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Synthesis and Stereochemistry of Some Heterocyclic Saturated Compounds Based on *l-p*-Nitrophenylserinol Skeleton (II).

1-Aza-3,7-dioxabicyclo[3.3.0.]octanes

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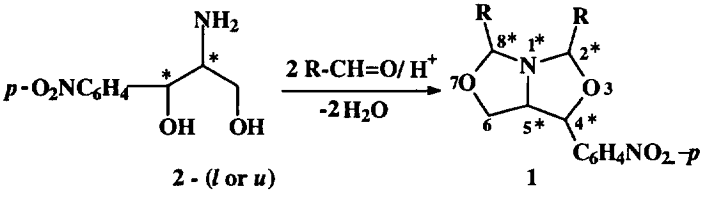
***Abstract*:** Total diastereoselective synthesis of 1-aza-4-(4-nitrophenyl)-3,7-dioxabicyclo[3.3.0] octanes bearing alkyl or aryl substituents at C^2 and C^8 is described as well as details concerning their stereochemistry. © 1997, Elsevier Science Ltd. All rights reserved.

INTRODUCTION

1-Aza-4-(4-nitrophenyl)- 2,8-(un)substituted-3,7-dioxabicyclo[3.3.0]octanes **1**, obtained from *l* (or *u*)-2-amino-1-(4-nitrophenyl)-propane-1,3-diol **2** (**Scheme 1**) exhibited some applicational interest during the period of the 1950's as possible intermediates in chloromycetine synthesis[1-6] or as building-blocks for chiral arylaminodiols, analogues of *l-p*-nitrophenylserinol[16].



Scheme 1

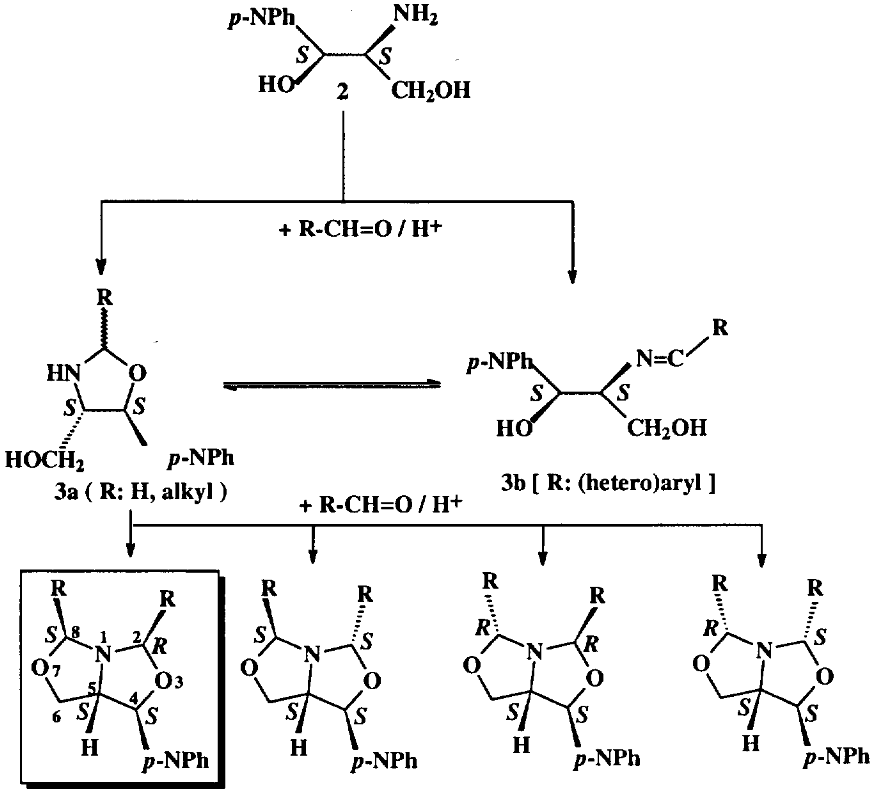
In the last time, along with the failure to synthesise chloromycetine, their use as plasticisers and additives for rubber were reported[8,9]. Few papers were dedicated to this subject and the only structural aspect pointed out was the conservation of the initial configuration of the starting *p*-nitrophenylserinol (designed as *d,l-threo* or *d,l-erythro*[1-7]). As depicted in **Scheme 1**, the double ring closure, starting from eighter *u*- or *l-p*-nitrophenylserinol **2**, would yield fused saturated heterocyclic structures with 1-3 more chiral centers than the starting aminodiol. They offer, besides their synthesis, interesting conformational and configurational features on which we will focus in this paper. Hereafter 2-amino-1-(4-nitrophenyl)-propane-1,3-diol **2**, will be referred to by its name from pharmaceutical chemistry of *l-p*-nitrophenylserinol; for the bicycloderivatives **1**, the title nomenclature is more convenient to the purpose of this paper than perhydro-1-(4-nitrophenyl)-oxazolo[3,4-*c*]oxazole.

