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Tetrahedron 62 (2006) 7339–7354
Tetrahedron

α-(3,7-Dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-ylmethoxy)-diazines. Part 2: Functionalisation via directed *ortho*-metallation and cross-coupling reactions

Camelia Berghian,[a,b] Eric Condamine,[b] Nelly Plé,[b] Alain Turck,[b] Ioan Silaghi-Dumitrescu,[c] Carmen Maiereanu[a,b] and Mircea Darabantu[a,b,*]

[a]*Department of Organic Chemistry, 'Babes-Bolyai' University, 11 Aranyi Jànos Str., RO-400028 Cluj-Napoca, Romania*
[b]*Institut de Recherche en Chimie Organique Fine (I.R.C.O.F.), Université de Rouen, BP 08, F-76131 Mont Saint-Aignan, France*
[c]*Department of Inorganic Chemistry, 'Babes-Bolyai' University, 11 Aranyi Jànos Str., RO-400028 Cluj-Napoca, Romania*

Received 13 March 2006; revised 1 May 2006; accepted 11 May 2006
Available online 8 June 2006

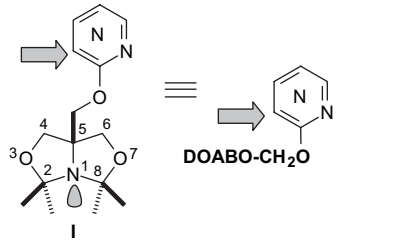
Abstract—The functionalisation of the title compounds via regioselective Directed *ortho*-Metallation (DoM) and cross-coupling reactions is studied. The compatibility of the 3,7-DiOxa-*r*-1-AzaBicyclo[3.3.0]Oct-*c*-5-ylmethoxy system (DOABO–CH_2O) to typical reaction conditions is established. Its role as Directed *ortho*-Metallation Group (DoMG) is examined, including competition with classical DoMGs, chlorine and methoxy. The chelating ability of some functionalised terms such as DOABO–CH_2O substituting chiral diarylmethanols and polyaza analogues of 2,6-terpyridine is discussed as intramolecular steric relationships determining configuration and aptitude to bind selectively transition metals, respectively.

1. Introduction

Advances in the field of Directed *ortho*-Metallation with organolithium reagents of azines and diazines have been recently reviewed.[1,2] This methodology, the so-called DoM reaction, allows access to functionalised π-deficient systems in clean, rapid, selective and high yielding transformations. In this context, of 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 is 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.

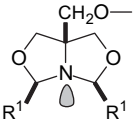
Hence, the objective of the present report is based on our previous acquired knowledge about the synthesis and stereochemistry of a new series of α-(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-ylmethoxy)-diazines **I** (Scheme 1),[8–11] aiming at their further functionalisation via DoM reactions.



I

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

Abbreviations:



R¹ = H: (2H)DOABO-CH_2O
R¹ = Ph: (2Ph)DOABO-CH_2O

Scheme 1.

We have recently reported the synthesis by double cross-coupling under Stille conditions[12,13] of a new class of polyaza analogues of 2,6-terpyridine possessing the

Keywords: Diazines; Oxazolidines; Metallation; Cross-coupling; NMR; Chirality.
* Corresponding author. Tel.: +40 264 59 38 33; fax: +40 264 59 08 18; e-mail addresses: darabantu@cluj.astral.ro; darab@chem.ubbcluj.ro

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doi:10.1016/j.tet.2006.05.032

2,6-disubstituted pyrazine as a central unit linked to various heteroaromatic systems as subunits.[14] Our ongoing efforts to prepare new aza polydentate 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 has been reported so far.

2. Results and discussion

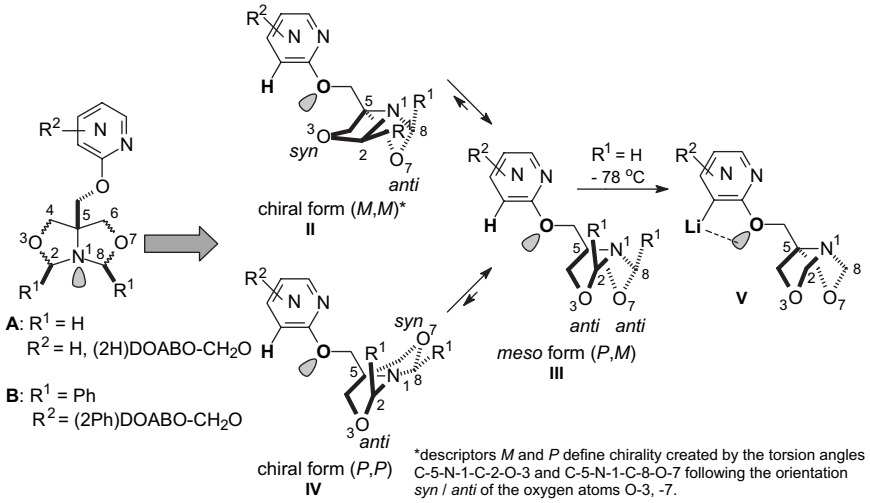
2.1. Functionalisation via directed *ortho*-metallation of α-(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-ylmethoxy)-diazines

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).

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

2.1.1. 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).

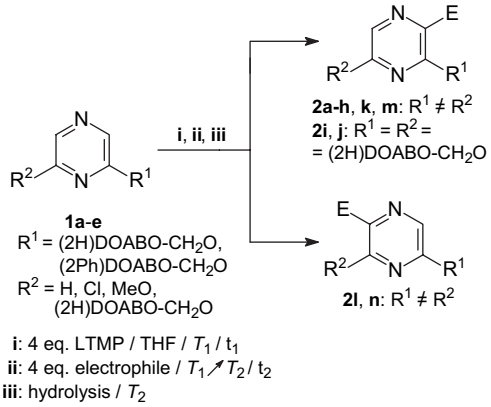
Treatment of **1a** with 1.1 equiv of LTMP (lithium-2,2,6,6,-tetramethylpiperidide) at −78 °C for 60 min as for 2-methoxypyrazine[17,18] followed by quenching with 20% DCl/D_2O (at −78 °C) afforded the starting material in 99% yield. Deuteriation was 84% at C-3′ if 2.1 equiv of LTMP were used. The best result, 98% deuterium incorporation in the crude product, was obtained with 4 equiv of LTMP (compound **2a**, Table 1). This excess could be explained by the high chelating ability at −78 °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).



Scheme 2.

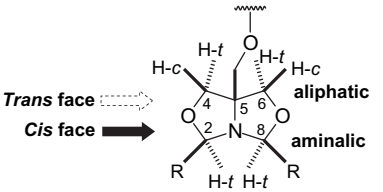
As seen previously,[8] the heterofacial cis fused double oxazolidine part of the compounds **A** (R^1=H) was flipping at room temperature (conformers **II**–**III**–**IV**) in an overall enantiomeric inversion. It became rigid on a large domain of low temperatures (273–173 K) with the potential chelating sites O-3, N-1 and O-7 orientated as a frozen nonchiral conformation **III**. In contrast, the *all-cis* C-2, C-5 and C-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 a 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 crystallographically-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', CIPE,[15,16] e.g., conformer **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



Scheme 3.

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



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

Entry	Starting material	R^1 / R^2	E	Products: Compd (%)	Products: Compd (%)	Conditions: t_1 (h)	T_1 (°C)	T_2 (°C)	t_2 (h)
1	**1a**	(2H)DOABO–CH_2O / H	D[a]	**2a** (98)[b]	—	1	−78	−78	—
			Ph–CH–OH	**2b** (79)	—	1	−78	rt	12
			Me–CH–OH	**2c** (41)	—	1	−78	−78	4.5
			Et[c]	**2d** (80)	—	1	−78	−78	1.5
			I	**2e** (68)	—	1	−78	−78	2
			Sn(*n*-Bu)$_3$[d]	**2f** (73)	—	1	−78	−78	2
			SPh[d]	**2g** (73)	—	1	−78	−78	2
2	**1b**	(2Ph)DOABO–CH_2O / H	Ph–CH–OH	**2h** (98)	—	1	−78	rt	12
3	**1c**	(2H)DOABO–CH_2O	D[a]	**2i** (71)[e]		0.5	0	—	—
		(2H)DOABO–CH_2O	Ph–CH–OH	**2j** (61)		2	−78	−50	10
4	**1d**	(2H)DOABO–CH_2O / Cl	Ph–CH–OH	**2k** (52) [67][f]	**2l** (26) [33]	1	−78	rt	12
5	**1e**	(2H)DOABO–CH_2O / MeO	Ph–CH–OH	**2m** (29) [41]	**2n** (41) [59]	1	−78	rt	12

[a] DCl 20% g/g (8 equiv) in D_2O solution were used.
[b] In round brackets, yields as isolated compounds after flash column chromatography; for **2a**, as deuterium incorporation in quantitatively isolated crude product (^{1}H NMR monitoring); for **2k–n**, as partial yields.
[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] Incorporation (50%) of deuterium with respect to the starting **1c**.
[f] In square brackets: contents according to the ^{1}H NMR spectra of the crude reaction mixtures.

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).

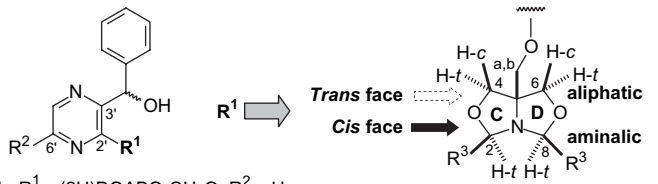
Products **2b**, **2c**, **2h**, **2j**, **2k** and **2m** have on *ortho* vicinity of a stereogenic centre versus the heterofacial DOABO skeleton. The ^{1}H NMR spectrum of **2b** showed the expected diastereotopic positions of the bicycle: C-2 versus C-8 and C-4 versus C-6. However, in the ^{1}H NMR spectrum of **2c** these relevant positions appeared almost undifferentiated. For this reason, we considered it of interest to continue our study by using mainly benzaldehyde as the electrophile and the structure of the chiral diarylmethanols of type **2b** closer to the DOABO–CH_2O group intimate stereochemistry.[8]

The deuteriation of compound **1c**, possessing twice the (2H)DOABO–CH_2O environment (Table 1, entry 3) yielded **2i** as product, but fast decomposition of the reaction mixture was observed. Consequently, no reaction of the metallated compound **1c** occurred at 0 °C with benzaldehyde. In turn, at −78 °C, 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 equiv of LTMP were necessary (vs 2.2 equiv LTMP reported for 2,6-dimethoxypyrazine), we considered that these conditions are also associated with 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).

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 ^{1}H–^{13}C heteronuclear correlations (HSQC[21,22] and HMBC[23,24] 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 (2D ^{1}H–^{1}H NOESY[25,26] 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 ^{1}H magnetic nonequivalence as diastereotopicity (Δδ values) between the homofacial aminalic (or aliphatic)

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



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 of DOABO–CH_2O linkage	Solvent	δ (ppm)					Diastereotopicity as Δδ values (ppm) between labelled positions	
			Positions						
			Aminalic protons		Aliphatic protons		5-CH_aH_bO		
			H-2-*c*	H-8-*c*	H-4-*c*	H-6-*c*	H-a	On *cis* face	
			H-2-*t*	H-8-*t*	H-4-*t*	H-6-*t*	H-b	(2)–(8)	(4)–(6)
			Δδ (*c*-*t*)	Δδ (*c*-*t*)	Δδ (*c*-*t*)	Δδ (*c*-*t*)	Δδ (a–b)	On *trans* face	
			Ring	Ring	Ring	Ring		(2)–(8)	(4)–(6)
2b	C-2′	$CDCl_3$	4.36	4.29	3.64	3.28	4.26[a]	+0.07	**+0.36**
			4.31	4.25	3.64	3.38	4.14[a]	+0.06	+0.26
			+0.05	+0.04	0.00	−0.10	**0.12**		
			C	**D**	**C**	**D**			
2h	C-2′	$CDCl_3$	—	—	3.91	3.46	4.17	—	**+0.45**
			5.50	5.41	3.81	3.32	4.00	+0.09	+0.49
			—	—	+0.10	+0.14	**0.17**		
			C	**D**	**C**	**D**			
2j	C-2′	$CDCl_3$	4.39	4.34	3.69	3.33	4.23	+0.05	**+0.36**
			4.35	4.30	3.69	3.48	4.15	+0.05	+0.21
			+0.04	+0.04	0.00	−0.15	**0.08**		
			C	**D**	**C**	**D**			
		[D_6]benzene	4.23	4.16	3.52	3.28	3.99	+0.07	**+0.24**
			4.02	3.98	3.52	3.38	3.89	+0.04	+0.14
			+0.21	+0.18	0.00	−0.10	**0.10**		
			C	**D**	**C**	**D**			
	C-6′	$CDCl_3$	4.46	4.45	3.83	3.82	4.27	+0.01	+0.01
			4.40	4.39	3.83	3.82	4.23	+0.01	+0.01
			+0.06	+0.06	0.00	0.00	0.04		
		[D_6]benzene	4.28	4.27	3.67	3.65	4.08	+0.01	+0.02
			4.05	4.05	3.59	3.58	3.98	0.00	+0.01
			+0.23	+0.22	+0.08	+0.07	0.10		

[a] Assigned arbitrarily.

