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α-(3,7-DIOXA-*r*-1-AZABICYCLO[3.3.0]OCT-*c*-5-YL METHOXY)-DIAZINES (I): SYNTHESIS AND STEREOCHEMISTRY. EXTENTION IN *s*-TRIAZINE SERIES♦

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Abstract: The synthesis of the title compounds, consisting in the replacement of chlorine in commercial α-chlorodiazines and cyanuryl chloride by the 3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-ylmethoxy group (Williamson method) is described. The stereochemistry of this new series is analysed in terms of different conformational chirality exhibited in solution (^{1}H DNMR) *vs.* solid state (X-Ray Diffractometry), *meso* against chiral forms respectively. In solid state, the inclusion capacity of some chiral networks as well as their supramolecular aggregation is pointed out.

Keywords: *pyrazines, pyrimidines, s-triazines, oxazolidines, NMR, chirality, X-Ray Diffractometry.*

INTRODUCTION

The 3,7-dioxa-1-azabicyclo[3.3.0]octane heterocyclic saturated system **A** is readily available by double cyclocondensation between TRIS® (2-amino-2-hydroxymethyl-1,3-

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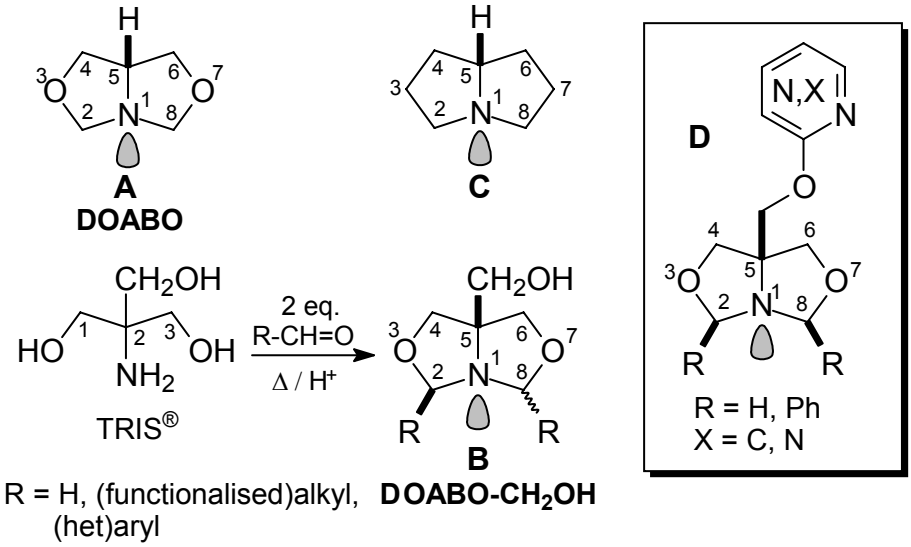
propandiol) and carbonyl compounds, yielding 5-hydroxymethyl-3,7-dioxa analogous **B** of the core alkaloid, namely *pyrrolizidine* **C** (*Scheme 1*) [1-4].



Scheme 1.

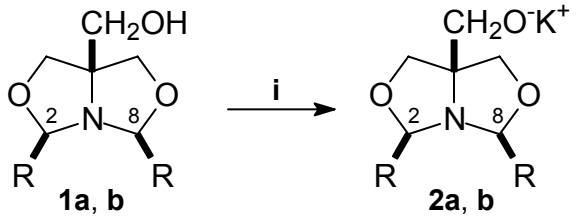
Although compounds having **A** as basic skeleton are of high biological interest, fertilisers, biocides, pesticides and anticancer agents [5-14], only few of the results reported previously validated this class as appropriate for further functionalisation. The later was ensured classically by the *a priori* selection of the substituted starting carbonyl compound, usually an aldehyde (*Scheme 1*). Only compounds **A** bearing a hydroxymethyl group at C-5 (*e.g.* **B**, *Scheme 1*) were mentioned to be suitable for functionalisation at this site by acylation [3-5, 7, 8, 12, 15], thionation [16] and by Dess-Martin oxidation [13]. Depending on the new group linked at C-5, the reported structures are all of pharmaceutical [7, 8, 12, 13] and of supramolecular interest [17].
Succeeding to our developments in synthesis and stereochemistry of substituted 3,7-**Di**-**O**xa-*r*-1-**A**za-**B**icyclo[3.3.0]-*c*-5-**O**ctanes[♣] (hereafter throughout abbreviated as **DOABO**, *Scheme 1*) [18-20], we recently established that some compounds of type **B** (*Scheme 1*, R = H, Ph) can be easily converted into 5-alkoxymethyl derivatives, *via* potassium alkoxides, in much milder conditions than those used earlier by Broadbent in 1976 (Williamson method) [7, 20]. Not only were they efficient nucleophiles against aliphatic halo compounds, but in a single testing example, against a α-chloro-π-deficient system such as 2,6-dichloropyrazine [20]. An extension of this result required a larger series of competent substrates. Referring to our previous data about the nucleophilic replacement of chlorine in certain π-deficient systems [26, 27], we considered certain α-chlorodiazines and cyanuryl chloride as a challenging choice for investigating more elaborated building blocks with potential biological and / or supramolecular interest. Hence, we preliminarily report here the synthesis and stereochemistry of a new class as 3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-ylmethoxydi(*s*-tri)azines **D** (*Scheme 1*).

[♣]Stereochemical descriptor ***r*** (reference) is used in order to simplify discussion arising from the basic stereochemistry of this molecule as *cis* fused double oxazolidine system, the lone pair at N-1 being the fiducial substituent.[21] This spatial arrangement, together with the absence of pyramidal inversion at N-1 are already very well documented.[7,11,18-20,22-25]

RESULTS AND DISCUSSION

Syntheses

Two known DOABO derivatives **1a, b** [19, 20] were reacted with potassium hydride in conditions depicted in *Scheme 2*.



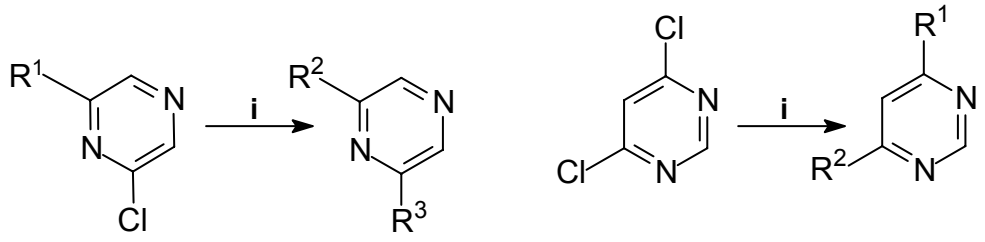
a: R = H; **b**: R = Ph

i: 1.05 eq. KH / THF / 40 °C / 1.0 - 1.5 hrs.

Abbreviations:
R = H: (2H)DOABO-CH_2O
R = Ph: (2Ph)DOABO-CH_2O

Scheme 2.

The study of the reaction between potassium alkoxides **2a, b** and α-chlorodiazines was performed by using throughout 1.05 × n equivalents of **2a, b** / equivalent of diazine possessing "n" chlorine atoms. All syntheses were systematically TLC and NMR monitored. New type compounds were prepared in pyrazine, pyrimidine and *s*-triazine series (*Scheme 3*, *4*, *Table 1 - 3*).



3a, b **4a-f** **5a-c**

3a: R^1 = H
3b: R^1 = Cl

i: **2a, b** / THF, *T*(°C), t (hrs.)

Scheme 3.

Only **2a** exhibited a "methoxide-like reactivity" regarding the quantitative results. Indeed, in a competitive experiment, equimolar amounts of 2-chloropyrazine **3a** : **2a** : potassium methoxide gave the equimolar ratio between 2-methoxypyrazine and **4a**. When **2b**, having C-2, -8 disubstituted DOABO unit with phenyl groups was used as nucleophile, the yields decreased slightly, **4a** (85 %) *vs.* **4b** (79 %). The unfavourable influence of substitution at C-2, -8 was best illustrated when the results of the on-pot replacement of the two chlorine atoms in 2,6-dichloropyrazine, **2b** *vs.* **2a** were compared. Treatment of **3b** with 2.1 eq. of **2b** yielded a complex mixture of monochloro derivative **4c**, the (2Ph)DOABO-CH_2O substituting pyrazinone **4d** (issued most probably from the partial hydrolysis of **4c** during the aqueous work-up) and, in traces

only, the desired product **4e**. Using **2a** as nucleophile, compound **4f** was obtained in a clean procedure as was described in a previous publication of us [20].

Table 1. *Results in the synthesis of α-(3,7-dioxa-r-1-azabicyclo[3.3.0]oct-c-5-ylmethoxy)-pyrazines. Preparation of compounds* ***4a-f***

Reaction	Product 4a-f		*T* (°C)	t (hrs.)	Yield (%)
	R^2	R^3			
3a + **2a** → **4a**	H	(2H)DOABO-CH_2O	40	16	85
3a + **2b** → **4b**	H	(2Ph)DOABO-CH_2O	60	20	79
3b + **2b** → **4c**	Cl	(2Ph)DOABO-CH_2O	65	52	34[a]
→ **4d**	OH	(2Ph)DOABO-CH_2O			17[a]
→ **4e**	(2Ph)DOABO-CH_2O	(2Ph)DOABO-CH_2O			8[a]
3b + **2a** → **4f**	(2H)DOABO-CH_2O	(2H)DOABO-CH_2O	65 r.t.	3 14	76

[a]Partial conversions of **3b** based on the efective amounts isolated by column chromatography.

