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FIRST EXAMPLE OF 1-AZA-3,7-DIOXABICYCLO[3.3.0]OCTANE-5-YL-METHOXY SYSTEM AS DIRECTED *ORTHO*-METALLATION GROUP

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ABSTRACT. The first synthetic and stereochemical approach (supported by NMR data) is described for two title compounds by complete regioselective metallation of some π-deficient systems of type pyrazine bearing a 1-aza-3,7-dioxabicyclo[3.3.0]octane-5-yl-methoxy fragment as directed *ortho*-metallating group.

1. INTRODUCTION

Advances in the field of directed *ortho*-metallation with organo lithium reagents of azines and diazines have been recently and comprehensively reviewed.[1,2] The exploit of this methodology (the so called **DoM** reaction) is now widely documented as of fundamental synthetic importance in order to access functionalised π-deficient systems in clean, rapid, selective and high yields transformation.

In this context, of a crucial relevance are the Directed *ortho*-Metallation Groups (**DoMG**s) whose increasing diversity makes in our days the method overall attractive. Thus, halo-, trifluoromethyl-, oxygen- (OH, OR, $OCONR_2$, $OSONR_2$), sulphur- (SO_2NR_2, SO_nR, n=1, 2), nitrogen- (NHCOR, NHCOOR), carbon- (COOH, CONHR, $CONR_2$, COR, >C=N-OH etc) based DoMGs revealed their synthetic utility (**Scheme 1**).

Few examples are known in which the DoMG was a heterocyclic saturated system: 1,3-dioxane-2-yl (in pyrazine and pyridine series);[4,5] 1,3-dioxolane-2-yl,[6] pyrrolidine-1-yl[7] and piperidine-1-yl[8] (in pyridine series). However, their use was described primarily to mask (as protecting groups) carbonyl and amino functionality linked *ortho* to the reaction site rather than connected to a peculiar stereochemistry of the DoMGs of this type.

Following our findings in the field of synthesis and stereochemistry of substituted 1-**A**za-3,7-**D**ioxa**B**icyclo[3.3.0]**O**ctanes[9-12] (hereafter abbreviated simply as **ADBO**), we established that *r*-1-aza-*c*-5-hydroxymethyl-3,7-dioxabicyclo[3.3.0]octane[*] **5-HOCH$_2$-ADBO** as well as certain C-2, -8 substituted analogues can be easily and selectively converted to 5-hetaryloxymethyl derivatives of ADBO *via* their corresponding potassium alkoxides upon treatment with (poly)chloro π-deficient systems.[14] Next, we decided to test their aptitude in the metallation methodology applied to some new synthesised 5-hetaryloxymethyl compounds, *e.g.* in pyrazine series.

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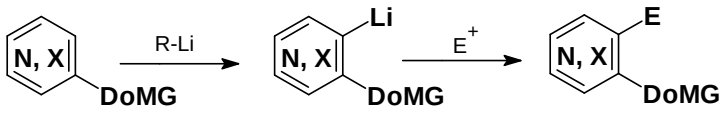
[*] Stereochemical descriptors ***r*** (referenece) and ***c*** (*cis*) are used according to I.U.P.A.C. in order to simplify discussion arising from the basic stereochemistry of this molecule as *cis* fused double oxazolidine system (lone pair at N-1 is the fiducial substituent).[13]



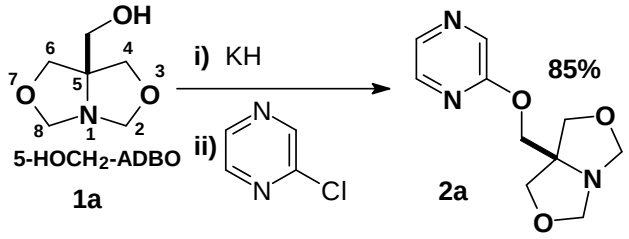
X = C, N

Scheme 1

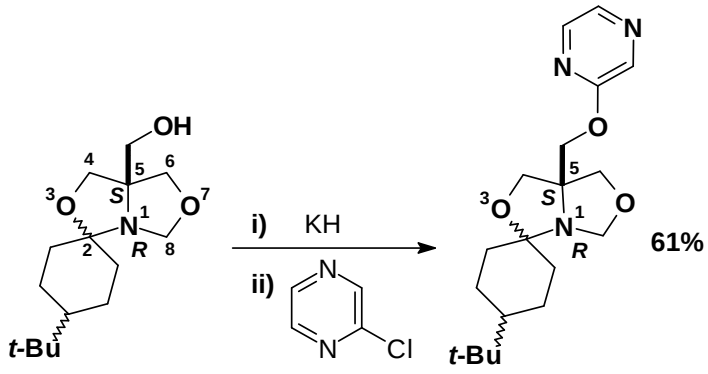
2. RESULTS AND DISCUSSION

2.1. Synthesis of *r*-1-aza-3,7-dioxa-*c*-5-pyrazinyloxymethyl-bicyclo [3.3.0]octanes

Starting from the ADBO derivatives **1a** and **1b**, the ADBO substituting pyrazines **2a** and **2b** were prepared succeeding our synthetic protocol (**Scheme 2**).[14] As yields demonstrated, it worked well also with 2-chloropyrazine. One must observe the stereochemistry of the starting material, the spiranic ADBO **1b**, which was used as racemate (in **Scheme 2** and hereafter throughout just one enantiomer 1*R**,5*S** is depicted) and as non separable mixture of diastereomers 94:6 **1b-*cis*** and **1b-*trans*** (O-3 and *t*-Bu group as references).



