

# FIRST EXAMPLE OF LONG DISTANCE STEREOCONTROLLED SYNTHESIS IN 1-AZA-3,7-DIOXABICYCLO[3.3.0]OCTANE SERIES

Carmen Maierceanu,<sup>a</sup> Mircea Darabantu,<sup>a\*</sup> Eric Condamine,<sup>b</sup> Gérard Plé,<sup>b</sup> Yvan Ramondenc,<sup>b</sup> Marijana Fazekas,<sup>a</sup> Monica Pintea<sup>a</sup> and Camelia Berghian<sup>c</sup>

<sup>a</sup> "Babes-Bolyai" University, Department of Organic Chemistry, 11 Aranyi János str., RO-3400 Cluj-Napoca, Romania

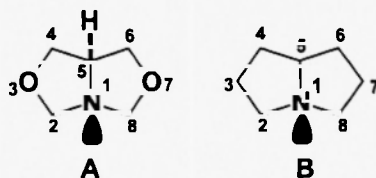
<sup>b</sup> Université de Rouen, Institut de Recherche en Chimie Organique Fine (I. R. C. O. F.), 76131 Mont Saint-Aignan, France

<sup>c</sup> "Babes-Bolyai" University, Department of Inorganic Chemistry, 11 Aranyi János str., RO-3400 Cluj-Napoca, Romania

**Abstract:** The diastereoselective synthesis of (1*R*\*,1'*S*\*,2*S*\*,2'*R*\*,5*S*\*,5'*R*\*,8*R*\*,8'*S*\*)-bis-1,4-{1-aza-5-methyl-8-(4-nitrophenyl)-3,7-dioxabicyclo[3.3.0]octane-2-yl}benzene is described as the first example of a long distance stereocontrolled synthesis of this type of structure. The thermodynamic control of the reaction together with complete NMR evidence to support the stereochemistry of this compound are discussed.

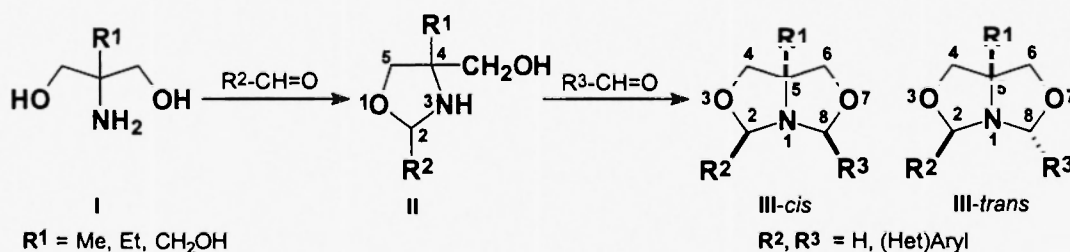
## INTRODUCTION

The 1-aza-3,7-dioxabicyclo[3.3.0]octane heterocyclic saturated system **A** (Scheme 1) as an easily available analogue of the core alkaloid pyrrolizidine **B** is known since the pioneering works of Senkus (1, 2), Pierce (3, 4) and Bergmann (5).



Scheme-1

The early title derivatives of **A** are classically obtained by direct two step condensation between *C*-2-substituted-2-amino-1,3-propanediols (the so called "serinols") and carbonyl compounds, mainly aldehydes (Scheme 2) (1, 2).



Scheme-2

Depending on the type of hydroxymethyl groups in **I**, homotopic ( $R^1 = \text{CH}_2\text{OH}$ ) or enantiotopic ( $R^1 = \text{Me, Et}$ ), the treatment of commercial *C*-2-substituted serinols **I** with 1 eq. of an aldehyde provides (non) isolable (epimeric) oxazolidines **II**. The second ring closure affords the substituted 1-aza-3,7-dioxabicyclo[3.3.0]octane **III** possessing an already very well documented stereochemistry of the bicyclic skeleton (Scheme 1) (6 – 11): a configurationally stable *cis* fused double oxazolidine system [H-5 in **A** (or  $R^1$  in **III**) and the lone pair of the bridged nitrogen as references]. All (hetero)atoms in **A** (Scheme 1) are prostereogenic to build a heterofacial molecule. According to these basic steric requirements, the disposal of the ligands  $R^2$  vs.  $R^3$  can be in a simplified way seen as *cis* or

\* darab@chem.ubbcluj.ro; darabantu@cluj.astral.ro; Tel.: 00 40 264 59 38 33; Fax. 00 40 264 59 08 18

*trans* relationship (Scheme 2). One must however observe that if  $R^2 \neq R^3$  both *cis* and *trans* diastereomers are polychiral structures ( $N^*-1, C^*-2, -5, -8$ ). If  $R^2 = R^3$ , III-*trans* is still chiral whereas III-*cis* becomes a *meso* form (9, 10).