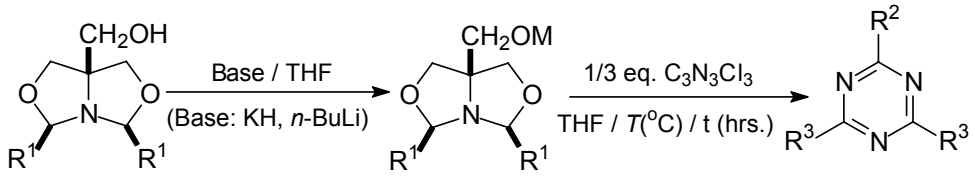
Next, the 4,6-dichloropyrimidine produced the series **5a-c** (*Scheme 3*, *Table 2*).

Table 2. *Results in the synthesis of α-(3,7-dioxa-r-1-azabicyclo[3.3.0]oct-c-5-ylmethoxy)-pyrimidines. Preparation of compounds* ***5a-c***

Compound	R^1	R^2	*T* (°C)	t (hrs.)	Yield (%)
5a	(2H)DOABO-CH_2O	(2H)DOABO-CH_2O	45	24	81
5b	(2Ph)DOABO-CH_2O	(2Ph)DOABO-CH_2O	65	21	31[a]
5c	(2Ph)DOABO-CH_2O	Cl			23[a]

[a]Partial conversions of 4,6-dichloropyrimidine based on the efective amounts isolated by column chromatography.

With **2a** as nucleophile, the synthesis of **5a** occurred with good yield. As in the α-chloropyrazine series, the use of **2b** gave different results since complete replacement of chlorine was possible but with low yield: the separable mixture of **5b** and **5c** was obtained, suggesting that the second substitution of chlorine in **5c** was difficult.
Based on literature data reporting the reaction between alcohols and cyanuryl chloride in neutral or basic conditions, we also attempted the one-pot trisubstitution of chlorine in cyanuryl chloride using our nucleophiles (*Scheme 4*, *Table 3*) [28-31].



1a, **b** — **a**: R^1 = H; **b**: R^1 = Ph

2a-d — **a**: R^1 = H, M = K; **b**: R^1 = Ph, M = K; **c**: R^1 = H, M = Li; **d**: R^1 = Ph, M = Li

6a, **b**; **7a**, **b** — **6a**: R^2 = Cl, R^3 = (2H)DOABO-CH_2O; **6b**: R^2 = Cl, R^3 = (2Ph)DOABO-CH_2O; **7a**: R^2 = R^3 = (2H)DOABO-CH_2O; **7b**: R^2 = R^3 = (2Ph)DOABO-CH_2O

Scheme 4.

A crucial dependence on the substitution at C-2, -8 on the DOABO group combined with a modulated nucleophilicity as K (**2a**, **2b**) or Li (**2c**, **2d**) alkoxide form was observed. The mass spectra of **6a**, **7a** (ESI and FAB^+ respectively) fully confirmed the envisaged structures. The bias between **6b** and **7b** could also be solved by MS-(FAB^+) spectrometry only. Next, with the isolated **6a**, **7a**, **6b** and **7b** in our hands, the content of the crude reaction mixtures (*Table 3*) based on their ^{1}H NMR spectra was determined.

Table 3. *Results in the synthesis of α-(3,7-dioxa-r-1-azabicyclo[3.3.0]oct-c-5-ylmethoxy)-s-triazines. Preparation of compounds* ***6a, 6b, 7a, 7 b***

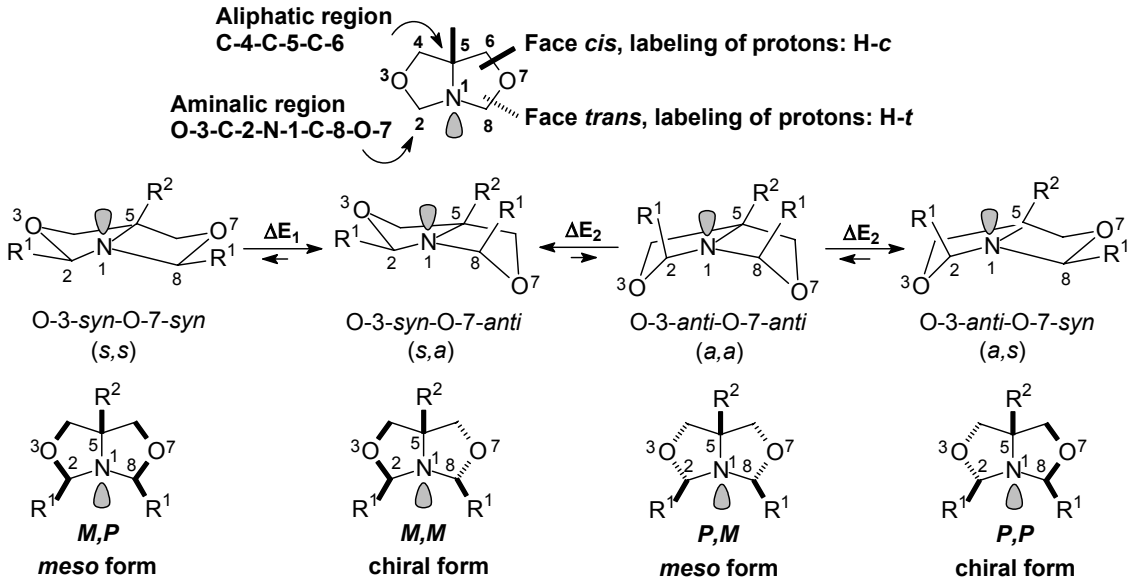
Starting material	**Nucleophile**	***T*** **(°C)**	**t (hrs.)**	**Results**	
				Compounds in crude r.m. (%)	**Yield (%)**
1a	**2a**	65	36	**6a** (100)	34
	2c	-78 → r.t.	20	**7a** (100)	82
1b	**2b**	0 65	1 40	**7b** (51); **6b** (10); **1b** (39)	37
	2d	-60 → r.t. r.t. 65	20 48 4	**7b** (46); **6b** (8); **1b** (46)	29

Stereochemistry

Preliminary conformational considerations

As pyrrolizidine **C** (*Scheme 1*), the skeleton of its 3,7-dioxa analogous **A** is heterofacial. All its (hetero)atoms are prostereogenic centres [20]. Except H-5, the substitution test of any of the hydrogen atoms generates configurational chirality [19, 20]. The basic molecule itself **A**, a *cis* fused double oxazolidine system, as well as its *c*-C-5-achiral monosubstituted derivatives (*e.g.* **B**, R = H, *Scheme 1*), can exist in a number of flexible conformations upon pseudorotation occurring at each oxazolidine ring. Few experimental studies confirmed this flipping [19, 20, 23] since determining the frozen conformation in solution is a quite difficult task. Our previous results of the *ab initio* RHF/6-31G* calculations [19, 20] predicted that the DOABO skeleton is involved in three different conformational equilibriums depicted in *Scheme 7*.

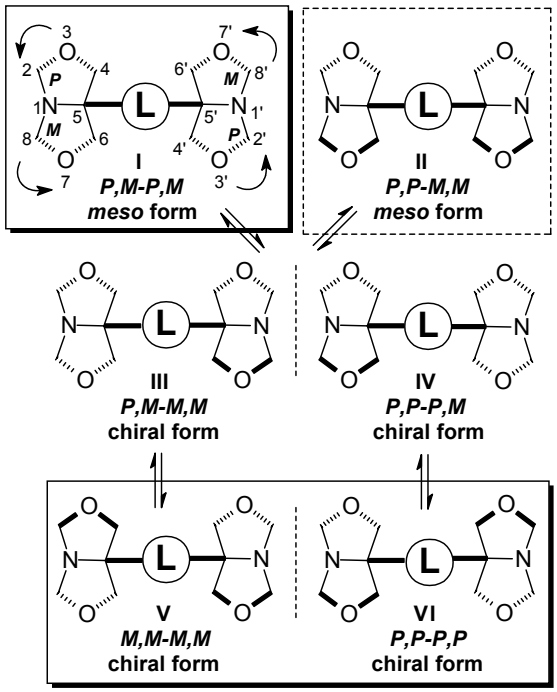
They suggested the oriented flexibility of the bicycle, ascertained as *a single oxazolidine ring inversion / equilibrium*. It occurs regardless of the *configurational* nature, *achiral* or *non-chiral*, of the structure. The four stereoisomers were discriminated based on the sense of puckering in the two oxazolidine rings, *syn*/*anti* O-3/O-7, revealed as fused *O*-envelope conformers. The substitution test shows that the steric relationships between homofacial protons, aminalic H-2, -8 or aliphatic H-4, -6, are different in the two types of conformers, *enantiotopic* in diastereomeric *meso* forms (*s*,*s*) or (*a*,*a*) but *diastereotopic* in chiral forms (*a*,*s*) or (*s*,*a*).



Type of structure	Configuration	ΔE_1 (kJ/mol)[a]	ΔE_2 (kJ/mol)[a]
R^1 = H; R^2 = CH_2OH (**1a**), MOM	Achiral	-18.87	-5.48
R^1 = Ph; R^2 = CH_2OH (**1b**), MOM	Non-chiral (*meso* form) 1*r*,2*R*,5*s*,8*S*	-14.86	-8.54

[a]Typical ΔE values in vacuum and gas phase [19, 20].

