α-(3,7-DIOXA-*r*-1-AZABICYCLO[3.3.0]OCT-*c*-5-YLMETHOXY)-DIAZINES (II): FUNCTIONALISATION *VIA* DIRECTED *ORTHO*-METALLATION AND CROSS-COUPLING REACTIONS♦

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Abstract: The functionalisation of the title compounds *via* regioselective Directed *ortho*-Metallation (DoM), cross-coupling and the compatibility of the 3,7-DiOxa-*r*-1-AzaBicyclo[3.3.0]Oct-*c*-5-ylmethoxy system (DOABO-CH_2O) to the reactions typical conditions are preliminarily reported. Its role as Directed *ortho*-Metallation Group (DoMG) is examined. The chelating ability of some functionalised terms as DOABO-CH_2O substituting chiral diarylmethanols and polyaza analogous of 2,6-terpyridine is discussed as intramolecular steric relationships determining configuration and aptitude to bind selectively transition metals respectively.

Keywords: *pyrazines, pyrimidines, pyridazines, oxazolidines, metallation, cross-coupling, NMR, chirality.*

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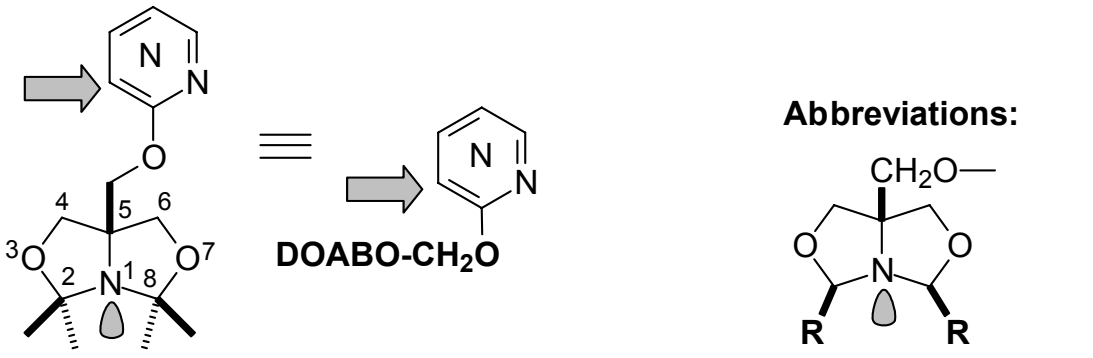
INTRODUCTION

Advances in the field of Directed *ortho*-Metallation with organo lithium reagents of azines and diazines have been recently reviewed [1, 2]. This methodology, the so-called *DoM reaction*, allows the access to functionalised π-deficient systems in clean, rapid, selective and high yielding transformations. In the context, of a crucial relevance are the *Directed ortho-Metallation Groups* (*DoMGs*) whose increasing diversity makes the method overall attractive. Few examples are known in which the DoMG was a heterocyclic saturated system: 1,3-diox-2-yl (in pyrazine and pyridine series) [3, 4], 1,3-dioxol-2-yl [5], pyrrolidin-1-yl [6] and piperidin-1-yl [7] (in pyridine series). However, their role appeared to us as protecting groups of the carbonyl and amino functionality linked *ortho* to the reaction site rather than connected to a peculiar stereochemistry of the DoMGs of this type.

Hence, the objective of the present preliminary report is based on our previous acquired knowledge about the synthesis and stereochemistry of a new series as α-(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-ylmethoxy)-diazines **I** (*Scheme 1*) [8-11], aiming at their further functionalisation *via* DoM reactions.



I

3,7-**DiO**xa-*r*-1-**Aza**bicyclo[3.3.0]**O**ct-*c*-5-ylmethoxy

R = H: (2H)DOABO-CH_2O

R = Ph: (2Ph)DOABO-CH_2O

Scheme 1.

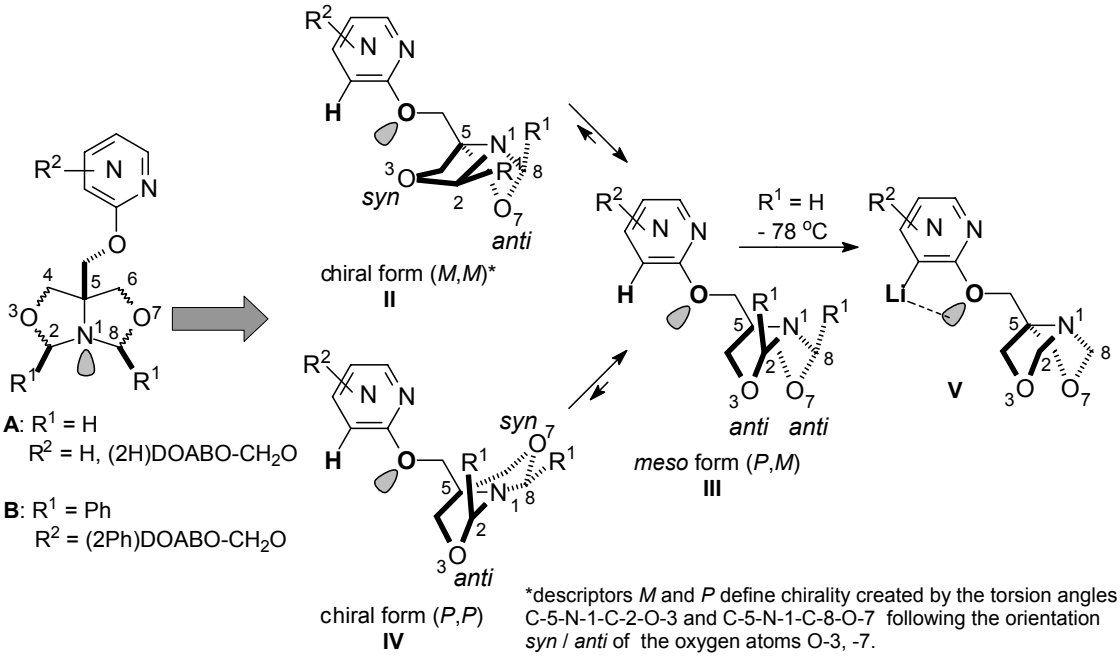
On the other hand, we have recently reported the synthesis by double cross-coupling under Stille conditions [12, 13] of a new class of polyaza analogous of 2,6-terpyridine possessing the 2,6-disubstituted pyrazine as central unit linked to various heteroaromatic systems as subunits [14]. Our ongoing efforts to prepare new aza polydentated architectures prompted us, as another objective, to test the 3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-ylmethoxy fragments α-substituting the building blocks, pyrazines, pyrimidines and pyridazines.

No such chemistry assisted by the DOABO heterocyclic system was reported so far.

RESULTS AND DISCUSSION

Functionalisation *via* directed *ortho*-metallation of α-(3,7-dioxa-*r*-1-azabicyclo [3.3.0]oct-*c*-5-ylmethoxy)-diazines

Our study started from the stereochemistry, supported by ^{1}H DNMR performed in [D_8]THF and X-Ray Diffractometry [8], of the DOABO group attached at the α position of a diazine by a methoxy like unit, *e.g.* compounds of type A and B (*Scheme 2*). As seen previously [8], the heterofacial *cis* fused double oxazolidine part of the compounds A (R^1 = H) was flipping at room temperature (conformers II-III-IV) in an overall enantiomeric inversion. It became rigid on a large domain of low temperatures (273 – 173 K) with the potential chelating sites O-3, N-1 and O-7 oriented as a frozen non-chiral conformation III. In contrast, the *all cis* C-2, -5, -8 trisubstituted DOABO analogue B (R^1 = Ph) was flipping still at 173 K. By lowering the temperature, the common conformational feature for structures A and B was the progressive orientation of the *c*-5-diazinyloxymethyl moiety in near coplanar *s-trans out* arrangement, bisecting the DOABO skeleton. Consequently, coplanarity also involved the *ortho* diazine proton and the lone pair of the oxygen atom in the CH_2O linkage, as also proved by the crystalographically-determined structures of type **A** and **B** [8]. So, the CH_2O connection could coordinate the lithium atom to the lone pair of its oxygen atom to bring the base into close vicinity of the *ortho* diazine hydrogen and to provoke its removal ("Complex Induced Proximity Effect", C.I.P.E. [15, 16], *e.g.* conformer **V**, *Scheme 2*).

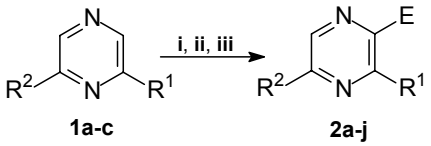


Scheme 2.

With these premises, we investigated the metallation in two series, pyrazine and pyrimidine, bearing at the α-positions the DOABO-CH_2O groups. Whenever available, a comparison with the behaviour in DoM conditions of the methoxy group α-substituting diazines was made.

Functionalisation of α-(3,7-dioxa-r-1-azabicyclo[3.3.0]oct-c-5-ylmethoxy)-pyrazines

The testing experiments were carried out on compound **1a** (*Scheme 3*, *Table 1*).