Following our initial findings in the domain of the synthesis and stereochemistry of the azadioxabicyclooctane system, we recently described (12) the versatile behaviour of the double oxazolidines of type II (derived from terephthalaldehyde) in complex ring-chain tautomerism equilibria (13). On the other hand, there are very few examples of compounds of type III prepared by using two different aldehydes ( $R^2 \neq R^3$ ) (7, 10). Moreover, a "dimeric" structure in this class was but once described by us (10).

For the present communication, our attention focused on terephthalaldehyde as the first aldehyde (Scheme 2) followed, in the second step, by *p*-nitrobenzaldehyde. Our option for the last one was motivated by the already reported genotoxicity of the nitro group in oxazolidine derivatives (14, 15).

## RESULTS AND DISCUSSION

### 1. Synthesis

The present study started from our previously reported condensation products 2 – 4a-c obtained from terephthalaldehyde and the serinols 1a-c (Scheme 3) (12). We note that the identity of the starting materials was different in solid state (IR spectra performed as suspension in nujol) than in solution (high resolution NMR in DMSO- $d_6$ ). Thus, from 1a, the double Schiff base 2a was detected in solution as major product (82 %) and exclusively as such in solid state. In solution, the isomerisation 2a  $\rightarrow$  3a  $\rightarrow$  4a slowly occurred to afford the tautomeric mixture 2a 36 %, 3a 47 % and 4a 17 % in equilibrium. From 1b, a spontaneous equilibrium state was observed in DMSO- $d_6$ : 2b 13 %, 3b 30 % and 4b 57 %. In solid state, the product appeared as an authentic double oxazolidine 4b. Finally, TRIS 1c yielded only the corresponding double oxazolidine 4c (IR spectroscopy); in solution, 4c was also largely dominant as a component of a spontaneous equilibrium: 86% 4c and 14 % 3c.

From the isolated 2-4, the attempt to a subsequent ring closure upon treatment with 2 eq. of *p*-nitrobenzaldehyde was straightforward. The thermodynamic conditions were used: up to 24 hours in refluxing toluene with continuous removal of water (*p*-Ts-OH as catalyst). Since the NMR spectra of the crude reaction mixtures provided very complicated appearance, the conversions in Scheme 3 were calculated based on the effective amounts of products separated by flash column chromatography.

The results showed a significant dependence on the initial ring-chain tautomerism between 2  $\rightarrow$  3  $\rightarrow$  4.

