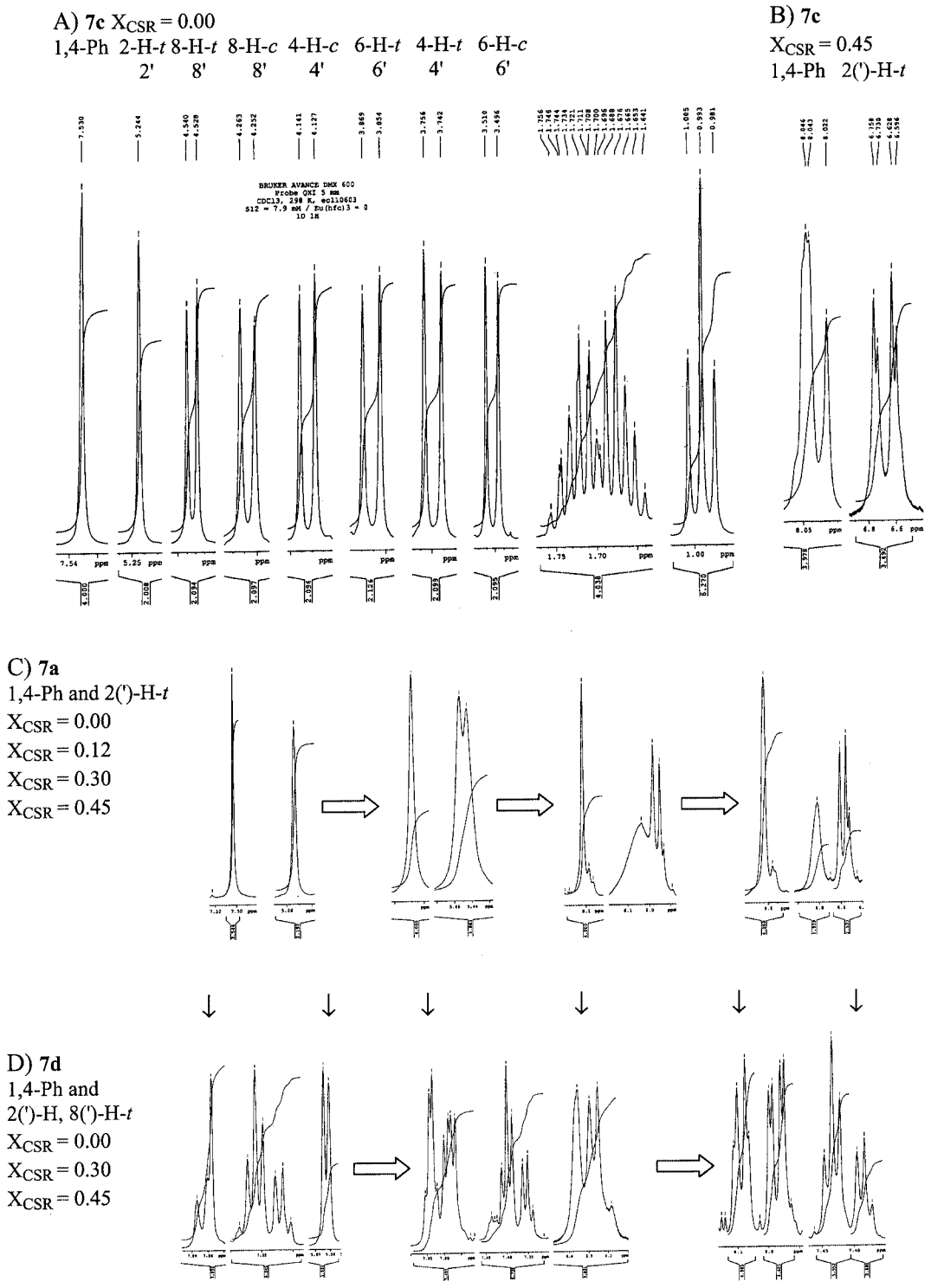


Figure 3. ^{1}H NMR spectra of compounds **7c** (A, B), **7a** (C, details) and **7d** (D, details) before and after addition of increasing amounts of Eu(hfc)$_3$ (see also Table 2)

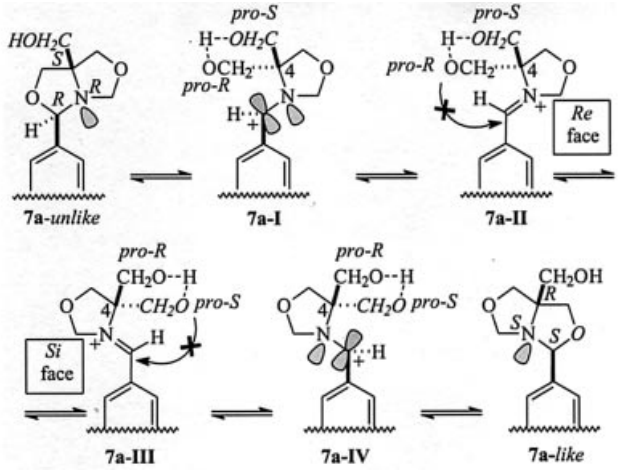
$$\delta_{obsd.} = \delta_{\mathbf{7a}}X_{\mathbf{7a}} + \delta_{Comp.}X_{CSR} \quad (6)$$

The obtained value, $\delta_{Comp.} \approx 9.50$ ppm, suggests the close proximity between the lanthanide cation and the aromatic ring, which suggests that the global stereochemistry of the whole molecule most probably is *like*; in addition to the two bridged nitrogen atoms, the two hydroxymethyl groups should be strongly involved in this preferred *in* rotamer arrangement (Scheme 6).

However, scepticism prevented us from extrapolating this result to complete diastereoselectivity in the synthesis of the compound **7a** because, as we previously reported, its precursor **5a** (Scheme 4), which raises the same problem of

global stereochemistry, showed a rather rapid equilibration between the *like* and *unlike* diastereoisomers, even on the 600-MHz NMR spectroscopic time scale.[26] A simplified molecular modeling in series **5a**−**c** and **7a**−**c**, by neglecting the geminal substituents at C-4(′) and C-5(′), respectively (Scheme 4), provided about the same small difference between the *like* and *unlike* forms in both cases: $\Delta E \approx 0.4$ kJ/mol (0.1 kcal/mol).

Consequently, in the case of **7a**, our diagnosis consists again of the presence, in solution, of both the free 1:1 diastereoisomers *like* and *unlike* in a dynamic equilibrium. On the other hand, a complete isomerisation of *unlike* → *like* spontaneously occurred upon complexation by $Eu(hfc)_3$. If so, this situation represents just another case of the rapid double ring−ring tautomerism in oxazolidine series that we recently described,[26,32] but it shifts completely towards **7a**-*like* in the presence of Eu^{3+} (Scheme 12).



Scheme 12

Thus, the interconversion between *like* and *unlike global stereochemistry* appears to be crucially influenced by the all-*cis* arrangement required by the *local stereochemistry* in each terminal bicyclic system because a complete inversion of three chiral centres must take place. The diastereoselective ring opening of the (*E*)-iminium cation (**7a-II**), which has diastereotopic faces, allowed no interaction between the rear *pro-R* nucleophile on the front-side *Re* face to provide the *cis* relationship between the phenyl ring and the *pro-S* nucleophile (*lk* topicity). The situation was reversed in **7a-III**: the *pro-S* nucleophile should attack on the *Si* face of the (*E*)-iminium cation (*lk* topicity). Hence, some free rotation around the $N-C_{benzyl}$ bond should occur and the existence of carbocations with diastereotopic faces (**7a-I** and **7a-II**) as intermediates is reasonable; they allow the *lk* topicity interaction for the ring closure.

Globally, it must be observed that during the equilibration, the two hydroxymethyl groups, which possess opposite prochiralities, replace one another. Obviously, the proposed pathway in Scheme 12 was not possible for **7b** and **7c** since the oxazolidine C-4 position is prostereogenic in **7a**, but it is stable stereogenic in **7b** and **7c**.

In the synthesis of compounds **7d** and **7e**, we encountered a complete *unlike* diastereoselectivity, as evidenced by their NMR spectra in the presence of $Eu(hfc)_3$ (Figure 3D: **7d**). The bulkiness of the two phenyl rings linked at C-8(′) might be responsible for this *global stereochemistry*. More stable and selective electrophiles, such as benzyl carbocations, were involved with dual consequences: higher yields than in the **7a**−**c** series (Scheme 4), but a failure to obtain the C-8/C-8′ diphenyl analogue of **7a**. Instead, the double transaminalisation product **2d**-*cis* was isolated with poor yield.