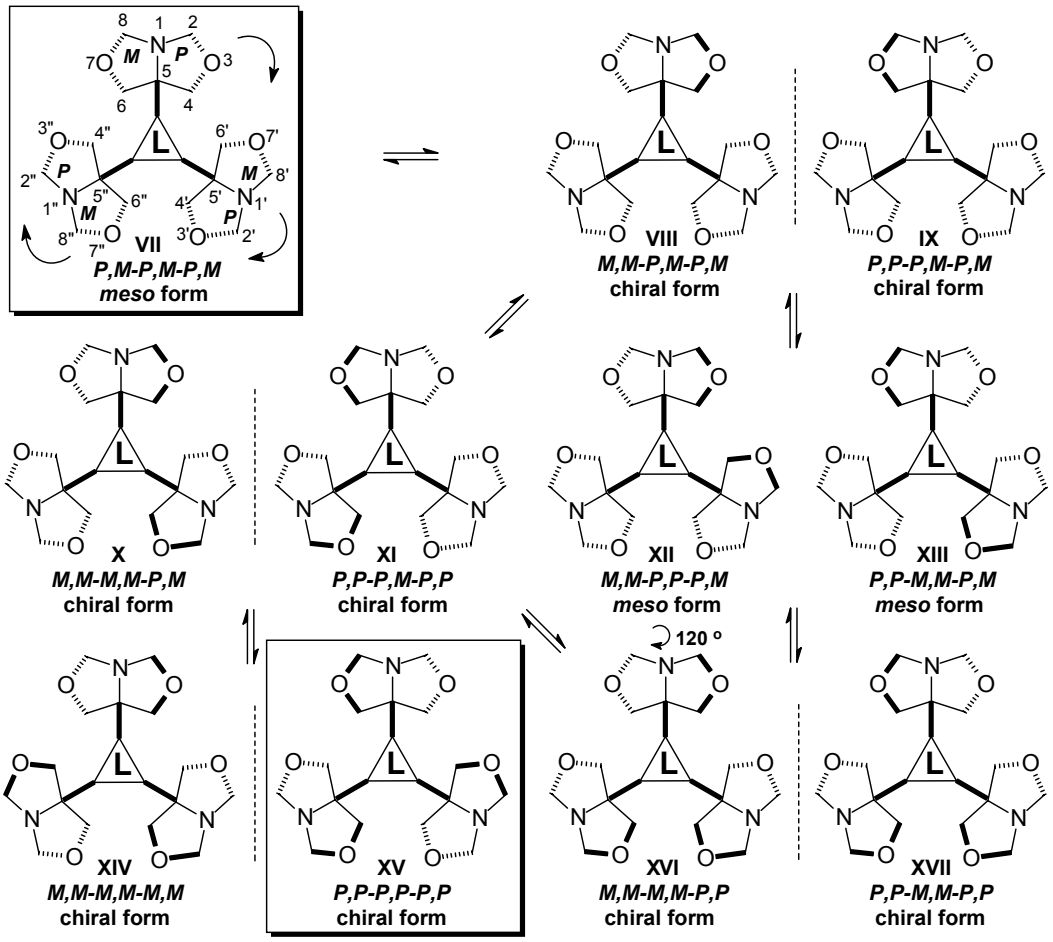
Scheme 7.



Scheme 8.

In order to designate enantiomeric and *meso* form conformations, the two torsion angles in the aminalic part of the skeleton, C-5-N-1-C-2-O-3 and C-5-N-1-C-8-O-7 were selected and defined by using the helicity rules descriptors *M* and *P*. As shown in *Scheme 7*, the occurrence of the *meso* (*M,P*) conformer can be reasonably ruled out since it was found much less stable than the alternative *meso* (*P,M*) diastereomer and the chiral conformers (*M,M*) ≡ (*P,P*). Only the equilibriums (*M,M*) ⇆ (*P,M*) ⇆ (*P,P*), consisting of two diastereomeric inversions and, overall, an enantiomeric interconversion, are to be considered. However, the magnitude of the corresponding ΔE_2 values precluded an *a priori* assignment of the frozen conformation, in gas phase as well as in solution [20]. We note that the apparently restrictive rotation about the C-O-C bonds only was proved by our inspection

of some earlier X-Ray crystallographically determined structures in this class [20, 24, 25].



Scheme 9.

For the present study, we enlarged the analysis to compounds comprising two, even three identical DOABO units tied together by an achiral linker **L** (*Scheme 8, 9*).* Obviously, the linker should be highly symmetric, *i.e.* C_{nh}, C_{nv} groups, such as di(tri)methoxy-di(*s*-tri)azine fragments. They are statistically achiral, considering the angular geometry of the –O-CH_2- sequence.

The stereoisomerism depicted in *Scheme 8, 9* is exacerbated although, by neglecting all the DOABO *meso* (*M,P*) type forms (*Scheme 7*), the conformational analysis is simplified. In this purpose, we applied our previous proposal, namely *local stereochemistry*, referring to compounds possessing only one DOABO unit (*Scheme 7*) and *global stereochemistry* defining molecules built on two or three DOABO units (*Scheme 8, 9*) [20]. In this approach, "dimeric" DOABO derivatives can exist as two *global meso* forms, **I** and **II**, and four *global* chiral forms, two racemates **III**-**IV** and **V**-

* In *Scheme 8, 9*, the DOABO homomorphic substitution at C-2, -8 was omitted for reason of simplicity.

VI. "Trimeric" DOABO derivatives, the *s*-triazines **7a**, **7b**, provide three *global meso* forms, **VII**, **XII** and **XIII**, and eight *global chiral* forms, four racemates, **VIII-IX**, **X-XI**, **XIV-XV** and **XVI-XVII**. The common feature is that each conformer **I** → **VI** and **VII** → **XVII** can be generated, step by step, *in a single oxazolidine ring inversion / equilibrium*, following statistically the pathways depicted in *Scheme 8, 9*.

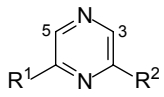
Determining the stereochemistry in solution by ^{1}H-DNMR

A stereochemical analysis, focused on compounds **4a**, **4f**, **5a**, **5b**, **7a** and **7b** was carried out by ^{1}H DNMR at low temperature (293 – 173 K) in [D_8]THF on 400 MHz time scale. The results (*Table 4*, *5*), as rate constant at coalescence (k_c) and the free enthalpy of activation ($\Delta G^{\neq}$) of DOABO ring inversion were available by applying the Eyring equations [21, 32].

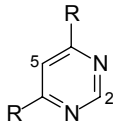
At room temperature, all compounds were flipping structures mediating the conformtations depicted in *Scheme 7-9*. Therefore, all data in *Table 4, 5* refer to *a single oxazolidine ring inversion / equilibrium* placed in different environments, created by the number of DOABO units (1-3) / compound. Based on the very small $\mathbf{\Delta E_2}$ values (*Scheme 7*), all equilibriums were seen as first order reactions and equally populated. Upon cooling, the (2H)DOABO groups could be ananchomerised below 273 K following the spectral sequence AB →A_2→AB (*Table 4*). The two "internal clocks", aminalic C-2(8) and aliphatic C-4(6) methylenes were "synchronised", except in the case of the most crowded compound **7a**. In contrast, the (2Ph)DOABO groups could be frozen only in the case of the trisubstituted *s*-triazine **7b**. No coalescence was displayed by the (2Ph)DOABO-CH_2O fragments disubstituting the pyrimidine **5b**. The calculated $\Delta G^{\neq}$ values were in agreement with literature data [33]. Their magnitude also confirmed the faster flipping aptitude of the structures (2Ph)DOABO against (2H)DOABO, for example our starting materials **1b** against **1a** [20].

The frozen conformations detected were all mono, double or triple *local meso* (*P,M*) forms DOABO conformers, building *global meso* forms of type **I** (*Scheme 8*, **4f** and **5a**) and of type **VII** (*Scheme 9*, **7a**, **7b**). The isochronous aminalic or aliphatic homofacial protons (*Table 4*), which were found throughout enantiotopic, motivate this conclusion.