i) 1 eq. KH, THF, 1.5 hrs., 40 °C; **ii)** 1 eq. 2-chloropyrazine, 16 hrs. 40 °C



1b-*cis*, -*trans*
94 : 6

2b-*cis*, - *trans*
75 : 25

i) 1.05 eq. KH, THF, 1.5 hrs., 45 °C; **ii)** 1.1 eq. 2-chloropyrazine, 2 hrs., reflux; **iii)** 12 hrs., r.t.

Scheme 2

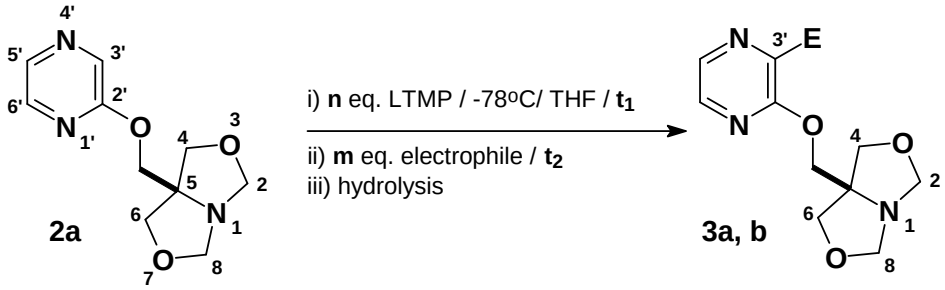
Following the chemistry depicted in **Scheme 2**, **1b** afforded **2b** as a diastereomeric mixture, 75:25 **2b-*cis* : 2b-*trans***. The ratio was calculated from the ^{1}H NMR spectrum of the isolated product by means of the well-separated peaks in the heteroaromatic zone; that is, all other relevant signals belonging to the two *cis* (*trans*) spiro-ADBO environment were completely overlapped. We explained simply this new diastereomeric ratio by the fact that crude **2b** (isolated in 96% yield) was directly crystallised from ligroine in which the *cis* diastereomer seemed to be more soluble. We opted for this alternative since the separation by column chromatography of C-2, -8 substituted ADBO derivatives often fails; indeed, too small were the differences between their R_f values together with decomposition on silica gel (see EXPERIMENTAL).[11]

2.2. Functionalisation by metallation

The metallation of the compounds **2a**, **2b** was straightforward.

The first attempt was carried on compound **2a** (**Scheme 3**).

In this purpose, we considered the comparative data focusing on the metallation of 2-methoxypyrazine.[15,16] Treatment of **2a** with 1.1 eq. of LTMP (4,4,6,6-**l**ithio**t**etra**m**ethyl**p**iperidide, as for 2-methoxypyrazine) at -78^{o}C for 60 min. followed by quench with 20% DCl/D_2O (at -78 ^{o}C) afforded the starting material in 99% yield. Deuteration was 84% at C-3' if 2.1 eq. of LTMP were used, as revealed by the ^{1}H NMR spectrum of the crude reaction mixture. The best result (98% deuterium incorporation in the crude product) was obtained with 4 eq. of LTMP (compound **3a**).



Compound	E	n	t_1	m	t_2	Temp. (^{o}C)	Yield[a] (%)
3a	D[b]	1.1	60	8.0	-	-78	0
	D	2.1	60	8.0	-	-78 to r.t.	84
	D	4.0	60	8.0	-	-78	98
3b	Ph-CHOH	4.0	60	4.0	Overnight	-78 to r.t.	79

[a] as isolated pure compounds, after flash column chromatography and subsequent recrystallisation (**3b**); for **3a**, as deuterium incorporation in the quantitatively isolated crude product (^{1}H NMR monitoring)