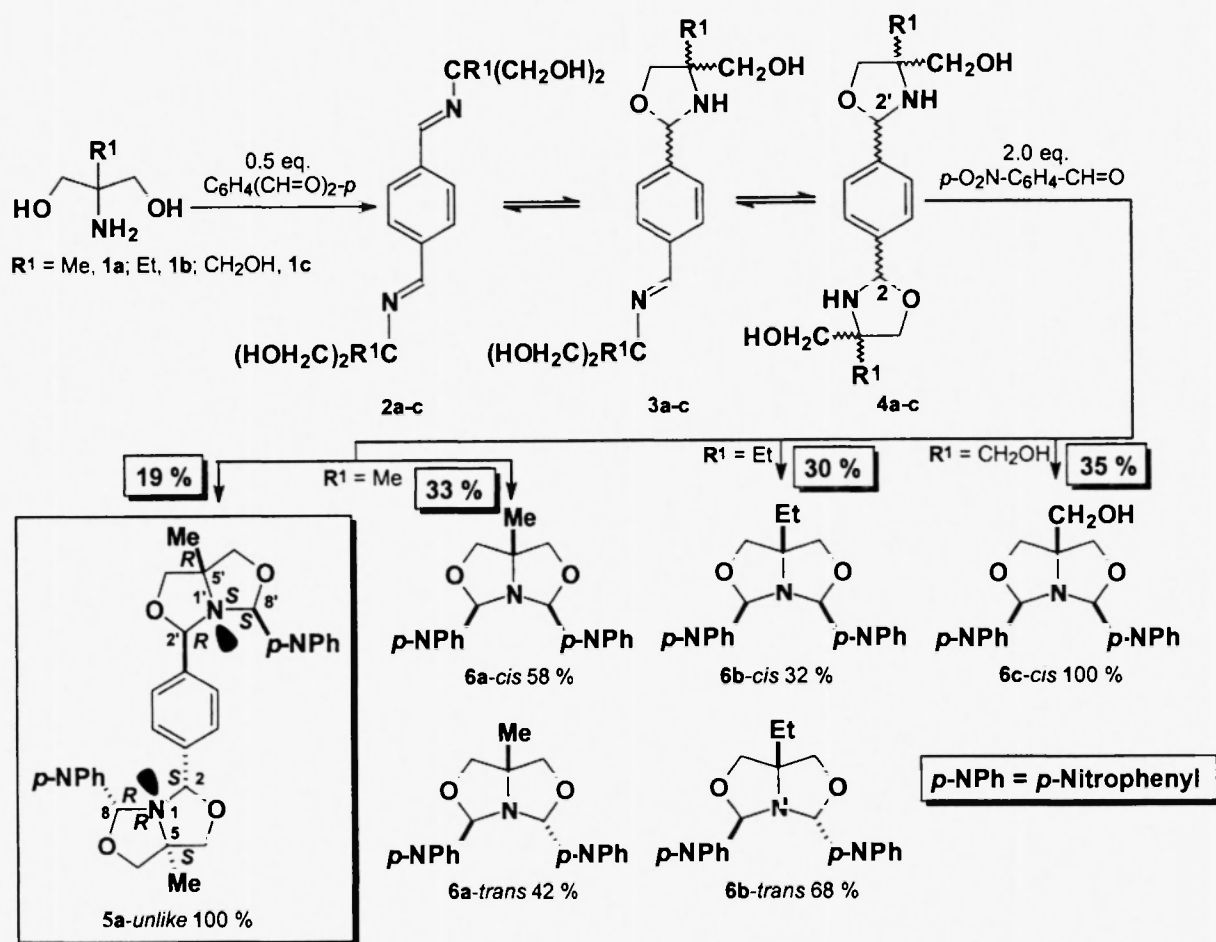
Only from 2a-4a, possessing the double Schiff-base 2a as major component, we did succeed to obtain the desired "dimer" 5a. Its stereochemistry elucidated as *unlike* (with respect to the chiral centers C-2, -2') will be discussed later on. The side non-separable mixture of diastereomers 6a-*cis* and 6a-*trans* was the effect of a almost non diastereoselective transamination. We checked the accuracy of this composition by direct synthesis (not depicted in Scheme 3): thus, 1a with 2 eq. of *p*-nitrobenzaldehyde, in identical condition provided, in quantitative yield, the same mixture of diastereomers of 6a with a comparable composition: 51 % 6a-*cis* vs. 49 % 6a-*trans*, calculated from the crude  $^1\text{H}$  NMR spectrum of the reaction mixture.

In turn, starting from 2-4b or 2-4c (Scheme 3) transamination was the restricted process: only the mixture of diastereomers 6b-*cis* vs. 6b-*trans* 32:68 and single 6c-*cis* were isolated after column chromatography respectively.

The same inspection of the validity of these results as in the case of 6a showed interesting features: indeed, treatment of 1b with 2 eq. of *p*-nitrobenzaldehyde afforded 6b-*cis* and 6b-*trans* in a comparable 40:60 molar ratio. In contrast, the direct reaction between TRIS 1c and 2 eq. of *p*-nitrobenzaldehyde to yield diastereoselectively only the *trans* analogue of 6c we already discussed elsewhere (10). This result is not consistent with the present transamination product: 6c as 100 % *cis* (Scheme 3). We concluded that, in this case only, the mechanism of the transamination should be different than in the direct synthesis, presumably because of the free hydroxymethyl group still present in a final structure of type 6c.