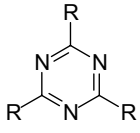
Table 4**: [1]H DNMR data [δ (ppm), [D8]THF] of compounds **4a, 4f, 5a, 5b, 7a, 7b



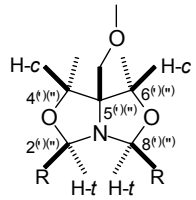
4a: R^1 = H, R^2 = (2H)DOABO-CH_2O
4f: R^1 = R^2 = (2H)DOABO-CH_2O



5a: R = (2H)DOABO-CH_2O
5b: R = (2Ph)DOABO-CH_2O



7a: R = (2H)DOABO-CH_2O
7b: R = (2Ph)DOABO-CH_2O



R = H-*c*, (2H)DOABO-CH_2O
R = Ph, (2Ph)DOABO-CH_2O

No.	T_i (K) $T_{coales.}$ (K) $T_{calc.}$ (K)[a]	δ Aminalic methylenes[b] H-2(8)$^{(')(")}$-*c*	H-2(8)$^{(')(")}$ -*t*	δ Aliphatic methylenes[c] H-4(6)$^{(')(")}$-*c*	H-4(6)$^{(')(")}$-*t*	δ[d] Hetar.
4a	293	4.42	4.40	3.84	3.81	H-3: 8.20
	268	4.41		3.83		H-3: 8.21
	253	4.42	4.40	3.84	3.82	H-3: 8.23
4f	293	4.42	4.40	3.84	3.81	H-3, -5: 7.78
	263	4.41		3.82		H-3, -5: 7.79
	183	4.45	4.38	3.88	3.81	H-3, -5: 7.85
5a	293	4.39	4.38	3.78	3.76	H-5: 6.12
	273	4.39		3.77		H-5: 6.15
	173	4.45	4.35	3.85	3.76	H-5: 6.35
7a	293	4.40	4.38	3.78		-
	273	4.39		3.80	3.78	-
	213	4.43	4.37	3.84	3.76	-
5b	293	-	5.59	4.00	3.91	H-5: 5.75
	173	-	5.58	3.96	3.96	H-5: 6.12
7b	293	-	5.58	3.98	3.92	-
	233	-	5.58	3.96		-
	193	-	5.58	3.99	3.94	-

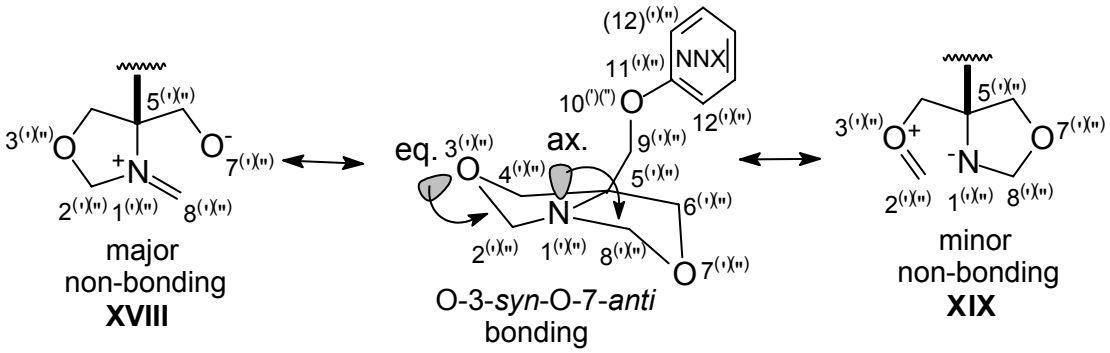
[a]Temperature at which the parameters Δν and ^2J were extracted from the spectrum and used for calculation of parameters k_c and $\Delta G^{\neq}$. [b]Doublets with ^2J = 5.2 – 5.6 Hz and singlets in **5b**, **7b** above T_i and below $T_{coales.}$. [c]Doublets with ^2J = 8.4 – 9.0 Hz. [d]Protons having *ortho* relationships with DOABO-CH_2O groups.

Table 5**: [1]H DNMR data, k_c (s^{-1}) and $\Delta G^{\neq}$ (kJ/mol) values of DOABO oxazolidine ring inversion in compounds **4a, 4f, 5a, 5b, 7a** and **7b

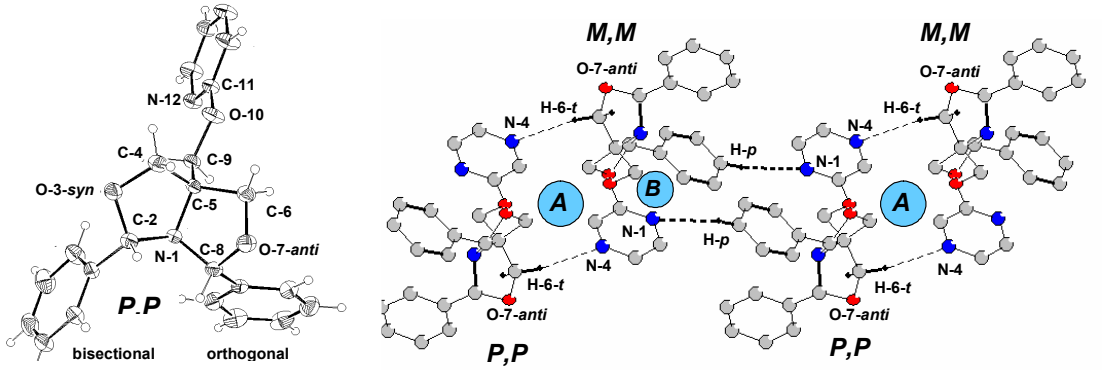
No.	Oxazolidine ring inversion data										
	CH_2 groups in aminalic zones					CH_2 groups in aliphatic zones					
	T_{coales} (K)	T_{calc} (K)	Δν (Hz)	^2J (Hz)	k_c (s^{-1})	T_{coales} (K)	T_{calc} (K)	Δν (Hz)	^2J (Hz)	k_c (s^{-1})	$\Delta G^{\neq}$ (kJ/mol)
4a	268	253	6.8	5.6	68.0	268	253	9.0	9.0	105.7	55.5
4f	263	183	28.8	5.2	139.8	263	183	29.0	8.6	159.1	53.2
5a	273	173	38.1	5.4	179.1	273	173	37.9	8.7	192.9	54.8
7a	273	213	23.0	5.4	117.3	293	213	29.4	8.9	162.5	59.3
5b	-	-	-	-	-	173	-	-	-	-	-
7b	-	-	-	-	-	233	193	19.9	9.1	132.8	47.1

Determining the stereochemistry in solid state by X-Ray Diffractometry

Compounds **4b**, **4f**, **5b** and **7b** supplied crystals suitable for study by X-Ray Diffractometry (*Scheme 10*, *Figure 1-4*).



Scheme 10.



1-1 ***1-2***

Figure 1. ***1-1***: *ORTEP viewing of compound* ***4b***; ***1-2***: *the non-bonding interactions in the elementary cell.*

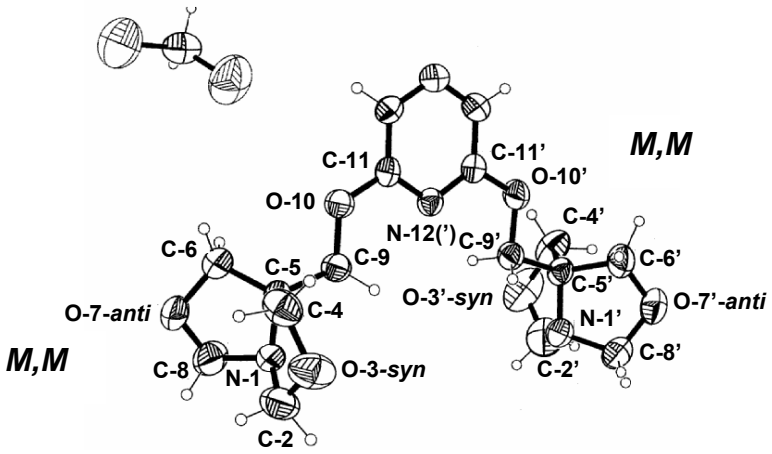
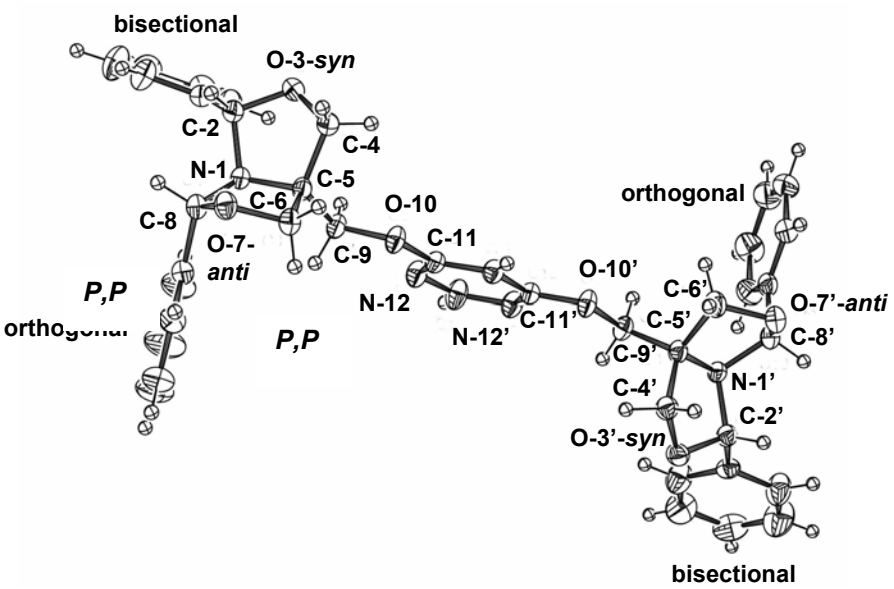
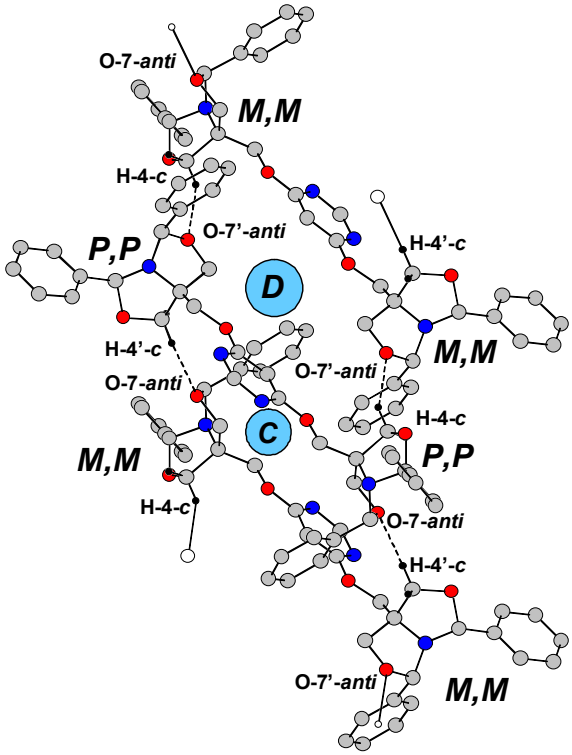


Figure 2. *ORTEP viewing of compound chiral* ***4f***.