2.4. Determining the Stereochemistry in the Solid State by X-ray Diffractometry

The compounds **2a**, **2d**-*trans*, **4** and **7c** provided crystals appropriate for investigation by X-ray diffractometry. Their determined X-ray structures are presented in Figures 4−7 together with selected bond lengths. The relevant delocalising interactions lp→σ* (E_{del}) issued from the NBO analysis are listed in Table 3.[33,34]

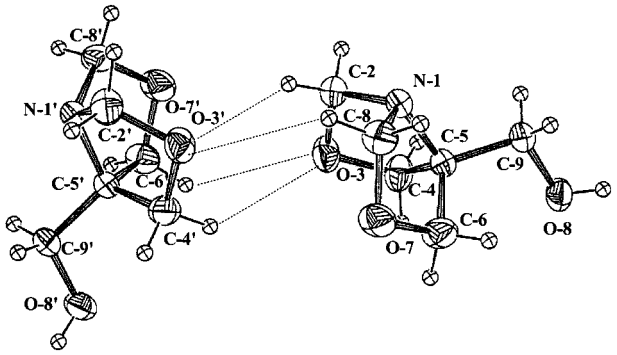


Figure 4. The X-ray crystallographically determined structure of compound **2a** and selected bond lengths [A]: N-1−C-5 1.499(3), N-1′−C-5′ 1.499(2), N-1−C-2 1.474(3), N-1′−C-2′ 1.467(3), C-2−O-3 1.420(3), C-2′−O-3′ 1.417(3), O-3−C-4 1.433(3), O-3′−C-4′ 1.416(3), N-1−C-8 1.466(3), N-1′−C-8′ 1.457(3), C-8−O-7 1.420(3), C-8′−O-7′ 1.415(3), O-7−C-6 1.420(3), O-7′−C-6′ 1.417(3)

In the solid state, compounds **2a** and **4** exist as unexpected aggregates that arise, in each case, because of a certain *global stereochemistry* based on an appropriate *local stereochemistry* of the bicyclic systems (Scheme 5). Thus, the elementary cell of **2a** is a dimeric form of two units: *left* and *right* (Figure 4).

Both forms have the same O-3(′)-*anti*−O-7(′)-*anti* envelope frozen conformation (*out* rotamers), which are close to the one predicted theoretically for **2a**-*a*,*a*-**II** (Scheme 6): twice *meso* form (Scheme 5). However, the two units are not quite identical because the *left* unit is slightly smaller and less puckered than the *right* unit. The *meso*/*meso global stereochemistry* appeares to be required for the non-bond-

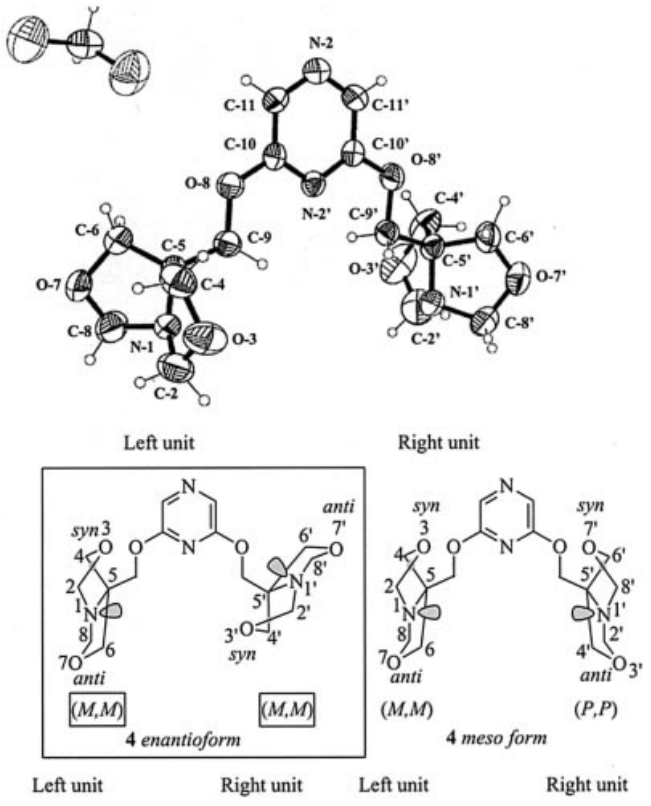


Figure 5. The X-ray crystallographically determined structure of compound **4** and selected bond lengths [Å]: *chiral*-**4**: N-1−C-5 1.493(3), N-1′−C-5′ 1.480(3), N-1−C-2 1.454(4), N-1′−C-2′ 1.466(4), C-2−O-3 1.398(4), C-2′−O-3′ 1.355(5), O-3−C-4 1.440(4), O-3′−C-4′ 1.443(5), N-1−C-8 1.448(4), N-1′−C-8′ 1.454(4), C-8−O-7 1.403(4), C-8′−O-7′ 1.405(4), O-7−C-6 1.430(3), O-7′−C-6′ 1.420(4); *meso*-**4**: N-1−C-5 1.493(3), N-1′−C-5′ 1.480(3), N-1−C-2 1.466(4), N-1′−C-2′ 1.454(4), C-2−O-3 1.62(3), C-2′−O-3′ 1.398(4), O-3−C-4 1.21(2), O-3′−C-4′ 1.440(4), N-1−C-8 1.448(4), N-1′−C-8′ 1.454(4), C-8−O-7 1.403(4), C-8′−O-7′ 1.318(19), O-7−C-6 1.430(3), O-7′−C-6′ 1.55(2)

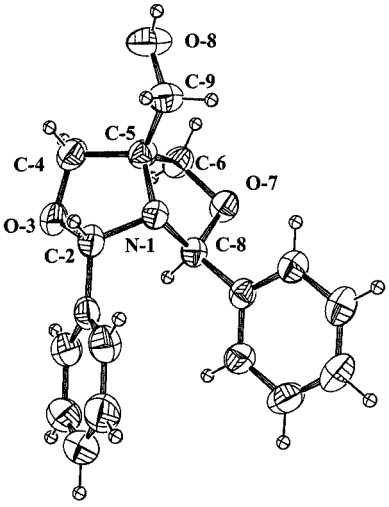


Figure 6. The X-ray crystallographically determined structure of compound **2d**-*trans* and selected bond lengths [Å]: N-1−C-5 1.4935(17), N-1−C-2 1.4693(16), C-2−O-3 1.4287(16), O-3−C-4 1.4282(18), N-1−C-8 1.4855(16), C-8−O-7 1.4187(15), O-7−C-6 1.4329(16)

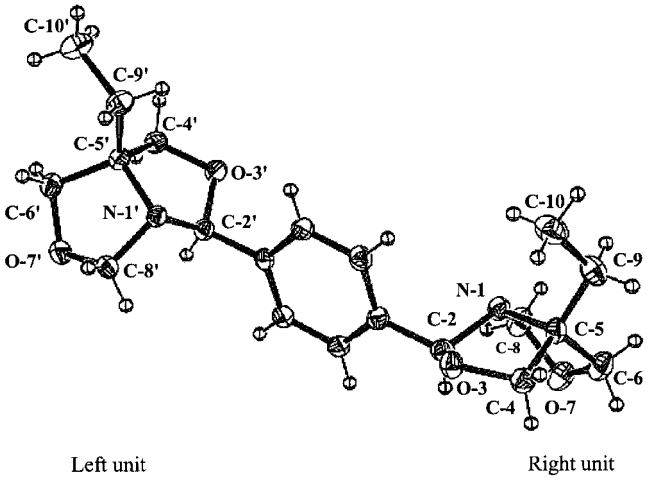


Figure 7. The X-ray crystallographically determined structure of compound **7c** and selected bond lengths [Å]: N-1−C-5 1.493(4), N-1′−C-5′ 1.498(3), N-1−C-2 1.479(3), N-1′−C-2′ 1.467(3), C-2−O-3 1.407(3), C-2′−O-3′ 1.419(3), O-3−C-4 1.436(3), O-3′−C-4′ 1.433(3), N-1−C-8 1.454(4), N-1′−C-8′ 1.449(3), C-8−O-7 1.426(4), C-8′−O-7′ 1.428(3), O-7−C-6 1.409(4), O-7′−C-6′ 1.428(3)

ing intermolecular interactions revealed by the crystalline network, between the aminalic O-3 and O-3′ atoms and both types of *trans* (pseudoequatorial) hydrogen atoms: aminalic 2-H/8-H-*t* and aliphatic 4′-H/6′-H-*t*. The interatomic >O···H−CH< distances have about the same magnitude. Four interactions were detected: 2.875 Å between O-3−6′-H-*t* and 2.720 Å between O-3−4′-H-*t*; 2.748 Å between O-3′−8-H-*t* and 2.407 Å between O-3′−2-H-*t*.