1a-c **2a-j**

1a: R^1 = (2H)DOABO-CH_2O, R^2 = H
1b: R^1 = (2Ph)DOABO-CH_2O, R^2 = H
1c: R^1 = R^2 = (2H)DOABO-CH_2O

R^1 = (2H)DOABO-CH_2O, R^2 = H
2a: E = D
2b: E = PhCHOH
2c: E = MeCHOH
2d: E = Et
2e: E= I
2f: E = Sn(*n*-Bu)$_3$
2g: E = SPh

R^1 = (2Ph)DOABO-CH_2O, R^2 = H
2h: E = PhCHOH

R^1 = R^2 = (2H)DOABO-CH_2O
2i: E = D

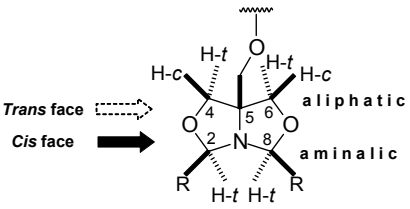
R^1 = R^2 = (2H)DOABO-CH_2O
2j:E = PhCHOH

i: 4 eq. LTMP / THF / T_1 / t_1 ; **ii**: 4 eq. electrophile / $T_1 \nearrow T_2$ / t_2; **iii**: hydrolysis / T_2

Scheme 3.

Table 1. *Results of the functionalisation via directed ortho-metallation of α-(3,7-dioxa-r-1-azabicyclo[3.3.0]oct-c-5-ylmethoxy)-pyrazines. Preparation of compounds* ***2a-j***

Entry	Products (Yields %)	Conditions			
		t_1 (hrs.)	T_1 (^{o}C)	T_2 (^{o}C)	t_2 (hrs.)
1	**2a** (98)[a,b]	1	-78	-78	-
	2b (79)	1	-78	r.t.	12
	2c (41)	1	-78	-78	4.5
	2d (80)[c]	1	-78	-78	1.5
	2e (68)	1	-78	-78	2
	2f (73)[d]	1	-78	-78	2
	2g (73)[d]	1	-78	-78	2
2	**2h** (98)	1	-78	r.t.	12
3	**2i** (71)[a,e]	0.5	0	-	-
	2j (61)	2	-78	-50	10



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

[a]8 eq. as DCl 20 % g/g in D_2O solution were used; [b]for **2a**, as deuterium incorporation in quantitatively isolated crude product (^{1}H NMR monitoring); [c]MeI as electrophile; less than 10 % of the intermediate methyl derivative was detected in the crude reaction mixture (^{1}H NMR monitoring). [d]ClSn(*n*-Bu)$_3$ (for **2f**) and Ph_2S_2 (for **2g**) as electrophiles; [e]50 % incorporation of deuterium with respect to the starting **1c**.

Treatment of **1a** with 1.1 eq.of LTMP (lithium-2,2,6,6,-tetramethylpiperidide) at -78 ^{o}C for 60 min. as for 2-methoxypyrazine [17, 18] followed by quench with 20 % DCl/D_2O (at –78 ^{o}C) afforded the starting material in 99 % yield. Deuteriation was 84 % at C-3' if 2.1 eq. of LTMP were used. The best result, 98 % deuterium incorporation in the crude product, was obtained with 4 eq. of LTMP (compound **2a**, *Table 1*). This excess could be explained by the high chelating ability at -78 ^{o}C of the frozen *meso* form (*P,M*) conformation of the (2H)DOABO-CH_2O group of **1a** (R^1 = R^2 = H, **III** → **V**, *Scheme 2*). Keeping in mind these experimental conditions, the lithiated compound **1a**, upon treatment with various electrophiles, afforded the products **2b-g** (*Table 1*, entry 1) with satisfactory to good yields and complete *ortho* regioselectivity indicating that the (2H)DOABO-CH_2O moiety acted as an effective DoMG.

The flipping (2Ph)DOABO-CH_2O fragment (*Scheme 2*) was also an authentic DoMG, as proved by the excellent result in the synthesis of compound **2h** (*Table 1*, entry 2).

Products **2b**, **2c**, **2h** and **2j** have on *ortho* vicinity of a stereogenic centre *vs.* the heterofacial DOABO skeleton. The ^1H NMR spectrum of **2b** evidenced the expected diastereotopic positions of the bicycle: C-2 *vs.* C-8 and C-4 *vs.* C-6. However, in the ^1H NMR spectrum of **2c** these relevant positions appeared almost no differentiated. For this reason, we considered of interest to continue our study by using mainly benzaldehyde as electrophile and the structure of the chiral diarylmethanols of type **2b** closer to the DOABO-CH_2O group intimate stereochemistry [8, 9].

The deuteriation of the compound **1c**, possessing twice the (2H)DOABO-CH_2O environment (*Table 1*, entry 3) yielded as product **2i** but fast decomposition of the reaction mixture was observed. Consequently, no reaction of the metallated compound **1c** occurred at 0 ^oC with benzaldehyde. In turn, at -78 ^oC, in contrast with the result observed with 2,6-dimethoxypyrazine [19, 20], the reaction gave the compound **2j** in a satisfactory yield. Taking into account that 4 eq. of LTMP were necessary (*vs.* 2.2 eq. LTMP reported for 2,6-dimethoxypyrazine), we considered these conditions also associated to the increased chelating ability of the double frozen *meso* form (*P,M*) of **1c** (R^1 = H, R^2 = (2H)DOABO-CH_2O, **III** → **V**, *Scheme 2*).

The compound **2j** was investigated by high resolution NMR in order to discriminate the two regioisomeric *ortho*-(C-2') and *para*-(C-6') (2H)DOABO-CH_2O groups with respect to the C-3'-α-hydroxybenzyl chiral centre. Individual ^1H-^{13}C heteronuclear correlations, HSQC and HMBC experiments, and the assignment of the homofacial bicyclic protons as -*c*(*cis*) or -*t*(*trans*) with respect to the lone pair at N-1 in each (2H)DOABO environment by 2 D ^1H-^1H NOESY experiments, were established. The results are collected in *Table 2* together with those supporting two other terms of the series, compounds **2b** and **2h**.

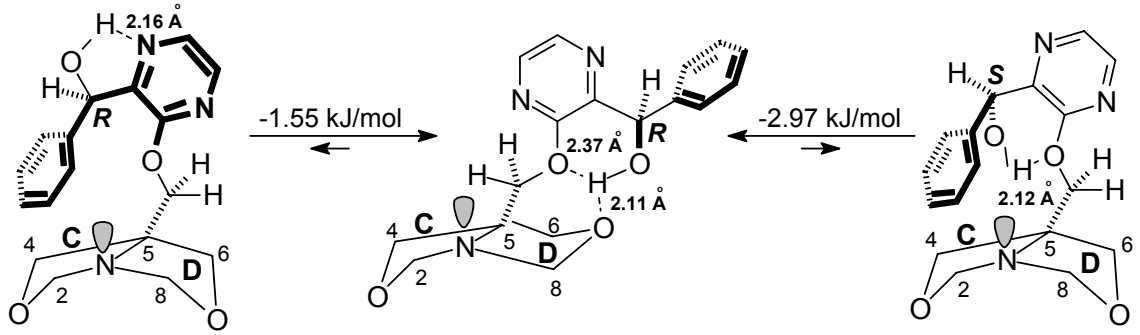
Only the *ortho*-linked DOABO-CH_2O groups exhibited significant ^1H magnetic non-equivalence as diastereotopicity (Δδ values) between the homofacial aminalic (or aliphatic) protons. It must be observed that it was more important in the *cis* aliphatic part of the bicycle, and, on the whole, even with respect to the Δδ (a-b) value revealed by the exocyclic methylene *c*-5-OCH-a, H-b. The presence of the phenyl groups at C-2, -8 in **2h** strongly increased the diastereotopicity.

In compound **2j**, for the remote *para* (2H)DOABO-CH_2O group, the discussed diastereotopicity was negligible. Therefore, besides NOESY experiments, the diastereotopicity criterion appeared to us a useful as rapid tool to discriminate regioisomers in this class of compounds.

The study of the *ortho* (2H)DOABO-CH_2O group in compound **2j** by 2 D ^1H – ^1H NOESY experiments made possible to differentiate the two oxazolidine environments, labelled arbitrarily **C** and **D**. The geminal anisochrony at C-6 Δδ (*c-t*) (ring **D**) was significant in comparison with C-4 (ring **C**) where no geminal anisochrony was found even at 500 MHz resolution. The same finding was valid for **2b** but not for **2h**. In

compounds **2b** and **2j**, by neglecting the absence of the geminal anisochrony at C-4, all *cis* oriented protons were more deshielded than the corresponding *trans* ones, except the reverse situation at C-6. Hence, we assigned ring **D** to be sterically closer to the anisotropy created by the *ortho* α-hydroxybenzyl group. The same discrimination in the case of **2h** might be envisaged cautiously.

For the simplest term **2b**, the assignment of a favoured configuration of the C-3'-chiral centre, associated to an appropriate conformation of the adjacent DOABO skeleton was attempted by means of *ab initio* molecular orbital calculation with full geometry optimisation (level RHF/6-31G*, *Scheme 4*).



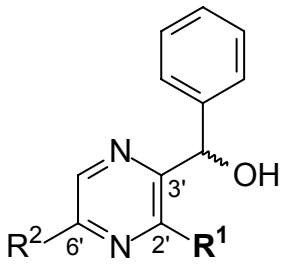
Scheme 4.