3-1.



3-2.

***Figure 3**. **3-1**: ORTEP viewing of compound **5b**; **3-2**: the non-bonding interactions in the network*

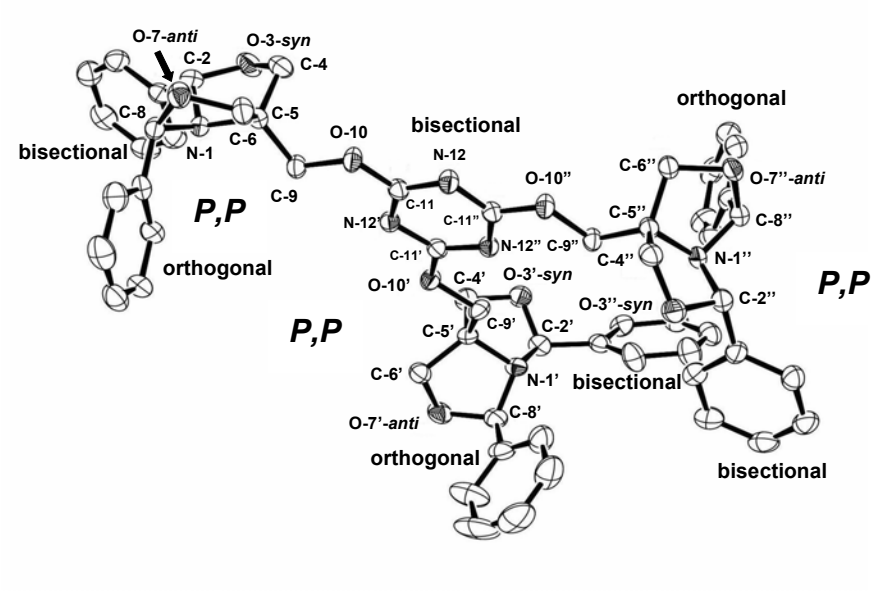


***Figure 4**. ORTEP viewing of compound **7b**.*

Inspection of all ORTEP diagrams showed exclusively the chiral O-*syn*-O-*anti* opposite orientation of the two *cis* fused oxazolidine rings as *O*-envelope conformers. The corresponding torsion angles C-4$^{(')(")}$-C-5$^{(')(")}$-N-1$^{(')(")}$-C-2$^{(')(")}$ and C-6$^{(')(")}$-C-5$^{(')(")}$-N-1$^{(')(")}$-C-8$^{(')(")}$ were small enough, ranging between 0.19 – 7.2 ^{o}. In contrast, the torsion angles in the aminalic zone, used to assign the conformational chirality of the DOABO skeleton (*Scheme 7, 11*), were noteworthy, 16.8 – 28.9 ^{o} in O-3$^{(')(")}$-*syn* rings and 21.3 – 28.0 ^{o} in O-7$^{(')(")}$-*anti* rings.

The torsion angles describing the rotamerism of the *c*-5$^{(')(")}$-di(*s*-tri)azinyloxymethyl motif pointed to its almost coplanar, bisectional, s-*trans* and *out* arrangement with respect to the medium plane of the bicycle. The most significant deviations from coplanarity, 13 – 17 ^{o}, were observed regarding the s-*trans* conformation of the bulky substituents about the bonds C-9$^{(')(")}$-O-10$^{(')(")}$. The rest of deviations were considerably smaller, 0.2 – 6.0 ^{o}.

We note that this spatial arrangement, found in solid state, should also be plausible in solution, but as non-chiral *meso* (*P,M*) form-s-*trans out* rotamer. Indeed, upon cooling (*Table 4*), the diazine protons, having an *ortho* vicinity with the DOABO-CH_2O groups, were all deshielded as environment created by their near coplanarity with one of the lone pair of the oxygen atoms in the CH_2O connections.

We also observed that the chirality of the DOABO skeleton was, in fact, the major consequence of a cross *endo*-anomeric effect, consisting in two and identically oriented delocalisations in the *syn*-*anti* aminalic part of the bicycle (*Scheme 10*).

Thus, the contraction of the bonds N-1$^{(')(")}$-C-8$^{(')(")}$ *vs.* N-1$^{(')(")}$-C-5$^{(')(")}$ (selected as reference), was significant in all compounds, around 0.030 Å. It has been recently explained by Pavia [25] and then by us [20] in terms of a hyperconjugative interaction

(*endo*-anomeric effect) involving the orbitals lpN-1$^{(')(")}$ax.(donor) → σ*C-8$^{(')(")}$-O-7$^{(')(")}$ (acceptor). It was due to their near antiperiplanar position created by the frozen oxazolidine O-*anti*-envelope conformation. The corresponding major non-bonding structure **XVIII** suggests the increased basicity of the O-7$^{(')(")}$-*anti* atom.

A second noticeable contraction was detected regarding this time the bonds O-3$^{(')(")}$-C-2$^{(')(")}$. They were shorter than O-7$^{(')(")}$-C-8$^{(')(")}$ with about 0.17 Å, covering however a larger domain of fluctuation, 0.05 – 0.050 Å. As above, this contraction originates in the O-*syn*-envelope geometry of the ring favouring the close to antiperiplanar arrangement of the orbitals lpO-3$^{(')(")}$eq. → σ*C-2$^{(')(")}$-N-1$^{(')(")}$, hence a second as weaker delocalising interaction. The matching minor non-bonding structure is **XIX** and consistent to a lower basicity of the O-3$^{(')(")}$-*syn* atom.

However, the essential characteristic of our polysubstituted compounds **4f**, **5b** and **7b** in solid state was their crystallisation as *global chiral* forms. The same sense of chirality is exposed by the DOABO groups in duplicate (**4f**, **5b**) and in triplicate (**7b**) (*Figure 2-4*). The network of **4f** consisted in *global chiral* form units of type **V** (*Scheme 8*) in a high occupation factor, 0.87 and *global meso* form units (not depicted, type **II**, *Scheme 8*) in a low occupation factor, 0.13. Compound **4f** was a non-stoichiometric solvate of dichloromethane, located in the channels of the network with an occupation factor of 0.96. The dominant incidence of *global chiral* against *meso* form units appeared to us mandatory to the inclusion aptitude of *chiral* **4f**. Indeed, the alternative *meso* **4f** structure exhibited strong geometric distortions; discussed previously by us [20] hence, lower inclusion ability.

Stronger dichloromethane incorporating capacity manifested the network of the *s*-triazine **7b** (*Figure 4*), found as triple chiral form of type **XV** (*Scheme 9*). It was ascertained to be a stable equimolar adduct with dichloromethane (omitted in *Figure 4* for reason of simplicity).

Important non-bonding interactions were identified in the networks of compounds **4b** and **5b**.

The elementary cell of **4b** was a tetramer (*Figure 1-2*), based on two different types of intermolecular interactions, (**a**) and (**b**). The interatomic distances that we associated to these interactions are: (**a**) H-6-*t*(DOABO)…N-4(pyrazine) 2.550(3) Å and N-1(pyrazine)…H-*para*(C-2-*pseudo*-equatorial-bisectional phenyl ring) 2.636(2) Å. They are smaller than the corresponding sum of the van der Waals radii (ΣvdW N…H) 2.74 Å [34]. The interactions (**a**) close two identical cavities ***A***, meanwhile the interactions (**b**) lock the central cavity ***B***. Two **4b** partners, having an opposite sense of chirality of the DOABO groups, are the building blocks of each cavity.

The network of compound **5b** was a polymeric structure (*Figure 3-2*) in which the non-bonding interactions between the **5b** units are of the same type H-4'-*c*…O-7-*anti* 2.464(1) Å and H-4-*c* …O-7'-*anti* 2.449(1) Å, (ΣvdW O…H 2.60 Å) [34]. Their magnitude is slightly different since the two DOABO groups in monomeric **5b** were geometrically not quite identical. Consequently, two cavities labeled ***C*** and ***D*** are

observed, comprising each two **5b** units with a reverse sense of the *global chirality* one against the other.

CONCLUSIONS

The Williamson procedure is a simple methodology starting from *c*-5-hydroxymethyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]octanes in reaction with α-chlorodiazines and cyanuryl chloride. The nucleophilicity of the DOABO-CH_2OH reagents in alkoxide form depends on the type of substituents at positions C-2, -8 of the bicycle and the cation against the π-deficiency of the substrates. The conformation analysis of some structures by X-Ray Diffractometry and ^{1}H DNMR indicates exclusively a chiral against *meso* form frozen conformation of the DOABO skeleton in solid state *vs.* solution respectively. The cross *endo*-anomeric effect in the aminalic O-C-N-C-O DOABO sequence is responsible for the chiral conformation in solid state. The rotamerism of the *c*-5-di(*s*-tri)azinyloxymethyl group against bicycle is bisectional and s-*trans out*. In solid state, an inclusion aptitude of the solvent by the chiral networks is found as well as non-bonding interaction creating specific self-assembly. The attempt at exploiting these findings in synthesis will be discussed in part II of our preliminary report.