### 2. The NMR discrimination of the compound 5a as *unlike* diastereomer

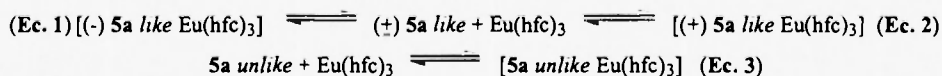
The discrimination of the compound 5a as *like* or *unlike* form was gradually solved by using enantiomerically pure  $\text{Eu}(\text{hfc})_3$  {Europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]} as Chiral Shift Reagent (CSR) (16). Preliminary  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of the isolated 5a by flash column chromatography revealed just one structure fully consistent with both the envisaged "dimeric" diastereomers *like* (racemate) or *unlike* (Figure 1). NOE-diff experiments located the stereochemistry of each



Scheme-3

terminus azadioxabicyclooctane unit as *all cis* concerning the ligands attached at C-2(<sup>1</sup>), -5(<sup>1</sup>), -8(<sup>1</sup>) in a *cis* fused double oxazolidine system.

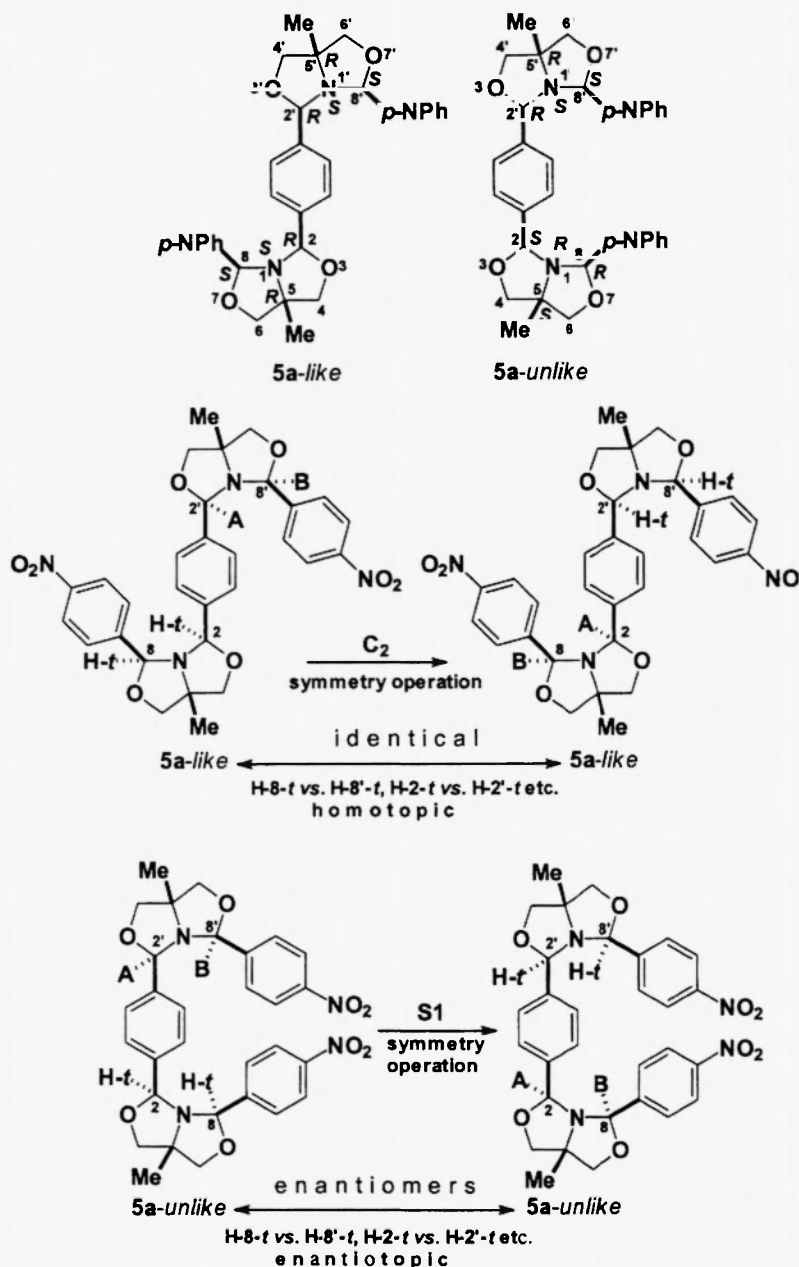
In the second step of our examination, by progressive adding of  $\text{Eu}(\text{hfc})_3$ , the data provided by high-resolution  $^1\text{H}$  NMR (600 MHz) spectra were rationalised based on an introductory configuration analysis of the compound **5a**, as steric relationships issued from the substitution test in both free *like* or *unlike* diastereomer (Scheme 4; for the *like* diastereomer, just one enantiomer is depicted) (17)-(19). Then, the expected interactions with the CSR were examined (Ec. 1-3). They are resumed below.