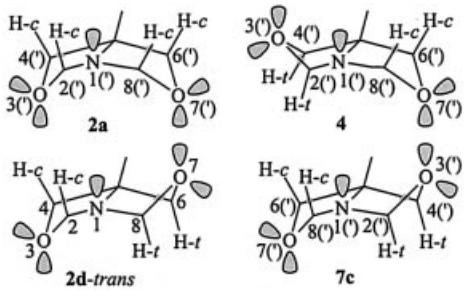
We were interested in the magnitude of the energy of these interactions (EI) starting from the optimised total geometry of the dimer (level RHF/6-31G*) from which the total electronic energy of each unit was extracted. The result suggests a stabilisation (dimer vs. two completely independent units) of 18.5 kJ/mol. Since the basis set superposition error (BSSE) usually affects this value, we also estimated it by the Counterpoise correction for BSSE[35] (10.5 kJ/mol); i.e., the EI is about 8.0 kJ/mol (1.91 kcal/mol), which is still significant.

The expected intermolecular hydrogen bond between the hydroxymethyl group from each unit and the bridged nitrogen atoms of the adjacent dimer was 2.100 Å.

Concerning the geometry of this type of bicyclic system, which was recently exemplified in the literature by **2d**-*cis* in terms of anomeric effects in the aminalic zone,[24,36,37] compound **2a** encounters twice the appropriate steric conditions for this purpose because of the O-3(′)-*anti*−O-7(′)-*anti* disposal in the two oxazolidine rings; it favours two hyperconjugative interaction: $lp_{N\text{-}1(')} \rightarrow \sigma^*_{C\text{-}2(')-O\text{-}3(')}$ and $lp_{N\text{-}1(')} \rightarrow \sigma^*_{C\text{-}8(')-O\text{-}7(')}$.

Their calculated magnitude (Table 3) was undoubtedly small enough and quite different [as the reverse ones: $lp_{O\text{-}3(')eq.} \rightarrow \sigma^*_{N\text{-}1(')-C\text{-}2(')}$ and $lp_{O\text{-}7(')eq.} \rightarrow \sigma^*_{N\text{-}1(')-C\text{-}8(')}$] when compared to the other terms of the series. In turn, four other delocalisations $lp_{O\text{-}ax.} \rightarrow \sigma^*_{C-H\text{-}c(axial)}$ appeared more significant. Similar remarks (Table 3) apply for the

Table 3. Results of NBO analysis and the main delocalising interactions (selected as $E_{del} > 25$ kJ/mol) in the region [C-4(′)−O-3(′)−C-2(′)−N-1(′)−C-8(′)−O-7(′)−C-6(′)] for the compounds **2a**, **2d**-*trans*, **4** and **7c**



lp donors	Acceptors (σ*) and E_{del} (kJ/mol)									
	C-2–O-3		C-8–O-7		N-1–C-2		N-1–C-8		C-2–2-H	
	2′	3′	8′	7′	1′	2′	1′	8′	2′	2′
2a										
N-1(′)	38.09		40.47							
O-3(′)-ax									41.98 (*c*)[a]	
O-3(′)-eq					29.55					
O-7(′)-ax										
O-7(′)-eq							29.05			
4										
N-1(′)			38.42						26.36 (*t*)	
O-3(′)-ax									36.87 (*t*)	
O-3(′)-eq					30.93					
O-7(′)-ax										
O-7(′)-eq							27.62			
2d-*trans*										
N-1	46.38									
O-3-ax									40.72 (*c*)	
O-3-eq					31.93					
O-7-ax										
O-7-eq							31.73			
7c										
N-1′			47.21						27.03 (*t*)	
O-3′-ax									37.67 (*t*)	
O-3′-eq					31.60					
O-7′-ax										
O-7′-eq							30.51			
N-1			47.63						27.33 (*t*)	
O-3-ax									38.59 (*t*)	
O-3-eq					35.86					
O-7-ax										
O-7-eq							29.76			

lp donors	Acceptors (σ*) and E_{del} (kJ/mol)							
	C-8–8-H		C-4–4-H		C-6–6-H			
	8′	8′	4′	4′	6′	6′		
2a								
N-1(′)								
O-3(′)-ax			42.82 (*c*)					
O-3(′)-eq								
O-7(′)-ax	41.77 (*c*)				42.94 (*c*)			
O-7(′)-eq								
4								
N-1(′)								
O-3(′)-ax			23.48 (*t*)					
O-3(′)-eq								
O-7(′)-ax	36.45 (*c*)				39.97 (*c*)			
O-7(′)-eq								
2d-*trans*								
N-1	25.41 (*t*)							
O-3-ax			39.64 (*c*)					
O-3-eq								
O-7-ax	42.61 (*t*)				38.51 (*t*)			
O-7-eq								
7c								
N-1′								
O-3′-ax			32.77 (*t*)					
O-3′-eq								
O-7′-ax	30.68 (*c*)				33.65 (*c*)			
O-7′-eq								
N-1								
O-3-ax			32.23 (*t*)					
O-3-eq								
O-7-ax	30.64 (*c*)				36.75 (*c*)			
O-7-eq								

[a] Disposition [*c* (*cis*) or *t* (*trans*)] of the depicted hydrogen atom; see also Table 1.

(pseudo)axial protons 2-H-*c* and 8-H-*t* in **2d**-*trans* where the elongation of the C-2−2-H-*c* and C-8−8-H-*t* bonds was observed (0.98 vs. 0.97 Å).[34] Bond lengths supported these assignments: more important was the contraction of each of the N-1(′)−C-8(′) bonds, relative to each N-1(′)−C-2(′) bond, with respect to the "reference" N-1(′)−C-5(′) bond: 0.033 and 0.042 Å vs. 0.025 and 0.032 Å, respectively.

The pyrazine derivative **4** (Figure 5) was established as a non-stoichiometric solvate of dichloromethane (used to develop crystals): one molecule of solvent was captured in the channels of the network with an occupation factor of 0.96.

This chelating aptitude was also based on a peculiar *global stereochemistry*: the elementary cell as *chiral* against *meso*. Accordingly, the intermolecular interactions imposed a certain *local stereochemistry*: each dioxaazabicyclooctane unit had the same O-3(′)-*syn*−O-7(′)-*anti* chiral frozen conformation (Scheme 5). Two crystalline diastereoisomeric forms were detected. In Figure 5, *chiral*-**4** is shown as the major structure (87%); the *meso* form of **4** has a minor occurrence (13%). In *chiral*-**4**, the two units (*left* and *right*) are different enough with respect to their main bond lengths, especially for the N-1(′)−C-5(′) and C-2(′)−O-3(′) bonds. On the basis of this criterion, the contractions of the C−O bonds in the aminalic part, mainly in the O-3(′)-*syn* rings, were the result of the hyperconjugation $lp_{O\text{-}3(')\text{-eq.}} \rightarrow \sigma^*_{N\text{-}1(')-C\text{-}2(')}$ (30.93 kJ/mol) being more important than in the O-7(′)-*anti*-oriented oxazolidines: $lp_{O\text{-}7(')\text{-eq.}} \rightarrow \sigma^*_{N\text{-}1(')-C8(')}$ (27.62 kJ/mol). The occurrence of the already "classic" interaction,[24] $lp_{N\text{-}1(')} \rightarrow \sigma^*_{C\text{-}8(')-O\text{-}7(')}$ [responsible for the

contraction of N-1(′)−C-8(′) bonds vs. N-1(′)−C-5(′), 0.045 and 0.026 Å, supported by 38.42 kJ/mol, Table 3], was also relevant.

The changing of the *global stereochemistry* from *chiral*-**4** to the global *meso* form of **4** involves important distortions of the C−O bonds in both the *right* and *left* units. Consequently, this alternative architecture was less stable and has a lower chelating aptitude. The molecule of dichloromethane was also found to be distorted, especially with respect to the H−C−Cl angles: 115.3 and 103.0 ° in *chiral* **4**; 109.0 and 101.0° in *meso* **4**. We note that the position of its hydrogen atoms was not calculated, but, rather, located from subsequent difference Fourier synthesis and refined isotropically. Some differences are worth mentioning with reference to the bond lengths: C−Cl, 1.711 Å in *chiral*-**4** and 1.746 Å in *meso*-**4**; C−H, 0.94 Å in *chiral*-**4** and 1.05 Å in *meso*-**4**.

Moreover, the inclusion of dichloromethane was crucial for the above structural investigation: the network was stable only in the presence of the solvent.

The geometry of compound **2d**-*trans* in the solid state (Figure 6) revealed the expected *out*-(hydroxymethyl) rotamer and the two phenyl rings linked in a *trans*-pseudodiequatorial position with bisectional orientation. These last details agree with the calculated structure (**2d**-*trans*-*a*,*s*; Scheme 7).

The length of the bonds in the aminalic motif allow us to make two applicable assignments.

(i) In comparison with **2a**, a stronger anomeric effect in the O-3-*anti*-oxazolidine ring $lp_{N\text{-}1} \rightarrow \sigma^*_{C\text{-}2-O\text{-}3}$ was estimated by calculation (ΔE_{del} = +5.91 kJ/mol; Table 3), although the contractions of the N-1−C-2 and N-1−C-5 bonds were about the same: 0.029 Å in **2a**, 0.024 Å in **2d**-*trans*

(ii) In turn, a comparison between E_{del} values at C-2 [(*S**) configuration, direct $lp_{N\text{-}1} \rightarrow \sigma^*_{C\text{-}2-O\text{-}3}$ and reverse $lp_{O\text{-}3\text{-}eq} \rightarrow \sigma^*_{N\text{-}1-C\text{-}2}$] and C-8 [(*S**) configuration, $lp_{O\text{-}7\text{-}eq} \rightarrow \sigma^*_{N\text{-}1-C\text{-}8}$] suggest that C-2 is a stronger anomeric centre than C-8.