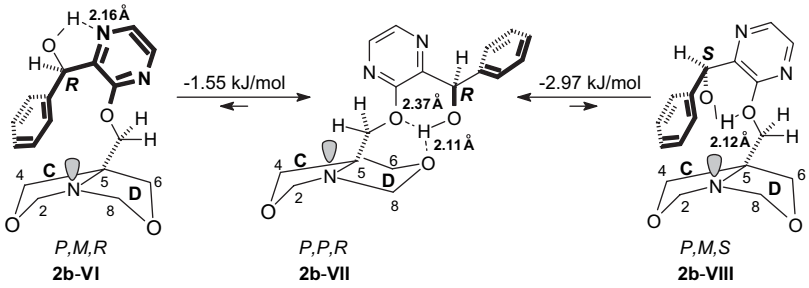
protons. It must be observed that it was more important in the *cis* aliphatic part of the bicycle, and, on the whole, even with respect to the Δδ (a–b) value revealed by the exocyclic methylene *c*-5-OCH-a, H-b. The presence of the phenyl groups at C-2 and C-8 in **2h** strongly increased the diastereotopicity.

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 as a useful and rapid tool to discriminate regioisomers in this class of compounds.

The study of the *ortho* (2H)DOABO–CH_2O group in compound **2j** by 2D ^{1}H–^{1}H NOESY experiments made it 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* orientated protons were more deshielded than the corresponding *trans* ones, except the reverse situation observed 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).

Three distinct conformers were found, **2b-VI**, **2b-VII** and **2b-VIII**. They were all orthogonal rotamers regarding the



Scheme 4.

orientation of the pyrazine ring. The magnitudes of the total ΔE values (<3 kJ mol^{-1}) 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' with a more deshielding influence on both faces of the bicycle faces with respect to oxazolidine **C** against **D**, e.g., H-4 versus H-6 and H-2 versus H-8. Comparable NMR data applied for the *ortho* (2H)DOABO–CH_2O group in compound **2j** were observed (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.

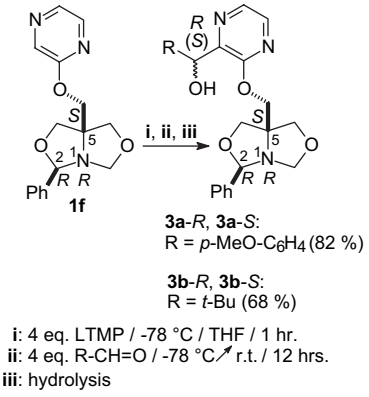
The NMR based stereochemical assignments for compounds **2b**, **2j** could be extrapolated for all synthesised chiral diarylmethanols having an *ortho* correspondence between the α-hydroxybenzyl and (2H)DOABO–CH_2O groups. Indeed, they all exhibited only small fluctuations of the DOABO chemical shifts in comparison with **2b** and **2j**.

The competition as DoMGs, (2H)DOABO–CH_2O against chlorine and methoxy, respectively, was also investigated (Table 1).

Starting from **1d** (entry 4), no trace of a deuteriated derivative was detected when the reaction mixture was quenched with DCl/D_2O, after several attempts: 4 equiv of LTMP (lithiation at −78 °C for 1, 6 even 14 h). In contrast, upon treatment of the reaction mixture with benzaldehyde at −78 °C, and slow evolution to room temperature, the regioisomers **2k** and **2l** were obtained in good yield with the competitive regioselectivity similar to 2-chloro-6-methoxypyrazine.[18] Thus, the synthesis of compounds **2k** and **2l** proved the in situ trapping when benzaldehyde was used as an electrophile. The easily separable compounds **2k** and **2l** were also easily discriminated based on ^{1}H NMR diastereotopicity criterion: it was around 0.31 ppm on the aliphatic motif of the DOABO *cis* face in **2k** but negligible in **2l** (0.01 ppm).

The competitive metallation of **1e** (entry 5) indicated comparable powers of orientation of the methoxy versus (2H)DOABO–CH_2O groups. The result was also reliable with the role played by the 5-OCH_2 group in creating CIPE, similar to an authentic DoMG, methoxy. In order to discriminate the nonseparable regioisomeric products **2m**+**2n**, the variable diastereotopicity in the aliphatic (2H)DOABO sequences was crucial. It was 0.38 versus 0.25 ppm (*cis* vs *trans* face) in **2m** but undetectable in **2n**.

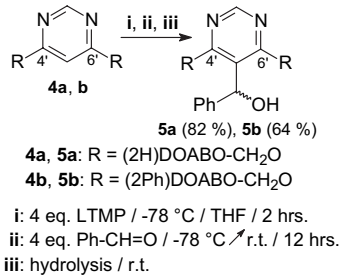
The lithiation of chiral **1f** (depicted as 1*R*,2*R*,5*S* enantiomer in Scheme 5), followed by quenching with anisaldehyde or pivalaldehyde resulted in the absence of diastereoselectivity, the equimolar nonseparable mixture of diastereomers **3a**-*R*+**3a**-*S* or **3b**-*R*+**3b**-*S* being isolated in each case (50:50, 1*R*,2*R*,5*S*,*R*:1*R*,2*R*,5*S*,*S*).



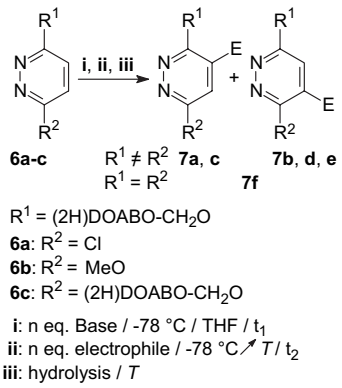
Scheme 5.

We explained this lack of diastereoselectivity by the stabilisation of the lithiated **1f** as *s-trans out* bisectional rotamer (**II**–**IV**, R^1(C-2)=Ph, R^1(C-8)=H, Scheme 2). Hence, the reaction site was significantly remote from the DOABO chiral centres N-1, C-2 and C-5.

2.1.2. 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 6).



Scheme 6.



Scheme 7.

The behaviour of 4′,6′-disubstituted compounds **4a** and **4b** was compared.

Starting from **4a**, 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% **5a** and 34% **4a**.

In the case of **4b**, 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 **5b** during isolation by flash column chromatography.

We rationalised these results as correlated with the different conformational behaviour of the DOABO systems in metallation conditions (**4a** vs **4b**) and to the in situ trapping of the electrophile in the case of **4a**.

2.1.3. Functionalisation of α-(3,7-dioxa-*r*-1-azabicyclo-[3.3.0]oct-*c*-5-ylmethoxy)-pyridazines. In the pyridazine series, the competitive *ortho*-metallation assisted by the (2H)DOABO–CH_2O group versus chlorine and methoxy, respectively, was studied.

Lithium-*N*,*N*-*tert*-butyl-(1-isopropylpentyl)amide (called 'LB_1', p*K*a=38.3 in THF), more hindered and basic than LDA and LTMP (p*K*a=35.7 and 37.3, respectively), was previously used for the claimed improved regioselective metallation of 3-chloro-6-methoxypyridazine.[27] Therefore, we tested the deuteriation of the analogous **6a** in identical conditions (2.2 equiv LB_1 at −78 °C, reaction time 30 min). The unreacted **6a** was recovered in almost quantitative yield. By using 4 equiv LB_1, the regioselectivity was poor (entry 1, compounds **7a**, and **7b**). The content of the crude reaction mixture was calculated based on the ^{1}H NMR spectrum, which displayed well-separated signals in the aromatic part: H-4′ and H-5′ at 7.37 6.97 ppm (d, *J*=9.2 Hz), respectively, in **6a**; H-5′ at 7.37 ppm (s) in **7a**; H-5′ at 6.97 ppm (s) in **7b**. Then, the global composition was checked and established in proportional correlation with the intensity of the singlet located at 3.86 ppm, assigned to DOABO methylenes C-4, C-6 in all **6a**, **7a** and **7b** environments (Scheme 7, Table 3).

Hence, the same metallating reagent, LTMP, as in the pyrazine and pyrimidine series, was again used (Table 3).

Compounds **7c** and **7d** were obtained with good global yield (entry 1), but with low *ortho* regioselectivity mandatory to the (2H)DOABO–CH_2O group in competition with chlorine. It was rather comparable with the already reported competition of methoxyethoxy versus chloro (*ortho* to chloro:*ortho* to methoxyethoxy as 32:48),[28] than methoxy versus chloro in the pyridazine series (*ortho* to chloro:*ortho* to methoxy as 20:80).[27,29] The individual assignment of the regioisomers **7c** and **7d** was unproblematic since the DOABO group exhibited different ^{1}H NMR diastereotopicity between homofacial aliphatic protons only in **7c**: $\Delta\delta$= 0.33 ppm (*cis* face) and 0.26 ppm (*trans* face). These $\Delta\delta$ values were 0.00 ppm in **7d**.

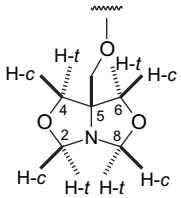
The functionalisation of the pyridazine **6b** was seen as the most illustrative competition between the methoxy against (2H)DOABO–CH_2O group because the sites to be deprotonated had *ortho* relationship (entry 2). The reaction occurred with complete *ortho* to methoxy regioselectivity. Identification of the product **7e** was based on its 2D ^{1}H–^{1}H NOESY[25,26] spectrum supporting the observation that, in the alicyclic region of the spectrum, poor or no diastereotopicity was evidenced in [D_6]benzene and $CDCl_3$. That is, the chiral centre was linked farther from the *ortho* position with respect to the (2H)DOABO–CH_2O group. In this case, the different steric hindrance against the bulky base LTMP, promoted by the two chelating oxygen-fragments, MeO and 5-OCH_2 in (2H)DOABO–CH_2O, became noteworthy.

We expected to better estimate this effect by the metallation of the symmetric 3′,6′-disubstituted pyridazine **6c** (entry 3). Unfortunately, despite dilution (more than 10^{-2} M in THF) and progressive increasing of the molar ratio **6c**:LTMP (4→8 equiv), the reaction mixture constantly was a very fine suspension of **6c**, from −78 °C to room temperature. For the largest excess of the metallating reagent, after column chromatography, a nonseparable mixture **6c+7f** was isolated.

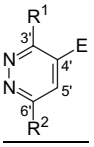
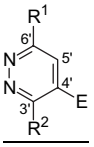
2.2. Functionalisation of α-(3,7-dioxa-*r*-1-azabicyclo-[3.3.0]oct-*c*-5-ylmethoxy)-α-chlorodiazines by cross-coupling reactions under Stille conditions

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 8, Table 4).