For reason of simplicity, from the isochronous nuclei 1→1(<sup>1</sup>) to 8→8(<sup>1</sup>) the discussion was hereafter limited to benzyl H-2(<sup>1</sup>), -8(<sup>1</sup>)-*t* and aromatic protons since their spectral appearance was the most convincing

Thus, if **5a** had been a *like* diastereomer, the *internal homotopic* H-2(<sup>1</sup>), -8(<sup>1</sup>)-*t* and anisogamous (17) 1,4-phenylene protons (Ec. 1, 2, Scheme 4), remained upon complexation *external* as such (two singlets) whereas the *internal enantiotopic* protons H-2(<sup>1</sup>), -8(<sup>1</sup>)-*t* of **5a unlike** rendered *external diastereotopic* (four singlets) as became the 1,4-phenylene ones (one AA'XX' system). Next, after complexation, the two *p*-nitrophenyl groups were still *internal homotopic* in **5a like** (one AA'XX' coupling pattern) but *external diastereotopic* in **5a unlike** (two AA'XX' systems).

Keeping in mind these assignments, one can conclude that the compound **5a** was an authentic *unlike* (*meso*) form (Table 1, Figure 2A-C). We also considered the data listed in Table 1 as describing the chelating ability of the compound **5a**; indeed they were



Scheme 4

(deshielding influence, Table 1, entry 5). The calculated deshielding for the aromatic protons linked *ortho* vs. benzyl positions was also significant (+ 0.39 and + 0.47 ppm) in comparison to the aromatic protons linked *ortho* vs. the nitro group (+ 0.06 ppm).

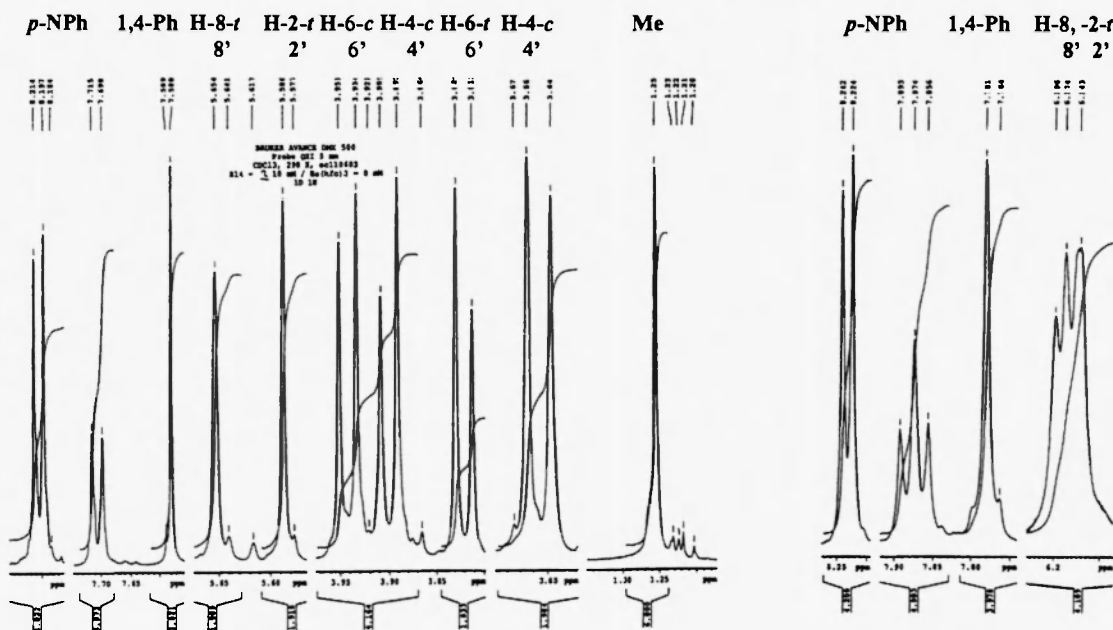
## CONCLUSIONS

In summary, the first example of a diastereoselective linkage of two 1-aza-3,7-dioxabicyclo[3.3.0]octane units in the aminallic zone of the molecule by a 1,4-phenylene fragment as *unlike* global stereochemistry was described. Starting from a double 1,3-oxazolidine possessing the 1,4-phenylene unit as 2,2' linkage, the additional double ring closure upon treatment with an

**Table-1:** Relevant  $^1\text{H}$  NMR data (as Chemical Shifts,  $\delta$  ppm and deshielding influence  $\Delta\delta$ , ppm) of the compound **5a** and in the presence of  $\text{Eu}(\text{hfc})_3$  (600 MHz,  $\text{CDCl}_3$ ,  $25^\circ\text{C}$ ).