There are experimental data to corroborate this feature:

(i) The epimerisation of the C-2 carbon centre in single or double (spiro)1,3-oxazolidines during their equilibration in simple or double ring−chain or ring−ring tautomerism, as we have reported previously:[20,26,32,38] this position is under simultaneous double N- and O-hyperconjugative influence[39]

(ii) The greater thermodynamic stability of *cis*- vs. *trans*-C-2,C-8-di(hetero)aryl diastereoisomers of types **2d** and **3e** (Schemes 7 and 9), which we have established recently by the diastereoselectivities observed in their thermodynamically controlled syntheses: epimerisation at C-2 from the (*S**) to (*R**) configuration, less hyperconjugated to provide the dominant all-*cis* double ring closure, with the exception of (Het)Ar fragments (*p*-nitrophenyl and 4-Py), which are unable to stabilise benzylic carbocations.[20,21]

In the case of compound **7c** (Figure 7), the presence of the non-polar ethyl group, in lieu of the hydroxymethyl group at position C-5, brought about no obvious change in the basic features.

The two bicyclic units (*left* and *right*) were again not identical, presumably because of the different orientation of the ethyl group: the *left* unit was typically an *out* rotamer while the *right* one's orientation was *in*. The major difference between the "dimer" **7c** and **2a** (or **2d**-*trans*) was found in both the O-3(′)-*syn* and O-7(′)-*anti* rings: the greatest contraction of N-1(′)−C-8(′) bonds relative to N-1(′)−C-5(′) bonds (0.039 Å and 0.049 Å, respectively) was evidenced by the greatest hyperconjugations: $lp_{N\text{-}1(')} \rightarrow \sigma^*_{C\text{-}8(')-O\text{-}7(')}$, E_{del} = 47.21 and 47.63 kJ/mol. The calculated effects in O-3(′)-*syn* rings, $lp_{O\text{-}3(')\text{-}eq} \rightarrow \sigma^*_{N\text{-}1(')-C\text{-}2(')}$ (35.86 and 31.60 kJ/mol), were also important and relevant: they both imply the stereogenic C-2(′) centres.

Contractions of the bonds C-2(′)−O-3(′) and C-8−O-7(′) (0.019 and 0.009 Å, respectively) provided support for the above values of E_{del}. It must be noted that all of these hyperconjugative interactions were oriented in an opposite global sense (*like global stereochemistry*) that is responsible, most probably, for the preferred crystallisation of **7c** as the *like* diastereoisomer.

3. Conclusion

The investigation of the 5-substituted 3,7-dioxa-1-azabicyclo[3.3.0]octanes involves various points of view that are coherently connected if we consider the conformational chirality of the basic skeleton and its flexibility around the C−O−C bonds as essential features. The latter depends on the chelating aptitude of the solvent and the orientation (*in* or *out* rotamers) of a hydroxymethyl group linked at position C-5. The energetic barrier of the ring inversion is influenced by the polarity of this substituent and the solvent. The observation of two fused 1,3-oxazolidine O-envelope conformers provides a useful local stereochemical approach for the analysis of the dioxaazabicyclooctane system because good-to-excellent agreements exist between the theoretical calculations and experimental data. Anomeric effects in the O−CH_2−N motif can explain the versatile reactivity of this system: (long-distance) diastereoselection in synthesis, epimerisation and ring-chain tautomerism. Relevant intra- and intermolecular chelations are responsible for aggregates possessing an appropriate *global stereochemistry*.

4. Experimental Section

General: Melting points are uncorrected; they were determined with an ELECTROTHERMAL® instrument. NMR spectra were recorded with a Bruker® AM 300 instrument operating at 300 and 75 MHz for ^1H and ^{13}C nuclei, respectively. Dynamic NMR spectra were performed with a Bruker® AM 400 instrument operating at 400 and 100 MHz for ^1H and ^{13}C nuclei, respectively, with each step decreasing the temperature by 10 K and without spinning. The assignments of the *global stereochemistry* of compounds **7a**−**e** were performed with a Bruker® DMX 600 instrument operating at 600 MHz for ^1H nuclei, without spinning. All NMR spectra were

measured in anhydrous, commercially available, deuterated solvents. No $SiMe_4$ was added; chemical shifts were measured against the solvent peak. All chemical shifts (δ values) are given throughout in ppm; all coupling patterns ($^nJ_{H,H}$ values) are given throughout in Hz. TLC was performed by using aluminium sheets coated with silica gel 60 F_{254} (Merck®); flash column chromatography was conducted on silica gel Si 60 (40−63 μm, Merck®). IR spectra were performed with a Perkin−Elmer® 16 PC FTIR spectrometer. Only relevant absorptions are listed [throughout in cm^{-1}: weak (w), medium (m) or (s) strong]. Mass spectra (MS) were recorded with an ATI-Unicam Automass® apparatus, fitted (or not) with a GC/mass coupling system (high-resolution J&W column, 30 m, 0.25 mm ID, flow rate: 1.2 mL·min^{-1}). Molecular orbital calculations: the conformational space of the systems was investigated by using the "Conformer Distribution" facility (MMFF force field) from Spartan'o2. (Spartan'o2, Wavefunction, Inc. Irvine, CA). The set of conformers thus generated was subjected, within the same package, to full geometry optimization at the RHF/6-31G* ab initio level. The default convergence criteria (energy = 0.000001 hartrees, rms gradient = 0.000450 hartrees/bohr) were imposed throughout all the ab initio computations. Natural bond orbital analysis[33] was conducted using the Gaussian 98 system[40] run under Linux. Single-point calculations were performed at the gas-phase geometries by resorting to the Polarized Continuum Model (PCM) of Tomassi as implemented in the Gaussian 98 system.[41] The syntheses of the known compounds **2a**−**c**, **2d**-*cis*, **2d**-*trans* and **2e**-*cis* have been reported previously by Senkus (1945),[1] Crabb (1973)[16] and by us (2000).[21] Assignment of the *local stereochemistry* for the compounds **4**, **6a**−**c** and **7a**−**e** was made by NOE difference and NOESY experiments. Labelling of protons as *c* (*cis*) or *t* (*trans*) was made throughout as defined in Table 1 and Figures 1−7. For compounds **2f**-*cis*, **3a**−**d**, **3e**,**f**-*cis*, **4** and **6a**−**c**, the lone pair of electrons at N-1 was designed as the fiducial substituent and is labelled as *r* (reference); the other ligands are labelled as *c* (*cis*) or *t* (*trans*) with respect to the fiducial substituent.

X-ray Diffractometry: CCDC-196937, -196938, -199978 and -196939 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk]. **2a** (CCDC-196937): Unit cell parameters: $a = 7.5309(2)$ $b = 9.8209(2)$ $c = 18.4736(3)$, space group $P2_12_12_1$. **2d-*trans*** (CCDC-196938): Unit cell parameters: $a = 9.53770(10)$ $b = 10.37930(10)$ $c = 31.1495(4)$, space group *Pbca*. **4** (CCDC-199978): Unit cell parameters: $a = 12.251$ $b = 11.072$ $c = 15.243$, space group $P2_1/n$. **7c** (CCDC-196939): Unit cell parameters: $a = 10.4775(2)$ $b = 13.0614(3)$ $c = 13.5611(3)$, space group $P2_12_12_1$.