Three distinct conformers were found, **2b-VI**, **2b-VII** and **2b-VIII**. They were all orthogonal rotamers regarding the orientation of the pyrazine ring. The magnitudes of the total ΔE values (< 3 kJ/mol) were too small to predict the most stable spatial arrangement but each of them was in agreement with two remarks, supported by ^{1}H NMR data (*Table 2*):

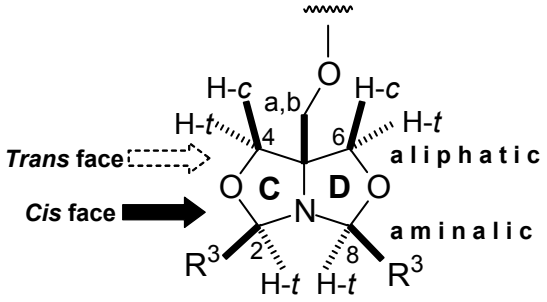
i) In conformers **2b-VI** and **2b-VIII**, the geometry of the two aromatic rings provided a "cage" of a more deshielding influence on both faces of the bicycle faces with respect to oxazolidine **C** against **D** *e.g.* H-4 *vs.* H-6 and H-2 *vs.* H-8. Very comparable NMR data applied for the *ortho* (2H)DOABO-CH_2O group in compound **2j** (*Table 2*). This stereochemistry (*P,M,R*) and (*P,M,S*) also facilitated the development of the expected intramolecular hydrogen bonds (benzyl)O-H…N-4'(pyrazine) and (benzyl)O-H…O-CH_2(DOABO).

ii) In conformer **2b-VII**, the chiral centre was, this time, closer to oxazolidine unit **D**. Hence, the geminal anisochrony at C-6 was noticeable; meanwhile almost no geminal anisochrony was exhibited by the methylene C-4. Moreover, the conformational chirality *P,P* of the DOABO skeleton appeared in relationship with the *R* configuration of the chiral centre since they together made possible two six membered chelate intramolecular hydrogen bonds.

Table 2. *Discriminating ^{1}H NMR assignments in the case of compounds* ***2b****,* ***2h*** *and* ***2j***



R1



2b: R^1 = (2H)DOABO-CH_2O, R^2 = H
2h: R^1 = (2Ph)DOABO-CH_2O, R^2 = H
2j: $R^1 = R^2$ = (2H)DOABO-CH_2O

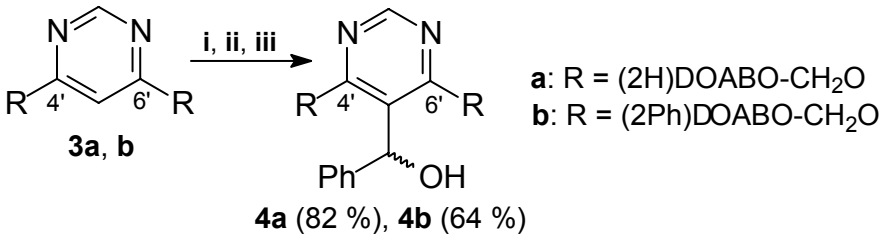
R^3 = H-*c*: (2H)DOABO-CH_2O
R^3 = Ph: (2Ph)DOABO-CH_2O

Compd. Position[a] Solvent	**δ (ppm) Positions** **Aminalic protons**		**Aliphatic protons**		**5-CH_aH_bO**	**Diastereotopicity as Δδ values (ppm) between labelled positions**	
	H-2-*c* H-2-*t* Δδ (*c*-*t*) Ring	H-8-*c* H-8-*t* Δδ (*c*-*t*) Ring	H-4-*c* H-4-*t* Δδ (*c*-*t*) Ring	H-6-*c* H-6-*t* Δδ (*c*-*t*) Ring	H-a H-b Δδ (a-b)	On *cis* face (2) – (8) (4) – (6) On *trans* face (2) – (8)	(4) – (6)
2b C-2'[a] $CDCl_3$	4.36 4.31 +0.05 **C**	4.29 4.25 +0.04 **D**	3.64 3.64 0.00 **C**	3.28 3.38 -0.10 **D**	4.26[b] 4.14[b] **0.12**	+0.07 +0.06	**+0.36** +0.26
2h C-2' $CDCl_3$	- 5.50 - **C**	- 5.41 - **D**	3.91 3.81 +0.10 **C**	3.46 3.32 +0.14 **D**	4.17 4.00 **0.17**	- +0.09	**+0.45** +0.49
2j C-2' $CDCl_3$	4.39 4.35 +0.04 **C**	4.34 4.30 +0.04 **D**	3.69 3.69 0.00 **C**	3.33 3.48 -0.15 **D**	4.23 4.15 **0.08**	+0.05 +0.05	**+0.36** +0.21
2j C-2' $[D_6]$ benzene	4.23 4.02 +0.21 **C**	4.16 3.98 +0.18 **D**	3.52 3.52 0.00 **C**	3.28 3.38 -0.10 **D**	3.99 3.89 **0.10**	+0.07 +0.04	**+0.24** +0.14
2j C-6' $CDCl_3$	4.46 4.40 +0.06	4.45 4.39 +0.06	3.83 3.83 0.00	3.82 3.82 0.00	4.27 4.23 0.04	+0.01 +0.01	+0.01 +0.01
2j C-6' $[D_6]$ benzene	4.28 4.05 +0.23	4.27 4.05 +0.22	3.67 3.59 +0.08	3.65 3.58 +0.07	4.08 3.98 0.10	+0.01 0.00	+0.02 +0.01

[a]Positions of the DOABO-CH_2O group connection to the pyrazine ring; [b]Assigned arbitrarily.

Functionalisation of α-(3,7-dioxa-r-1-azabicyclo[3.3.0]oct-c-5-ylmethoxy)-pyrimidines

The DoMG aptitude of the DOABO-CH_2O group substituting a diazine ring was also investigated in the pyrimidine series (*Scheme 5*).



i: 4 eq. LTMP / -78 °C / THF / 2 hrs.; **ii**: 4 eq. Ph-CH=O / -78 °C ↗ r.t. / 12 hrs.
iii: hydrolysis / r.t.

Scheme 5.

The behaviour of 4',6'-disubstituted compounds **3a**, **3b** was compared. Starting from **3a**, having, at -78 °C, the two (2H)DOABO units blocked as *meso* form (*P,M*) conformers (**III**, *Scheme 2*) [8], no reaction was observed at this temperature. A slow progress was detected by TLC monitoring only if the reaction mixture was gently warmed up to room temperature. The NMR spectrum of the crude reaction mixture indicated a content of about 66 % **4a** and 34 % **3a**. In the case of **3b**, whose (2Ph)DOABO units were still flipping at – 78 °C (R^1 = Ph, **II-III-IV**, *Scheme 2*) [8], the reaction reached completion at this temperature. The smaller yield (64 %) was due to the partial decomposition of the product **4b** during isolation by flash column chromatography. We rationalised these results as correlated with the different conformational behaviour of the DOABO systems in metallation conditions (**3a** *vs.* **3b**) and to the *in situ* trapping of the electrophile in the case of **3a**.

Functionalisation of α-(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-ylmethoxy)-α-chloro-diazines by cross-coupling reactions under Stille conditions

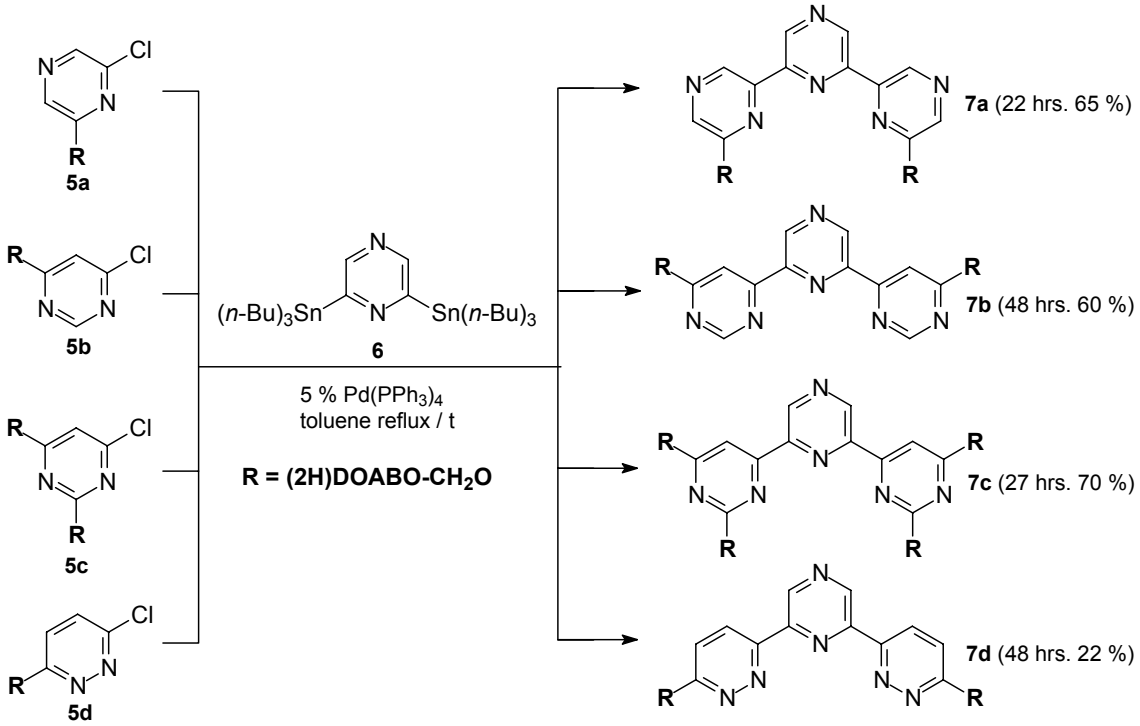
In this section, our preliminary results concerning the synthesis and coordination ability of four polyaza heterocycles possessing the (2H)DOABO-CH_2O group as peripheral sites is described (*Scheme 6*).