[b] 8 eq. DCl as 20% g/g D_2O solution was used

Scheme 3

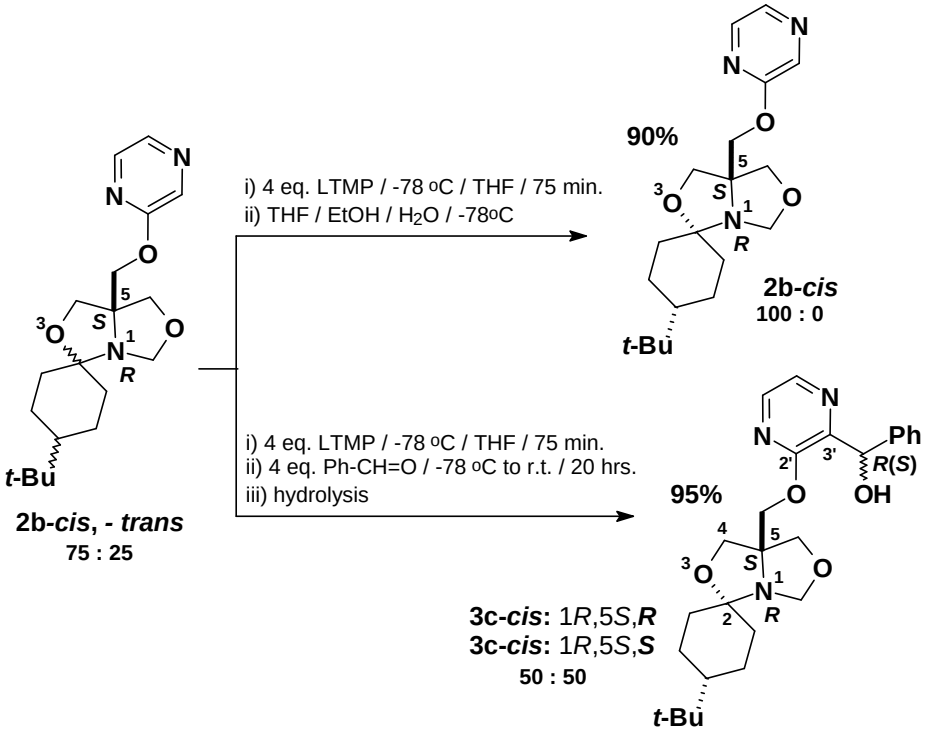
In identical conditions, the lithio-derivative of **2a**, upon treatment with benzaldehyde as electrophile, yielded the chiral diarylmethanol **3b** with good yield and complete *ortho*-regioselectivity.

The NMR spectra of **3b** nicely displayed the expected diastereotopic positions (as $\Delta\delta$ values) in the ADBO moiety: C-2 *vs.* C-8 and C-4 *vs.* C-6. We have seen of interest our study by selecting benzaldehyde as typical electrophile since the synthesis of the chiral diaryl methanols of type **3b** appeared to us closer to 5-OCH_2-ADBO intimate structure, including its above exhibited ability as **DoMG**.[11]

Our option was then supported by the results obtained when metallation of the mixture **2b-*cis*** and **2b-*trans*** was carried out. We figured that more details about the behaviour of azadioxabicyclooctane system as **DoMG** could be obtained if a diastereomeric compound built on this skeleton was involved. That is, the chiral spiro-ADBO compound **2b** was chosen as apt for this tentative (**Scheme 4**).

Metallation of **2b** quantitatively yielded, after work up, the crude equimolar mixture of two compounds **3c** (*de* 0%, 100% *ortho*-regioselectivity). However, by flash column chromatography, they were eluted together, although it was twice performed.

Hence, we focused on identification of the compounds **3c**.



Scheme 4

Initial inspection of their ^{1}H NMR spectrum evidenced two stereoisomers with excellent partition of all peaks in the aliphatic region but complete overlapping in the heteroaromatic zone.

Two hypothesis were selected to be more plausible:

i) 3c should be a 1:1 mixture of *cis* and *trans* diastereomers each having the same configuration of the α-hydroxybenzyl chiral center (*e.g.* 1:1 *R-cis* and *R-trans* or 1:1 *S-cis* and *S-trans*); this would involve not only a complete asymmetric induction but also an isomerisation *cis* → *trans* of the spiranic skeleton (from 75:25 in **2b** to 50:50 in **3c**).

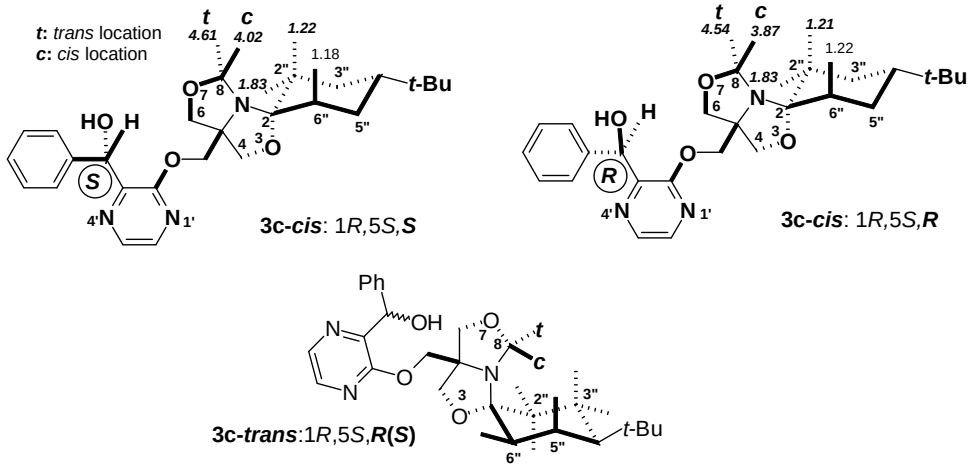
ii) 3c should be a 1:1 mixture of either *cis* or *trans* diastereomers having an opposite configuration (*R* or *S*) of the α-hydroxybenzyl chiral center (*e.g.* 1:1 *R-cis* and *S-cis* or 1:1 *R-trans* and *S-trans*); this would involve no steric predilection towards a certain diastereoselectivity but a complete isomerisation either *cis* → *trans* or *trans* → *cis* from **2b** to **3c**.