General Procedure for the Preparation of Compounds 3a−d, 3e-*cis*, 3f-*cis* and 4: Potassium hydride (for the synthesis of compounds **3a**−**d**: 1.400 g as 30% oily suspension, 0.421 g, 100%, 10.50 mmol; for the synthesis of compounds **3e**-*cis* and **3f**-*cis*: 0.683 g as 30% oily suspension, 0.205 g, 100%, 5.12 mmol) was suspended with stirring in freshly distilled THF (50 mL) under nitrogen. Finely powdered *c*-5-(hydroxymethyl)-3,7-dioxa-*r*-1-azabicyclo[3.3.0]octane (**2a**) (1.450 g, 10.00 mmol) [or *c*-5-(hydroxymethyl)-*c*-2,*c*-8-diphenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]octane (**2d**-*cis*) (1.450 g, 4.88 mmol)] was added at room temperature. The resulting fine suspension was warmed at 40 °C for 1.5−2.0 h (until no more hydrogen was formed) and then cooled to room temperature to afford a fine, white suspension in a clear solution. The corresponding electrophile [Schemes 3 and 4: for the synthesis of compounds **3a**−**c**: R^2X (11.00 mmol); for the synthesis of **3d**: 1,2-ethylene glycol ditosylate (4.76 mmol) or tosyl chloride (11.00 mmol); for the synthesis of the compound **4**: 2,6-dichloropyrazine (4.76 mmol); for the synthesis of compounds **3e**-*cis* and **3f**-*cis*: R^2X (5.37 mmol)] was added as a solution in freshly distilled THF (10 mL) at room temperature. The reaction mixture was warmed at 55−60 °C for 10−15 min, then left to cool slowly, while maintaining stirring, to room temperature overnight (12−24 h). TLC monitoring indicated the starting materials were absent or in small traces only (double visualisation: first UV 254 nm for compounds **3c**−**e**-*cis*, **3f**-*cis* and **4**, then an I_2 bath; single visualisation in an I_2 bath for compounds **3a** and **3b**). During condensation, the reaction mixture turned brown and potassium halide was formed abundantly. The reaction was quenched at room temperature by adding water (100 mL) and dichloromethane (100 mL) with vigorous stirring. After separation, the organic layer was washed with water (about 3 × 50 mL) to pH = 7.5−8.0 and then dried ($MgSO_4$). After filtering, the organic solution was concentrated under vacuum to dryness to yield the crude product, which was purified by flash column chromatography or crystallised directly from an appropriate solvent to yield the title compounds **3a**−**d**, **3e**-*cis*, **3f**-*cis* and **4**.

***c*-5-(Methoxymethyl)-3,7-dioxa-*r*-1-azabicyclo[3.3.0]octane (3a):** Yield 33%, yellowish oil (flash column chromatography; pentane/acetone, 1:1). $C_7H_{13}NO_3$ (159.19): calcd. C 52.81, H 8.23, N 8.80; found C 52.59, H 8.50, N 9.06. R_f (50% pentane/acetone) = 0.70. IR (CH_3Cl film, NaCl): $\tilde{\nu}$ = 2921 (s), 2857 (m), 1737 (w), 1470 (w), 1387 (w), 1263 (w), 1120 (w), 1074 (w), 1019 (w), 798 (w) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.34 (s, 3 H, OCH_3), 3.40 (s, 2 H, 5-CH_2O), 3.75 (s, 4 H, 4-H, 6-H-*c*, -*t*), 4.38 (d, $^2J_{H,H}$ = 5.5 Hz, 2 H, 2-H, 8-H-*c*), 4.42 (d, $^2J_{H,H}$ = 5.5 Hz, 2 H, 2-H, 8-H-*t*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 59.9 (1 C, OCH_3), 72.2 (1 C, C-5), 74.7 (2 C, C-4, C-6), 76.4 (1 C, 5-CH_2O), 88.5 (2 C, C-2, C-8) ppm. MS (CI, CH_4): *m*/*z* (%) = 205 (24), 149 (55), 129 (8), 97 (18), 79 (18), 57 (100).

***c*-5-(Ethoxymethyl)-3,7-dioxa-*r*-1-azabicyclo[3.3.0]octane (3b):** Yield 66%, yellowish oil (flash column chromatography; pentane/Et_2O, 2:1). $C_8H_{15}NO_3$ (173.21): calcd. C 55.47 H 8.73, N 8.09; found C 55.22, H 9.13, N 8.33. R_f (66% pentane/Et_2O) = 0.80. IR (CH_3Cl film, NaCl): $\tilde{\nu}$ = 2975 (m), 2932 (s), 2863 (s), 1653 (w), 1636 (w), 1465 (m), 1445 (w), 1374 (m), 1363 (m), 1352 (m), 1274 (m), 1176 (s), 1157 (s), 1110 (s), 1045 (s), 1022 (s), 929 (s), 877 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.06 (t, $^3J_{H,H}$ = 7.0 Hz, 3 H, OCH_2CH_3), 3.37 (s, 2 H, 5-CH_2O), 3.40 (q, $^3J_{H,H}$ = 7.0 Hz, 2 H, OCH_2CH_3), 3.67 (s, 4 H, 4-H, 6-H-*c*,-*t*), 4.29 (d, $^2J_{H,H}$ = 5.3 Hz, 2 H, 2-H, 8-H-*c*), 4.33 (d, $^2J_{H,H}$ = 5.3 Hz, 2 H, 2-H, 8-H-*t*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 15.3 (1 C, CH_2CH_3), 67.4 (1 C, CH_2CH_3), 72.2 (1 C, C-5), 74.2 (1 C, 5-CH_2O), 74.8 (2 C, C-4, C-6), 88.4 (2 C, C-2, C-8) ppm. MS (CI, CH_4): *m*/*z* (%) = 174 (70) [M^+ + 1], 128 (25), 114 (100), 99 (7), 86 (15), 58 (25).

***c*-5-(Benzyloxymethyl)-3,7-dioxa-*r*-1-azabicyclo[3.3.0]octane (3c):** Yield 40%, yellowish oil (flash column chromatography; Et_2O/heptane, 3.5:1.0). $C_{13}H_{17}NO_3$ (235.28): calcd. C 66.36, H 7.28, N 5.95; found C 66.59, H 7.15, N 6.22. R_f (78% Et_2O/heptane) = 0.65. IR (CH_3Cl film, NaCl): $\tilde{\nu}$ = 2939 (s), 2866 (s), 1502 (w), 1461 (m), 1364 (m), 1286 (w), 1217 (m), 1189 (m), 1102 (s), 1051 (s), 1036 (s), 936 (s), 798 (w), 756 (s), 706 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.50 (s, 2 H, 5-CH_2O), 3.80 (s, 4 H, 4-H, 6-H-*c*,-*t*), 4.40 (d, $^2J_{H,H}$ = 5.5 Hz, 2 H, 2-H, 8-H-*c*), 4.44 (d, $^2J_{H,H}$ = 5.5 Hz, 2 H, 2-H, 8-H-*t*), 4.53 (s, 2 H, OCH_2Ph), 7.28−7.34 (m, 5 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 72.3 (1 C, C-5), 73.9 (1 C, 5-CH_2O), 74.1 (1 C, OCH_2Ph), 75.0 (2 C, C-4, C-6), 88.5 (2 C, C-2, C-8), 128.1 (2 C, CH arom.), 128.2 (2 C, CH arom.), 128.9

(1 C, CH arom.), 138.2 (1 C, Cq arom.) ppm. MS (CI, CH_4): *m*/*z* (%) = 236 (100) [M^+ + 1], 158 (10), 129 (29), 114 (96), 91 (90), 58 (36).

***c*-5-(Tosyloxymethyl)-3,7-dioxa-*r*-1-azabicyclo[3.3.0]octane (3d):** Yield 70%, yellowish crystalline powder, m.p. 124−125 °C (direct crystallisation from Et_2O). $C_{13}H_{17}NSO_5$ (299.34): calcd. C 52.16, H 5.72, N 4.68; found C 51.81, H 6.05, N 4.98. R_f (78% Et_2O/heptane) = 0.65. IR (CH_3Cl film, NaCl): $\tilde{\nu}$ = 2856 (w), 1636 (s), 1357 (m), 1186 (m), 1166 (s), 1135 (w), 1045 (m), 971 (m), 927 (w), 840 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.44 (s, 3 H, CH_3), 3.70 (d, $^2J_{H,H}$ = 9.2 Hz, 2 H, 4-H, 6-H-*c*), 3.73 (d, $^2J_{H,H}$ = 9.2 Hz, 2 H, 4-H, 6-H-*t*), 3.99 (s, 2 H, 5-CH_2O), 4.33 (d, $^2J_{H,H}$ = 5.5 Hz, 2 H, 2-H, 8-H-*c*), 4.38 (d, $^2J_{H,H}$ = 5.5 Hz, 2 H, 2-H, 8-H-*t*), 7.35 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H, Ts), 7.77 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H, Ts) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 22.1 (1 C, CH_3), 71.3 (1 C, C-5), 72.5 (1 C, 5-CH_2O), 74.0 (2 C, C-4, C-6), 88.2 (2 C, C-2, C-8), 128.4 (2 C, CH, Ts), 130.4 (2 C, CH, Ts), 132.7 (1 C, Cq, Ts), 145.7 (1 C, Cq, Ts) ppm. MS (CI, CH_4): *m*/*z* (%) = 300 (3) [M^+ + 1], 146 (40), 128 (100), 93 (22), 65 (17).