Thus, the 2,6-bis(tri-*n*-butylstannyl)pyrazine **6** was reacted under Stille conditions as double cross-coupling with the (2H)DOABO-CH_2O fragments α-substituting the α-chlorodiazines **5a-d**. Their syntheses, together with that of the starting **6** were previously reported by us [8, 14, 21, 22].

The target compounds were the 2,6-bis(diazinyl)pyrazines **7a-d**.

Very clean reactions accompanied the preparation of the compounds **7a**, **7c**. In turn, separation of **7b** and **7d** as pure analytical samples was more cumbersome than expected because they were contaminated by side products, homocoupling and hetero-homocoupling derivatives [23]. With pure **7a-d** in our hands, their coordination ability

against two transition metals, Zn^{2+} and Eu^{3+}, was examined. The first results of this exploratory study, carried out by means of UV spectroscopy, are collected in *Table 3*.



Scheme 6.

The measurements were performed in acetonitrile by using initial concentration of the compounds **7a-d** as 4×10^{-5} M. UV spectra were recorded for each 0.2 eq. of the salt added as 3×10^{-4} M solution, the final number of equivalents of the salt being 2.0 in all cases. Successive high dilutions were required by the very low solubility of our compounds in acetonitrile.

The UV data indicated that the terpyrazine **7a** was inert against both cations (entries 1-5). The compound **7b** was an efficient ligand for both Zn^{2+} and Eu^{3+}. The consecutive UV spectra showed a relevant bathochromic effect as $\Delta\lambda_{max.} = 26$ nm for Zn^{2+}(entry 7 *vs.* 6) and 16 nm for Eu^{3+} (entry 9 *vs.* 6) until 1 eq. of M^{n+} was added and the saturation was reached (entries 8, 10). Two isosbestic points were displayed in each case. Accordingly, two successive equilibriums including the free **7b** and its complex [**7b**]:[M^{n+}] (1:1 stoichiometry) were proposed.

The compound **7c**, possessing twice the number of (2H)DOABO-CH_2O groups, was a selective ligand (*Figure 1*). The UV monitoring of its behaviour in the presence of increased amounts of M^{n+}, indicated only with Zn^{2+} a strong bathochromic effect as $\Delta\lambda_{max.}$= 49 nm (entry 12 *vs.* 11) and two isosbestic points located at 236 and 318 nm. The same stoichiomery of the complex as above, [**7c**]:[Zn^{2+}] = 1:1 in equilibrium with the free **7c**, *via* an intermediate, was plausible. No modification of the UV spectrum was observed in the presence of Eu^{3+} (entries 14,15).

Table 3. *Relevant UV data about the coordination ability of compounds* ***7a-d***

Entry No.	Salt	Metal eq. M^{n+}	Absorptions as λ(nm) (log ε)	Isosbestic points λ(nm)
1 **7a**	**7a** only	0.0	242 (4.10); 323 (4.27)	
2	+ $Zn(BF_4)_2$	1.0	242 (4.10); 323 (4.25)	
3		2.0	242 (4.11); 324 (4.26)	
	Final stoichiometry **7a**: Zn^{2+} : none			
4	+ $EuCl_3 \times 6\ H_2O$	1.0	242 (4.11); 323 (4.25)	
5		2.0	241 (4.13); 322 (4.25)	
	Final stoichiometry **7a**: Eu^{3+} : none			
6 **7b**	**7b** only	0.0	209 (4.63); 246 (4.17); 293 (4.18)	
7	+ $Zn(BF_4)_2$	1.0	211 (4.65); 319 (4.23)	
8		2.0	211 (4.67); 319 (4.24)	
	Final stoichiometry **7b**: Zn^{2+} = 1:1			226 305
9	+ $EuCl_3 \times 6\ H_2O$	1.0	210 (4.72); 309 (4.22)	
10		2.0	211 (4.75); 310 (4.26)	
	Final stoichiometry **7b**: Eu^{3+} = 1:1			230 311
11 **7c**	**7c** only	0.0	203 (4.68); 250 (4.25); 298 (4.27)	
12	+ $Zn(BF_4)_2$	1.0	205 (4.66); 335 (4.33); 347 (4.33)	
13		2.0	205 (4.66); 335 (4.33); 345 (4.41)	
	Final stoichiometry **7c**: Zn^{2+} = 1:1			236 318
14	+ $EuCl_3 \times 6\ H_2O$	1.0	203 (4.68); 250 (4.25); 298 (4.24)	
15		2.0	203 (4.68); 250 (4.24); 298 (4.24)	-
	Final stoichiometry **7c**: Eu^{3+} : none			
16 **7d**	**7d** only	0.0	209 (4.48); 252 (4.39); 297 (4.24)	
17	+ $Zn(BF_4)_2$	1.0	212 (4.45); 234 (4.41); 257 (4.36)	
18		1.6	213 (4.46); 234 (4.40); 263 (4.36); 347 (4.04)	
19		2.0	213 (4.47); 234 (4.45); 265 (4.37); 347 (4.05)	263 280
	Final stoichiometry **7d**: Zn^{2+} = 1:1.5			334
20	+ $EuCl_3 \times 6\ H_2O$	1.0	209 (4.48); 252 (4.41); 285 (4.26)	
21		2.0	209 (4.48); 252 (4.41); 283 (4.26)	-
	Final stoichiometry **7d**: Eu^{3+} : none			

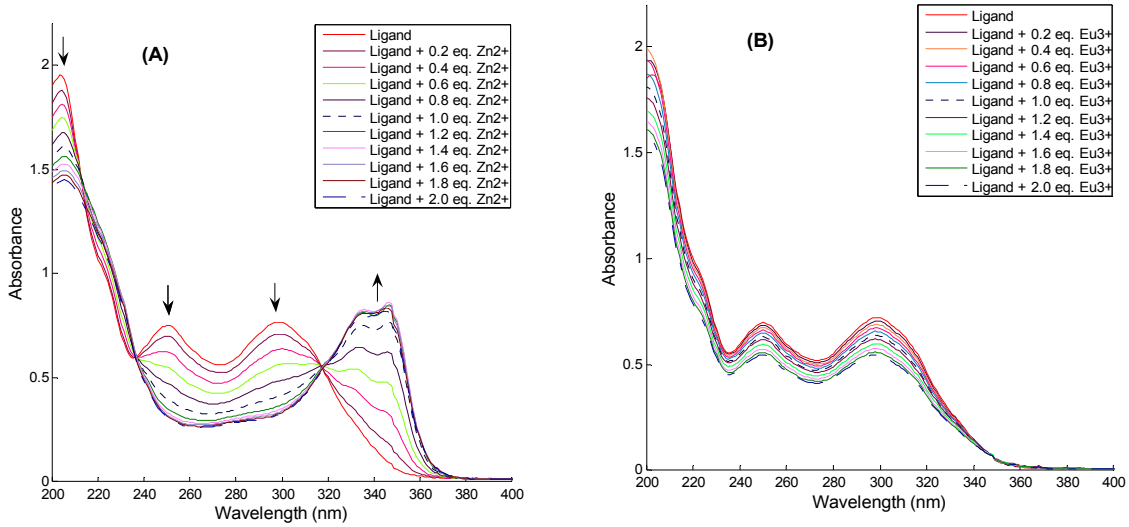


Figure 1. *UV spectra of compound* ***7c*** *in the presence of progressive increased concentration of* Zn^{2+} *as* $Zn(BF_4)_2$ ***(A)*** *and* Eu^{3+} *as* $EuCl_3 \times 6H_2O$ ***(B)***.

Finally, the bis(pyridazinyl)pyrazine **7d** was not only a selective ligand but the stoichiometry of its coordination with Zn^{2+} showed an increased chelating ability as [**7d**]:[Zn^{2+}] = 1:1.5 (entry 18). Consequently, besides the bathochromic effect as $\Delta\lambda_{max.}$ = 50 nm (entries 16-19), three isosbestic points were found, consistent with the occurrence of three successive equilibriums.

CONCLUSIONS

The 3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-ylmethoxydiazines can be highly functionalised on the diazine site *via* Directed *ortho*-Metalation reaction. The DOABO-CH_2O architecture acts as a DoMG since the 5-OCH_2 moiety creates CIPE. The later is is favoured by the orientation of the diazinyloxymethyl fragment as bisectional and coplanar *s-trans out* rotamer. Although the metallation conditions are very different from those previously reported for methoxydiazines, the results appear quite similar. By appropriate choice of the electrophile, elaborated chiral diarylmethanols are prepared. They exhibit stereospecific relationships between configurational and conformational chirality of the molecule creating internal six membered chelate hydrogen bonds. The DOABO-CH_2O group α-substituting diazines is also compatible with cross-coupling reactions providing aza analogous of terpyridine with selective coordinating ability against transition metals.