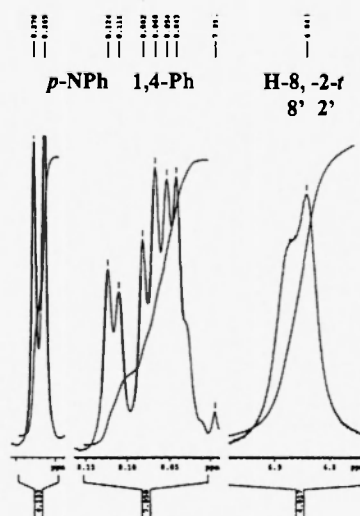
| Entry            | $X_{\text{CSR}}^a$ | $\text{H-8}(\prime)-t^b$ | $\text{H-2}(\prime)-t$ | $p$ -Nitrophenyl                    | 1,4-Ph     |
|------------------|--------------------|--------------------------|------------------------|-------------------------------------|------------|
| 1                | 0.00               | 5.65                     | 5.59                   | 8.21 <sup>c</sup> 7.71 <sup>d</sup> | 7.58       |
| 2                | 0.22               | 6.20;6.17; 6.14; 6.14    |                        | 8.23; 8.23 7.88; 7.86               | 7.79; 7.77 |
| 3                | 0.33               | 6.42; 6.39; 6.39; 6.39   |                        | 8.25; 8.25 7.96; 7.94               | 7.88; 7.86 |
| 4                | 0.45               | 6.84                     |                        | 8.27; 8.27 8.12; 8.08               | 8.06; 8.04 |
| $\Delta\delta$ 5 | -                  | +1.22 <sup>e</sup>       |                        | +0.06 +0.39                         | +0.47      |

<sup>a</sup>Molar fraction of the CSR; <sup>b</sup>As  $t$  (*trans*) disposal with respect with the lone pair of the bridged nitrogen (fiducial substituent); <sup>c</sup>Protons with *ortho* linkage with respect to the nitro group; <sup>d</sup>Protons with *meta* linkage with respect to the nitro group [*ortho* to the benzyl positions C-2( $\prime$ ), -8( $\prime$ )]; <sup>e</sup>As difference between averaged max.  $\delta$  values ( $X_{\text{CSR}}=0.45$ ) and initial  $\delta$  value ( $X_{\text{CSR}}=0.00$ ).

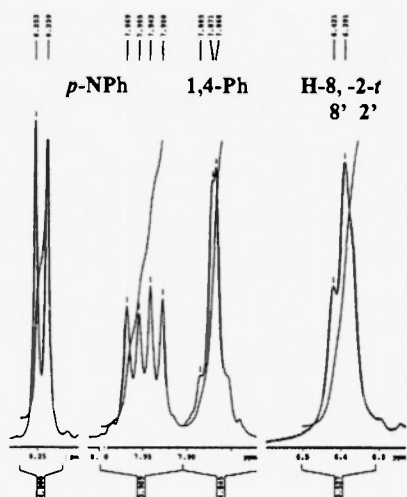


**Figure-1:**  $^1\text{H}$  NMR spectrum of the compound **5a** ( $X_{\text{CSR}} = 0.00$ )

**Figure-2A:**  $X_{\text{CSR}} = 0.22$



**Figure-2C:**  $X_{\text{CSR}} = 0.45$



**Figure-2B:**  $X_{\text{CSR}} = 0.33$

electrophile of type *p*-nitrobenzaldehyde can promote:

- a complete *all cis local diastereoselectivity* with respect to each azadioxabicyclooctane unit.
- a complete *unlike global diastereoselectivity* under thermodynamic control.