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



(2H)DOABO-CH_2O

Entry	Starting material	R^1 / R^2	E	Products: Compd ()	Products: Compd ()	*n*	Base	t_1 (min)	*T* (°C)	t_2 (h)
1	**6a**	(2H)DOABO–CH_2O Cl	D[a] Ph–CH–OH	**7a** [15][b] **7c** (53)[d] [63]	**7b** [32] **7d** (31) [37]	4 4	LB_1[c] LTMP	60 90	−78 rt	— 14
2	**6b**	(2H)DOABO–CH_2O MeO	Ph–CH–OH	—	**7e** (78)	4	LTMP	70	rt	16
3	**6c**	(2H)DOABO–CH_2O (2H)DOABO–CH_2O	Ph–CH–OH	**7f** [36]		8	LTMP	120	rt	24

[a] DCl 20% g/g (8 equiv) in D_2O solution was used.
[b] In square brackets: contents according to the ^1H NMR spectra of the crude reaction mixtures; 53% of starting **6a** in the mixture **7a+7b**: 64% of starting **6c** as a mixture with **7f**.
[c] Lithium-*N,N-tert*-butyl-(1-isopropylpentyl)amide.
[d] In round brackets, yields as isolated compounds after flash column chromatography; for **7c** and **7d** as partial yields.

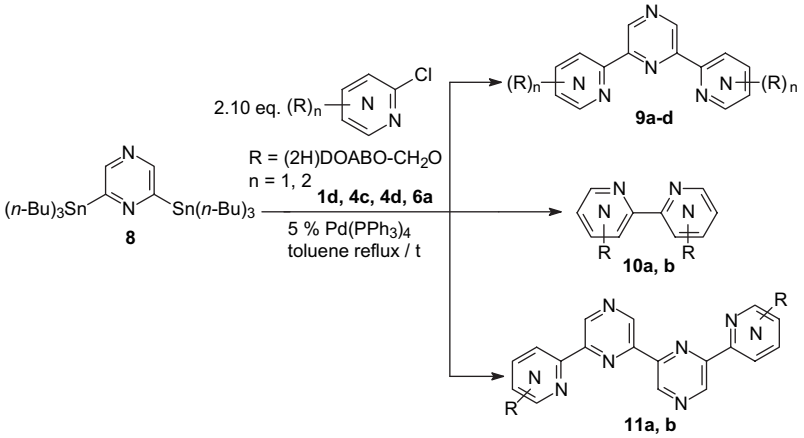
Thus, the 2,6-bis(tri-*n*-butylstannyl)pyrazine **8** was reacted under Stille conditions as double cross-coupling with the (2H)DOABO–CH_2O fragments α-substituting the α-chloro-diazines **1d**, **4c**, **4d** and **6a**. Their syntheses, together with that of the starting **8** were previously reported by us.[8,14]

The target compounds were 2,6-bis(diazinyl)pyrazines **9a–d**.

Very clean reactions accompanied the preparation of the compounds **9a** and **9c**. In turn, separation of **9b** and **9d** as pure analytical samples was more cumbersome than expected because they were contaminated by side products, homocoupling **10a** and **10b** and hetero–homocoupling derivatives **11a** and **11b**. As shown in Table 4, the compounds **10a**, **10b**, **11a** and **11b** were assigned on the basis of their well-separated signals in the ^1H NMR (aromatic zone) and MS spectra of the crude reaction mixtures.

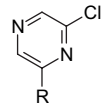
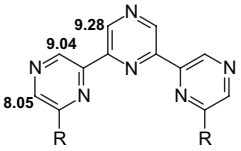
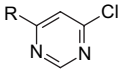
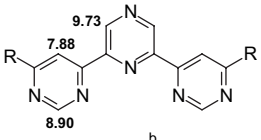
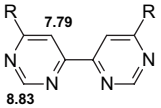
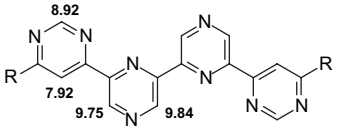
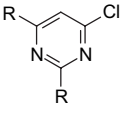
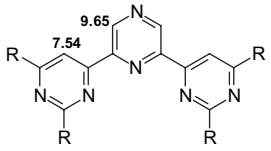
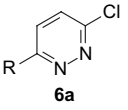
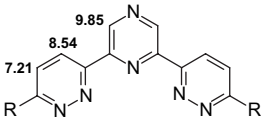
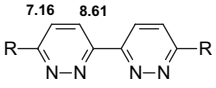
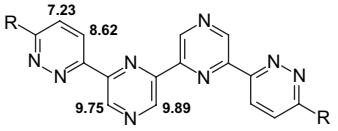
With the pure **9a–d** in our hands, their coordination ability against two transition metals, Zn^{2+} and Eu^{3+}, was examined. The first results of this exploratory study, carried out by means of UV spectroscopy, are collected in Table 5.

The measurements were performed in acetonitrile by using 4×10^{-5} M as initial concentration of the compounds **9a–d**. UV spectra were recorded for each 0.2 equiv of the salt



Scheme 8.

Table 4. Results in the cross-coupling reactions of compounds **1d**, **4c**, **4d** and **6a**. Preparation of compounds **9a–d**

Entry	Starting material	t (h)	Yield (%)	Main products	Side products	
1	 **1d**	22	65	 **9a**[a]		
2	 **4c**	48	60	 **9b** (82%)[b]	 **10a** (6%)	 **11a** (12%)
3	 **4d**	27	70	 **9c**		
4	 **6a**	48	22	 **9d** (50%)	 **10b** (35%)	 **11b** (15%)

[a] R=(2H)DOABO–CH_2O.
[b] Contents issued from the ^{1}H NMR spectra of the crude reaction mixtures.

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 **9a** was inert against both cations (entries 1–5).

Compound **9b** 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 equiv of M^{n+} was added and the saturation was reached (entries 8 and 10). Two isosbestic points were displayed in each case. Accordingly, two successive equilibriums including the

Table 5. Relevant UV data about the coordination ability of compounds **9a–d**

Entry	Ligand L	Salt	Metal (equiv M^{n+})	Absorptions as λ (nm) (log ε)	Isosbestic points λ (nm)		Proposed stoichiometry L:M
1	**9a**	**9a** 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)	—		—
4		+$EuCl_3\times6H_2O$	1.0	242 (4.11); 323 (4.25)			
5			2.0	241 (4.13); 322 (4.25)	—		—
6	**9b**	**9b** 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)			1:1
8			2.0	211 (4.67); 319 (4.24)	226	305	
9		+$EuCl_3\times6H_2O$	1.0	210 (4.72); 309 (4.22)			1:1
10			2.0	211 (4.75); 310 (4.26)	230	311	
11	**9c**	**9c** 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)			1:1
13			2.0	205 (4.66); 335 (4.33); 345 (4.41)	236	318	
14		+$EuCl_3\times6H_2O$	1.0	203 (4.68); 250 (4.25); 298 (4.24)	—		—
15			2.0	203 (4.68); 250 (4.24); 298 (4.24)			
16	**9d**	**9d** 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)	263	280	1:1.5
19			2.0	213 (4.47); 234 (4.45); 265 (4.37); 347 (4.05)	334		
20		+$EuCl_3\times6H_2O$	1.0	209 (4.48); 252 (4.41); 285 (4.26)			
21			2.0	209 (4.48); 252 (4.41); 283 (4.26)	—		—

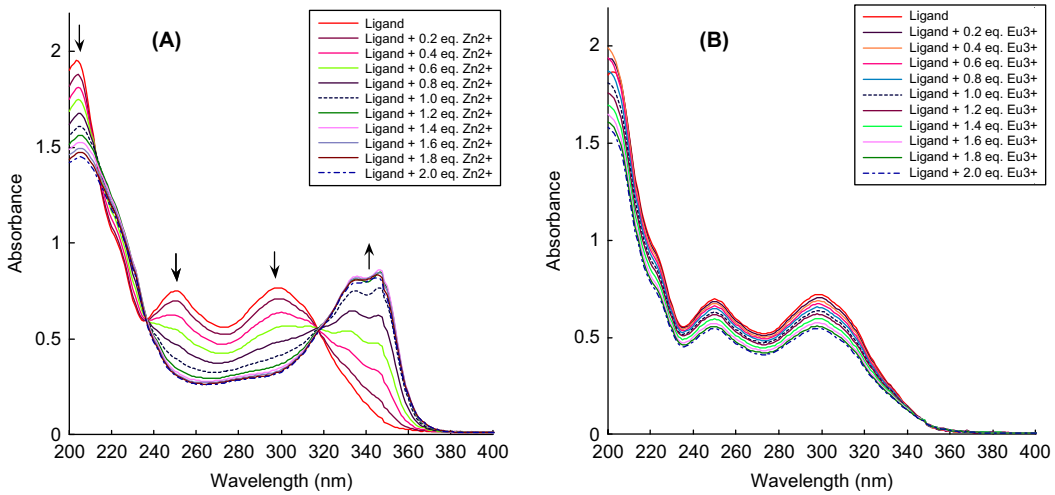


Figure 1. UV spectra of compound **9c** in the presence of progressive increased concentration of Zn^{2+} as $Zn(BF_4)_2$ (**A**) and Eu^{3+} as $EuCl_3 \cdot 6H_2O$ (**B**).

free **9b** and its complex [**9b**]:[M^{n+}] (1:1 stoichiometry) were proposed.

Compound **9c**, possessing twice the number of (2H)DOABO–CH_2O groups, was a selective ligand (Fig. 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 at $\Delta\lambda_{max.}$=49 nm (entry 12 vs 11) and two isosbestic points located at 236 and 318 nm. The same stoichiometry of the complex as above, [**9c**]:[Zn^{2+}]=1:1 in equilibrium with the free **9c**, via an intermediate, was plausible. No modification of the UV spectrum was observed in the presence of Eu^{3+} (entries 14 and 15).

Finally, the bis(pyridazinyl)pyrazine **9d** was not only a selective ligand but the stoichiometry of its coordination with Zn^{2+} showed an increased chelating ability as [**9d**]:[Zn^{2+}]=1:1.5 (entry 18). Consequently, besides the bathochromic effect at $\Delta\lambda_{max.}$=50 nm (entries 16–19), three isosbestic points were found, consistent with the occurrence of three successive equilibriums.

3. 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*-metallation reaction. The DOABO–CH_2O architecture, alone or in competition with chloro or methoxy groups, acts as a DoMG since the 5-OCH_2 moiety creates CIPE. The latter 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 analogues of terpyridine with selective coordinating ability against transition metals.

4. Experimental

4.1. General

Melting points are uncorrected; they were carried out on an ELECTROTHERMAL® 9100 instrument. Current NMR spectra were recorded on a Brucker® AM300 (300 MHz ^1H, 75 MHz ^{13}C). NMR analysis for the 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 FTIR spectrometer. Only relevant absorptions are listed [throughout in cm^{-1}: weak (w), medium (m) or strong (s)]. 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. Microanalyses were performed on a Carlo Erba® CHNOS 1160 apparatus. All synthesis was performed under dry nitrogen atmosphere. THF was freshly distilled from Na/benzophenone prior to use. All solvents and starting materials were of commercial quality.

UV spectra were compiled by using SPECFIT/32® and Varian Carry Winuv® programs.

Molecular orbital calculations for the compound **2b**: the conformational space of these systems has been investigated by using the 'Conformer Distribution' facility (MMFF force field) from Spartan'o2. [Spartan'o2, Wavefunction, Inc. Irvine, CA]. The set of conformers thus generated has been subjected, within the same package, to full geometry optimisation at the RHF/6-31G* ab initio level. The default convergence criteria (Energy = 0.000001 hartrees, rms gradient = 0.000450 hartrees/bohr) have been imposed throughout for all the ab initio computations.

The syntheses of the starting materials **1a–f**, **4a–d** and **6a–c** was described elsewhere.[8,11]

4.2. General procedure for the preparation of compounds 2a–j, 3a, 3b, 5a, 5b and 7a–f by Directed *ortho*-Metallation methodology

In 25–50 mL (Note 1) THF and with vigorous stirring, 2,2,6,6-tetramethylpiperidine (HTMP) (0.688 mL, 0.565 g 100%, 0.576 g 98%, 4 mmol) was injected. The solution was cooled at −10 to −15 °C and 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 to −15 °C for additional 15 min and then cooled to −78 °C. The starting DOABO–CH_2O substituting diazine (1.00 mmol) as a THF solution (2–10 mL, Note 1) was introduced. Specific conditions to perform the reaction are presented in Tables 1 and 3 and Schemes 5 and 6 (Note 2). 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 °C or very slow evolution was observed, the reaction mixture was let to reach very gently the room temperature.