RESULTS AND DISCUSSION

1. Synthesis

Eleven 1-aza-4-(4-nitrophenyl)-2,8-(un)substituted-3,7-dioxabicyclo[3.3.0]octanes **1a-k** were prepared in order to evaluate a possible diastereoselectivity of the ring closures[10-11]. As depicted in **Scheme 2**, four diastereomers are theoretically possible based on the assumption that no epimerization occurs concerning the chiral centers of the substrate, as reported in the literature[1-5]. Each compound was isolated as a single diastereomer which, according to the initial configuration (1*S*,2*S*) of the aminodiol **2**, was unambiguously assigned as diastereomer **1** (1*R*,2*R*,4*S*,5*S*,8*S*) (see **2. Stereochemistry**). The general method of Senkus[11] was used (stoichiometric mixture of aminodiol and aldehyde, or a slight excess of the latter, in benzene, under reflux with a Dean-Stark trap; *p*-TsOH was generally used as catalyst). The same experimental route was discussed by Pedrazzoli and Tricerri[2], Bergmann and Resnick[3], Edgerton and Coll.[6,7]. Based mainly on our data, two distinct behaviours may be observed (**Scheme 2**):

A. If **R** was (hetero)aryl, Schiff-bases of **3b** type were isolable intermediates (synthesis of **1** may start from these compounds). The first ring closure occurs from the Schiff bases **3b** according to the ring-chain tautomerism, previously reported[12], *via* the oxazolidine derivative **3a**. No epimerization occurred at carbon C^1 because the secondary hydroxyl group underwent a nucleophilic addition to the iminic function. The influence of the substituent on the aromatic ring was in complete agreement with this fact. Thus, only Schiff bases having substituents with positive σ^+-values (and/or K=[ring]/[chain] more than 0.200) afforded bicycloderivatives. On the contrary, substituents with negative σ^+ values would fail in this ring closure; that is, unreacted Schiff base were obtained instead of bicycloderivatives if **R** was: *p*(*o*)-HOC_6H_4, *p*-$Me_2NC_6H_4$, *p*-$MeOC_6H_4$[7]. Similar



1 (2*R*,4*S*,5*S*,8*S*) 1 (2*S*,4*S*,5*S*,8*S*) 1 (2*R*,4*S*,5*S*,8*R*) 1 (2*S*,4*S*,5*S*,8*R*)

***p*-NPh** is the symbol of the *p*-nitrophenyl group

R (yield %): H (92) **1a**; Ph (55) **1b**; *o*-ClC$_6$H$_4$ (40) **1c**; *o*-O$_2$NC$_6$H$_4$ (66) **1d**; *p*-O$_2$NC$_6$H$_4$ (11) **1e**; β-naphthyl (22) **1f**; 2-Py (61) **1g**; 3-Py (67) **1h**; 4-Py (62) **1i**; Ph-CH$_2$ (50) **1j**; *i*-Pr (63) **1k**; compounds **1c, d, 1f-k** are new ones.