***c*-5-(Methoxymethyl)-*c*-2,*c*-8-diphenyl-3,7-dioxa-*r*-1-azabicyclo-[3.3.0]octane (3e-*cis*):** Yield 30%, yellowish crystalline powder, m.p. 73−74 °C (flash column chromatography; pentane/Et_2O, 1:1). $C_{19}H_{21}NO_3$ (311.38): calcd. C 73.29, H 6.80, N 4.52; found C 73.55, H 7.11, N 4.41. R_f (50% pentane/Et_2O) = 0.75. IR (CH_3Cl film, NaCl): $\tilde{\nu}$ = 2995 (m), 2884 (s), 1466 (m), 1392 (m), 1314 (w), 1199 (m), 1111 (s), 927 (m), 701 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.17 (s, 3 H, OCH_3), 3.27 (s, 2 H, 5-CH_2O), 3.80 (s, 2 H, 4-H, 6-H-*t*), 3.96 (d, $^2J_{H,H}$ = 9.0 Hz, 2 H, 4-H, 6-H-*c*), 5.47 (s, 2 H, 2-H, 8-H-*t*), 7.22−7.30 (m, 6 H, Ph), 7.42−7.44 (m, 4 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 59.8 (1 C, OCH_3), 73.5 (1 C, C-5), 74.0 (2 C, C-4, C-6), 78.0 (1 C, 5-CH_2O), 97.5 (2 C, C-2, C-8), 128.6 (4 C, CH arom.), 128.7 (4 C, CH arom.), 128.9 (2 C, CH arom.), 140.1 (2 C, Cq, Ph) ppm. MS (CI, CH_4): *m*/*z* (%) = 312 (7) [M^+ + 1], 266 (95), 234 (42), 206 (100), 160 (20), 105 (50), 77 (46), 51 (34).

***c*-5-(Benzyloxymethyl)-*c*-2,*c*-8-diphenyl-3,7-dioxa-*r*-1-azabicyclo-[3.3.0]octane (3f-*cis*):** Yield 40%, yellowish crystalline powder, m.p. 84−85 °C (flash column chromatography; Et_2O/heptane, 1.5:1.0). $C_{25}H_{25}NO_3$ (387.48): calcd. C 77.49, H 6.50, N 3.61; found C 77.81, H 6.88, N 3.44. R_f (60% Et_2O/heptane) = 0.70. IR (CH_3Cl film, NaCl): $\tilde{\nu}$ = 3041 (w), 2866 (m), 1457 (m), 1203 (m), 1097 (s), 1033 (m), 743 (s), 701 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.67 (s, 2 H, 5-CH_2O), 3.82 (d, $^2J_{H,H}$ = 9.0 Hz, 2 H, 4-H, 6-H-*t*), 3.98 (d, $^2J_{H,H}$ = 9.0 Hz, 2 H, 4-H, 6-H-*c*), 4.32 (s, 2 H, OCH_2Ph), 5.46 (s, 2 H, 2-H, 8-H-*t*), 7.11−7.26 (m, 11 H, Ph), 7.39−7.41 (m, 4 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 73.6 (1 C, C-5), 73.9 (1 C, 5-CH_2O), 74.1 (2 C, C-4, C-6), 75.5 (1 C, O*C*H_2Ph), 97.6 (2 C, C-2, C-8), 127.6 (4 C, CH arom.), 127.9 (2 C, CH arom.), 128.1 (1 C, CH arom.), 128.7 (4 C, CH arom.), 128.8 (2 C, CH arom.), 128.9 (2 C, CH arom.), 138.4 (1 C, Cq, Ph), 140.1 (2 C, Cq, Ph) ppm. MS (CI, CH_4): *m*/*z* (%) = 388 (99) [M^+ + 1], 266 (15), 91 (50).

2,6-Bis[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (4): Yield 81%, yellowish crystalline powder, m.p. 151−152 °C (direct crystallisation from pentane). $C_{16}H_{22}N_4O_6$ (366.37): calcd. C 52.45, H 6.05, N 15.29; found C 52.11, H 5.75, N 15.66. R_f (50% acetone/ligroin) = 0.70. IR (CH_3Cl film, NaCl): $\tilde{\nu}$ = 2945 (m), 2862 (s), 1584, (w), 1532 (s), 1425 (s), 1316 (m), 1266 (m), 1185 (s), 1136 (m), 1094 (m), 1013 (s), 918 (m), 701 (w) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.86 (s, 8 H, 4-H, 4′-H, 6-H, 6′-H-*c*,-*t*), 4.30 (s, 4 H, 5-CH_2O), 4.44 (d, $^2J_{H,H}$ = 5.3 Hz, 4 H, 2-H, 2′-H, 8-H, 8′-H-*t*), 4.50 (d, $^2J_{H,H}$ = 5.3 Hz, 4 H, 2-H, 2′-H, 8-H, 8′-H-*c*), 7.79 (s, 2 H, 3-H, 5-H pyrazine) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 69.3 (2 C, 5-CH_2O), 71.8 (2 C, C-5, C-5′), 74.5 (4 C, C-4, C-4′, C-6, C-6′), 88.4 (4 C, C-2, C-2′, C-8, C-8′), 125.7 (2 C, C-3, C-5, pyrazine), 158.2 (2 C, C-2, C-6 pyrazine) ppm. MS (EI, 70 eV): *m*/*z* (%) = 366 (< 1) [M^+], 336 (4), 305 (4), 238 (8), 163 (10), 128 (100), 114 (75), 98 (28), 68 (50), 41 (76).

Typical Procedure for the Synthesis of Compounds 7a−e; Preparation of the Compound 7c: Solid 1,4-bis[4-ethyl-4-(hydroxymethyl)-1,3-oxazolidin-2-yl]benzene (**5c**) (0.600 g, 1.78 mmol), paraformaldehyde (0.108 g, 3.6 mmol) and catalytic *p*-toluenesulfonic acid were heated under reflux in toluene (25 mL) using a Dean−Stark trap until no further water separated (about 12 h; TLC monitoring, pentane/acetone, 3.5:1.0; visualisation: UV 254 nm). The solution was cooled to room temperature, neutralised with solid Na_2CO_3 and filtered and then the solvent was completely evaporated under vacuum. The yellow oily residue was separated by flash column chromatography to yield the following fractions (order of elution): compound **6c** (0.077 g, 17% conversion with respect to **5c**), compound **7c** (0.400 g, 62% conversion with respect to **5c**) and compound **2c** (0.074 g, total conversion: 17 + 6 = 23% with respect to **5c**).

***c*-2-(4-Formylphenyl)-*c*-5-(hydroxymethyl)-3,7-dioxa-*r*-1-azabicyclo-[3.3.0]octane (6a):** Yield 27%, yellowish crystalline powder, m.p. 100−101 °C (flash column chromatography; EtOAc/pentane, 3:1). $C_{13}H_{15}NO_4$ (249.27): calcd. C 62.54, H 6.01, N 5.61; found C 62.26, H 5.86, N 5.35. R_f (75% EtOAc/pentane) = 0.55. IR (CH_3Cl film, NaCl): $\tilde{\nu}$ = 3441 (s), 2930 (m), 2870 (s), 1696 (s), 1610 (m), 1576 (w), 1427 (w), 1360 (w), 1299 (m), 1207 (s), 1156 (m), 1089 (s), 1016 (s) 916 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.46 (br. s, 1 H, OH), 3.58 (br. s, 2 H, 5-CH_2O), 3.66 (d, $^2J_{H,H}$ = 9.0 Hz, 1 H, 6-H-*c*), 3.77 (d, $^2J_{H,H}$ = 9.0 Hz, 1 H, 4-H-*t*), 3.88 (d, $^2J_{H,H}$ = 9.0 Hz, 1 H, 6-H-*t*), 4.19 (d, $^2J_{H,H}$ = 9.0 Hz, 1 H, 4-H-*c*), 4.23 (d, $^2J_{H,H}$ = 7.2 Hz, 1 H, 8-H-*c*), 4.53 (d, $^2J_{H,H}$ = 7.2 Hz, 1 H, 8-H-*t*), 5.25 (s, 1 H, 2-H-*t*), 7.60 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H, H arom.), 7.84 (d, $^3J_{H,H}$ = 8.1, 2 H, H arom.), 9.97 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 65.3 (1 C, 5-CH_2O), 72.2 (1C, C-6), 74.7 (1 C, C-5), 74.9 (1 C, C-4), 85.5 (1 C, C-8), 98.4 (1 C, C-2), 128.1 (2 C, CH arom.), 130.4 (2 C, CH arom.), 137.2 (1 C, Cq arom.), 146.4 (1 C, Cq arom.), 192.4 (1 C, CHO) ppm. MS (EI, 70 eV): *m*/*z* (%) = 218 (100) [$M^+ - CH_2OH$], 119 (18).