The reaction mixture was quenched according to one of the following variants:

A In the case of deuteriated compounds **2a** and **7a**, **7b**, the reaction was quenched at −78 °C (0 °C in the case of **2i**) with 8 equiv of DCl as 20% g/g solution in D_2O. Then it was allowed 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 °C with 10 mL 1:1 v/v THF:EtOH. Then it was allowed to reach room temperature. The next work up was made according to variant **C**.

C For the rest of the compounds, the reaction mixture 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) and 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 ^1H NMR as a crude reaction mixture. For deuteriated compounds **2a**, **2i** and **7a**, **7b** conclusions were provided at this stage (Note 3). For the rest of the compounds, the mixtures were purified by column chromatography to yield the title compounds (Note 4).

Note 1 THF 25 (50) mL for diazines possessing one (two, respectively) DOABO fragment(s).

Note 2 After the accumulation time, usually clear coloured solutions were obtained as follows: **1a**, **1e** (yellow → reddish-brown), **1b** (yellow → orange), **1c** (orange at −78 °C and brown at 0 °C), **1d** (reddish orange), **1f** (yellow → reddish-yellow), **4a**, **4b** (no change), **6a** (bright yellow → reddish violet with LiB_1, reddish orange with LTMP), **6b** (red) and **6c** (pale reddish).

Note 3 For mono deuteriated compounds **2a** and **2i** the magnitude of the corresponding integral is given in each case as percentages with respect to the most intense signal. For **7a** and **7b**, see the text.

Note 4 CARE! After column chromatography, almost all compounds were preliminarily obtained as viscous pale yellowish oils. They were then crystallised from ligroin:ether mixtures (about 1:1 v/v) or pentane. Crystallisations take place over a long time (1–7 days). All melting points, elementary analysis, NMR, IR and MS spectra refer to crystalline isolated structures. The TLC monitoring of all reactions and separations by column chromatography evidenced very weak absorption in UV (254 nm). Concentrated samples were used.

4.2.1. 3-[^2H]-2-[(3,7-Dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (2a). Yield 98%. δ_H (300 MHz, $CDCl_3$) *heteroaromatic*: 8.23 (1H, d, *J*=1.1 Hz, H-3, 1.7%), 8.13 (1H, d, *J*=3.0 Hz, H-5, 93%), 8.06 (1H, d, *J*=2.8 Hz, H-6, 100%). MS (EI, 70 eV) *m/z* (rel int. %): (M^++1) 225 (5), 207 (5), 177 (4), 128 (100%), 98 (9).

4.2.2. *rac*-3-(α-Hydroxybenzyl)-2-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (2b). Yield 79%. Yellowish crystalline powder, mp 84–85 °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 (1H, d, *J*=2.8 Hz, H-5), 7.96 (1H, d, *J*=2.8 Hz, H-6), 7.30–7.10 (5H, m, Ph), 5.71 (1H, d, *J*=4.7 Hz, C*H*OH), 5.05 (1H, d, *J*=4.7 Hz, OH); *DOABO–CH_2O*: 4.36 (1H, d, *J*=5.7 Hz, H-2-*c*), 4.31 (1H, d, *J*=5.7 Hz, H-2-*t*), 4.29 (1H, d, *J*=6.4 Hz, H-8-*c*), 4.26 (1H, d, *J*=10.9 Hz, 5-OCH_aH$_b$), 4.25 (1H, d, *J*=6.4 Hz, H-8-*t*), 4.14 (1H, d, *J*=10.9 Hz, 5-OCH$_a$$H_b$), 3.64 (2H, s, H-4-*c*, H-4-*t*), 3.38 (1H, d, *J*=9.0 Hz, H-6-*t*), 3.28 (1H, d, *J*=9.0 Hz, H-6-*c*); δ_C (75 MHz, $CDCl_3$) *(hetero)aromatic*: 156.8 (1C, C-2), 146.2 (1C, C-3), 141.9 (1C, Cq., Ph), 140.3 (1C, C-6), 135.5 (1C, C-5), 128.9 (2C, CH, Ph), 128.5 (1C, CH, Ph), 127.6 (2C, CH, Ph); *DOABO–CH_2O*: 88.4, 88.3 (2C, C-2, C-8), 74.32, 74.28 (2C, C-4, C-6), 71.9 (1C, CHOH), 71.6 (1C, C-5), 69.3 (1C, 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).

4.2.3. *rac*-3-(1-Hydroxyeth-1-yl)-2-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (2c). Yield 41%. White crystalline powder, mp 79–80 °C (Et_2O:ligroin 1:1 v/v) (column chromatography, eluent AcOEt:ligroin 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 (1H, d, *J*=2.3 Hz, H-5), 7.97 (1H, d, *J*=2.3 Hz, H-6), 4.94 (1H, q, *J*=6.4 Hz, C*H*OH), 3.83 (1H, br s, OH); *DOABO–CH_2O*: 4.49 (2H,

d, J=5.5 Hz, H-2, H-8-*c*), 4.43 (2H, d, J=5.5 Hz, H-2, H-8-*t*), 4.40 (1H, d, J=10.7 Hz, 5-OCH_aH$_b$), 4.35 (1H, d, J=10.7 Hz, 5-OCH$_a$$H_b$), 3.85 (2H, d, J=9.4 Hz, H-4, H-6, H-*c*), 3.82 (2H, d, J=9.4 Hz, H-4, H-6, H-*t*), 1.42 (3H, d, J=6.4 Hz, CH$_3$); δ_C (75 MHz, $CDCl_3$) *heteroaromatic*: 156.8 (1C, C-2), 148.5 (1C, C-3), 139.8 (1C, C-6), 135.8 (1C, C-5); *DOABO–CH$_2$O*: 88.6 (2C, C-2, C-8), 74.2 (2C, C-4, C-6), 72.0 (1C, C-5), 69.0 (1C, 5-OCH$_2$), 65.7 (1C, CHOH), 22.6 (1C, CH$_3$). δ_H (300 MHz, [D$_6$]bezene) *DOABO–CH$_2$O*: 4.27 (1H, d, J=5.3 Hz, H-2-*c*), 4.25 (1H, d, J=5.3 Hz, H-8-*c*), 4.19 (1H, d, J=10.9 Hz, 5-OCH_aH$_b$), 4.10 (1H, d, J=10.9 Hz, 5-OCH$_a$$H_b$), 4.06 (2H, d, J=5.5 Hz, H-2, H-8-*t*), 3.50 (2H, d, J=9.4 Hz, H-4, H-6-*c*), 3.45 (2H, d, J=9.4 Hz, H-4, H-6-*t*). 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).

4.2.4. 3-Ethyl-2-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (2d). Yield 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 (1H, d, J=2.6 Hz, H-5), 7.83 (1H, d, J=2.6 Hz, H-6); *DOABO–CH$_2$O*: 4.46 (2H, d, J=5.5 Hz, H-2, H-8-*c*), 4.42 (2H, d, J=5.5 Hz, H-2, H-8-*t*), 4.32 (2H, s, 5-OCH$_2$), 3.83 (2H, d, J=9.0 Hz, H-4, H-6-*c*), 3.81 (2H, d, J=9.0 Hz, H-4, H-6-*t*), 2.73 (2H, q, J=7.5 Hz, CH_2CH$_3$), 1.19 (3H, t, J=7.5 Hz, CH$_2$CH_3); δ_C (75 MHz, $CDCl_3$) *heteroaromatic*: 158.0 (1C, C-2), 149.1 (1C, C-3), 138.2 (1C, C-6), 136.6 (1C, C-5); *DOABO–CH$_2$O*: 88.8 (2C, C-2, C-8), 74.4 (2C, C-4, C-6), 72.0 (1C, C-5), 68.9 (1C, 5-OCH$_2$), 26.1 (1C, *C*H$_2$CH$_3$), 11.6 (1C, CH$_2$*C*H$_3$). MS (CI) *m/z* (rel int. %): (M^++14) 256 (5), 251 (<1), 235 (9), 221 (18), 141 (100), 128 (24), 115 (14).

4.2.5. 3-Iodo-2-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (2e). Yield 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 (2H, s, H-5, H-6); *DOABO–CH$_2$O*: 4.56 (2H, d, J=5.3 Hz, H-2, H-8-*c*), 4.46 (2H, d, J=5.3 Hz, H-2, H-8-*t*), 4.36 (2H, s, 5-OCH$_2$), 3.93 (2H, d, J=9.0 Hz, H-4, H-6-*c*), 3.89 (2H, d, J=9.0 Hz, H-4, H-6-*t*); δ_C (75 MHz, $CDCl_3$) *heteroaromatic*: 158.9 (1C, C-2), 139.8 (1C, C-6), 138.4 (1C, C-5), 108.0 (1C, C-3); *DOABO–CH$_2$O*: 88.9 (2C, C-2, C-8), 74.3 (2C, C-4, C-6), 71.8 (1C, C-5), 70.4 (1C, 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).

4.2.6. 3-Tri-*n*-butylstannyl-2-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (2f). Yield 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 (1H, d, J=2.6 Hz, H-5), 7.84 (1H, dd, J=2.6, 5.1 Hz, H-6); *DOABO–CH$_2$O*: 4.47 (2H, d, J=5.3 Hz, H-2, H-8-*c*), 4.42 (2H, d, J=5.3 Hz, H-2, H-8-*t*), 4.31 (2H, s, 5-OCH$_2$), 3.84 (4H, dd as t, J=8.7 Hz, H-4, H-6, H-c, H-*t*), 1.54–1.44 (6H, m, CH$_2$CH_2CH$_2$CH$_3$), 1.32–1.20 (6H, m, CH$_2$CH$_2$CH_2CH$_3$), 1.14–1.07 (6H, m, CH_2CH$_2$*C*H$_2$CH$_3$), 0.82 (9H, t, J=7.3 Hz, CH$_2$CH$_2$CH$_2$CH_3); δ_C (75 MHz, $CDCl_3$) *heteroaromatic*: 164.5 (1C, C-3), 160.8 (1C, C-2), 139.7 (1C, C-6), 138.9 (1C, C-5); *DOABO–CH$_2$O*: 88.6 (2C, C-2, C-8), 75.0 (2C, C-4, C-6), 71.9 (1C, C-5), 69.6 (1C, 5-OCH$_2$), 29.4 (3C, CH$_2$*C*H$_2$CH$_2$CH$_3$), 27.7 (3C, CH$_2$CH$_2$*C*H$_2$CH$_3$), 14.1 (3C, CH$_2$CH$_2$CH$_2$*C*H$_3$), 10.4 (3C, *C*H$_2$CH$_2$CH$_2$CH$_3$). 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).

4.2.7. 2-[(3,7-Dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)-methoxy]-3-thiophenylpyrazine (2g). Yield 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 (1H, d, J=2.6 Hz, H-5), 7.74 (1H, d, J=2.6 Hz, H-6), 7.53–7.50 (2H, m, Ph), 7.40–7.39 (3H, m, Ph); *DOABO–CH$_2$O*: 4.57 (2H, d, J=5.5 Hz, H-2, H-8-*c*), 4.47 (2H, d, J=5.5 Hz, H-2, H-8-*t*), 4.43 (2H, s, 5-OCH$_2$), 3.92 (2H, d, J=8.9 Hz, H-4, H-6-*c*), 3.87 (2H, d, J=8.9 Hz, H-4, H-6-*t*); δ_C (75 MHz, $CDCl_3$) *(hetero)aromatic*: 155.8 (1C, C-2), 146.8 (1C, C-3), 137.1 (1C, C-6), 136.3 (1C, C-5), 135.5 (2C, CH, Ph), 129.64 (2C, CH, Ph), 129.55 (1C, CH, Ph), 128.7 (1C, Cq., Ph); *DOABO–CH$_2$O*: 88.9 (2C, C-2, C-8), 74.4 (2C, C-4, C-6), 71.9 (1C, C-5), 69.5 (1C, 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).