Scheme 2

assumptions were suggested by Pedrazzoli and Tricerri[2], based on direct inspection of the mesomeric structures, to illustrate the stability of the arylideneamino conjugated system against cyclization (no data). The observed diastereoselectivity was treated from the following points of view:

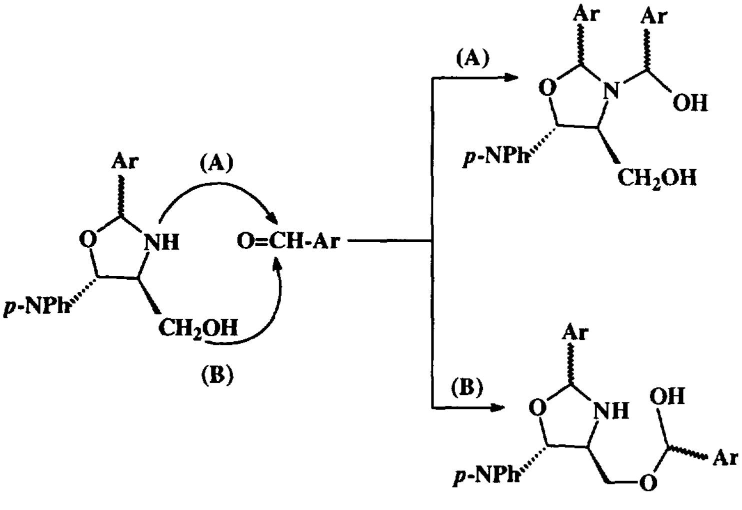
a) as a normal global process under thermodynamic control [to yield the less hindered configuration **1** (2*R*,4*S*,5*S*,8*S*)].

b) as intrinsic feature of the whole reactant system, including both reactants and experimental conditions used. In a test reaction, with benzaldehyde, (**Scheme 1**) all four diastereomers were isolated as a stable mixture

1 but the major diastereomer was anyhow **1b** (2*R*,4*S*,5*S*,8*S*) (about 32%, from the 360MHz ^{1}H-RMN spectrum[13]).

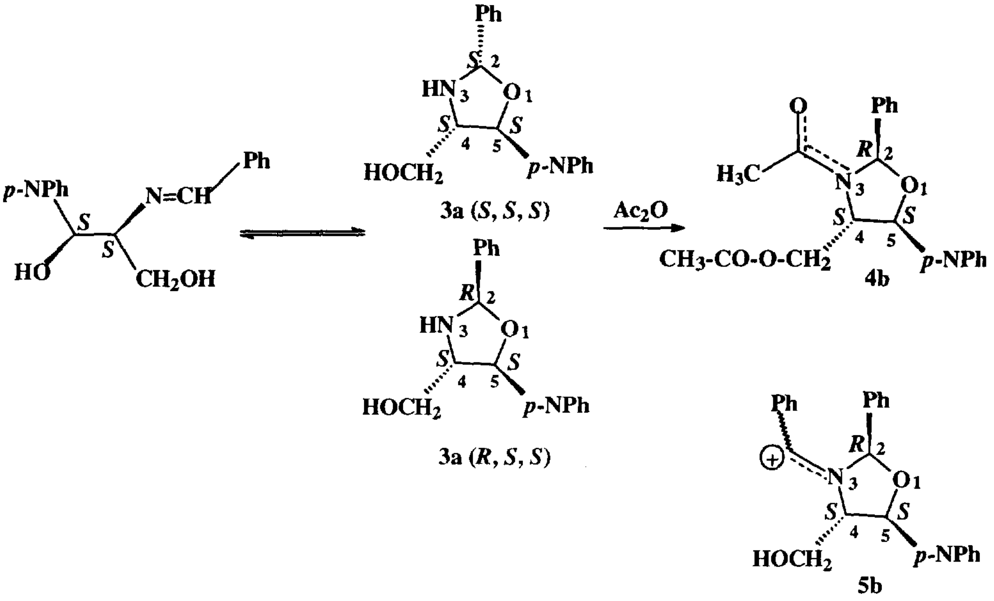
Similarly, all four diasteromers **1e** were detected by TLC-control at the beginning of the reaction with *p*-nitrobenzaldehyde (**Scheme 2**) [no special separation was needed at the end of the reaction because of rapid decomposition of the organic mixture to yield the intermediate Schiff base and a small amount of **1e** (2*R*,4*S*,5*S*,8*S*)]. To improve the diastereoselectivity, *o*-substituted benzaldehydes were chosen and only **1c, d, f** (2*R*,4*S*,5*S*,8*S*) forms were isolated with reasonable yields. However, complete diastereoselectivity was also observed when pyridinealdehydes were used, to give unitary **1h-j** bicycloderivatives. To conclude, the behaviour of benzaldehyde may be seen as an exception and not a rule.