***c*-2-(4-Formylphenyl)-*c*-5-methyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]-octane (6b):** Yield 53%, yellow oil (flash column chromatography; pentane/acetone, 4:1). $C_{13}H_{15}NO_3$ (233.27): calcd. C 66.83, H 6.42, N 5.99; found C 67.12, H 6.24, N 6.27. R_f (80% pentane/acetone) = 0.65. IR (CH_3Cl film, NaCl): $\tilde{\nu}$ = 2970 (w), 2864 (m), 2729 (w), 1701 (s), 1608 (m), 1577 (w), 1376 (m), 1299 (m), 1205 (s), 1160 (m), 1098 (m), 1027 (m), 919 (w) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.29 (s, 3 H, CH_3), 3.37 (d, $^2J_{H,H}$ = 8.7 Hz, 1 H, 6-H-*c*), 3.76 (d, $^2J_{H,H}$ = 8.3 Hz, 1 H, 4-H-*t*), 3.85 (d, $^2J_{H,H}$ = 8.7 Hz, 1 H, 6-H-*t*), 3.88 (d, $^2J_{H,H}$ = 8.3 Hz, 1 H, 4-H-*c*), 4.29 (d, $^2J_{H,H}$ = 6.9 Hz, 1 H, 8-H-*c*), 4.52 (d, $^2J_{H,H}$ = 6.9 Hz, 1 H, 8-H-*t*), 5.27 (s, 1 H, 2-H-*t*), 7.62 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H, H arom.), 7.82 (d, $^3J_{H,H}$ = 8.7, 2 H, H arom.), 9.96 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 24.0 (1 C, CH_3), 70.5 (1 C, C-5), 75.9 (1C, C-6), 78.0 (1 C, C-4), 85.7 (1 C, C-8), 98.9 (1 C, C-2), 128.2 (2 C, CH arom.), 130.2 (2 C, CH arom.), 136.9 (1 C, Cq arom.), 147.3 (1 C, Cq arom.), 192.4 (1 C, CHO) ppm. MS (CI, CH_4): *m*/*z* (%) = 234 (100) [M^+ + 1], 203 (13), 135 (14), 100 (18), 69 (19).

***c*-5-Ethyl-*c*-2-(4-formylphenyl)-3,7-dioxa-*r*-1-azabicyclo[3.3.0]octane (6c):** Yield 17%, yellow oil (flash column chromatography; pentane/acetone, 4:1). $C_{14}H_{17}NO_3$ (247.29): calcd. C 67.90, H 6.87, N 5.65; found C 68.22, H 6.54, N 5.88. R_f (80% pentane/acetone) = 0.50. IR (CH_3Cl film, NaCl): $\tilde{\nu}$ = 2965 (s), 2930 (s), 2860 (s), 1701 (s), 1609 (s), 1579 (w), 1356 (m), 1298 (m), 1205 (s), 1157 (s), 1103 (s), 1046 (s), 1014 (s), 925 (s), 836 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.90 (t, $^3J_{H,H}$ = 7.5 Hz, 3 H, CH_2CH_3), 1.59 (m, 2 H, CH_2CH_3), 3.43 (d, $^2J_{H,H}$ = 8.8 Hz, 1 H, 6-H-*c*), 3.57 (d, $^2J_{H,H}$ = 8.5 Hz, 1 H, 4-H-*t*), 3.80 (d, $^2J_{H,H}$ = 8.8 Hz, 1 H, 6-H-*t*), 4.03 (d, $^2J_{H,H}$ = 8.5 Hz, 1 H, 4-H-*c*), 4.22 (d, $^2J_{H,H}$ = 6.9 Hz, 1 H, 8-H-*c*), 4.49 (d, $^2J_{H,H}$ = 6.9 Hz, 1 H, 8-H-*t*), 5.24 (s, 1 H, 2-H-*t*), 7.62 (d, $^3J_{H,H}$ = 8.1 Hz, 2 H, H arom.), 7.82 (d, $^3J_{H,H}$ = 8.1, 2 H, H arom.), 9.95 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 9.4 (1 C, CH_2CH_3), 30.4 (1 C, CH_2CH_3), 74.1 (1 C, C-5), 74.4 (1 C, C-6), 76.3 (1 C, C-4), 85.6 (1 C, C-8), 98.7 (1 C, C-2), 128.3 (2 C, CH arom.), 130.2 (2 C, CH arom.), 137.0 (1 C, Cq arom.), 147.2 (1 C, Cq arom.), 192.3 (1 C, CHO) ppm. MS (CI, CH_4): *m*/*z* (%) = 247 (27) [M^+ + 1], 218 (90), 158 (8), 119 (29), 83 (100), 56 (37).

(1*R,1′*R**,2*R**,2′*R**,5*S**,5′*S**)-1,4-Bis{5-(hydroxymethyl)-3,7-dioxa-1-azabicyclo[3.3.0]oct-2-yl}benzene (7a-*like*) and (1*S**,1′*R**,2*S**,2′*R**,5*R**,5′*S**)-Bis-1,4-{5-(hydroxymethyl)-3,7-dioxa-1-azabicyclo-[3.3.0]oct-2-yl}benzene (7a-*unlike*):** Yield 27%, white crystalline powder, m.p. 140−141 °C (flash column chromatography; EtOAc/pentane, 3:1). $C_{18}H_{24}N_2O_6$ (364.40): calcd. C 59.27, H 6.58, N 7.68; found C 59.56, H 6.33, N 7.48. R_f (75% EtOAc/pentane) = 0.20. IR (CH_3Cl film, NaCl): $\tilde{\nu}$ = 3421 (s), 2867 (s), 1636 (m), 1363 (m), 1088 (s), 1017 (s), 913 (m) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 2.20 (br. s, 2 H, OH), 3.63 (br. s, 4 H, 5-CH_2O), 3.69 (d, $^2J_{H,H}$ = 9.0 Hz, 2 H, 6-H, 6′-H-*c*), 3.81 (d, $^2J_{H,H}$ = 9.0 Hz, 2 H, 4-H, 4′-H-*t*), 3.92 (d, $^2J_{H,H}$ = 8.4 Hz, 2 H, 6-H, 6′-H-*t*), 4.24 (d, $^2J_{H,H}$ = 9.0 Hz, 2 H, 4-H, 4′-H-*c*), 4.26 (d, $^2J_{H,H}$ = 6.8 Hz, 2 H, 8-H, 8′-H-*c*), 4.57 (d, $^2J_{H,H}$ = 6.8 Hz, 2 H, 8-H, 8′-H-*t*), 5.25 (s, 2 H, 2-H, 2′-H-*t*), 7.50 (s, 4 H, 1,4-phenylene) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 65.2 (2 C, 5-CH_2O), 71.9 (4 C, C-6, C-6′), 74.6 (2 C, C-5, C-5′), 74.9 (2 C, C-4, C-4′), 85.4 (2 C, C-8, C-8′), 98.8 (2 C, C-2, C-2′), 127.7 (4 C, CH arom.), 140.7 (2 C, Cq arom.) ppm. MS (EI, 70 eV): *m*/*z* (%): 350 (50) [M^+], 331 (68), 248 (30), 232 (12), 218 (12), 190 (15), 142 (18), 113 (35), 88 (100).

(1*R,1′*R**,2*R**,2′*R**,5*S**,5′*S**)-1,4-Bis{5-methyl-3,7-dioxa-1-azabicyclo[3.3.0]oct-2-yl}benzene (7b-*like*) and (1*S**,1′*R**,2*S**,2′*R**,5*R**,5′*S**)-1,4-Bis{5-methyl-3,7-dioxa-1-azabicyclo[3.3.0]oct-2-yl}-benzene (7b-*unlike*):** Yield 40%, white crystalline powder, m.p. 126−127 °C (flash column chromatography; pentane/acetone, 4:1). $C_{18}H_{24}N_2O_4$ (332.40): calcd. C 64.98, H 7.22, N 8.42; found C 65.22, H 6.92, N 8.36. R_f (80% pentane/acetone) = 0.40. IR (CH_3Cl film, NaCl): $\tilde{\nu}$ = 2964 (s), 2928 (s), 2853 (s), 1349 (m), 1161 (m), 1105 (s), 1054 (s), 1030 (s), 990 (m), 918 (m) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.369 (s, 3 H, CH_3), 1.372 (s, 3 H, CH_3), 3.43 (d, $^2J_{H,H}$ = 9.0 Hz, 2 H, 6-H, 6′-H-*c*), 3.81 (d, $^2J_{H,H}$ = 8.4 Hz, 2 H, 4-H, 4′-H-*t*), 3.91 (d, $^2J_{H,H}$ = 9.0 Hz, 2 H, 6-H, 6′-H-*t*), 3.98 (d, $^2J_{H,H}$ = 8.4 Hz, 2 H, 4-H, 4′-H-*c*), 4.33 (d, $^2J_{H,H}$ = 6.6 Hz, 2 H, 8-H, 8′-H-*c*), 4.57 (d, $^2J_{H,H}$ = 6.6 Hz, 2 H, 8-H, 8′-H-*t*), 5.28 (s, 2 H, 2-H, 2′-H-*t*), 7.53 (s, 4 H, 1,4-phenylene) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 24.2 (2 C, CH_3), 70.3 (2 C, C-5, C-5′), 76.0 (2 C, C-6, C-6′), 78.1 (2 C, C-4, C-4′), 85.5 (2 C, C-8, C-8′), 99.4 (2 C, C-2, C-2′), 127.7 (4 C, CH arom.), 141.1 (2 C, Cq arom.) ppm. MS (EI, 70 eV): *m*/*z* (%) = 332 (60) [M^+], 302 (20), 234 (40), 128 (20), 99 (38), 69 (100).