4.2.8. *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). Yield 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 (1H, d, J=2.4 Hz, H-5), 7.92 (1H, d, J=2.4 Hz, H-6), 7.43–7.38 (4H, m, Ph), 7.24–7.15 (9H, m, Ph), 7.10–7.08 (2H, m, Ph), 5.55 (1H, d, J=3.8 Hz, C*H*–OH), 4.99 (1H, d, J=3.8 Hz, OH); *DOABO–CH$_2$O*: 5.50 (1H, s, H-2-*t*), 5.41 (1H, s, H-8-*t*), 4.17 (1H, d, J=10.2 Hz, 5-OCH_aH$_b$), 4.00 (1H, d, J=10.2 Hz, 5-OCH$_a$$H_b$), 3.91 (1H, d, J=8.9 Hz, H-4-*c*), 3.81 (1H, d, J=9.4 Hz, H-4-*t*); 3.46 (1H, d,

J=9.2 Hz, H-6-*c*), 3.32 (1H, d, *J*=9.2 Hz, H-6-*t*); δ_C (75 MHz, $CDCl_3$) *(hetero)aromatic*: 156.7 (1C, C-2), 145.8 (1C, C-3), 141.8 (1C, Cq., Ph), 140.4 (1C, C-6), 139.6 (1C, Cq., Ph), 139.4 (1C, Cq., Ph), 135.2 (1C, C-5), 129.1 (1C, CH, Ph), 129.0 (2C, CH, Ph), 128.9 (1C, CH, Ph), 128.8 (4C, CH, Ph), 128.6 (1C, CH, Ph), 127.7 (2C, CH, Ph), 127.6 (2C, CH, Ph), 127.5 (2C, CH, Ph); *DOABO–CH_2O*: 98.0, 97.2 (2C, C-2, C-8), 73.7 (1C, C-5), 73.3, 72.9 (2C, C-4, C-6), 71.8 (1C, CHOH), 70.5 (1C, 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).

4.2.9. 3-[^2H]-2,6-Bis[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (2i). Yield 71%. δ_H (300 MHz, $CDCl_3$) *heteroaromatic*: 7.79 (1H, s, H-5, 50%). MS (EI, 70 eV) *m/z* (rel int. %): (M^++1) 368 (10), 279 (<1), 212 (<1), 128 (100), 98 (4).

4.2.10. *rac*-3-(α-Hydroxybenzyl)-2,6-bis[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (2j). Yield 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 (1H, s, H-5), 7.28–7.16 (5H, m, Ph); 5.69 (1H, br s, C*H*OH), 4.81 (1H, br s, OH); *DOABO–CH_2O linked at C-2*: 4.39 (1H, d, *J*=5.5 Hz, H-2-*c*), 4.35 (1H, d, *J*=5.5 Hz, H-2-*t*), 4.34 (1H, d, *J*=5.5 Hz, H-8-*c*), 4.30 (1H, d, *J*=5.5 Hz, H-8-*t*), 4.23 (1H, d, *J*=10.6 Hz, 5-OC$H_a$$H_b$), 4.15 (1H, d, *J*=10.6 Hz, 5-OCH_aH_b), 3.69 (2H, s, H-4-c, H-4-*t*), 3.48 (1H, d, *J*=9.4 Hz, H-6-*t*), 3.33 (1H, d, *J*=9.4 Hz, H-6-*c*); *DOABO–CH_2O linked at C-6*: 4.46 (1H, d, *J*=5.3 Hz, H-2-*c*), 4.45 (1H, d, *J*=5.5 Hz, H-8-*c*), 4.40 (1H, d, *J*=5.3 Hz, H-2-*t*), 4.39 (1H, d, *J*=5.3 Hz, H-8-*t*), 4.27 (1H, d, *J*=10.6 Hz, 5-OC$H_a$$H_b$), 4.23 (1H, d, *J*=10.6 Hz, 5-OCH_aH_b), 3.83 (2H, s, H-4, H-*c*, H-*t*), 3.82 (2H, s, H-6, H-*c*, H-*t*); δ_C (75 MHz, $CDCl_3$) *(hetero)aromatic*: 158.1 (1C, C-6), 154.3 (1C, C-2), 142.7 (1C, Cq., Ph), 136.4 (1C, C-3), 128.8 (2C, CH, Ph), 128.3 (1C, CH, Ph), 127.3 (2C, CH, Ph), 123.2 (1C, C-5), 71.5 (1C, CHOH); *DOABO–CH_2O linked at C-2*: 88.3, 88.2 (2C, C-2, C-8), 74.3 (2C, C-4, C-6), 71.5 (1C, C-5), 69.3 (1C, 5-OCH_2); *DOABO–CH_2O linked at C-6*: 88.4 (2C, C-2, C-8), 74.4 (2C, C-4, C-6), 71.8 (1C, C-5), 69.7 (1C, 5-OCH_2). δ_H (500 MHz, [D_6]benzene) *(hetero)aromatic*: 7.62 (1H, s, H-5), 7.35 (2H, d, *J*=7.2 Hz, *ortho*-Ph), 7.09 (2H, m, *meta*-Ph), 7.02 (1H, m, *para*-Ph), 5.86 (1H, d, *J*=7.2 Hz, C*H*OH), 4.99 (1H, d, *J*=7.2 Hz, OH); *DOABO–CH_2O linked at C-2*: 4.23 (1H, d, *J*=5.5 Hz, H-2-*c*), 4.16 (1H, d, *J*=5.5 Hz, H-8-*c*), 4.02 (1H, d, *J*=5.5 Hz, H-2-*t*), 3.99 (1H, d, *J*=10.6 Hz, 5-OC$H_a$$H_b$), 3.98 (1H, d, *J*=5.5 Hz, H-8-*t*), 3.89 (1H, d, *J*=10.6 Hz, 5-OCH_aH_b), 3.52 (2H, s, H-4-*c*, H-4-*t*), 3.38 (1H, d, *J*=9.0 Hz, H-6-*t*), 3.28 (1H, d *J*=9.0 Hz, H-6-*c*); *DOABO–CH_2O linked at C-6*: 4.28 (1H, d, *J*=5.5 Hz, H-2-*c*), 4.27 (1H, d, *J*=5.5 Hz, H-8-*c*), 4.08 (1H, d, *J*=11.3 Hz, 5-OC$H_a$$H_b$), 4.05 (2H, d, *J*=5.5 Hz, H-2, H-8-*t*), 3.98 (1H, d, *J*=11.3 Hz, 5-OCH_aH_b), 3.67 (1H, d, *J*=9.0 Hz, H-4-*c*), 3.65 (1H, d *J*=9.0 Hz, H-6-*c*), 3.59 (1H, d, *J*=9.0 Hz, H-4-*t*), 3.58 (1H, d, *J*=9.0 Hz, H-6-*t*). δ_C (125 MHz, [D_6]benzene) *(hetero)aromatic*: 158.0 (1C, C-6), 154.3 (1C, C-2), 143.5 (1C, Cq., Ph), 137.1 (1C, C-3), 128.6 (2C, CH, *meta*-Ph), 127.9 (1C, CH, *para*-Ph), 127.4 (2C, CH, *ortho*-Ph), 122.6 (1C, C-5), 71.6 (1C, CHOH); *DOABO–CH_2O linked at C-2*: 87.88 (1C, C-8), 87.82 (1C, C-2), 73.96 (1C, C-6), 73.90 (1C, C-4), 71.4 (1C, C-5), 69.3 (1C, 5-OCH_2); *DOABO–CH_2O linked at C-6*: 88.0 (2C, C-2, C-8), 74.00 (1C, C-4), 73.96 (1C, C-6), 71.6 (1C, C-5), 69.7 (1C, 5-OCH_2). MS (EI, 70 eV) *m/z* (rel int. %): (M^+) 472 (<1), 344 (3), 212 (4), 128 (100), 98 (7).

4.2.11. *rac*-6-Chloro-3-(α-hydroxybenzyl)-2-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (2k). Yield 52%. White crystalline powder, mp 76–78 °C (Et_2O: pentane 1:1 v/v) (column chromatography, eluent ligroin: AcOEt 1:1 v/v). [Found: C, 55.89; H, 5.25; N, 11.81. $C_{17}H_{18}N_3O_4Cl$ requires: C, 56.13; H, 4.99; N, 11.55%]. R_f (50% ligroin:AcOEt) 0.50. ν_{max} (film NaCl): 3416 (s), 2857 (m), 1540 (m), 1422 (s), 1351 (s), 1173 (m), 1129 (m), 1041 (s), 930 (w), 749 (w), 700 (m) cm^{-1}. δ_H (300 MHz, $CDCl_3$) *(hetero)aromatic*: 8.15 (1H, s, H-5), 7.32–7.20 (5H, m, Ph), 5.76 (1H, br s, C*H*OH), 4.76 (1H, br s, OH); *DOABO–CH_2O*: 4.41 (1H, d, *J*=5.5 Hz, H-2-*c*), 4.36 (1H, d, *J*=5.5 Hz, H-2-*t*), 4.33 (1H, d, *J*=5.5 Hz, H-8-*c*), 4.32 (1H, d, *J*=5.5 Hz, H-8-*t*), 4.30 (1H, d, *J*=10.9 Hz, 5-OC$H_a$$H_b$), 4.21 (1H, d, *J*=10.9 Hz, 5-OCH_aH_b), 3.68 (2H, s, H-4-c, H-4-*t*), 3.47 (1H, d, *J*=9.0 Hz, H-6-*t*), 3.36 (1H, d, *J*=9.0 Hz, H-6-*c*); δ_C (75 MHz, $CDCl_3$) *(hetero)aromatic*: 155.6 (1C, C-2), 144.7 (1C, C-3), 144.2 (1C, C-6), 141.4 (1C, Cq., Ph), 134.3 (1C, C-5), 129.0 (2C, CH, Ph), 128.7 (1C, CH, Ph), 127.5 (2C, CH, Ph); *DOABO–CH_2O*: 88.40, 88.35 (2C, C-2, C-8), 74.11, 74.06 (2C, C-4, C-6), 71.8 (1C, CHOH), 71.5 (1C, C-5), 70.0 (1C, 5-OCH_2). δ_H (300 MHz, [D_6]benzene) *(hetero)aromatic*: *DOABO–CH_2O*: 4.28 (1H, d, *J*=5.5 Hz, H-2-*c*), 4.17 (1H, d, *J*=5.5 Hz, H-8-*c*), 4.10 (1H, d, *J*=5.5 Hz, H-2-*t*), 4.06 (1H, d, *J*=5.5 Hz, H-8-*t*), 3.97 (1H, d, *J*=10.6 Hz, 5-OC$H_a$$H_b$), 3.88 (1H, d, *J*=10.6 Hz, 5-OCH_aH_b), 3.51 (1H, d, *J*=9.0 Hz, H-4-*t*), 3.48 (1H, d *J*=9.0 Hz, H-4-*c*), 3.35 (1H, d *J*=9.0 Hz, H-6-*t*), 3.18 (1H, d, *J*=9.0 Hz, H-6-*c*). MS (EI, 70 eV) *m/z* (rel int. %): (M^+-1) 362.6 (3), 346 (100), 318 (6), 178 (6), 128 (93), 98 (65).