Complete systematic NMR investigations solved this very difficult problem.

In a first step, the ^{1}H and ^{13}C assignments for each of the compounds **3c** were realised by means of 2D homo- and heteronuclear NMR experiments: ^{1}H-^{15}N, ^{1}H-^{13}C (HSQC[17,18] and HMBC[19,20]), ^{1}H-^{1}H (COSY and TOWNY).[21,22] Next, the stereochemistry as *cis* or *trans* of **3c** was revealed by the correlation of the dipolar interactions observed in 2D ^{1}H-^{1}H (NOESY[23,24] and ROESY)[25,26] experiments with the protons estimated distances (Å) in all the possible modellised diastereomers, as described **i)** and **ii)** above.[27]

Obviously, this minute analysis was dedicated mainly to the spiranic oxazolidine motif in **3c**.

A good concordance we found between the estimated interatomic distances (Å) in the **3c-*cis***-1*R*,5*S*,*S*(*R*) diastereomer and the detectable dipolar interactions in 2D ^{1}H-^{1}H NMR experiments (**Scheme 5**).



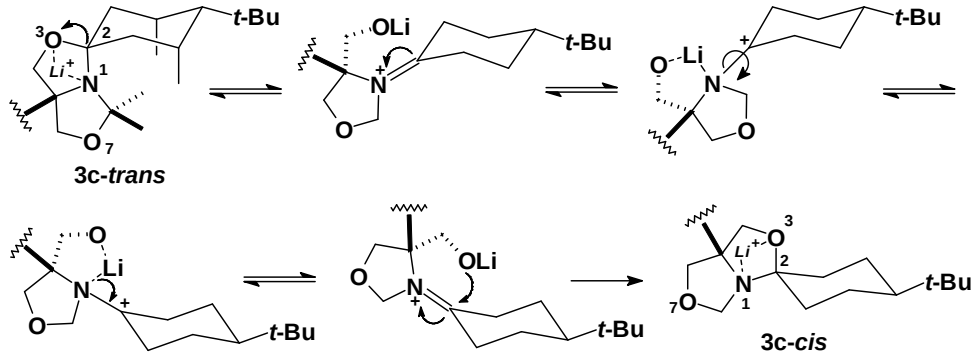
***italicised**:* positions (as δ, ppm) involved in relevant dipolar interaction as predicted by modellised structures and confirmed by NOSEY and ROESY experiments.

Scheme 5

We finished that the stereoisomers of type **3c** have both the same *cis* geometry, the single difference between them originating from the opposite configuration of the α-hydroxybenzyl chiral center.

Though our effort to use a chiral ADBO in an asymmetric synthesis failed (*de* 0%), we re-checked the validity of this conclusion by an alternative attempt (**Scheme 4**). In fact, it was not clear for us the change in stereochemistry of the spiranic ADBO from 75:25 *cis* : *trans* (in the starting **2b**) to 100:0 *cis* : *trans* (in **3c**). For this reason, we lithiated **2b** in the same and accurate conditions but we quenched the reaction with water. We isolated in 90% yield the crude product **2b** as unique *cis* diastereomer (^{1}H- and ^{13}C-NMR spectra monitoring).

This result supports our hypothesis concerning the interaction between ADBO and the Li-metallating reagent (*e.g.* chelation of Li by the most basic oxygen O-3 and N-1, followed by ring opening - ring closure) but observable only for configured azadioxabicyclooctane fragments (*e.g.* of type **2b** as proposed in **Scheme 6**).



Scheme 6

In the end, we note our verdict to be in agreement with the pioneering results of Pierce in 1951 (ring opening of the ADBO with Grignard reagents)[28,29] and our very recent assignments[11,30] (confirmed soon later by Pavia[31]): spontaneous-, Lewis acids- or even intramolecular hydrogen bonds-assisting stereoelectronic ring opening - ring closure in 2-substituted-1,3-oxazolidines.

3. CONCLUSION

The 1-aza-3,7-dioxabicyclo[3.3.0]octane-5-yl-methoxy group attached to pyrazine revealed clear and convincing aptitudes as Directed *ortho*-Metallating Group in the lithiation of these substrates. Although the quantitative and qualitative results seem similar with those previously reported for the methoxy analogous, the specific reaction conditions were enough different. Hence, azadioxabicyclooctane system itself can be considered as having a typical and versatile chelating behaviour against organo-lithium reagents, regardless its 5-yl-methoxy functionality. Organo-lithium reagents can assist ring opening-ring closure of the 1-aza-3,7-dioxabicyclo[3.3.0]octane system.

4. EXPERIMENTAL

General

Melting points are uncorrected; they were carried out on ELECTROTHERMAL® 9100 instrument.