EXPERIMENTAL

Current NMR spectra were recorded on a Brucker® AM300 (300 MHz ^{1}H, 75 MHz ^{13}C) instrument. ^{1}H DNMR analysis of compounds **4a**, **4f**, **5a**, **5b, 7a** and **7b** was carried out on a Brucker® AM400 (400 MHz ^{1}H, 100 MHz ^{13}C) instrument. TLC was performed by using aluminium sheets with silica gel 60 F_{254} (Merck®).; flash column chromatography was conducted on Silica gel Si 60 (40-63 μm, Merck®). All synthesis were performed under dry nitrogen atmosphere. THF was freshly distilled from Na/benzophenone prior to use. Crystallographic Data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC: compound **4b** CCDC 283623. Unit cell parameters: a 13.0640(11) b 8.8414(7) c 17.2561(14) space group P1 21/c 1(14). Compound **4f** CCDC 199978. Unit cell parameters: a 12.251 b 11.072 c 15.243 space group P2(1) / n. Compound **5b** CCDC 238894. Unit cell parameters: a 27.3536(3) b 11.8334 c 23.7369(3) space group C2/c. Compound **7b** CCDC 272371. Unit cell parameters: a 8.9574(2) b 12.2323(2) c 24.6520(4) space group P-1. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk] [35-37].
The ^{1}H NMR assignments of compounds **4a**, **4f**, **5a**, **5b, 7a** and **7b** are listed in *Table 4*. The synthesis of compound **4f** was reported by us elsewhere [20]. The step by step exploring of the synthesis of compounds **6a**, **6b**, **7a** and **7b** is reported elsewhere [35-37].

General procedure for the preparation of compounds 4a-e, 5a-c

In a 100 mL three necked round bottom flask potassium hydride (1.000 g as 30% oily suspension, 0.300 g 100%, 7.48 mmol) was rapidly introduced and washed with stirring three times with dry ligroin (optionally pentane, hexane) (30 mL). THF (50 mL) was then introduced with stirring to yield a fine grey suspension. Fine powdered *c*-5-hydroxymethyl-3,7-dioxa-1-azabicyclo[3.3.0]-*c*-5-octanes **1a, b** (7.12 mmol) was added and the mixture was heated at 40 ^{o}C for 1.0-1.5 hrs. until no more hydrogen was formed and a fine suspension was obtained. The corresponding α-chlorodiazine (6.78/n mmoles, n = number of chlorine atoms to be replaced) was rapidly injected as THF (10 mL) solution, at room temperature (see *Table 1, 2* for temperatures and time reaction). The TLC monitoring was performed until the starting materials were absent or in small traces only. Double visualisation was required if **2a** was the nucleophile: first UV 254 nm, then I_2 bath, for the detection of **1a**. During condensation, the reaction mixture turned coloured and potassium chloride was formed. The reaction was quenched at room temperature with 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 then dried over $MgSO_4$. After filtering, the organic solution was evaporated under vacuum to dryness to yield the crude product, which was directly crystallised from an appropriate solvent or purified by flash column chromatography to yield the title compounds.

2-[(3,7-Dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (4a). (85 %) yellowish crystalline powder, mp 128 - 129 ^{o}C (pentane). [Found: C, 53.50; H, 6.09; N, 18.55. $C_{10}H_{13}N_3O_3$ requires: C, 53.81; H, 5.87; N, 18.82 %]. R_f (75 % ligroin/acetone) 0.40. ν_{max} (film NaCl) 2868 (m), 1524 (s), 1465 (m), 1413 (s), 1361 (m), 1289 (s), 1134 (m), 1032 (s), 1002 (s), 915 (s), 832 (m), 692 (m) cm^{-1}. δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 160.1 (1 C, C-2), 140.9 (1 C, C-6), 137.5 (1 C, C-3), 136.1 (1 C, C-5); *DOABO-CH_2O*: 88.6 (2 C, C-2, -8), 74.4 (2 C, C-4, -6), 71.9 (1 C, C-5), 69.0 (1 C, 5-OCH_2). MS (EI, 70 eV); m/z (rel. int. %): 223 (6), 178 (14), 163 (13), 114 (100), 98 (17), 86 (9), 68 (26), 58 (11), 42 (18), 41 (59).

2-[(*c*-2,*c*-8-Diphenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (4b). (79 %) yellowish crystalline powder, mp 134 - 136 ^{o}C (flash column chromatography, eluent ligroin : AcOEt 3:1 v/v). [Found: C, 70.17; H, 5.94; N, 10.95. $C_{22}H_{21}N_3O_3$ requires C, 70.38; H, 5.64; N, 11.19 %]. R_f (75 % ligroin/AcOEt) 0.56. ν_{max} (film KBr) 2877 (s), 1586 (m), 1540 (s), 1418 (s), 1388 (m), 1312 (s), 1135 (s), 1065 (s), 932 (s), 834 (s), 800 (m), 763 (s), 738 (s), 696 (s), 617 (m), 537 (m), 499 (w), 465 (m) cm^{-1}. δ_H (300 MHz $CDCl_3$) *(hetero)aromatic*: 8.09 (1 H, d, *J*=2.6 Hz, H-5), 8.04 (1 H, s, H-3), 8.01 (1 H, dd, *J*=2.6, 1.3 Hz, H-6), 7.52 (4 H, d, *J*=6.0 Hz, Ph), 7.36 - 7.30 (6 H, m, Ph); *DOABO-CH_2O*: 5.61 (2 H, s, H-2, -8-*t*), 4.27 (2 H, s, 5-OCH_2), 4.10 (2 H, d, *J*=9.0 Hz, H-4, -6-*c*), 4.00 (2 H, d, *J*=9.0 Hz, H-4, -6-*t*); δ_C (75 MHz $CDCl_3$) (*hetero)aromatic*: 160.1 (1 C, C-2), 140.8 (1 C, C-6), 139.7 (2 C, Cq., Ph), 137.4 (1 C, C-3), 136.1 (1 C, C-5), 129.0 (2 C, CH, Ph), 128.7 (4 C, CH, Ph), 127.6 (4 C, CH, Ph); *DOABO-CH_2O*: 97.8 (2 C, C-2, -8), 73.6 (2 C, C-4, -6), 73.3 (1 C, C-5), 70.2 (1 C, 5-OCH_2). MS (EI, 70 eV); m/z (rel. int. %): (M^+) 375 (<1), 269 (30), 173 (100), 155 (33), 128 (21).

2-Chloro-6-[(*c*-2,*c*-8-diphenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (4c). (as 34 % conversion of **3b**, *Table 1*) white crystalline powder, mp 128 - 129 ^{o}C (flash column chromatography, eluent ligroin : AcOEt 2:1 v/v). [Found: C, 64.59; H, 4.60; N, 10.51. $C_{22}H_{20}N_3O_3Cl$ requires: C, 64.47; H, 4.92; N, 10.25 %]; R_f (67 % ligroin/AcOEt) 0.35. ν_{max} (film KBr) 3060 (m), 2990 (m), 2878 (s), 1568 (s), 1528 (s), 1435 (s), 1409 (s), 1309 (s), 1209 (s), 1179 (s), 1131 (s), 1091 (s), 1064 (s), 1006 (s), 949 (m), 923 (s), 961 (s), 762 (s), 736 (s), 697 (s), 637 (m) cm^{-1}. δ_H (300 MHz $CDCl_3$) *(hetero)aromatic*: 8.14 (1 H, s, H-5), 7.89 (1 H, s, H-3); 7.54 – 7.52 (4 H, m, Ph), 7.40 – 7.31 (6 H, m, Ph); *DOABO-CH_2O*: 5.63 (2 H, s, H-2, -8-*t*), 4.30 (2 H, s, 5-OCH_2), 4.10 (2 H, d, *J*=9.0 Hz, H-4, -6-*c*), 4.00 (2 H, d, *J*=9.0 Hz, H-4, -6-*t*); δ_C (75 MHz $CDCl_3$) *(hetero)aromatic*: 159.0 (1 C, C-6), 145.7 (1 C, C-2), 139.5 (2 C, Cq., Ph), 136.1 (1 C, C-3), 133.3 (1 C, C-5), 129.0 (2 C, CH, Ph), 128.8 (4 C, CH, Ph), 127.5 (4 C, CH, Ph); *DOABO-CH_2O*: 97.9 (2 C, C-2, -8), 73.4 (2 C, C-4, -6), 73.2 (1 C, C-5), 70.6 (1 C, 5-OCH_2). MS (EI, 70 eV); m/z (rel. int. %): (M^+-1) 408 (<1), 267 (22), 266 (100), 160 (10), 105 (28).