4.2.12. *rac*-2-Chloro-3-(α-hydroxybenzyl)-6-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (2l). Yield 26%. White crystalline powder, mp 117–119 °C (Et_2O:pentane 1:1 v/v) (column chromatography, eluent ligroin:AcOEt 1:1 v/v). [Found: C, 56.44; H, 5.30; N, 11.29. $C_{17}H_{18}N_3O_4Cl$ requires: C, 56.13; H, 4.99; N, 11.55%]. R_f (50% ligroin:AcOEt) 0.35. ν_{max} (film NaCl): 3419 (s), 2868 (m), 1640 (w), 1566 (w), 1526 (w), 1446 (s), 1328 (s), 1169 (s), 1041 (s), 930 (w), 751 (s), 700 (m) cm^{-1}. δ_H (300 MHz, $CDCl_3$) *(hetero)aromatic*: 8.16 (1H, s, H-5), 7.35–7.20 (5H, m, Ph), 5.98 (1H, s, C*H*OH), 5.05 (1H, br s, OH); *DOABO–CH_2O*: 4.48 (1H, d, *J*=5.7 Hz, H-2-*c*), 4.47 (1H, d, *J*=5.7 Hz, H-8-*c*), 4.42 (2H, d, *J*=5.7 Hz, H-2, H-8-*t*), 4.35 (1H, s, 5-OC$H_a$$H_b$), 4.33 (1H, s, 5-$OCH_aH_b$), 3.84 (2H, s, H-4, H-*c*, H-*t*), 3.83 (2H, s, H-6, H-*c*, H-*t*); δ_C (75 MHz, $CDCl_3$) *(hetero)aromatic*: 158.5 (1C, C-6), 146.3 (1C, C-3), 143.1 (1C, C-2), 141.7 (1C, Cq., Ph), 132.1 (1C, C-5), 128.9 (2C, CH, Ph), 128.4 (1C, CH, Ph), 127.4 (2C, CH, Ph); *DOABO–CH_2O*:

88.6 (2C, C-2, C-8), 74.3 (2C, C-4, C-6), 71.9 (1C, CHOH), 71.8 (1C, C-5), 70.1 (1C, 5-OCH_2). δ_H (300 MHz, [D_6]benzene) *(hetero)aromatic*: 7.60 (1H, s, H-5), 7.43 (2H, d, *J*=7.2 Hz, Ph), 7.20–7.00 (3H, m, Ph), 6.10 (1H, s, C*H*OH), 4.35 (1H, br s, OH); *DOABO–CH_2O*: 4.24 (1H, d, *J*=5.5 Hz, H-2-*c*), 4.23 (1H, d, *J*=5.5 Hz, H-8-*c*), 4.05 (2H, d, *J*=5.5Hz, H-2, H-8-*t*), 3.98 (1H, s, *J*=10.7 Hz, 5-OC*H_a*H_b), 3.89 (1H, d, *J*=10.7 Hz, 5-OCH_aH_b), 3.51 (2H, s, H-4, H-*c*, H-*t*), 3.50 (2H, s, H-6, H-*c*, H-*t*). MS (EI, 70 eV) *m/z* (rel int. %): (M^+) 363.6 (3), 346 (8), 128 (100), 98 (15).

4.2.13. *rac*-3-(α-Hydroxybenzyl)-6-methoxy-2-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (2m) and *rac*-3-(α-hydroxybenzyl)-2-methoxy-6-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazine (2n). Nonseparable mixture as white crystalline powder, mp 114–119 °C (Et_2O) (column chromatography, eluent ligroin: AcOEt 1:1 v/v). [Found: C, 60.30; H, 5.62; N, 11.80. $C_{18}H_{21}N_3O_5$ requires: C, 60.16; H, 5.89; N, 11.69%]. R_f (50% ligroin:AcOEt) 0.32. ν_{max} (film KBr): 3224 (m), 2886 (w), 2863 (m), 1583 (m), 1410 (m), 1184 (m), 922 (m), 703 (s), 561 (m), 491 (w) cm^{-1}. *Regioisomer* ***2m*** (29%): δ_H (300 MHz, $CDCl_3$) *(hetero)aromatic*: 7.77 (1H, s, H-5), 7.32–7.16 (5H, m, Ph), 5.68 (1H, d, *J*=6.4 Hz, C*H*OH), 4.78 (1H, d, *J*=6.4 Hz, OH); *DOABO–CH_2O*: 4.41 (1H, d, *J*=4.5 Hz, H-2-*c*), 4.37 (1H, d, *J*=4.5 Hz, H-2-*t*), 4.36 (1H, d, *J*=4.5 Hz, H-8-*c*), 4.29 (1H, d, *J*=4.5 Hz, H-8-*t*), 4.26 (1H, d, *J*=10.6 Hz, 5-OC*H_a*H_b), 4.19 (1H, d, *J*=10.6 Hz, 5-OCH_aH_b), 3.88–3.83 (3H, m, OCH_3), 3.73 (1H, d, *J*=9.8 Hz, H-4-*c*), 3.70 (1H, d, *J*=9.8 Hz, H-4-*t*), 3.45 (1H, d, *J*=9.0 Hz, H-6-*t*), 3.35 (1H, d, *J*=9.0 Hz, H-6-*c*); δ_C (75 MHz, $CDCl_3$) *(hetero)aromatic*: 159.0 (1C, C-6), 154.4 (1C, C-2), 142.9 (1C, Cq., Ph), 135.5 (1C, C-3), 128.8 (2C, CH, Ph), 128.2 (1C, CH, Ph), 127.3 (2C, CH, Ph), 123.2 (1C, C-5); *DOABO–CH_2O*: 88.3, 88.2 (2C, C-2, C-8), 74.3 (2C, C-4, C-6), 71.6 (1C, C-5), 71.5 (1C, CHOH), 69.3 (1C, 5-OCH_2), 54.4 (1C, OCH_3). *Regioisomer* ***2n*** (41%): δ_H (300 MHz, $CDCl_3$) *(hetero)aromatic*: 7.71 (1H, s, H-3), 7.32–7.16 (5H, m, Ph), 5.82 (1H, d, *J*=7.4 Hz, C*H*OH), 4.55 (1H, d, *J*=7.4 Hz, OH); *DOABO–CH_2O*: 4.48 (1H, d, *J*=4.9 Hz, H-2-*c*), 4.47 (1H, d, *J*=4.9 Hz, H-8-*c*), 4.41 (2H, d, *J*=4.9 Hz, H-2, H-8-*t*), 4.31 (1H, d, *J*=8.5 Hz, 5-OC*H_a*H_b), 4.28 (1H, d, *J*=8.5 Hz, 5-OCH_aH_b), 3.88–3.83 (3H, OCH_3; 4H, H-4, H-6, H-*c*, H-*t*); δ_C (75 MHz, $CDCl_3$) *(hetero)aromatic*: 158.1 (1C, C-6), 155.3 (1C, C-2), 142.9 (1C, Cq., Ph), 137.1 (1C, C-5), 128.6 (2C, CH, Ph), 127.8 (1C, CH, Ph), 127.1 (2C, CH, Ph), 122.6 (1C, C-3); *DOABO–CH_2O*: 88.4 (2C, C-2, C-8), 74.5 (2C, C-4, C-6), 71.9 (1C, C-5), 70.8 (1C, CHOH), 69.5 (1C, 5-OCH_2), 54.1 (1C, OCH_3). MS (EI, 70 eV) *m/z* (rel int. %): 342 (9), 312 (4), 217 (5), 128 (100), 98 (10).

4.2.14. 3-[(*R)-4-Methoxy-α-hydroxybenzyl]-2-{[(1*R**,2*R**,5*S**)-2-phenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl]methoxy}-pyrazine (3a-*R*) and 3-[(*S**)-4-methoxy-α-hydroxybenzyl]-2-{[(1*R**,2*R**,5*S**)-2-phenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl]methoxy}-pyrazine (3a-*S*).** Nonseparable equimolar component mixture (82%) was obtained as yellow crystalline powder, mp 84–88 °C (column chromatography, eluent ligroin: AcOEt 2:1 v/v). [Found: C, 66.07; H, 5.76; N, 9.48. $C_{24}H_{25}N_3O_5$ requires: C, 66.19; H, 5.79; N, 9.65%]. R_f (67% ligroin:AcOEt) 0.20. ν_{max} (film KBr): 3449 (m), 2860 (m), 1611 (s), 1512 (s), 1418 (m), 1349 (w), 1256 (m), 1177 (m), 1028 (m), 911 (m), 853 (s), 754 (s), 701 (s), 615 (w), 571 (m), 494 (w) cm^{-1}. δ_H (300 MHz, $CDCl_3$) *(hetero)aromatic*: 8.17–8.15 (2H, m, H-5), 8.06–8.04 (2H, m, H-6), 7.50–7.43 (4H, m, Ph), 7.37–7.32 (6H, m, Ph), 7.18–7.12 (4H, m, Ph), 6.84–6.80 (4H, m, Ph), 5.75 (1H, d, *J*=6.4 Hz, C*H*–OH), 5.71 (1H, d, *J*=6.4 Hz, C*H*–OH), 5.00 (1H, d, *J*=6.4 Hz, OH), 4.94 (1H, d, *J*=6.4 Hz, OH); *DOABO–CH_2O*: 5.21 (1H, s, H-2-*t*), 5.16 (1H, s, H-2-*t*), 4.53 (1H, d, *J*=7.1 Hz, H-8-*c*), 4.49 (1H, d, *J*=7.1 Hz, H-8-*c*), 4.44 (1H, d, *J*=10.2 Hz, 5-OC*H_a*H_b), 4.41 (1H, d, *J*=10.2 Hz, 5-OCH_aH_b), 4.30 (1H, d, *J*=10.2 Hz, 5-OC*H_a*H_b), 4.296 (1H, d, *J*=9.0 Hz, H-4-*c*), 4.25 (1H, d, *J*=7.1 Hz, H-8-*t*), 4.22 (1H, d, *J*=10.2 Hz, 5-OCH_aH_b), 4.16 (1H, d, *J*=7.1 Hz, H-8-*t*), 3.95 (1H, d, *J*=9.0 Hz, H-4-*c*), 3.75 (2H, br s, H-4-*t*, H-6-*c*), 3.75 (3H, s, –OCH_3), 3.74 (3H, s, –OCH_3), 3.67 (1H, d, *J*=9.0 Hz, H-6-*c*), 3.62 (1H, d, *J*=9.0 Hz, H-4-*t*), 3.50 (1H, d, *J*=9.0 Hz, H-6-*t*), 3.26 (1H, d, *J*=9.0 Hz, H-6-*t*); δ_C (75 MHz, $CDCl_3$) *(hetero)aromatic*: 159.9, 159.8 (2C, 2C-2), 156.8 (2C, Cq., Ph), 146.4, 146.2 (2C, C-3), 140.3, 140.2 (2C, C-6), 139.5, 139.3 (2C, Cq., Ph), 135.4, 135.3 (2C, C-5), 134.1 (2C, Cq., Ph), 129.5, 128.9, 128.88, 128.8, 127.8, 127.78 (14C, CH, Ph), 114.4, 114.3 (4C, CH, Ph); *DOABO–CH_2O*: 99.2, 99.1 (2C, C-2), 85.1 (2C, C-8), 75.1 (2C, C-6), 73.5, 73.3 (2C, C-4), 72.3, 72.2 (2C, C-5), 71.3, 71.0 (2C, CHOH), 70.1, 69.6 (2C, 5-OCH_2), 55.7 (2C, –OCH_3). MS (ES^+) *m/z* (rel int. %): 422 (23), 313 (2), 295 (15), 237 (21), 202 (20), 146 (12).

4.2.15. 3-[(1*R)-2,2-Dimethyl-1-hydroxyprop-1-yl]-2-{[(1*R**,2*R**,5*S**)-2-phenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl]methoxy}-pyrazine (3b-*R*) and 3-[(1*S**)-2,2-dimethyl-1-hydroxyprop-1-yl]-2-{[(1*R**,2*R**,5*S**)-2-phenyl-3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl]methoxy}-pyrazine (3b-*S*).** Yield 68%. Nonseparable equimolar component mixture was obtained as white crystalline powder, mp 140–142 °C (column chromatography, eluent ligroin:AcOEt 2:1 v/v). [Found: C, 65.61; H, 7.21; N, 11.05. $C_{21}H_{27}N_3O_4$ requires: C, 65.45; H, 7.01; N, 10.91%]. R_f (67% ligroin:AcOEt) 0.48. ν_{max} (KBr film): 3436 (m), 2956 (m), 2868 (m), 1161 (m), 1585 (w), 1511 (s), 1418 (m), 1315 (w), 1028 (m), 917 (m), 830 (m), 755 (s), 700, (m), 576 (w) cm^{-1}. δ_H (300 MHz, $CDCl_3$) *(hetero)aromatic*: 8.16 (2H, d, *J*=2.6 Hz, H-5), 8.03–8.02 (2H, m, H-6), 7.52–7.49 (4H, m, Ph), 7.36–7.34 (6H, m, Ph); *DOABO–CH_2O*: 5.26 (1H, s, H-2-*t*), 5.25 (1H, s, H-2-*t*), 4.64 (1H, d, *J*=9.7 Hz, C*H*–OH), 4.61 (1H, d, *J*=9.7 Hz, C*H*–OH), 4.59 (1H, d, *J*=7.1 Hz, H-8-*c*), 4.58 (1H, d, *J*=7.1 Hz, H-8-*c*), 4.56 (1H, d, *J*=10.6 Hz, 5-OC*H_a*H_b), 4.48 (1H, d, *J*=10.6 Hz, 5-OC*H_a*H_b), 4.37 (1H, d, *J*=9.0 Hz, H-4-*c*), 4.35 (1H, d, *J*=7.1 Hz, H-8-*t*), 4.34 (2H, d, *J*=10.6 Hz, 5-OCH_aH_b), 4.33 (1H, d, *J*=7.1 Hz, H-8-*t*), 4.32 (1H, d, *J*=9.0 Hz, H-4-*c*), 4.06 (1H, d, *J*=9.0 Hz, H-6-*c*), 4.04 (1H, d, *J*=9.0 Hz, H-6-*c*), 3.83 (2H, d, *J*=9.0 Hz, H-4-*t*), 3.73 (1H, d, *J*=9.0 Hz, H-6-*t*), 3.70 (1H, d, *J*=9.0 Hz, H-6-*t*), 3.58 (1H, d, *J*=9.7 Hz, OH), 3.56 (1H, d, *J*=9.7 Hz, OH), 0.905, 0.900 (18H, s, CH_3); δ_C (75 MHz, $CDCl_3$) *(hetero)aromatic*: 157.0 (2C, C-2), 146.8 (2C, C-3), 139.9 (2C, C-6), 139.4 (2C, Cq., Ph), 136.1 (2C, C-5), 129.5, 128.8, 127.9, 127.8 (10C, CH,