Current NMR spectra were recorded on Brucker® AM300 instrument operating at 300 and 75 MHz for ^{1}H and ^{13}C nuclei respectively. NMR analysis for the compound **3c** was performed on Brucker® DMX500 instrument operating at 500 and 125 MHz for ^{1}H and ^{13}C nuclei respectively. No $SiMe_4$ was added; chemical shifts were measured against the solvent peak, throughout re-calibrated for $CDCl_3$ or C_6D_6. All NMR spectra were measured in anhydrous commercially available deuterated solvents. All chemical shifts (δ) values are given throughout in ppm; all coupling patterns (*J*) values are given throughout in Hz.

Labelling of the positions in the ADBO motif as c (cis) or t (trans) was made with respect to the fiducial substituent, the lone pair at N-1. Numbering of the position was made 1 → 8 for the ADBO fragment, 1' → 6' for the pyrazine ring and 1" → 6" for the spiranic cyclohexane.

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® 16 PC 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 (high-resolution J&W column, 30 m, 0.25 mm ID, flow rate: 1.2 mL min^{-1}).

All syntheses were performed under dry nitrogen atmosphere. THF was freshly distilled from Na/benzophenone prior to use. All solvents and starting materials were of commercial quality.

The modeling of the compounds **3c** was made by using Cerius-2 program: Cerius-2 Simulation Tool User's Reference, version 4.0. Molecular Simulation software for material science. Molecular Simulation Incorporated, San Diegao, CA, USA 1999.[27]

The synthesis and the conformational analysis of the compound **1b** we described in detail elsewhere.[11]

Typical procedure for the synthesis of the compounds 3a-c by Directed *ortho*-Metallation methodology

In 50 mL freshly distilled THF and under nitrogen atmosphere and with vigorous stirring, dry 2,2,6,6-tetramethylpiperidine (HTMP) from freshly opened bottle (0.688 mL, 0.565 g 100%, 0.576 g 98%, 4 mmol) was injected; the solution was cooled at (-10)-(-15 ^{o}C) in an ice bath 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 ADBO-substituting pyrazine **2a**, **b** (1.00 mmol) as freshly distilled THF solution (2-10 mL) was introduced. Specific conditions to perform the reaction are presented in **Schemes 3** and **4**. TLC monitoring was made as follows: 02-0.3 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. The reaction was quenched according to one of the following variant:

A. In the case of deuterated compound **3a** the reaction was quenched at -78 °C 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** (see below).

B. In the case of compounds **2b** the reaction was quenched at –78 °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** (see below).

C. In the case of compounds **3b, c**, 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 (2x15 mL) then the combined organic solution was washed with water (x25 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 deutherated compound **3a** (**Note 1**). For the rest of the compounds **3b**, **c**, the mixtures were purified by column chromatography to yield the title compounds **3b, c** (**Note 2**).

Note 1: for mono deuterated compound **3a** the magnitude of the corresponding integral is given as percentages with respect to the most intense signal.

Note 2: CARE! TLC monitoring of all reactions and separations by column chromatography evidenced very weak absorption in UV (254 nm); concentrated samples should be used.

Preparation of the compound 2b

The compound **2b** was prepared following the same protocol as for **2a**: from compound **1b** (as mixture of 96:4 *cis : trans* diastereomers, 0.650 g, 2.4 mmol) and potassium hydride (0.330 g as 30% KH, 0.100 g 100%, 2.5 mmol) in anhydrous THF (40 mL), upon treatement with chloropyrazine (0.236 mL, 0.297 g, 2.6 mmol, 2 hrs. at reflux then 12 hrs. at room temperature) and work up, 0.802 g the crude product **2b** was obtained. Subsequent recrystallisation from ligroine afforded 0.517 g of the title compound **2b** as a mixture of 75:25 *cis : trans* diastereomers.

2-{*r*-1-Aza-3,7-dioxabicyclo[3.3.0]octane-*c*-5-yl}-methoxypyrazine (2a) (85%) yellowish crystalline powder, mp 128-129 °C (pentane); [Found: C, 53.50; H, 6.09; N, 18.55. $C_{10}H_{13}N_3O_3$ requires: C, 53.81; H, 5.87; N, 18.82%]; R_f(75% ligroine/ acetone) 0.40; ν_{max} (film NaCl) 2868 (m), 1524 (s), 1465 (m), 1413 (s), 1361 (m), 1289 (s), 1134 (m), 1032 (s), 1002 (s), 915 (s), 832 (m), 692 (m) cm^{-1}. δ_H (300 MHz $CDCl_3$) *heteroaromatic*: 8.19 (1H, d, *J* =1.5 Hz, H-3), 8.09 (1H, d, *J* =3.0 Hz, H-5), 8.01 (1H, dd, *J* =1.5, 1.5 Hz, H-6); *alicyclic*: 4.47 (2H, d, *J* =5.7 Hz, H-2, -8-*c*), 4.41 (2H, d, *J* =5.7 Hz, H-2, -8-*t*), 4.33 (2H, s, 5-OC*H*$_2$), 3.83 (4H, s, H-4, -6, -*c*, -*t*); δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 160.1 (1C, C-2), 140.9 (1C, C-6), 137.5 (1C, C-3), 136.1 (1C, C-5); *alicyclic*: 88.6 (2C, C-2, -8), 74.4 (2C, C-4, -6), 71.9 (1C, C-5), 69.0 (1C, 5-O-*C*H_2). MS (EI, 70 eV); m/z (rel. int. %): 223 (6) [M^+], 178 (14), 163 (13), 114 (100), 98 (17), 86 (9), 68 (26), 58 (11), 42 (18), 41 (59).