On the other hand all bicycloderivatives **1a-k** exhibited more or less instability towards opening of the ring to give the corresponding structures of type **3b**. It was quite impossible to perform the ring closures under kinetic control because the unreacted intermediate, the Schiff base, was very difficult to be removed, as well as **2** from the crude reaction mixture. Thus, synthesis was performed till no more unreacted materials were detected (TLC monitored) or their amount seemed to remain constant. The reaction time was long enough (11-48h) to ensure equilibration between the different diastereomers of **1** .It is note worthy that after the first ring closure (assigned as a simple nucleophilic addition), which is non-diastereoselective, the second one (addition + substitution) can (or not) be *a priori* postulated from the first step of the cyclization (**Scheme 3**):



Scheme 3

It is obviously difficult to determine which pathway is preferred (**A**-through a *hemi*-aminal or **B**-through a *hemi*-acetal) as well as between SN_1 or SN_2 mechanism but a bulky nucleophile (secondary amino group) is always involved. Based on this assumption, the stable product of a model reaction involving both amino- and hydroxymethyl group was carried out. When the Schiff base **3b** (**R** = Ph) was treated with excess of acetic anhydride, no O^1-O^3-diacetylated Schiff base was isolated but a N-O-diacetyl derivative of its tautomeric oxazolidine **4b** (**Scheme 4**)[14]:



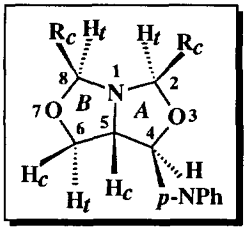
Scheme 4

Although the correct structure of the diacetylderivative **4b** was difficult to assign (see **2. Stereochemistry**), for the purpose of these investigations, it was very helpful. The ***R*** configuration at C^2 allowed presumptions that if a bulky substituent is linked first at N^3, a diastereoselective premise for the next ring closure would be achieved. Also (**Scheme 4**) the partial double bond N^3-C in the amide moiety might cause distortions of the oxazolidine ring (including the option for a certain configuration at C^2) as the same partial double bond would be required to stabilise the benzylic carbocation **5b**. Thus, route (**A**) (**Scheme 3**) seems to be more convenient from a diastereoselective point of view. Unfortunately, extension of diacetylation to other Schiff bases **3b** failed because their diacetyloxazolidines of type **4b** could be not obtained in crystalline form. In addition, even some bicycloderivatives bearing (hetero)aromatic substituents linked at C^2 and C^8 (**1e-i**) were difficult to be isolated in a crystalline form (in complete contradiction to the results of Edgerton and Coll.[6,7]).