Ph); *DOABO–CH_2O*: 99.3, 99.2 (2C, C-2), 85.3 (2C, C-8), 75.5, 75.4 (2C, C-4), 75.0, 74.9 (2C, CHOH), 73.6 (2C, C-6), 72.5 (2C, C-5), 70.2, 69.9 (2C, 5-OCH_2), 37.9 (2C, Cq., *t*-Bu), 26.3, 26.2 (6C, CH_3). MS (EI, 70 eV) *m/z* (rel int. %): (M^+) 385 (<1), 328 (23), 222 (30), 204 (100), 190 (83), 105 (13), 98 (60), 91 (20), 68 (54), 57 (26).

4.2.16. *rac*-5-(α-Hydroxybenzyl)-4,6-bis[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrimidine (5a). Yield 82% taking into account the recovered starting material **4a**; 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 (1H, s, H-2), 7.30–7.23 (5H, m, Ph), 6.05 (1H, s, C*H*OH), 4.20 (1H, br s, OH); *DOABO–CH_2O*: 4.42 (4H, d, *J*=5.3 Hz, H-2, H-8-*c*), 4.41 (2H, d, *J*=10.9 Hz, 5-OCH_aH_b), 4.35 (2H, d, *J*=10.9 Hz, 5-OCH_aH_b), 4.35 (2H, d, *J*=5.3 Hz, H-2-*t*), 4.34 (2H, d, *J*=5.3 Hz, H-8-*t*), 3.70 (2H, d, *J*=9.0 Hz, H-4-*c*), 3.66 (2H, d, *J*=9.0 Hz, H-4-*t*), 3.65 (2H, d, *J*=9.4 Hz, H-6-*t*), 3.61 (2H, d, *J*=9.0 Hz, H-6-*c*); δ_C (75 MHz, $CDCl_3$) *(hetero)aromatic*: 167.4 (2C, C-4, C-6), 156.4 (1C, C-2), 143.2 (1C, Cq., Ph), 128.8 (2C, CH, Ph), 127.7 (1C, CH, Ph), 125.5 (2C, CH, Ph), 107.4 (1C, C-5); *DOABO–CH_2O*: 88.34, 88.26 (2C, C-2, C-8), 73.8, 73.7 (2C, C-4, C-6), 71.9 (2C, C-5), 69.5 (2C, 5-OCH_2); 67.0 (1C, CHOH). MS (EI, 70 eV) *m/z* (rel int. %): (M^+-1) 471 (<1), 455 (50), 328 (8), 128 (100), 98 (5).

4.2.17. *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 (5b). Yield 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, $CDCl_3$) *(hetero)aromatic*: 8.31 (1H, s, H-2), 7.51–7.49 (8H, m, Ph), 7.34–7.30 (15H, m, Ph), 7.18 (2H, d, *J*=7.2 Hz, Ph), 5.93 (1H, d, *J*=10.8 Hz, C*H*OH), 3.08 (1H, d, *J*=10.8 Hz, OH); *DOABO–CH_2O*: 5.57, (2H, H-8-*t*), 5.55 (2H, s, H-2-*t*), 4.31 (2H, d, *J*=10.4 Hz, 5-OCH_aH_b), 4.25 (2H, d, *J*=10.4 Hz, 5-OCH_aH_b), 3.92 (2H, d, *J*=8.9 Hz, H-6-*c*), 3.81 (2H, d, *J*=8.9 Hz, H-6-*t*), 3.73 (2H, d, *J*=9.2 Hz, H-4-*c*), 3.69 (2H, d, *J*=9.2 Hz, H-4-*t*); δ_C (75 MHz, $CDCl_3$) *(hetero)aromatic*: 167.3 (2C, C-4, C-6), 156.5 (1C, C-2), 143.2 (1C, Cq., Ph), 139.34, 139.3 (4C, Cq., Ph), 129.1, 129.0, 128.8, 127.7, 127.6, 125.5, 125.2 (25C, CH, Ph), 107.2 (1C, C-5); *DOABO–CH_2O*: 97.6, 97.59 (4C, C-2, C-8), 73.3, 73.2 (4C, C-4, C-6), 73.0 (2C, C-5), 71.0 (2C, 5-OCH_2), 66.7 (1C, CHOH). MS (FAB^+) *m/z* (rel int. %): (M^++1) 778 (100), 760 (25).

4.2.18. 6-Chloro-4-[^{2}*H*]-3-[(3,7-dioxa-*r*-1-azabicyclo-[3.3.0]oct-*c*-5-yl)methoxy]-pyridazine (7a) and 3-chloro-4-[^{2}*H*]-6-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)-methoxy]-pyridazine (7b). Yield 47%. *Regioisomer* ***7a*** (15%): δ_H (300 MHz, $CDCl_3$) *aromatic*: 7.37 (1H, s, H-5). *Regioisomer* ***7b*** (32%): δ_H (300 MHz, $CDCl_3$) *aromatic*: 6.97 (1H, s, H-5). MS (EI, 70 eV) *m/z* (rel int. %): (M^++1) 259.6 (<1), 258 (<1), 257 (4), 196 (3), 157.5 (5), 128 (100), 98 (3).

4.2.19. *rac*-6-Chloro-4-(α-hydroxybenzyl)-3-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyridazine (7c) and *rac*-3-chloro-4-(α-hydroxybenzyl)-6-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyridazine (7d). Nonseparable component mixture was obtained as white crystalline powder, mp 154–167 °C (Et_2O:pentane 1:1 v/v) (column chromatography, eluent ligroin:acetone 1.8:1.0 v/v). [Found: C, 55.89; H, 5.21; N, 11.49. $C_{17}H_{18}N_3O_4Cl$ requires: C, 56.13; H, 4.99; N, 11.55%]. R_f (65% ligroin: acetone) 0.75. ν_{max} (film NaCl): 3417 (m), 3379 (s), 2868 (w), 1635 (m), 1586 (w), 1416 and 1414 (s), 1359 (s), 1095 (m), 1044 and 1041 (m), 930 and 928 (w), 754 and 749 (w), 703 (m) cm^{-1}. *Regioisomer* ***7c*** (53%): δ_H (300 MHz, $CDCl_3$) *(hetero)aromatic*: 7.69 (1H, s, H-5), 7.40–7.31 (3H, m, Ph), 7.28–7.20 (2H, m, Ph), 5.78 (1H, s, C*H*OH), 5.05 (1H, br s, OH); *DOABO–CH_2O*: 4.45 (1H, d, *J*=11.3 Hz, 5-OCH_aH_b), 4.44 (1H, d, *J*=5.5 Hz, H-2-*c*), 4.40 (1H, d, *J*=11.3 Hz, 5-OCH_aH_b), 4.39 (1H, d, *J*=5.5 Hz, H-2-*t*), 4.38 (1H, d, *J*=5.7 Hz, H-8-*c*), 4.34 (1H, d, *J*=5.7 Hz, H-8-*t*), 3.71 (2H, s, H-4-*c*, H-4-*t*), 3.45 (1H, d, *J*=9.0 Hz, H-6-*t*), 3.38 (1H, d, *J*=9.0 Hz, H-6-*c*); δ_C (75 MHz, $CDCl_3$) *(hetero)aromatic*: 161.6 (1C, C-3), 152.6 (1C, C-4), 140.2 (1C, Cq., Ph), 136.2 (1C, C-6), 129.4 (2C, CH, Ph), 128.0 (1C, C-5), 127.7 (1C, CH, Ph), 127.5 (2C, CH, Ph); *DOABO–CH_2O*: 88.4, 88.3 (2C, C-2, C-8), 74.1, 73.9 (2C, C-4, C-6), 71.7 (1C, C-5), 70.7 (1C, CHOH), 70.3 (1C, 5-OCH_2). *Regioisomer* ***7d*** (31%): δ_H (300 MHz, $CDCl_3$) *(hetero)aromatic*: 7.47 (1H, s, H-5), 7.40–7.31 (3H, m, Ph), 7.28–7.20 (2H, m, Ph), 5.90 (1H, s, C*H*OH), 5.05 (1H, br s, OH); *DOABO–CH_2O*: 4.53 (1H, d, *J*=5.7 Hz, H-2-*c*), 4.53 (2H, m, 5-OCH_aH_b), 4.52 (1H, d, *J*=5.7 Hz, H-8-*c*), 4.46 (2H, d, *J*=5.7 Hz, H-2, H-8-*t*), 3.90 (4H, s, H-4, H-6, H-*c*, H-*t*); δ_C (75 MHz, $CDCl_3$) *(hetero)aromatic*: 165.4 (1C, C-6), 150.5 (1C, C-4), 146.0 (1C, Cq., Ph), 140.4 (1C, C-3), 129.2 (2C, CH, Ph), 128.0 (2C, CH, Ph), 127.7 (1C, CH, Ph), 117.3 (1C, C-5); *DOABO–CH_2O*: 88.7 (2C, C-2, C-8), 74.4, 74.3 (2C, C-4, C-6), 72.1 (1C, CHOH), 71.9 (1C, C-5), 70.3 (1C, 5-OCH_2). MS (EI, 70 eV) *m/z* (rel int. %): (M^+) 363.6 (5), 346 (7), 128 (100), 98 (14).

4.2.20. *rac*-4-(α-Hydroxybenzyl)-3-methoxy-6-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyridazine (7e). Yield 78%. Yellowish crystalline powder, mp 44–46 °C (pentane) (column chromatography, eluent ligroin:acetone 1.5:1 v/v). [Found: C, 60.40; H, 5.99; N, 11.79. $C_{18}H_{21}N_3O_5$ requires: C, 60.16; H, 5.89; N, 11.69%]; R_f (60% ligroin:acetone) 0.40. ν_{max} (film NaCl): 3297 (s), 2945 (s), 2866 (s), 1620 (w), 1461 (s), 1412 (s), 1381 (s), 1227 (w), 1133 (w), 1023 (s), 928 (m), 751 (s), 700 (m) cm^{-1}. δ_H (300 MHz, $CDCl_3$) *(hetero)aromatic*: 7.28–7.15 (6H, m, pyridazine, Ph), 5.74 (1H, br s, C*H*OH), 4.28 (1H, br s, OH); *DOABO–CH_2O*: 4.37 (2H, d, *J*=5.7 Hz, H-2, H-8-*c*), 4.32 (2H, s, 5-OCH_aH_b), 4.31 (2H, d, *J*=5.7 Hz, H-2, H-8-*t*), 3.86 (3H, s, OCH_3), 3.76 (4H, s, H-4, H-6, H-c, H-*t*); δ_C (75 MHz, $CDCl_3$) *(hetero)aromatic*: 162.6 (1C, C-6), 159.9 (1C, C-3), 141.3 (1C, Cq., Ph), 138.5 (1C, C-4), 128.9 (2C, CH, Ph), 128.6 (1C, CH, Ph), 127.4

(2C, CH, Ph), 117.2 (1C, C-5); *DOABO–CH_2O*: 88.5 (2C, C-2, C-8), 74.4 (2C, C-4, C-6), 71.9 (1C, 5-OCH_2), 70.0 (1C, CHOH), 69.4 (1C, C-5), 55.0 (1C, OCH_3). δ_H (300 MHz, [D_6]benzene) *DOABO–CH_2O*: 4.46 (1H, d, *J*=10.7 Hz, 5-OC$H_a$$H_b$), 4.39 (1H, d, *J*=10.7 Hz, 5-OC$H_a$$H_b$), 4.26 (1H, d, *J*=5.3 Hz, H-2-*c*), 4.24 (1H, d, *J*=5.3 Hz, H-8-*c*), 4.054 (1H, d, *J*=5.3 Hz, H-2-*t*), 4.046 (1H, d, *J*=5.5 Hz, H-8-*t*), 3.66 (1H, d, *J*=8.7 Hz, H-4-*c*), 3.62 (1H, d, *J*=8.7 Hz, H-6-*c*), 3.57 (1H, d, *J*=8.7 Hz, H-4-*t*), 3.55 (1H, d, *J*=8.7 Hz, H-6-*t*). MS (EI, 70 eV) *m/z* (rel int. %): (M^+−1) 358 (10), 342 (20), 245 (15), 128 (100), 98 (9).