(1*R,5*S**)-2-{*r*-1-aza-*r*-3-oxa-7-oxa-2-(*c*-4-tertbutylspirocyclohexyl)-bicyclo [3.3.0] octane-*c*-5-yl}-methoxypyrazine (2b-*cis*)** and **(1*R**,5*S**)-2-{*r*-1-aza-*r*-3-oxa-7-oxa-2-(*t*-4-tertbutylspirocyclohexyl)-bicyclo[3.3.0]octane-*c*-5-yl}-methoxypyrazine (2b-*trans*)** (61%) yellow crystalline powder, mp 103-105 °C (as mixture of diastereomers *cis* : *trans* 75:25); [Found: C, 65.79; H, 8.19; N, 11.85. $C_{19}H_{29}N_3O_3$ requires: C, 65.68; H, 8.41; N, 12.09%]; R_f(75% ligroine/acetone) 0.60; ν_{max} (film NaCl) 2940 (s), 2857 (m), 1529

(s), 1465 (m), 1408 (s), 1284 (s), 1080 (w), 1005 (m), 909 (w) cm^{-1}. ***Diastereomer* 2b-*cis***: δ_H (300 MHz $CDCl_3$) *heteroaromatic*: 8.21 (1H, s, H-3), 8.11 (1H, d, *J*=3.0 Hz, H-5), 8.03 (1H, d, *J*=2.6 Hz, H-6); *alicyclic*: 4.79 (1H, d, *J*=7.5 Hz, H-8-*c*), 4.42 (1H, d, *J*=10.6 Hz, 5-OC*H*$_a$H$_b$), 4.29 (1H, d, *J*=10.6 Hz, 5-OCH$_a$*H*$_b$), 4.15 (1H, d, *J*=7.5 Hz, H-8-*t*), 4.04 (1H, d, *J*=9.2 Hz, H-4-*c*), 3.86 (1H, d, *J*=9.2 Hz, H-4-*t*), 3.77 (1H, d, *J*=8.7 Hz, H-6-*c*), 3.65 (1H, d, *J*=8.7 Hz, H-6-*t*), 1.97-1.79 (2H, m, cyclohexyl), 1.77-1.67 (1H, m, cyclohexyl), 1.60-1.45 (2H, m, cyclohexyl), 1.44-1.15 (3H, m, cyclohexyl), 1.03-0.89 (1H, m, cyclohexyl), 0.81 [9H, s, C(C*H*$_3$)$_3$]; δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 160.3 (1C, C-2), 140.8 (1C, C-6), 137.4 (1C, C-3), 136.2 (1C, C-5); *alicyclic*: 98.1 (1C, C-2), 82.0 (1C, C-8), 73.8 (1C, C-6), 72.0 (1C, C-5), 71.6 (1C, C-4), 69.7 (1C, 5-O-*C*H$_2$), 47.5 (1C, *C*H, cyclohexyl), 38.5, 32.7, 32.2, 24.7 (4x1C, *C*H$_2$ cyclohexyl), 28.0 [3C, C(*C*H$_3$)$_3$] , 24.5 [1C, *C*(CH$_3$)$_3$]. ***Diastereomer* 2b-*trans***: δ_H (300 MHz $CDCl_3$ only distinct peaks are listed) *heteroaromatic*: 8.09 (1H, s, H-5), 8.01 (1H, s, H-6); δ_C (75 MHz $CDCl_3$) *heteroaromatic*: 136.3 (1C, C-5); *alicyclic*: 96.2 (1C, C-2), 68.4 (1C, 5-OCH$_2$), 47.3 (1C, *C*H cyclohexyl), 37.8 (1C, *C*H$_2$ cyclohexyl). MS (EI, 70 eV); m/z (rel. int. %): 348 [M^+] (50), 334 (11), 318 (27), 292 (13), 252 (100), 234 (15), 222 (35), 194 (50), 165 (7), 152 (9), 98 (70).

2-{*r*-1-Aza-3,7-dioxabicyclo[3.3.0]octane-*c*-5-yl}-methoxy-[3-^{2}H]-pyrazine (3a) (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%); *alicyclic*: see compound **2a**. MS (EI, 70 eV); m/z (rel. int. %): 225 (5) [M^++1], 207 (5), 177 (4), 128 (100%), 98 (9).