6-[(*c*-2,*c*-8-Diphenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-1*H*-pyrazin-2-one (4d). (as 17 % conversion of **3b**, *Table 1*) white crystalline powder, mp 199 - 201 ^{o}C (flash column chromatography, eluent ligroin : AcOEt 1:1 v/v. [Found: C, 67.42; H, 5.63; N, 10.46. $C_{22}H_{21}N_3O_4$ requires: C, 67.51; H, 5.41; N, 10.74 %]. R_f (50 % ligroin/AcOEt) 0.60. ν_{max} (film KBr) 3062 (m), 2978 (m), 2877 (s), 2442 (s), 1822 (s), 1612 (s), 1537 (s), 1449 (s), 1376 (s), 1315 (s), 1269 (s), 1188 (s), 1135 (s), 1091 (s), 921 (s), 836 (s), 757 (s), 732 (s), 695 (s) cm^{-1}. δ_H (300 MHz $CDCl_3$) *(hetero)aromatic*: 7.77 (1 H, s, H-5), 7.62 (1 H, s, H-3); 7.52 – 7.50 (4 H, m, Ph), 7.36 – 7.27 (6 H, m, Ph), 7.03 (1 H, bs, NH); *DOABO-CH_2O*: 5.60 (2 H, s, H-2, -8-*t*), 4.17 (2 H, s, 5-OCH_2), 4.08 (2 H, d, *J*=9.0 Hz, H-4, -6-*c*), 3.98 (2 H, d, *J*=9.0 Hz, H-4, -6-*t*); δ_C (75 MHz $CDCl_3$) *(hetero)aromatic*: 158.1 (1 C, C-2), 157.0 (1 C, C-6), 139.6 (2 C, Cq., Ph), 129.1 (2 C, CH., Ph), 128.8 (4 C, CH., Ph), 127.6 (4 C, CH., Ph) 125.3 (1 C, C-3), 124.2 (1 C, C-5); *alicyclic*: 97.7 (2 C, C-2, -8), 73.6 (2 C, C-4, -6), 73.2 (1 C, C-5), 70.5 (1 C, 5-OCH_2); MS (EI, 70 eV); m/z (rel. int. %): (M^+) 391 (<5), 285 (50), 179 (15), 174 (100), 155 (13), 128 (17).

2,6-Bis[(*c*-2,*c*-8-diphenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (4e). (as 8 % conversion of **3b**, *Table 1*) white crystalline powder; this compound was isolated only as a non separable mixture(38 %) with **4d** (62 %) during the work up by flash column chromatography of the reaction between **3b** and **2b** (*Table 1*). δ_H (300 MHz $CDCl_3$) only distinct peaks are listed as *DOABO-CH_2O*: 5.63 (4 H, s, H-2, -8-*t*), 4.15 (4 H, s, 5-, 5'-OCH_2), 4.07 (4 H, d, *J*=9.1 Hz, H-4, -4', -6, -6'-*c*); δ_C (75 MHz $CDCl_3$) *(hetero)aromatic*: 139.7 (4 C, Cq., Ph), 125.0 (2 C, C-3, -5); *DOABO-CH_2O*: 73.2 (4 C, C-4, -4' -6, -6'). MS (EI, 70 eV); m/z (rel. int. %): (M^+) 670 (<1).

4,6-Bis[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrimidine (5a). (81 %) white crystalline powder, mp 146 - 148 ^{o}C (pentane). [Found: C, 52.70; H, 5.88; N, 14.98. $C_{16}H_{22}N_4O_6$ requires: C, 52.45; H, 6.05; N, 15.29 %]. R_f (75 % ligroin/acetone) 0.35. ν_{max} (film NaCl) 2950 (w), 2858 (m), 1593 (s), 1563 (s), 1457 (m), 1421 (m),

1341 (m), 1195 (m), 1137 (m), 1095 (m), 1039 (s), 933 (m), 674 (m) cm^{-1}. δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 171.0 (2 C, C-4, -6), 157.8 (1 C, C-2), 91.4 (1 C, C-5); *DOABO-CH_2O*: 88.6 (4 C, C-2, -2', -8, -8'), 74.4 (4 C, C-4, -4', -6, -6'), 71.9 (2 C, C-5, -5'), 69.4 (2 C, 5-, 5'-OCH_2). MS (EI, 70 eV); m/z (rel. int. %): (M^++1)367 (<1), 274 (3), 252 (2), 168 (8), 128 (100), 98 (4).

4,6-Bis[(*c*-2,*c*-8-diphenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrimidine (5b). (31 %) white crystalline powder, mp 176 - 178 °C (flash column chromatography, eluent ligroin : AcOEt 3:1 v/v). [Found: C, 71.53; H, 5.93; N, 8.07. $C_{40}H_{38}N_4O_6$ requires C, 71.63; H, 5.71; N, 8.35 %]. R_f (75 % ligroin/AcOEt) 0.59. ν_{max} (film KBr) 2876 (m), 1595 (s), 1455 (s), 1430 (m), 1314 (w), 1256 (s), 1166 (m), 1089 (m), 989 (w), 921 (m), 838 (s), 752 (m), 694 (m), 470 (m) cm^{-1}. δ_C (75 MHz $CDCl_3$) *(hetero)aromatic*: 170.8 (2 C, C-4, -4' -6, -6'), 157.8 (1 C, C-2), 139.6 (4 C, Cq., Ph), 129.0 (4 C, CH, Ph), 128.8 (8 C, CH, Ph), 127.6 (8 C, CH, Ph); *DOABO-CH_2O*: 97.8 (4 C, C-2, -2', -8, -8'), 73.6 (4 C, C-4, -4', -6, -6'), 73.2 (2 C, C-5, -5'), 70.7 (2 C, 5-, 5'-OCH_2). MS (EI, 70 eV); m/z (rel. int. %): (M^+) 670 (31), 692 (14), 564 (9), 280 (100).

4-Chloro-6-[(*c*-2,*c*-8-diphenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrimidine (5c). (23 %) yellowish crystalline powder, mp 145 - 147 °C (flash column chromatography, eluent ligroin : AcOEt 3:1 v/v). [Found: C, 64.32; H, 5.14; N, 10.19. $C_{22}H_{20}N_3O_3Cl$ requires C, 64.47; H, 4.92; N, 10.25 %]. R_f (75 % ligroin/AcOEt) 0.80. ν_{max} (film KBr) 3091 (m), 2874 (m), 1573 (s), 1454 (s), 1334 (m), 1258 (m), 1213 (m), 1088 (s), 1009 (s), 931 (w), 871 (w), 804 (m), 753 (s), 696 (s), 535 (w) cm^{-1}. δ_H (300 MHz $CDCl_3$) *(hetero)aromatic*: 8.50 (1 H, s, H-2), 7.51 - 7.48 (4 H, m, Ph), 7.37 - 7.28 (6 H, m, Ph), 6.53 (1 H, s, H-5); *DOABO-CH_2O*: 5.60 (2 H, s, H-2, -8-*t*), 4.33 (2 H, s, 5-OCH_2), 4.06 (2 H, d, *J*=9.0 Hz, H-4, -6-*c*), 3.96 (2 H, d, *J*=9.0 Hz, H-4, -6-*t*); δ_C (75 MHz $CDCl_3$) *(hetero)aromatic*: 170.0 (1 C, C-6), 161.3 (1 C, C-4), 158.5 (1 C, C-2), 139.5 (2 C, Cq., Ph), 129.1 (2 C, CH, Ph), 128.8 (4 C, CH, Ph), 127.5 (4 C, CH, Ph), 108.2 (1 C, C-5); *DOABO-CH_2O*: 97.8 (2 C, C-2, -8), 73.4 (2 C, C-4, -6), 73.1 (1 C, C-5), 70.8 (1 C, 5-OCH_2). MS (EI, 70 eV); m/z (rel. int. %): (M^++1) 410 (4), 386 (<1), 304 (100), 280 (42), 174 (98), 156 (23), 129 (11), 91 (18).

2-Chloro-4,6-bis[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-*s*-triazine (6a). (34 %) yellowish crystalline powder, mp 91.8 - 93.4 °C (flash column chromatography, eluent ligroin : acetone 2:1 v/v). [Found: C, 44.91; H, 5.19; N, 17.63. $C_{15}H_{20}N_5O_6Cl$ requires: C, 44.84; H, 5.02; N, 17.43 %]. R_f 0.75 (66 % ligroin/acetone). ν_{max} (KBr) 2971 (m), 2868 (s), 1731 (s), 1390 (m), 1252 (s), 1138 (m), 1038 (s), 926 (s), 885 (w), 792 (m), 673 (s), 610 (s), 505 (w) cm^{-1}. δ_H (300 MHz $CDCl_3$) 4.39 (4 H, s, H-2, -2', -8, -8'-*c*), 4.37 (4 H, s, H-2, -2', -8, -8'-*t*), 4.06 (4 H, s, 5-, 5'-OCH_2), 3.73 (4 H, d, *J*=9.0 Hz, H-4, -4', -6, -6'-*c*), 3.68 (4 H, d, *J*=9.0 Hz, H-4, -4', -6, -6'-*t*); δ_C (75 MHz $CDCl_3$) 171.0 (3 C, C-2, -4, -6 *s*-triazine), 88.6 (4 C, C-2, -2', -8, -8'), 74.2 (4 C, C-4, -4', -6, -6'), 71.5 (2 C, C-5, -5'), 66.9 (2 C, 5-, 5'-OCH_2). MS (EI), m/z (rel. int. %) 402 (< 1) [M^++1], 324 (38), 256 (57), 145 (58), 127 (100).