4.2.21. *rac*-4-(α-Hydroxybenzyl)-3,6-bis[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]octane-*c*-5-yl)methoxy]-pyridazine (7f). This compound was only identified in both the NMR spectra of the crude reaction mixture (together with the starting **6c**) and after unsuccessful attempt of separation by column chromatography (as mixture 36% **7f**+64% **6c**). δ_H (300 MHz, $CDCl_3$) *(hetero)aromatic, only distinct peaks are listed*: 7.35–7.20 (5H, m, Ph), 6.96 (1H, H-5), 5.72 (1H, br s, C*H*OH), 4.81 (1H, br s, OH); *DOABO–CH_2O C-3, C-6*: 4.52–4.30 (12H, irresolvable multiplet, H-2, H-8, H-*c*, H-*t*, 5-OCH_2); *DOABO–CH_2O linked at C-6*: 3.86 (4H, s, H-4, H-6, H-*c*, H-*t*); *DOABO–CH_2O linked at C-3*: 3.68 (2H, s, H-4-*c*, H-4-*t*), 3.43 (1H, d, *J*=9.0 Hz, H-6-*t*), 3.35 (1H, d, *J*=9.0 Hz, H-6-*c*); δ_C (75 MHz, $CDCl_3$) *(hetero)aromatic*: 162.9 (1C, C-3), 162.1 (1C, C-6), 159.4 (1C, C-4), 140.9 (1C, Cq., Ph), 129.2 (2C, CH, Ph), 129.1 (1C, CH, Ph), 127.5 (2C, CH, Ph), 117.9 (1C, C-5), 70.8 (1C, CHOH); *DOABO–CH_2O linked at C-3*: 88.4, 88.3 (2C, C-2, C-8), 74.3, 74.1 (2C, C-4, C-6), 71.8 (1C, 5-OCH_2), 69.7 (1C, C-5); *DOABO–CH_2O linked at C-6*: 88.7 (2C, C-2, C-8), 74.4 (2C, C-4, C-6), 71.9 (1C, 5-OCH_2), 69.8 (1C, C-5).

4.3. General procedure for the preparation of compounds 9a–d by cross-coupling under Stille conditions

In dry toluene (25 mL) and under a dry nitrogen atmosphere, 2,6-bis(tri-*n*-butylstannyl)pyrazine **8** 0.493 g (0.75 mmol) and chlorodiazine **1d**, **4c** and **6a** 0.405 g (1.575 mmol, 2.10 equiv) (0.630 g, 1.575 mmol, 2.10 equiv in the case of **4d**) were dissolved with stirring. $Pd(PPh_3)_4$ 0.091 g (0.079 mmol, 5% with respect to chlorodiazine) was rapidly added. The solution was heated at reflux for 22–48 h (Table 4) until the TLC monitoring (UV 254 nm) indicated the starting materials in traces only (compounds **9a**–**c**) or no more significant evolution of the reaction (in the case of compound **9d**), **8** (ligroin:AcOEt 50:1 v/v), **1d** (ligroin: AcOEt 2:1 v/v), **4c** and **6a** (ligroin:acetone 3:1 v/v), **4d** (ligroin:acetone 2:1 v/v). A second elution system was used to detect the desired products **9a**–**d** as shown below. During all the syntheses, Pd metal precipitated abundantly. The reaction mixture was filtered hot (100 °C) and the solids were washed (×50 mL) several times with hot EtOH. The combined organic filtrate was evaporated under vacuum and the solid residue was directly crystallised from an appropriate solvent or subjected to column chromatography to yield the title compounds **9a**–**d**.

4.3.1. 2,6-Bis{6′-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrazin-2′-yl}-pyrazine (9a). Yield 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 (2H, s, H-3, H-5), 9.04 (2H, s, H-3′), 8.05 (2H, s, H-5′); *DOABO–CH_2O*: 4.40 (4H, s, 5-OCH_2), 4.36 (4H, d, *J*=6.2 Hz, H-2, H-8-*c*), 4.33 (4H, d, *J*=6.2 Hz, H-2, H-8-*t*), 3.80 (8H, s, H-4, H-6, H-*c*, H-*t*); δ_C (75 MHz, CF_3CD_2OD) *heteroaromatic*: 157.0 (2C, C-6′), 146.4 (2C, C-2′), 143.5 (2C, C-2, C-6), 139.3 (2C, C-3, C-5), 133.1 (2C, C-5′), 131.2 (2C, C-3′); *DOABO–CH_2O*: 85.1 (4C, C-2, C-8), 71.2 (4C, C-4, C-6), 69.1 (2C, C-5), 65.1 (2C, 5-OCH_2). MS (FAB^+) *m/z* (rel int. %): (M^++1) 523 (14), 289 (100), 235 (30), 165 (48).

4.3.2. 2,6-Bis{6′-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrimidin-4′-yl}-pyrazine (9b). Yield 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 (2H, s, H-3, H-5), 8.90 (2H, s, H-2′), 7.88 (2H, s, H-5′); *DOABO–CH_2O*: 4.57 (4H, d, *J*=5.5 Hz, H-2, H-8-*c*), 4.55 (4H, s, 5-OCH_2), 4.50 (4H, d, *J*=5.5 Hz, H-2, H-8-*t*), 3.93 (8H, s, H-4, H-6, H-*c*, H-*t*); δ_C (75 MHz, $CDCl_3$) *heteroaromatic*: 170.6 (2C, C-6′), 162.1 (2C, C-4′), 158.8 (2C, C-2′), 148.1 (2C, C-2, C-6), 145.2 (2C, C-3, C-5), 105.4 (2C, C-5′); *DOABO–CH_2O*: 88.6 (4C, C-2, C-8), 74.3 (4C, C-4, C-6), 72.0 (2C, C-5), 69.3 (2C, 5-OCH_2). MS (FAB^+) *m/z* (rel int. %): (M^++1) 523 (10), 283 (<1), 136 (35), 128 (100).

4.3.3. 2,6-Bis{2′,6′-bis[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]-oct-*c*-5-yl)methoxy]-pyrimidin-4′-yl}-pyrazine (9c). Yield 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 (2H, s, H-3, H-5), 7.54 (2H, s, H-5′); *DOABO–CH_2O*: 4.56 (8H, d, *J*=5.3 Hz, H-2, H-8-*c*), 4.51 (8H, s, 5-OCH_2), 4.49 (4H, d, *J*=5.3 Hz, H-2, H-8-*c*), 4.47 (4H, d, *J*=5.3 Hz, H-2, H-8-*t*), 3.98 (8H, d, *J*=9.6 Hz, H-4, H-6-*c*), 3.89 (8H, d, *J*=9.6 Hz, H-4, H-6-*t*); δ_C (75 MHz, $CDCl_3$) *heteroaromatic*: 172.6 (2C, C-6′), 165.2 (2C, C-2′), 163.6 (2C, C-4′), 147.9 (2C, C-2, C-6), 145.2 (2C, C-3, C-5), 100.0 (2C, C-5′); *DOABO–CH_2O*: 88.6, 88.4 (8C, C-2, C-8), 74.7, 74.3 (8C, C-4, C-6), 71.9, 71.8 (4C, C-5), 71.0, 69.6 (4C, 5-OCH_2). MS (FAB^+) *m/z* (rel int. %): (M^++1) 809.8 (93), 459.9 (53), 391 (100).

4.3.4. 2,6-Bis{6′-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyridazin-3′-yl}-pyrazine (9d). Yield 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 (ligroin:acetone: ethanol 50:25:25) 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 (2H, s, H-3, H-5), 8.54 (2H, d, J=9.2 Hz, H-4′), 7.21 (2H, d, J=9.2 Hz, H-5′); *DOABO–CH_2O*: 4.73 (4H, s, 5-OCH_2), 4.59 (4H, d, J=5.7 Hz, H-2, H-8-*c*), 4.53 (4H, d, J=5.7 Hz, H-2, H-8-*t*), 3.96 (8H, s, H-4, H-6, H-*c*, H-*t*); δ_C (75 MHz, $CDCl_3$) *heteroaromatic*: 165.4 (2C, C-6′), 153.9 (2C, C-3′), 147.6 (2C, C-2, C-6), 143.3 (2C, C-3, C-5), 128.3 (2C, C-4′), 118.4 (2C, C-5′); *DOABO–CH_2O*: 88.8 (4C, C-2, C-8), 74.4 (4C, C-4, C-6), 72.0 (2C, C-5), 70.4 (2C, 5-OCH_2). MS (FAB^+) *m/z* (rel int. %): ($M+Na^+$) 545 (2), (M^++1) 523 (39), 283 (100), 128 (55), 95 (20).

4.3.5. 6,6′-Bis[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)-methoxy]-4,4′-bipyrimidine (10a). This compound was identified as side product in the crude reaction mixture of the synthesis of the compound **9a** in 6% occurrence. δ_H (300 MHz, $CDCl_3$) *heteroaromatic*: 8.83 (2H, s, H-2, H-2′), 7.79 (2H, s, H-5, H-5′). MS (FAB^+) *m/z* (rel int. %): (M^++1) 475 (<1), 289 (29).

4.3.6. 6,6′-Bis[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)-methoxy]-3,3′-bipyridazine (10b). This compound was identified as side product in the crude reaction mixture of the synthesis of the compound **9d** in 35% occurrence. δ_H (300 MHz, $CDCl_3$) *heteroaromatic*: 8.61 (2H, d, J=9.3 Hz, H-4, H-4′), 7.16 (2H, d, J=9.3 Hz, H-5, H-5′). MS (FAB^+) *m/z* (rel int. %): (M^++1) 445 (6).

4.3.7. 6,6′-Bis{6″-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyrimidin-4″-yl}-2,2′-bipyrazine (11a). This compound was identified as side product in the crude reaction mixture of the synthesis of the compound **9b** in 12% occurrence. δ_H (300 MHz, $CDCl_3$) *heteroaromatic*: 9.84 (2H, s, H-3, H-3′), 9.75 (2H, s, H-5, H-5′), 8.92 (2H, s, H-2″), 7.92 (2H, s, H-5″). MS (FAB^+) *m/z* (rel int. %): (M^++1) 630 (<1), 588 (<1), 564 (3).

4.3.8. 6,6′-Bis{6″-[(3,7-dioxa-*r*-1-azabicyclo[3.3.0]oct-*c*-5-yl)methoxy]-pyridazin-3″-yl}-2,2′-bipyrazine (11b). This compound was identified as side product in the crude reaction mixture of the synthesis of the compound **9d** in 15% occurrence. δ_H (300 MHz, $CDCl_3$) *heteroaromatic*: 9.89 (2H, s, H-3, H-3′), 9.75 (2H, s, H-5, H-5′), 8.62 (2H, d, J=9.2 Hz, H-4″), 7.23 (2H, d, J=9.2 Hz, H-5″). MS (FAB^+) *m/z* (rel int. %): 585 (<1), 564 (4).

Acknowledgements

The financial support from C.N.C.S.I.S. (Romania, Project 353/20, 2005) and A.U.F. (Project 6313PS571 2004, Bruxelles) is gratefully acknowledged.

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