## EXPERIMENTAL

### General

Melting point was uncorrected; it was carried out on ELECTROTHERMAL<sup>®</sup> instrument. Current NMR spectra were recorded on Bruker<sup>®</sup> AM 300 instrument operating at 300 and 75 MHz for <sup>1</sup>H and <sup>13</sup>C nuclei respectively. The assignments of the *global stereochemistry* of the compound 5a in the presence of Eu(hfc)<sub>3</sub> was performed on Bruker<sup>®</sup> DMX 600 instrument operating at 600 MHz for <sup>1</sup>H nuclei, without spinning. *No major problem of integration arising from the broadening linewidth, according to equation  $\delta\nu = \pi\Delta\omega \tau_{1/2}$  we encountered for the discussed signals (see text, ref. 16 and Figures 2A-C).* No SiMe<sub>4</sub> was added; chemical shifts were measured against the solvent peak. All chemical shifts ( $\delta$  values) are given throughout in ppm; all coupling patterns (<sup>n</sup>J<sub>H,H</sub> values) are given throughout in Hz. Labelling of the protons as *c* (*cis*) or *t* (*trans*) was made with respect to their disposal against the lone pair at N-1 and the C-5-Me group, as issued from NOE Experiments. TLC was performed by using aluminium sheets with silica gel 60 F<sub>254</sub> (Merck<sup>®</sup>); flash column chromatography was conducted on Silica gel Si 60 (40–63  $\mu$ m, Merck<sup>®</sup>). IR spectrum was performed on a Perkin-Elmer<sup>™</sup> 16 PC FT-IR spectrometer. Only relevant absorptions are listed [throughout in cm<sup>-1</sup>: weak (w), medium (m) or (s) strong]. Mass spectrum (MS) was recorded on an ATI-Unicam Automass<sup>®</sup> 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<sup>-1</sup>).

(1*R*\*,1'*S*\*,2*S*\*,2'*R*\*,5*S*\*,5'*R*\*,8*R*\*,8'*S*\*)-bis-1,4-{1-aza-5-methyl-8-(4-nitrophenyl)-3,7-dioxabicyclo[3.3.0]octane-2-yl}benzene (5a *unlike*) (19 %) yellow crystalline powder, mp 172–174 °C (flash column chromatography; eluent pentane : acetone 4:1). [Found: C, 62.92; H, 5.06; N, 10.11. C<sub>30</sub>H<sub>30</sub>N<sub>4</sub>O<sub>8</sub> requires C, 62.64; H, 5.22; N, 9.74 %]. *R*<sub>f</sub> (80 % pentane/acetone) 0.40. IR ( $\nu_{\max}$ , CH<sub>3</sub>Cl film, NaCl) 2966 (m), 2924 (m), 2866 (m), 1605 (w), 1518 (s), 1347 (s), 1204 (m), 1096 (s), 1025 (s), 855 (m) cm<sup>-1</sup>. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 1.26 (s, 6 H, CH<sub>3</sub>), 3.66 (d, <sup>2</sup>J<sub>H,H</sub> = 10.5 Hz, 2 H, H-4, -4'-*t*), 3.82 (d, <sup>2</sup>J<sub>H,H</sub> = 10.5 Hz, 2 H, H-6, -6'-*t*), 3.90 (d, <sup>2</sup>J<sub>H,H</sub> = 10.5 Hz, 2 H, H-4, -4'-*c*), 3.94 (d, <sup>2</sup>J<sub>H,H</sub> = 10.5 Hz, 2 H, H-6, -6'-*c*), 5.59 (s, 2 H, H-2, -2'-*t*), 5.65 (s, 2 H, H-8, -8'-*t*), 7.58 (s, 4 H, 1,4-phenylene), 7.71 (d, 4 H, <sup>2</sup>J<sub>H,H</sub> = 10.2 Hz, *p*-NPh), 8.21 (d, 4 H, <sup>2</sup>J<sub>H,H</sub> = 10.2 Hz, *p*-NPh). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 25 °C):  $\delta$  = 24.9 (2 C, CH<sub>3</sub>), 71.3 (2 C, C-5, -5'), 75.8 (2 C, C-4, -4'), 76.6 (2 C, C-6, -6'), 96.9 (2 C, C-2, -2'), 98.8 (2 C, C-8, -8'), 123.9 (4 C, CH arom.), 127.7 (4 C, CH arom.), 128.4 (4 C, CH arom.), 140.6 (2 C, Cq arom.), 147.8 (2 C, Cq arom.), 148.4 (2 C, Cq arom.). MS (EI, 70 eV); *m/z* (rel. int. %): 574 (45), 408 (5), 354 (<5), 220 (100), 150 (25), 98 (45).

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