2,4,6-Tris[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-*s*-triazine (7a) (82 %) white crystalline powder, mp 238.9 - 239.5 °C (Et_2O). [Found: C, 49.44; H, 5.98; N,

16.44. $C_{21}H_{30}N_6O_9$ requires: C, 49.41; H, 5.92; N, 16.46 %]. R_f 0.30 (50 % ligroin/acetone). ν_{max} (KBr) 3444 (m), 2969 (w), 2858 (s), 1589 (s), 1414 (s), 1334 (s), 1189 (m), 1141 (m), 1096 (s), 1044 (s), 1028 (s), 943 (m), 807 (s), 750 (m), 718 (w), 676 (m), 572 (m) cm^{-1}. δ_C (75 MHz $CDCl_3$) 173.3 (3 C, C-2, -4, -6 *s*-triazine), 88.5 (6 C, C-2, -2', -2", -8, -8', -8"), 74.3 (6 C, C-4, -4', -4", -6, -6', -6"), 71.5 (3 C, 5-, 5'-, 5"-OCH_2) 71.3 (3 C, C-5, -5', -5"); MS (ESI), m/z (rel. int. %) 532 [M^+-1+Na^+] (100), 511 (40) [M^+], 384(10).

2-Chloro-4,6-bis[(*c*-2,*c*-8-diphenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-triazine (6b) (8 %). δ_H (300 MHz $CDCl_3$) as detected from the mixture with **7b**: 5.59 (4 H, s, H-2, -8-*t*), 4.31 (4 H, s, 5-, 5'-OCH_2), 4.06 (4 H, d, *J*=9.2 Hz, H-4, -4', -6, -6'-*c*), 3.98 (4 H, d, *J*=9.2 Hz, H-4, -4', -6, -6'-*t*); δ_C (75 MHz $CDCl_3$), 171.8 (3 C, C-2, -4, -6 *s*-triazine), 139.3 (4 C, Cq., Ph), 127.5 (8 C, CH, Ph). MS (FAB^+), m/z (rel. int. %) 704 (20) [M^+-1].

2,4,6-Tris[(*c*-2,*c*-8-diphenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-*s*-triazine (7b) (37 %) white crystalline powder, mp 162.5 - 164.2 °C (flash column chromatography, eluent ligroin : acetone 3.5:1 v/v). [Found: C, 70.61; H, 5.70; N, 8.44. $C_{57}H_{54}N_6O_9$ requires: C, 70.80; H, 5.63; N, 8.69 %] R_f 0.40 (78 % ligroin/acetone). ν_{max} (KBr) 3063 (w), 2871 (m), 1571 (s), 1417 (s), 1334 (s), 1210 (m), 1131 (s), 1088 (m), 1068 (m), 922 (m), 820 (w), 762 (m), 735 (s), 698 (s) cm^{-1}. δ_C (75 MHz $CDCl_3$) 172.9 (3 C, C-2, -4, -6 *s*-triazine), 139.5 (6 C, Cq., Ph), 129.1 (6 C, CH, Ph), 128.8 (12 C, CH, Ph), 127.5 (12 C, CH, Ph), 97.6 (6 C, C-2, -2', -2", -8, -8', -8"), 73.6 (6 C, C-4, -4', -4", -6, -6', -6"), 72.8 (3 C, 5-, 5'-, 5"-OCH_2), 72.2 (3 C, C-5, -5', -5"); MS (FAB^+), m/z (rel. int. %) 967.9 (100) [M^++1].

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REFERENCES

1. Senkus, M.: *Journal of the American Chemical Society*, **1945**, **67**, 1515.
2. Senkus, M.: *U. S. Patent 2,401,196*; *Chemical Abstracts*, **1946**, **40**, P5446[4].
3. Pierce, S., Lunsford, D.C., Raiford Jr., R.W., Rush, J.L., Riley, D.W.: *Journal of the American Chemical Society*, **1951**, **73**, 2595.
4. Pierce, S., Lunsford, D.C.: *Journal of the American Chemical Society*, **1951**, **73**, 2596.
5. Tilford, C.H., Van Campen Jr., M.G., Shelton, R.S.: *Journal of the American Chemical Society*, **1947**, **69**, 2902.
6. Darabantu, M., Mager, S., Plé, G., Puscas, C.: *Heterocycles*, **1995**, **41**, 2327.
7. Broadbent, H.S., Burnham, W.S., Sheely, R.M., Olsen, R.K.: *Journal of Heterocyclic Chemistry*, **1976**, **13**, 337.
8. Barbulescu, N., Moga, S.G., Sintamarian, A., Cuza, O., Vasilescu, V.: *Romanian Patent 83, 939*; *Chemical Abstract*, **1985**, **102**, P149252r.

9. Nouguier, R., Crozet, M., Vanelle, P., Maldonado, J.: *Tetrahedron Letters*, **1985**, **26**, 5523.
10. Zayed, S. E.: *Pakistan Journal of Scientific and Industrial Research*, **1987**, **30**, 432; *Chemical Abstract*, **1988**, **108**, 94446y.
11. Vanelle, P., M. De Meo, M.P., Maldonado, J., Nouguier, R., Crozet, M.P., Laget, M., Dumenil, G.: *European Journal of Medicinal Chemistry*, **1990**, **25**, 241.
12. Mattson, A., Norin, T.: *Synthetic Communications*, **1994**, **24**, 1489.
13. Bonnet, D., Pascal, J., Grass-Masse, H., Melnyk, O.: *Tetrahedron Letters*, **2001**, **42**, 1875.
14. Japan, Jpn. Tokkyo Koho (**1996**) *JP 08325147*; *Chemical Abstracts*, **1997**, **126**, 139880.
15. Laurent, P.A., Riehl, M., Frazao, C.S.: *Bulletin de la Société Chimique de France*, **1967**, **10**, 3868.
16. Cobb, R.L.: *U. S. Patent 3,843,726*; *Chemical Abstracts*, **1975**, **82**, P861193t.
17. Cardona, C., Gawley, R. E.: *Journal of Organic Chemistry*, **2002**, **67**, 1411.
18. Darabantu, M., Plé, G., Mager, S., Gaina, L., Cotora, E., Mates, A., Costas, L.: *Tetrahedron*, **1997**, **53**, 1891.
19. Darabantu, M., Plé, G., Maiereanu, C., Silaghi-Dumitrescu, I., Ramondenc, Y., Mager, S.: *Tetrahedron*, **2000**, **56**, 3799.
20. Darabantu, M., Maiereanu, C., Silaghi-Dumitrescu, I., Toupet, L., Condamine, E., Ramondenc, Y., Berghian, C., Plé, G., Plé, N.: *European Journal of Organic Chemistry*, **2004**, **12**, 2644.
21. Eliel, E.L., Wilen, H.S.: *Stereochemistry of the Organic Compounds*; John Wiley & Sons, Inc., **1994**; pp 221-239, 488-507, 1017, 1199.
22. Cookson R.C., Crabb, T.A.: *Tetrahedron*, **1968**, **24**, 2385.
23. Crabb, T.A., Hall, M.J., Williams, R.O.: *Tetrahedron*, **1973**, **29**, 3389.
24. Brush, J.R., Magee, R.J., O'Connor, M.J., Teo, S.B., Geue, R.J., Snow, M.R.: *Journal of the American Chemical Society*, **1973**, 2034.
25. Monge, S., Sélambaron, J., Carré, F., Verducci, J., Roque, J. P., Pavia, A.A.: *Carbohydrate Research*, **2000**, **328**, 127.
26. Darabantu, M., Lequeux, T., Pommelet, J.C., Plé, N., Turck, A., Toupet, L.: *Tetrahedron Letters*, **2000**, **41**, 6763.
27. Darabantu, M., Lequeux, T., Pommelet, J.C., Plé, N., Turck, A.: *Tetrahedron*, **2001**, **57**, 739.
28. Dudley, J.R., Thuyrston, J.T., Schaefer, F.C., Holm-Hansen, D., Hull, C.J., Adams, P.: *Journal of the American Chemical Society*, **1951**, **73**, 2986.
29. Weber, A.J.M., Huysmans, W.G.B., Mijs, W.J., Bovee, W.M.M.J., Smidt, J., Vriend, J.: *Recueil des Travaux Chimiques des. Pays-Bas*, **1978**, **97**, 107.
30. Menicagli, R., Malanga, C., Peluso, P.: *Synthtic Communications*, **1994**, **24**, 2153.
31. Cronin, J.S., Ginah, F.O., Murray, R.A., Copp, D.J.: *Synthetic Communications*, **1996**, **26**, 3491.
32. Friebolin, H.: *Basic One- and Two Dimensional NMR Spectroscopy*; VCH Verlagsgesellschaft /VCH: Weinheim/New York, **1991**; pp. 271.
33. Riedell, F.G.: *Cyclic Organonitrogen Stereodynamics* Eds. J. B. Lambert, Y. Takeuchi; VCH, New York, **1992**; pp. 159.

34. Emsley, J.: *Die Elemente*; W. de Gruyter Editor, Berlin, New York, **1994**; pp. 166, 178, 206.
35. Berghian, C., Plé, N., Turck, A., Darabantu, M.: *Studia Universitatis "Babes-Bolyai" Serie Chemia*, **2005**, **1**, 201.
36. Berghian, C., Lameiras, P., Toupet, L., Condamine, E., Plé, N., Turck, A., Maiereanu, C., Darabantu, M.: **2006**, *Manuscript under revision*.
37. Berghian, C., Darabantu, M., Lameiras, P., Plé, N., Turck, A.: *Heterocyclic Communications*, **2005**, **11**, 517.