EXPERIMENTAL

Melting points are uncorrected; they were carried out on a ELECTROTHERMAL® 9100 instrument. Current NMR spectra were recorded on a Brucker® AM300 (300 MHz ^1H, 75 MHz ^{13}C). NMR analysis of compound **2j** was performed on a Brucker® DMX500 (500 MHz ^1H, 125 MHz ^{13}C). 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®). IR spectra were performed on a Perkin-Elmer® Paragom FT-IR spectrometer. Only relevant absorptions are listed [throughout in cm^{-1}: weak (w), medium (m) or (s) strong]. Mass spectra (MS) were recorded on an ATI-Unicam Automass® apparatus, fitted (or not) with a GC-mass coupling. UV spectra were measured on a VARIAN® CARY 100 SCANS instrument. UV spectra were compiled by using SPECFIT/32® and Varian Carry Winuv® programs. Microanalyses were performed on a Carlo Erba® CHNOS 1160 apparatus. All synthesis were performed under dry nitrogen atmosphere. THF was freshly distilled from Na/benzophenone prior to use.

The syntheses of the starting materials **1a-c, 3a, 3b, 5a-d** were described elsewhere [8, 21, 22]. Relevant ^1H NMR data of the compounds **2b**, **2h**, **2j** are collected in *Table 2*.

General procedure for the preparation of compounds 2a-j, 4a, 4b by Directed *ortho*-Metallation methodology

In 25-50 mL THF and and with vigorous stirring, 2,2,6,6-tetramethylpiperidine (HTMP) from (0.688 mL, 0.565 g 100 %, 0.576 g 98 %, 4 mmol) was injected. The solution was cooled at (-10)-(-15 ^{o}C) then *n*-BuLi (2.50 mL as 1.6 M solution in hexane, 4.00 mmol, optionally 1.54 mL as 2.6 M in hexane) was injected. The clear yellowish solution was stirred at (-10)-(-15 ^{o}C) for additional 15 min., then cooled at -78 ^{o}C. The starting DOABO-CH_2O substituting diazine (1.00 mmol) as THF solution (2-10 mL was introduced. Specific conditions to perform the reaction are presented in *Table 1* and *Scheme 3*, *5*). TLC (UV 254 nm) monitored all syntheses as follows: 0.2-0.3 mL from the reaction mixture were rapidly quenched with 2 mL 1:1 v/v mixture ethyl acetate (optionally ether): water. The sample was collected from the organic layer after vigorous stirring and separation. If no reaction occurred at – 78 ^{o}C or very slow evolution was observed, the reaction mixture was let to reach very gently the room temperature. The reactions were quenched according to one of the following variant:
A. In the case of deuteirated compound **2a** the reaction was quenched at -78 ^{o}C (0 ^{o}C in the case of **2i**) with 8 eq. of DCl as 20 % g/g solution in D_2O. Then it was let to reach the room temperature. The next work up was made according to variant **C**.
B. In the case of compounds **2c-g**, the reaction was quenched at -78 ^{o}C with 10 mL 1:1 v/v THF : EtOH. Then it was let to reach the room temperature. The next work up was made according to variant **C**.
C. For the rest of the compounds, the reaction was quenched at room temperature with 100 mL 1:1 v/v dichloromethane : water. After separation, the aqueous layer was extracted with dichloromethane (2×15 mL) then the combined organic solution was washed with water (× 25 mL) to neutrality. After drying on $MgSO_4$ and filtering, the dichloromethane solution was evaporated under vacuum to dryness. The obtained oily residue was analysed by NMR as crude reaction mixture. For deuteriated compounds **2a**, **2i** conclusions were provided at this stage. For the rest of the compounds, the mixtures were purified by column chromatography to yield the title compounds.

***Rac*-3-(α-hydroxybenzyl)-2-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (2b).** (79 %) Yellowish crystalline powder, mp 84 - 85 ^{o}C (pentane), (column chromatography, eluent AcOEt : ligroin 20:1 v/v). [Found: C, 61.79; H, 6.10; N, 12.45. $C_{17}H_{19}N_3O_4$ requires: C, 61.99; H, 5.81; N, 12.76 %]. R_f (95 % AcOEt/ligroin) 0.40. ν_{max} (film NaCl) 3600 (s), 2863 (w), 2356 (w), 1540 (w), 1419 (s), 1320 (w), 1176 (m), 1093 (w), 1042 (s), 925 (m), 700 (s) cm^{-1}. δ_H (300 MHz $CDCl_3$) *(hetero)aromatic*: 8.07 (1 H, d, *J* =2.8 Hz, H-5), 7.96 (1 H, d, *J* =2.8 Hz, H-6), 7.30 - 7.10 (5 H, m, Ph); 5.71 (1 H, d, *J*=4.7 Hz, C*H*OH), 5.05 (1 H, d, *J*=4.7 Hz, OH); δ_C (75 MHz $CDCl_3$) *(hetero)aromatic*: 156.8 (1 C, C-2), 146.2 (1 C, C-3), 141.9 (1 C, Cq., Ph), 140.3 (1 C, C-6), 135.5 (1 C, C-5), 128.9 (2 C, CH, Ph), 128.5 (1 C, CH, Ph), 127.6 (2 C, CH, Ph); *DOABO-CH_2O*: 88.4, 88.3 (2 C, C-2, -8), 74.32, 74.28 (2 C, C-4, -6), 71.9 (1 C, CHOH), 71.6 (1 C, C-5), 69.3 (1 C, 5-OCH_2) MS (EI, 70 eV); m/z (rel. int. %): (M^+-1) 328 (3), 312 (100), 281.9 (13), 254.8 (10), 211.7 (11), 186.8 (8), 128 (75), 98 (32).

***Rac*-3-(1-hydroxyeth-1-yl)-2-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (2c).** (41 %) White crystalline powder, mp 79 - 80 ^{o}C (Et_2O: ligroin 1:1 v/v),

(column chromatography, eluent AcOEt : ligroine 20:1 v/v). [Found: C, 53.94; H, 6.41; N, 15.39. $C_{12}H_{17}N_3O_4$ requires: C, 53.92; H, 6.41; N, 15.72 %]. R_f (95 % AcOEt/ligroin) 0.19. ν_{max} (film KBr) 3414(s), 2853 (s), 1544 (m), 1417 (s), 1342 (s), 1306 (s), 1271 (m), 1175 (s), 1136 (s), 1103 (s), 1064 (s), 1038 (s), 1004 (s), 944 (m), 916 (s), 854 (w), 765 (w), 678 (m), 617 (w) cm^{-1}. δ_H (300 MHz $CDCl_3$) *heteroaromatic*: 8.05 (1 H, d, *J* =2.3 Hz, H-5), 7.97 (1 H, d, *J* =2.3 Hz, H-6), 4.94 (1 H, q, *J*=6.4 Hz, C*H*OH), 3.83 (1H, bs, OH); *DOABO-CH_2O*: 4.49 (2 H, d, *J* =5.5 Hz, H-2, -8-*c*), 4.43 (2 H, d, *J* =5.5 Hz, H-2, -8-*t*), 4.40 (1 H, d, *J*=10.7 Hz, 5-OCH_aH_b), 4.35 (1 H, d, *J*=10.7 Hz, 5-OCH_aH_b), 3.85 (2 H, d, *J*=9.4 Hz, H-4, -6, -*c*), 3.82 (2 H, d, *J*=9.4 Hz, H-4, -6, -*t*), 1.42 (3 H, d, *J*=6.4 Hz, CH_3); δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 156.8 (1 C, C-2), 148.5 (1 C, C-3), 139.8 (1 C, C-6), 135.8 (1 C, C-5); *DOABO-CH_2O*: 88.6 (2 C, C-2, -8), 74.2 (2 C, C-4, -6), 72.0 (1 C, C-5), 69.0 (1 C, 5-OCH_2), 65.7 (1 C, CHOH), 22.6 (1 C, CH_3). MS (EI, 70 eV); m/z (rel. int. %): (M^+) 267 (6), 222 (12), 207 (15), 128 (18), 114 (100), 98 (20), 86 (10), 68 (21).