***Rac*-2-{*r*-1-aza-3,7-dioxabicyclo[3.3.0]octane-*c*-5-yl}-methoxy-3-α-hydroxy benzylpyrazine (3b)** (79% after column chromatography, 51% after recrystallisation) yellowish crystalline powder, mp 84-85 °C (column chromatography, eluent AcOEt : ligroine 20:1 v/v then recrystallisation from pentane); [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/ligroine) 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); 5.71 (1H, d, *J*=4.7 Hz, C*H*OH), 5.05 (1H, d, *J*=4.7 Hz, O*H*); *alicyclic*: 4.36 (1H, d, *J* =5.7 Hz, H-8-*c*), 4.31 (1H, d, *J* =5.7 Hz, H-8-*t*), 4.29 (1H, d, *J* =6.4 Hz, H-2-*c*), 4.26 (1H, d, *J*=10.9 Hz, 5-OC*H*$_a$H$_b$), 4.25 (1H, d, *J* =6.4 Hz, H-2-*t*), 4.14 (1H, d, *J*=10.9 Hz, 5-OCH$_a$*H*$_b$), 3.64 (2H, s, H-6-*c*, -*t*), 3.38 (1H, d, *J*=9.0 Hz, H-4-*t*), 3.28 (1H, d, *J*=9.0 Hz, H-4-*c*); δ_C (75 MHz $CDCl_3$) *(hetero)aromatic*: 156.8 (1C, C-2), 146.2 (1C, C-3), 141.9 (1C, C-q arom.), 140.3 (1C, C-5), 135.5 (1C, C-6), 128.9 (2C, *C*H arom.), 128.5 (1C, *C*H arom.), 127.6 (2C, *C*H arom.); *alicyclic*: 88.4 [1C, C-2(8)], 88.3 [1C, C-(2)8], 74.32 [1C, C-4(6)], 74.28 [1C, C-(4)6], 71.9 (1C, *C*HOH), 71.6 (1C, C-5), 69.3 (1C, 5-O*C*H$_2$). MS (EI, 70 eV); m/z (rel. int. %): 328 (3) [M^+-1], 312 (100), 281.9 (13), 254.8 (10), 211.7 (11), 186.8 (8), 128 (75), 98 (32).

***Rac*-(*R**,1*R**,5*S**)-2-{*r*-1-aza-*r*-3-oxa-7-oxa-2-(*c*-4-tertbutylspirocyclohexyl)-bicyclo[3.3.0]octane-*c*-5-yl}-methoxy-3-α-hydroxybenzylpyrazine (3c-*cis*-1*R*,5*S*,*R*)** and ***Rac*-(*S**,1*R**,5*S**)-2-{*r*-1-aza-*r*-3-oxa-7-oxa-2-(*t*-4-tertbutylspirocyclohexyl)-bicyclo [3.3.0]octane-*c*-5-yl}-methoxy-3-α-hydroxybenzylpyrazine (3c-*cis*-1*R*,5*S*,*S*)** (95%) white crystalline powder, mp 96-98 °C (column chromatography, eluent ligroine :