(1*R,1′*R**,2*R**,2′*R**,5*S**,5′*S**)-1,4-Bis{5-ethyl-3,7-dioxa-1-azabicyclo[3.3.0]oct-2-yl}benzene (7c-*like*) and (1*S**,1′*R**,2*S**,2′*R**,5*R**,5′*S**)-1,4-Bis{5-ethyl-3,7-dioxa-1-azabicyclo[3.3.0]oct-2-yl}benzene (7c-*unlike*):** Yield 62%, yellowish crystalline powder, m.p. 109−110 °C (as *like* form) (flash column chromatography: pentane/acetone, 4:1). $C_{20}H_{28}N_2O_4$ (360.45): calcd. C 66.64, H 7.83, N 7.77; found C 66.29, H 8.11, N 7.44. R_f (80% pentane/acetone) = 0.25. IR (CH_3Cl film, NaCl): $\tilde{\nu}$ = 2924 (s), 2962 (s), 2848 (s), 1460 (m), 1431 (m), 1349 (m), 1292 (m), 1209 (m), 1152 (m), 1107 (s), 1055 (s), 1013 (s), 908 (m) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 0.99 [dd (app t), $^3J_{H,H}$ = 7.2 Hz, 6 H, CH_2CH_3], 1.67 (m, $^3J_{H,H}$ = 7.2, $^2J_{H,H}$ = 14.4 Hz, 4 H, CH_2CH_3), 1.73 (m, $^3J_{H,H}$ = 7.2, $^2J_{H,H}$ = 14.4 Hz, 4 H, CH_2CH_3), 3.50 (d, $^2J_{H,H}$ = 8.7 Hz, 2 H, 6-H, 6′-H-*c*), 3.75 (d, $^2J_{H,H}$ = 8.4 Hz, 2 H, 4-H, 4′-H-*t*), 3.86 (d, $^2J_{H,H}$ = 8.7 Hz, 2 H, 6-H, 6′-H-*t*), 4.13 (d, $^2J_{H,H}$ = 8.4 Hz, 2 H, 4-H, 4′-H-*c*), 4.26 (d, $^2J_{H,H}$ = 6.9 Hz, 2 H, 8-H, 8′-H-*c*), 4.53 (d, $^2J_{H,H}$ = 6.9 Hz, 2 H, 8-H, 8′-H-*t*), 5.24 (s, 2 H, 2-H, 2′-H-*t*), 7.53 (s, 4 H, 1,4-phenylene) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 9.4 (2 C, CH_2CH_3), 30.5 (2 C, CH_2CH_3), 73.9 (2 C, C-5, C-5′), 74.5 (2 C, C-6, C-6′), 76.4 (2 C, C-4, C-4′), 85.3 (2 C, C-8, C-8′), 99.1 (2 C, C-2, C-2′), 127.8 (4 C, CH arom.), 141.0 (2 C, Cq arom.) ppm. MS (EI, 70 eV): *m*/*z* (%) = 360 (55) [M^+], 331 (65), 248 (30), 232 (10), 218 (10), 190 (15), 142 (15), 113 (35), 105 (10), 98 (5), 91 (8), 88 (100), 77 (5).

(1*S,1′*R**,2*S**,2′*R**,5*R**,5′*S**,8*R**,8′*S**)-1,4-Bis{5-methyl-8-phenyl-3,7-dioxa-1-azabicyclo[3.3.0]oct-2-yl}benzene (7d-*unlike*):** Yield 62%, white crystalline powder, m.p. 171−172 °C (flash column chromatography; pentane/acetone, 4:1). $C_{30}H_{32}N_2O_4$ (484.60): calcd. C 74.28, H 6.60, N 5.78; found C 74.60, H 6.42, N 5.44. R_f (80% pentane/acetone) = 0.40. IR (CH_3Cl film, NaCl): $\tilde{\nu}$ = 3412 (s), 2966 (s), 2924 (s), 2867 (s), 1649 (w), 1377 (m), 1304 (m), 1209 (s), 1097 (s), 1024 (s) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 1.27 (s, 6 H, CH_3), 3.72 and 3.74 (d, $^2J_{H,H}$ = 9.0 Hz, 4 H, 4-H, 4′-H-*t* and 6-H, 6′-H-*t*), 3.89 (d, $^2J_{H,H}$ = 9.0 Hz, 4 H, 4-H, 4′-H-*c*, 6-H, 6′-H-*c*), 5.58 and 5.59 (s, 4 H, 2-H, 2′-H-*t* and 8-H, 8′-H-*t*), 7.30−7.39 (m, 6 H, phenyl), 7.56 (s, 4 H, 1,4-phenylene), 7.56−7.57 (m, 4 H, phenyl) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 25.1 (2 C, CH_3), 71.1 (2 C, C-5, C-5′), 76.2 and 76.3 (4 C, C-4, C-4′ and C-6, C-6′), 98.2 and 98.5 (4 C, C-2, C-2′ and C-8, C-8′), 127.6 (2 C, CH arom.), 127.7 (4 C, CH arom.), 128.6 (4 C, CH arom.), 128.7 (4 C, CH arom.), 140.4 (2 C, Cq arom.), 140.7 (2 C, Cq arom) ppm. MS (CI, CH_4): *m*/*z* (%) = 485 (100) [M^+ + 1], 407 (38), 379 (12), 204 (56), 175 (54).

(1*S,1′*R**,2*S**,2′*R**,5*R**,5′*S**,8*R**,8′*S**)-1,4-Bis{5-ethyl-8-phenyl-3,7-dioxa-1-azabicyclo[3.3.0]oct-2-yl}benzene (7e-*unlike*):** Yield 64%, yellow crystalline powder, m.p. 122−125 °C (flash column chromatography; pentane/acetone, 5:1). $C_{32}H_{36}N_2O_4$ (512.65): calcd. C 74.89, H 7.02, N 5.46; found C 74.52, H 6.86, N 5.22. R_f (83% pentane/acetone) = 0.40. IR (CH_3Cl film, NaCl): $\tilde{\nu}$ = 3417 (s), 2963 (s), 2928 (s), 2862 (s), 1384 (m), 1306 (m), 1211 (s), 1099 (s), 1018 (s), 922 (m) cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 0.86 (t, $^3J_{H,H}$ = 7.6 Hz, 6 H, CH_2CH_3), 1.53 (q, $^3J_{H,H}$ = 7.6 Hz, 4 H, CH_2CH_3), 3.83 and 3.84 (d, $^2J_{H,H}$ = 8.4 Hz, 4 H, 4-H, 4′-H-*t* and 6-H, 6′-H-*t*), 3.86 and 3.87 (d, $^2J_{H,H}$ = 8.4 Hz, 4 H, 4-H, 4′-H-*c* and 6-H, 6′-H-*c*), 5.57 and 5.57 (s, 4 H, 2-H, 2′-H-*t* and 8-H, 8′-H-*t*), 7.3−7.37 (m, 6 H, phenyl), 7.53 (s, 4 H, 1,4-phenylene), 7.53−7.56 (m, 4 H, phenyl) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 9.8 (2 C, CH_2CH_3), 31.3 (2 C, CH_2CH_3), 74.6 (4 C, C-4, C-4′, C-6, C-6′), 74.9 (2 C, C-5, C-5′), 97.8 and 98.0 (4 C, C-2, C-2′ and C-8, C-8′), 127.5 (2 C, CH arom.), 127.6 (4 C, CH arom.), 128.6 (4 C, CH arom.), 128.7 (4 C, CH arom.) 140.4 (2 C, Cq arom.), 140.6 (2 C, Cq arom) ppm. MS (CI, CH_4): *m*/*z* (%) = 513 (100) [M^+ + 1], 483 (< 5), 435 (32), 406 (14), 218 (30), 190 (34).

***c*-5-Ethyl-*c*-2,*c*-8-diphenyl-3,7-dioxa-*r*-1-aza-bicyclo[3.3.0]octane (2f-*cis*):** This compound was identified in small traces in the crude reaction mixture obtained from the synthesis of **7e** in about 6% conversion with respect to the starting material, **5c**, together with the corresponding amount of terephthalaldehyde. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.84 (t, $^3J_{H,H}$ = 7.2 Hz, CH_2CH_3), 1.52 (q, $^3J_{H,H}$ = 7.2 Hz, CH_2CH_3), 3.83 (s, 4 H, 4-H, 6-H-*c*,-*t*), 5.55 (s, 2 H, 2-H, 8-H-*t*), 7.34−7.52 (m, 10 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 9.7 (1 C, CH_2CH_3), 31.4 (1 C, CH_2CH_3), 76.7 (2 C, C-4, C-6), 97.9 (2 C, C-2, C-8), 127.4 (2 C, CH arom.), 127.6 (4 C, CH arom.), 128.5 (4 C, CH arom.), 140.4 (2 C, Cq, Ph) ppm.

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