3-Ethyl-2-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (2d). (80 %) Yellowish crystalline powder, mp 31 - 35 °C (pentane), (column chromatography, eluent AcOEt : ligroin 20:1 v/v). [Found: C, 57.09; H, 7.15; N, 16.55. $C_{12}H_{17}N_3O_3$ requires: C, 57.36; H, 6.82; N, 16.72 %]. R_f (95 % AcOEt/ligroin) 0.40. ν_{max} (film KBr) 2976.1, 2858 (s), 1548 (s), 1418 (s), 1334 (s), 1184 (s), 1147 (s), 1099 (s), 1043 (s), 1020 (w), 1003 (s), 925 (s), 846 (m), 748 (m), 665 (m) cm^{-1}. δ_H (300 MHz $CDCl_3$) *heteroaromatic*: 7.98 (1 H, d, *J* =2.6 Hz, H-5), 7.83 (1 H, d, *J* =2.6 Hz, H-6); *DOABO-CH_2O*: 4.46 (2 H, d, *J* =5.5 Hz, H-2, -8-*c*), 4.42 (2 H, d, *J* =5.5 Hz, H-2, -8-*t*), 4.32 (2 H, s, 5-OCH_2), 3.83 (2 H, d, *J* =9.0 Hz, H-4, -6-*c*), 3.81 (2 H, d, *J*=9.0 Hz, H-4, -6-*t*), 2.73 (2 H, q, *J*=7.5 Hz, C$H_2$$CH_3$), 1.19 (3 H, t, *J*=7.5 Hz, CH_2CH_3); δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 158.0 (1 C, C-2), 149.1 (1 C, C-3), 138.2 (1 C, C-6), 136.6 (1 C, C-5); *DOABO-CH_2O*: 88.8 (2 C, C-2, -8), 74.4 (2 C, C-4, -6), 72.0 (1 C, C-5), 68.9 (1 C, 5-OCH_2), 26.1 (1 C, C$H_2$$CH_3$), 11.6 (1 C, CH_2CH_3). MS (CI); m/z (rel. int. %): (M^++14) 256 (5), 251 (<1), 235 (9), 221 (18), 141 (100), 128 (24), 115 (14).

3-Iodo-2-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (2e). (68 %) Yellow crystalline powder, mp 71 - 72 °C (pentane), (column chromatography, eluent AcOEt : pentane 4:1 v/v). [Found: C, 34.55; H, 3.45; N, 11.97. $C_{10}H_{12}N_3O_3I$ requires: C, 34.40; H, 3.46; N, 12.04 %]; R_f (75 % AcOEt/pentane) 0.55. ν_{max} (film KBr) 2980 (w), 2872 (s), 1510 (s), 1443 (m), 1404 (s), 1354 (s), 1344 (s), 1330 (s), 1161 (s), 1092 (s), 1041 (s), 1018 (m), 988 (m), 931 (m), 913 (m), 851 (m), 713 (m), 631 (w), 454 (m) cm^{-1}. δ_H (300 MHz $CDCl_3$) *heteroaromatic*: 7.94 (2 H, s, H-5, -6); *DOABO-CH_2O*: 4.56 (2 H, d, *J* =5.3 Hz, H-2, -8-*c*), 4.46 (2 H, d, *J* =5.3 Hz, H-2, -8-*t*), 4.36 (2 H, s, 5-OCH_2), 3.93 (2 H, d, *J* =9.0 Hz, H-4, -6-*c*), 3.89 (2 H, d, *J*=9.0 Hz, H-4, -6-*t*); δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 158.9 (1 C, C-2), 139.8 (1 C, C-6), 138.4 (1 C, C-5), 108.0 (1 C, C-3); *DOABO-CH_2O*: 88.9 (2 C, C-2, -8), 74.3 (2 C, C-4, -6), 71.8 (1 C, C-5), 70.4 (1 C, 5-OCH_2). MS (EI, 70 eV); m/z (rel. int. %): (M^+) 349 (4), 304 (5), 289 (15), 261 (5), 222 (40), 205 (5), 128 (14), 114 (100), 98 (28), 86 (10), 68 (30).

3-Tri-*n*-butylstannyl-2-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (2f). (73 %) Yellow oil (column chromatography, eluent ligroin : AcOEt 2:1). [Found: C, 51.29; H, 7.95; N, 8.25. $C_{22}H_{39}N_3O_3Sn$ requires: C, 51.58; H, 7.67; N, 8.20 %]. R_f (66 % ligroin/AcOEt) 0.60. ν_{max} (film NaCl) 2955 (s), 2928 (s), 2855 (s), 1559 (w), 1503 (m), 1463 (w), 1389 (s), 1342 (s), 1326 (s), 1294 (m), 1155 (s), 1100 (s), 1088 (s), 1047 (m), 1025 (m), 1002 (m), 931 (m), 865 (w), 843 (w), 749 (w), 693 (w), 601 (w) cm^{-1}. δ_H (300 MHz $CDCl_3$) *heteroaromatic*: 8.26 (1 H, d, *J* =2.6 Hz, H-5), 7.84 (1 H, dd, *J* =2.6, 5.1 Hz, H-6); *DOABO-CH_2O*: 4.47 (2 H, d, *J* =5.3 Hz, H-2, -8-*c*), 4.42 (2 H, d, *J* =5.3 Hz, H-2, -8-*t*), 4.31 (2 H, s, 5-OCH_2), 3.84 (4 H, dd as t, *J* =8.7 Hz, H-4, -6, -c, -*t*), 1.54 - 1.44 (6 H, m, $CH_2CH_2CH_2CH_3$), 1.32 - 1.20 (6 H, m, $CH_2CH_2CH_2CH_3$), 1.14 - 1.07 (6 H, m, $CH_2CH_2CH_2CH_3$), 0.82 (9 H, t, *J*=7.3 Hz, $CH_2CH_2CH_2CH_3$); δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 164.5 (1 C, C-3), 160.8 (1 C, C-2), 139.7 (1 C, C-6), 138.9 (1 C, C-5); *DOABO-CH_2O*: 88.6 (2 C, C-2, -8), 75.0 (2 C, C-4, -6), 71.9 (1 C, C-5), 69.6 (1 C, 5-OCH_2), 29.4 (3 C, $CH_2CH_2CH_2CH_3$), 27.7 (3 C, $CH_2CH_2CH_2CH_3$), 14.1 (3 C, $CH_2CH_2CH_2CH_3$), 10.4 (3 C, $CH_2CH_2CH_2CH_3$). MS (EI, 70 eV); m/z (rel. int. %): (M^+) 512 (<1), 456 (M^+-C_4H_9, 100), 329 (5), 229 (5), 215 (16), 177 (15), 128 (36), 114 (30), 98 (75), 86 (<5), 68 (35).

2-[(3,7-Dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-3-thiophenylpyrazine (2g). (73 %) Yellow crystalline powder, mp 102 - 103 °C (ligroin), (column chromatography, eluent AcOEt : ligroin 20:1 v/v); [Found: C, 57.91; H, 5.24; N, 12.64. $C_{16}H_{17}N_3SO_3$ requires: C, 58.00; H, 5.17; N, 12.68 %]. R_f (95 % AcOEt/ligroin) 0.70. ν_{max} (film KBr) 2871 (m), 1517 (s), 1476 (m), 1440 (w), 1409 (s), 1360 (s), 1175 (s), 1130 (w), 1105 (s), 1059 (m), 1046 (s), 1022 (m), 932 (s), 916 (s), 897 (w), 750 (s), 693 (m), 681 (w), 457 (w). δ_H (300 MHz $CDCl_3$) *(hetero)aromatic*: 7.85 (1 H, d, *J* =2.6 Hz, H-5), 7.74 (1 H, d, *J* =2.6 Hz, H-6), 7.53-7.50 (2 H, m, Ph), 7.40-7.39 (3 H, m, Ph); *DOABO-CH_2O*: 4.57 (2 H, d, *J* =5.5 Hz, H-2, -8-*c*), 4.47 (2 H, d, *J* =5.5 Hz, H-2, -8-*t*), 4.43 (2 H, s, 5-OCH_2), 3.92 (2 H, d, *J* =8.9 Hz, H-4, -6-*c*), 3.87 (2 H, d, *J*=8.9 Hz, H-4, -6-*t*); δ_C (75 MHz $CDCl_3$) *(hetero)aromatic*: 155.8 (1 C, C-2), 146.8 (1 C, C-3), 137.1 (1 C, C-6), 136.3 (1 C, C-5), 135.5 (2 C, CH, Ph), 129.64 (2 C, CH, Ph), 129.55 (1 C, CH, Ph), 128.7 (1 C, Cq., Ph); *DOABO-CH_2O*: 88.9 (2 C, C-2, -8), 74.4 (2 C, C-4, -6), 71.9 (1 C, C-5), 69.5 (1 C, 5-OCH_2). MS (EI, 70 eV); m/z (rel. int. %): (M^+) 331 (15), 222 (20), 203 (9), 187 (5), 160 (7), 128 (100), 121 (5), 114 (33), 98 (20), 86 (7), 77 (10), 68 (28).