acetone 4:1 v/v then, crystallisation from pentane as non separable 1:1 mixture of diastereomers labelled as **3c-*cis*-1*R*,5*S*,*R*** and **3c-*cis*-1*R*,5*S*,*S*** respectively, see **Scheme 4** and **5**); [Found: C, 69.11; H, 8.19; N, 8.97. $C_{26}H_{35}N_3O_4$ requires: C, 68.85; H, 7.78; N, 9.26%]; R_f (80%ligroine/acetone) 0.60 and 0.40; ν_{max} (film NaCl) 3431 (s), 2945 (m), 2857 (m), 1638 (m), 1416 (s), 1080 (m), 1023 (m), 700 (s) cm^{-1}. *The hereafter reported NMR data refer to labelling of the molecular positions as described in* **Scheme 5**. ***Diastereomer* 3c-*cis*-1*R**,5*S**,*S****: δ_H (500 MHz C_6D_6) *(hetero)aromatic*: 7.66 (1H, d *J*=3.0 Hz, H-5'), 7.53 (1H, d, *J*=2.5 Hz, H-6'), 7.26 (2H, m, *ortho* phenyl), 7.05 (2H, m, *meta* phenyl), 6.98 (1H, m, *para* phenyl); *alicyclic*: 4.61 (1H, d, *J*=7.5 Hz, H-8-*t*), 4.28 (1H, d, *J*=10.5 Hz, 5-OCH_aH$_b$), 4.02 (1H, d, *J*=8.0 Hz, H-8-*c*), 4.00 (1H, d, *J*=12.0 Hz, 5-OCH$_a$$H_b$), 3.55 (1H, d, *J*=8.5 Hz, H-6-*t*), 3.44 (1H, d, *J*=9.0 Hz, H-4-*t*), 3.41 (1H, d, *J*=8.5 Hz, H-6-*c*), 3.37 (1H, d, *J*=9.0 Hz, H-4-*c*), 1.83 (1H, ddd, *J*=3.2, 6.4, 12.6 Hz, H-2"-eq.), 1.77 (1H, ddd, *J*=3.0, 6.5, 12.6 Hz, H-6"-eq.), 1.22 (1H, m, H- H-2"-ax.), 1.18 (1H, m, H-6"-ax.), 1.50 (4H, m, H-3", -5", -ax., -eq.), 0.83 [9H, s, C(CH_3)$_3$], 0.81 (1H, m, H-4"-ax.); δ_C (125 MHz C_6D_6) *(hetero)aromatic*: 157.56 (1C, C-2'), 143.3 (1C, C-3'), 143.2 (1C, C-q phenyl), 140.5 (1C, C-5'), 135.49 (1C, C-6'), 129.2 (2C, *meta C*H phenyl), 128.7 (1C, *para C*H phenyl); 128.3 (2C, *ortho C*H phenyl); *alicyclic*: 98.4 (1C, C-2), 82.2 (1C, C-8), 73.9 (1C, C-6), 72.8 (1C, C-4), 71.18 (1C, 5-O-*C*H$_2$), 70.91 (1C, C-5), 48.03 (1C, C-4"), 39.6 (1C, C-6"), 32.91 [1C, *C*(CH$_3$)$_3$], 32.32(1C, C-2"), 28.36 [3C, C(*C*H$_3$)$_3$], 25.33 (1C, C-5"), 25.04 (1C, C-3"); δ_N (500 MHz C_6D_6): 96.9 (1N, N-1), 281.3 (1N, N-1'), 319.4 (1N, N-4"). ***Diastereomer* 3c-*cis*-1*R**,5*S**,*R****: δ_H (500 MHz C_6D_6) *(hetero)aromatic*: 7.66 (1H, d *J*=3.0 Hz, H-5'), 7.53 (1H, d, *J*=2.5 Hz, H-6'), 7.27 (2H, m, *ortho* phenyl), 7.05 (2H, m, *meta* phenyl), 6.98 (1H, m, *para* phenyl); *alicyclic*: 4.54 (1H, d, *J*=7.5 Hz, H-8-*t*), 4.18 (1H, d, *J*=10.5 Hz, 5-OCH_aH$_b$), 4.14 (1H, d, *J*=10.5 Hz, 5-OCH$_a$$H_b$), 3.87 (1H, d, *J*=8.0 Hz, H-8-*c*), 3.80 (1H, d, *J*=9.0 Hz, H-4-*t*), 3.56 (1H, d, *J*=9.0 Hz, H-4-*c*), 3.34 (1H, d, *J*=8.5 Hz, H-6-*t*), 3.06 (1H, d, *J*=8.5 Hz, H-6-*c*), 1.89 (1H, ddd, *J*=3.2, 6.5, 13.8 Hz, H-6"-eq.), 1.83 (1H, ddd, *J*=3.2, 6.4, 12.6 Hz, H-2"-eq.), 1.22 (1H, m, H- H-6"-ax.), 1.21 (1H, m, H-2"-ax.), 1.50 (4H, m, H-3", -5", -ax., -eq.), 0.83 [9H, s, C(CH_3)$_3$], 0.84 (1H, m, H-4"-ax.); δ_C (125 MHz C_6D_6) *aromatic*: 157.61 (1C, C-2'), 147.1 (1C, C-3'), 143.0 (1C, C-q phenyl), 140.5 (1C, C-5'), 135.46 (1C, C-6'), 129.2 (2C, *meta C*H phenyl), 128.7 (1C, *para C*H phenyl); 128.3 (2C, *ortho C*H phenyl); *alicyclic*: 98.4 (1C, C-2), 82.0 (1C, C-8), 73.9 (1C, C-6), 72.8 (1C, C-4), 71.18 (1C,C-5), 70.91 (1C, 5-O*C*H$_2$), 48.06 (1C, C-4"), 32.95 [1C, *C*(CH$_3$)$_3$], 32.6 (1C, C-6"), 32.3 (1C, C-2"), 28.38 [3C, C(*C*H$_3$)$_3$], 25.36 (1C, C-5"), 25.07 (1C, C-3"); δ_N (500 MHz C_6D_6): 96.7 (1N, N-1), 281.3 (1N, N-1'), 319.4 (1N, N-4"). MS (EI, 70 eV); m/z (rel. int. %): 454 [M^++1] (65), 436 (20), 423 (18), 300 (40), 282 (75), 252 (100), 222 (18), 185 (13), 128 (95), 98 (77).

Isomerisation of (1*R,5*S**)-2-{*r*-1-aza-*r*-3-oxa-7-oxa-2-(*t*-4-tertbutylspirocyclo hexyl)-bicyclo[3.3.0]octane-*c*-5-yl}-methoxypyrazine (2b-*trans*) into (1*R**,5*S**)-2-{*r*-1-aza-*r*-3-oxa-7-oxa-2-(*c*-4-tertbutylspirocyclohexyl)-bicyclo[3.3.0]octane-*c*-5-yl}-methoxypyrazine (2b-*cis*)**

According to the typical procedure for metallation and the same reaction conditions (**Scheme 4**), the mixture was quenched with water as 1:1:1 v/v/v mixture with EtOH/THF at –78 ^oC. After typical preliminary work up, the isolated compound (in 90% yield as *crude product*) exhibited identical NMR spectra with only the major

component **2b-*cis*** from the already described mixture **2b-*cis*, -*trans***. After identification, the compound was simply crystallised from pentane; mp 77-78 ^{o}C. Scale up of the synthesis: 0.5 mmol mixture **2b-*cis*, -*trans***.

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