***Rac*-3-(α-hydroxybenzyl)-2-[(*c*-2,*c*-8-diphenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (2h).** (98 %) Yellow crystalline powder, mp 88 - 90 °C (column chromatography, eluent ligroin : AcOEt 2:1 v/v). [Found: C, 72.47; H, 5.52; N, 8.81. $C_{29}H_{27}N_3O_4$ requires: C, 72.33; H, 5.65; N, 8.73 %]. R_f (67 % ligroin/AcOEt) 0.60. ν_{max} (film KBr) 3401 (m), 2875 (m), 1547 (s), 1423 (m), 1211 (m), 831 (s), 739 (s), 696 (s), 634 (w), 534 (w) cm^{-1}. δ_H (300 MHz $CDCl_3$) *(hetero)aromatic*: 8.03 (1 H, d, *J*=2.4 Hz, H-5), 7.92 (1 H, d, *J*=2.4 Hz, H-6), 7.43 - 7.38 (4 H, m, Ph), 7.24 - 7.15 (9 H, m, Ph), 7.10 - 7.08 (2 H, m, Ph), 5.55 (1 H, d, *J*=3.8 Hz, C*H*-OH), 4.99 (1 H, d, *J*=3.8 Hz, OH); δ_C (75 MHz $CDCl_3$) *(hetero)aromatic*: 156.7 (1 C, C-2), 145.8 (1 C, C-3), 141.8 (1 C, Cq., Ph), 140.4 (1 C, C-6), 139.6 (1 C, Cq., Ph), 139.4 (1 C, Cq., Ph), 135.2 (1 C, C-5), 129.1 (1 C, CH, Ph), 129.0 (2 C, CH, Ph), 128.9 (1 C, CH, Ph), 128.8 (4 C, CH, Ph), 128.6 (1 C, CH, Ph), 127.7 (2 C, CH, Ph), 127.6 (2 C, CH, Ph), 127.5 (2

C, CH, Ph); *DOABO-CH_2O*: 98.0, 97.2 (2 C, C-2, -8), 73.7 (1 C, C-5), 73.3, 72.9 (2 C, C-4, -6), 71.8 (1 C, CHOH); 70.5 (1 C, 5-OCH_2). MS (EI, 70 eV); m/z (rel. int. %): (M^+-1) 480 (<1), 464 (4), 376 (22), 358 (34), 281 (70), 174 (100), 156 (11).

***Rac*-3-(α-hydroxybenzyl)-2,6-bis[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (2j).** (61 %) White crystalline powder, mp 172 - 174 °C (Et_2O : pentane 1:1), (column chromatography, eluent ligroin : acetone 1:1 v/v). [Found: C, 58.80; H, 5.69; N, 11.86. $C_{23}H_{28}N_4O_7$ requires: C, 58.47; H, 5.97; N, 11.86 %]. R_f (50 % ligroin/acetone) 0.75. ν_{max} (film NaCl) 3600 (s), 2852 (s), 1537 (m), 1452 (s), 1413 (s), 1315 (s), 1142 (m), 1039 (m), 925 (m) cm^{-1}. δ_H (300 MHz $CDCl_3$) *(hetero)aromatic*: 7.40 (1 H, s, H-5), 7.28 - 7.16 (5 H, m, Ph); 5.69 (1 H, bs, C*H*OH), 4.81 (1 H, bs, OH); δ_C (75 MHz $CDCl_3$) *(hetero)aromatic*: 158.1 (1 C, C-6), 154.3 (1 C, C-2), 142.7 (1 C, Cq., Ph), 136.4 (1 C, C-3), 128.8 (2 C, CH, Ph), 128.3 (1 C, CH, Ph), 127.3 (2 C, CH, Ph), 123.2 (1 C, C-5); 71.5 (1 C, CHOH); *DOABO-CH_2O linked at C-2*: 88.3, 88.2 (2 C, C-2, -8), 74.3 (2 C, C-4, -6), 71.5 (1 C, C-5), 69.3 (1 C, 5-O*C*H_2); *DOABO-CH_2O linked at C-6*: 88.4 (2 C, C-2, -8), 74.4 (2 C, C-4, -6), 71.8 (1 C, C-5), 69.7 (1 C, 5-OCH_2). δ_H (500 MHz [D_6]benzene) *(hetero)aromatic*: 7.62 (1 H, s, H-5), 7.35 (2 H, d, *J*=7.2 Hz, *ortho*-Ph), 7.09 (2 H, m, *meta*-Ph), 7.02 (1 H, m, *para*-Ph); 5.86 (1 H, d, *J*=7.2 Hz, C*H*OH), 4.99 (1 H, d, *J*=7.2 Hz, OH); δ_C (125 MHz [D_6]benzene) *(hetero)aromatic*: 158.0 (1 C, C-6), 154.3 (1 C, C-2), 143.5 (1 C, Cq., Ph), 137.1 (1 C, C-3), 128.6 (2 C, CH, *meta*-Ph), 127.9 (1 C, CH, *para*-Ph), 127.4 (2 C, CH, *ortho*-Ph), 122.6 (1 C, C-5); 71.6 (1 C, CHOH); *DOABO-CH_2O linked at C-2*: 87.88 (1 C, C-8), 87.82 (1 C, C-2), 73.96 (1 C, C-6), 73.90 (1 C, C-4), 71.4 (1 C, C-5), 69.3 (1 C, 5-OCH_2); *DOABO-CH_2O linked at C-6*: 88.0 (2 C, C-2, -8), 74.00 (1 C, C-4), 73.96 (1 C, C-6), 71.6 (1 C, C-5), 69.7 (1 C, 5-OCH_2). MS (EI, 70 eV); m/z (rel. int. %): (M^+) 472 (<1), 344 (3), 212 (4), 128 (100), 98 (7).

***Rac*-5-(α-hydroxybenzyl)-4,6-bis[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrimidine (4a).** (82 % taking into account the recovered starting material **3a**; total conversion: 71 %). White crystalline powder, mp 121 - 122 °C (Et_2O : pentane 1:1 v/v), (column chromatography, eluent acetone). [Found: C, 58.71; H, 6.02; N, 11.87. $C_{23}H_{28}N_4O_7$ requires: C, 58.47; H, 5.97; N, 11.86 %]. R_f (100 % acetone) 0.80. ν_{max} (film NaCl) 3431 (s), 2925 (m), 2857 (s), 1574 (s), 1442 (m), 1300 (w), 1101 (s), 1011 (w), 1023 (w), 925 (w) cm^{-1}. δ_H (300 MHz $CDCl_3$) *(hetero)aromatic*: 8.34 (1 H, s, H-2), 7.30 - 7.23 (5 H, m, Ph); 6.05 (1 H, s, C*H*OH), 4.20 (1 H, bs, OH); *DOABO-CH_2O*: 4.42 (4 H, d, *J* =5.3 Hz, H-2, -8-*c*), 4.41 (2 H, d, *J*=10.9 Hz, 5-OCH_aH_b), 4.35 (2 H, d, *J*=10.9 Hz, 5-OCH_aH_b), 4.35 (2 H, d, *J* =5.3 Hz, H-2-*t*), 4.34 (2 H, d, *J* =5.3 Hz, H-8-*t*), 3.70 (2 H, d, *J*=9.0 Hz, H-4-*c*), 3.66 (2H, d *J*=9.0 Hz, H-4-*t*), 3.65 (2 H, d *J*=9.4 Hz, H-6-*t*), 3.61 (2 H, d, *J*=9.0 Hz, H-6-*c*); δ_C (75 MHz $CDCl_3$) *(hetero)aromatic*: 167.4 (2 C, C-4, -6), 156.4 (1 C, C-2), 143.2 (1 C, Cq., Ph), 128.8 (2 C, CH, Ph), 127.7 (1 C, CH, Ph), 125.5 (2 C, CH, Ph), 107.4 (1 C, C-5); *DOABO-CH_2O*: 88.34, 88.26 (2 C, C-2, -8), 73.8, 73.7 (2 C, C-4, -6), 71.9 (2 C, C-5), 69.5 (2 C, 5-OCH_2); 67.0 (1 C, CHOH). MS (EI, 70 eV); m/z (rel. int. %): (M^+-1) 471 (<1), 455 (50), 328 (8), 128 (100), 98 (5).

***Rac*-5-(α-hydroxybenzyl)-4,6-bis[(*c*-2-*c*-8-diphenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0] oct-*c*-5-yl)methoxy]-pyrimidine (4b).** (64 %) White crystalline powder mp 165 - 167 °C (flash column chromatography, eluent ligroin : AcOEt 3.5:1 v/v). [Found: C, 72.50; H, 5.90; N, 7.45. $C_{47}H_{44}N_4O_7$ requires: C, 72.66; H, 5.71; N, 7.21 %]. R_f (77 % ligroin/AcOEt) 0.51. ν_{max} (film KBr) 3580 (w), 2866 (m), 1578 (s), 1442 (s), 1304 (m), 1106 (s), 1064 (m), 945 (w), 916 (m), 718 (w), 699 (m) cm^{-1}. δ_H (300 MHz $CDCl_3$) *heteroaromatic*: 8.31 (1 H, s, H-2), 7.51 - 7.49 (8 H, m, Ph), 7.34 - 7.30 (15 H, m, Ph), 7.18 (2 H, d, *J*=7.2 Hz, Ph), 5.93 (1 H, d, *J*=10.8 Hz, C*H*OH), 3.08 (1 H, d, *J*=10.8 Hz, OH); *DOABO-CH_2O*: 5.57, (2 H, H-8-*t*), 5.55 (2 H, s, H-2-*t*), 4.31 (2 H, d, *J*=10.4 Hz, 5-OCH_aH$_b$), 4.25 (2 H, d, *J*=10.4 Hz, 5-OCH$_a$$H_b$), 3.92 (2 H, d, *J*=8.9 Hz, H-6-*c*), 3.81 (2 H, d, *J*=8.9 Hz, H-6-*t*), 3.73 (2 H, d, *J*=9.2 Hz, H-4-*c*), 3.69 (2 H, d, *J*=9.2 Hz, H-4-*t*); δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 167.3 (2 C, C-4, -6), 156.5 (1 C, C-2), 143.2 (1 C, Cq., Ph), 139.34, 139.3 (4 C, Cq., Ph), 129.1, 129.0, 128.8, 127.7, 127.6, 125.5, 125.2 (25 C, CH, Ph), 107.2 (1 C, C-5); *DOABO-CH_2O*: 97.6, 97.59 (4 C, C-2, -8), 73.3, 73.2 (4 C, C-4, -6), 73.0 (2 C, C-5), 71.0 (2 C, 5-OCH_2), 66.7 (1 C, CHOH). MS (FAB^+); m/z (rel. int. %): (M^++1) 778 (100), 760 (25).

General procedure for the preparation of compounds 7a-d by cross-coupling under Stille conditions

In dry toluene (25 mL) and under dry nitrogen atmosphere, 0.493 g (0.75 mmol) 2,6-bis(tri-*n*-butylstannyl)pyrazine **6** and 0.405 g (1.575 mmol, 2.10 eq.) chlorodiazine **5a**, **5b**, **5d** (0.630 g, 1.575 mmol, 2.10 eq. in the case of **5c**) were dissolved with stirring. $Pd(PPh_3)_4$ 0.091 g (0.079 mmol, 5 % with respect to chlorodiazine **5a-d**) was rapidly added. The solution was heated at reflux for 22 – 48 hrs. untill the TLC monitoring (UV 254 nm) indicated the starting materials in traces only (compounds **7a-c**) or no more significant evolution of the reaction (in the case of compound **7d**): **6** (ligroin : AcOEt 50:1 v/v), **5a** (ligroin AcOEt 2:1 v/v), **5b** and **5d** (ligroin : acetone 3:1 v/v), **5c** (ligroin : acetone 2:1 v/v). A second elution system was used to detect the desired products **7a-d** as shown below in each case. During all syntheses, Pd metal precipitated abundantly. The reaction mixture was filtered hot (100 °C) and the solids were washed (x 50 mL) several times with hot EtOH. The combined organic filtrate was evaporated under vacuum and the solid residue was directly crystalised from an appropriate solvent or subjected to column chromatography to yield the title compounds **7a-d**.

2,6-Bis{6'-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazin-2'-yl}-pyrazine (7a). (65 %) Grey crystalline powder, mp 218 °C (dec., EtOH). [Found: C, 55.25; H, 5.15; N, 21.55. $C_{24}H_{26}N_8O_6$ requires: C, 55.17; H, 5.02; N, 21.45 %]. R_f (95 % dichloromethane/ethanol) 0.52. ν_{max} (film KBr) 3401 (m), 2875 (m), 1539 (s), 1402 (s), 1369 (m), 1215 (s), 939 (s), 898 (w), 782 (m), 730 (w) cm^{-1}. δ_H (300 MHz CF_3CD_2OD) *heteroaromatic*: 9.28 (2 H, s, H-3, -5), 9.04 (2 H, s, H-3'), 8.05 (2 H, s, H-5'); *DOABO-CH_2O*: 4.40 (4 H, s, 5-OCH_2), 4.36 (4 H, d, *J*=6.2 Hz, H-2, -8-*c*), 4.33 (4 H, d, *J*=6.2 Hz, H-2, -8-*t*), 3.80 (8 H, s, H-4, -6, -*c*, -*t*); δ_C (75 MHz CF_3CD_2OD) *heteroaromatic*: 157.0 (2 C, C-6'), 146.4 (2 C, C-2'), 143.5 (2 C, C-2, -6), 139.3 (2 C, C-3, -5), 133.1 (2 C, C-5'), 131.2 (2 C, C-3'); *DOABO-CH_2O*: 85.1 (4 C, C-2, -8), 71.2 (4 C, C-4, -6), 69.1 (2 C, C-5), 65.1 (2 C, 5-OCH_2). MS (FAB^+); m/z (rel. int. %): (M^++1) 523 (14), 289 (100), 235 (30), 165 (48).

2,6-Bis{6'-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrimidin-4'-yl}-pyrazine (7b). (60 %) Yellowish crystalline powder, mp 222 - 225 °C (flash column chromatography, AcOEt 100 %). [Found: C, 55.10; H, 5.10; N, 21.50. $C_{24}H_{26}N_8O_6$ requires: C, 55.17; H, 5.02; N, 21.45 %]; R_f (100 % AcOEt) 0.42. ν_{max} (film KBr) 3468 (w), 2864 (m), 1598 (s), 1538 (s), 1427 (s), 1346 (m), 1316 (w), 1096 (s), 753 (m), 680 (w), 569 (w) cm^{-1}. δ_H (300 MHz $CDCl_3$) *heteroaromatic*: 9.73 (2 H, s, H-3, -5), 8.90 (2 H, s, H-2'), 7.88 (2 H, s, H-5'); *DOABO-CH_2O*: 4.57 (4 H, d, *J*=5.5 Hz, H-2, -8-*c*), 4.55 (4 H, s, 5-OCH_2), 4.50 (4 H, d, *J*=5.5 Hz, H-2, -8-*t*), 3.93 (8 H, s, H-4, -6, -*c*, -*t*); δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 170.6 (2 C, C-6'), 162.1 (2 C, C-4'), 158.8 (2 C, C-2'), 148.1 (2 C, C-2, -6), 145.2 (2 C, C-3, -5), 105.4 (2 C, C-5'); *DOABO-CH_2O*: 88.6 (4 C, C-2, -8), 74.3 (4 C, C-4, -6), 72.0 (2 C, C-5), 69.3 (2 C, 5-OCH_2). MS (FAB^+); m/z (rel. int. %): (M^++1) 523 (10), 283 (<1), 136 (35), 128 (100).

2,6-Bis{2',6'-bis[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrimidin-4'-yl}-pyrazine (7c). (70 %) Grey crystalline powder, mp 190 °C (dec.). [Found: C, 53.35; H, 5.37; N, 17.50. $C_{36}H_{44}N_{10}O_{12}$ requires: C, 53.46; H, 5.48; N, 17.32 %]. R_f (50 % acetone/dichloromethane) 0.56. ν_{max} (film KBr) 3477 (m), 2954 (m), 2867 (s), 1572 (s), 1440 (w), 1407 (m), 1329 (s), 1118 (m), 1043 (m), 929 (m), 750 (m), 676 (w) cm^{-1}. δ_H (300 MHz $CDCl_3$) *heteroaromatic*: 9.65 (2 H, s, H-3, -5), 7.54 (2 H, s, H-5'); *DOABO-CH_2O*: 4.56 (8 H, d, *J*=5.3 Hz, H-2, -8-*c*), 4.51 (8 H, s, 5-OCH_2), 4.49 (4 H, d, *J*=5.3 Hz, H-2, -8-*c*), 4.47 (4 H, d, *J*=5.3 Hz, H-2, -8-*t*), 3.98 (8 H, d, *J*=9.6 Hz, H-4, -6-*c*), 3.89 (8 H, d, *J*=9.6 Hz, H-4, -6-*t*); δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 172.6 (2 C, C-6'), 165.2 (2 C, C-2'), 163.6 (2 C, C-4'), 147.9 (2 C, C-2, -6), 145.2 (2 C, C-3, -5), 100.0 (2 C, C-5'); *DOABO-CH_2O*: 88.6, 88.4 (8 C, C-2, -8); 74.7, 74.3 (8 C, C-4, -6); 71.9, 71.8 (4 C, C-5); 71.0, 69.6 (4 C, 5-O*C*H_2). MS (FAB^+); m/z (rel. int. %): (M^++1) 809.8 (93), 459.9 (53), 391 (100).

2,6-Bis{6'-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyridazin-3'-yl}-pyrazine (7d). (22 %).Yellow crystalline powder, mp 190 °C (dec.) (flash column chromatography, eluent ligroin : acetone : ethanol 2:1:1 v/v/v). [Found: C, 55.32; H, 4.97; N, 21.30. $C_{24}H_{26}N_8O_6$ requires: C, 55.17; H, 5.02; N, 21.45%]. R_f (50/25/25 ligroin/acetone/ethanol) 0.48. ν_{max} (film KBr) 3400 (m), 2871 (m), 1593 (m), 1417 (s), 1378 (w), 1310 (s), 1134 (m), 1098 (m), 930 (m), 860 (w), 753 (w) cm^{-1}. δ_H (300 MHz $CDCl_3$) *heteroaromatic*: 9.85 (2 H, s, H-3, -5), 8.54 (2 H, d, *J*=9.2 Hz, H-4'), 7.21 (2 H, d, *J*=9.2 Hz, H-5'); *DOABO-CH_2O*: 4.73 (4 H, s, 5-OCH_2), 4.59 (4 H, d, *J*=5.7 Hz, H-2, -8-*c*), 4.53 (4 H, d, *J*=5.7 Hz, H-2, -8-*t*), 3.96 (8 H, s, H-4, -6, -*c*, -*t*); δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 165.4 (2 C, C-6'), 153.9 (2 C, C-3'), 147.6 (2 C, C-2, -6), 143.3 (2 C, C-3, -5), 128.3 (2 C, C-4'), 118.4 (2 C, C-5'); *DOABO-CH_2O*: 88.8 (4 C, C-2, -8), 74.4 (4 C, C-4, -6), 72.0 (2 C, C-5), 70.4 (2 C, 5-OCH_2). MS (FAB^+); m/z (rel. int. %): ($M+Na^+$) 545 (2), (M^++1) 523 (39), 283 (100), 128 (55), 95 (20).

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