B. If **R** was alkyl, haloalkyl, substituted oxazolidines **3a** have been suggested as intermediates[2,3,10,11] (**Scheme 2**) . There is insufficient data on the subject[2,14] regarding the correct structure assignment and, combined with our previous results[15], these are also seen to be unstable compounds. For this reason, we have preferred the one pot synthesis [molar ratio aldehyde:(1*S*,2*S*)-*p*-nitrophenylserinol about 2.2-2.1:1] by using

Senkus' method[11]. Bicycloderivatives **1a, j, k** were obtained as single (2*R*,4*S*,5*S*,8*R*) diastereomer too.We have previously described our synthetic investigations of compound **1a**[13]. To compare our above synthetic results with similar data from literature, condensation of TRIS (α, α, α-trimethylolaminomethane)[16-24] and of some (un)substituted-2-aminopropane-1,3-diols with carbonyl compounds[7,10,21,25-27] was considered appropriate. The general route (**Scheme 2**) has been the subject of different approaches (including obvious contradictions[24]). The analogous 1-aza-3,7-dioxabicyclo[3.3.0]octanes were generally not reported as complex polychiral structures but, sometimes, as simple *cis-trans* diastereomers[7,20,22,25-27] with no comment regarding ring-chain tautomerism.

2. Stereochemistry



Rather exciting results were obtained from NMR data to clarify the configuration of the prepared bicycloderivatives.Chemical shifts and coupling constants are shown in **Tables 1** and **2** resp. For unitary discussion, the *p*-nitrophenyl group, as a permanent substituent, was chosen as reference and heterocyclic protons linked at $C^{2,5,6,8}$ are designed with *c* (*cis*) and *t* (*trans*) indexes with respect to ***p*-NPh**.

Table 1: ^{1}H-chemical Shifts (δ ppm) of the Heterocyclic Protons in compounds **1a-k** (Solvent $CDCl_3$)

Compound	H_4	H_{5c}	H_{6c}	H_{6t}	H_{8t}	H_{2t}	$\Delta\delta(H_{2t}$-$H_{8t})$
1a*	4.56(d)	3.56(m)	4.09(dd)	3.88(dd)	4.38(d)	4.57(d)	0.19
1b**	4.97(d)	3.74(m)	4.08(dd)	3.89(dd)	5.67(s)	5.76(s)	0.09
1c	4.96(d)	3.92(m)	4.09(dd)	3.87(dd)	6.14(s)	6.16(s)	0.02
1d	4.88(d)	3.71(m)	4.05(q)	3.71(m)	6.43(s)	6.61(s)	0.18
1e	4.98(d)	3.76(m)	4.14(dd)	3.83(dd)	5.71(s)	5.81(s)	0.10
1f	5.06(d)	3.86(m)	4.17(dd)	4.00(dd)	5.91(s)	5.99(s)	0.08
1g	5.03(d)	3.93(m)	4.18(dd)	4.13(dd)	5.88(s)	5.96(s)	0.08
1h	4.97(d)	3.75(m)	4.12(dd)	3.84(dd)	5.69(s)	5.78(s)	0.09
1i	4.94(d)	3.70(m)	4.11(dd)	3.81(dd)	5.65(s)	5.71(s)	0.06
1j***	4.58(d)	3.44(m)	3.91(dd)	4.00(dd)	4.64(t)	4.76(t)	0.12
1k****	4.61(d)	3.43(m)	3.94(dd)	3.98(dd)	4.27(d)	4.43(d)	0.16

(d) doublet; (m) multiplet (in most cases as triplet of doublets); (dd) doublet of doublets; (t) triplet; (s) singlet

*Additional data:H_{2c}:4.90; H_{8c}:4.66. Chemical shifts for the analogue of *l*-phenylserinol (Crabb and Coll.[25], 1973) as follows: H_4:4.55; H_{5c}:3.58; H_{6c}:4.04; H_{6t}:3.73; H_{8t}:4.23; H_{2t}:4.47

**The major diastereomer (32%)

***Diastereotopicity (Δδ) of the methylenes groups adjacent to C^2 and C^8 resp. is the same: 0.23ppm.

****Diastereotopicity (Δδ) of the methyl groups at C^2 and C^8 resp.: 0.05 and 0.02ppm.

Table 2: Coupling Constants *J* (H,H Hz) of the Heterocyclic Protons in Compounds **1a-k**

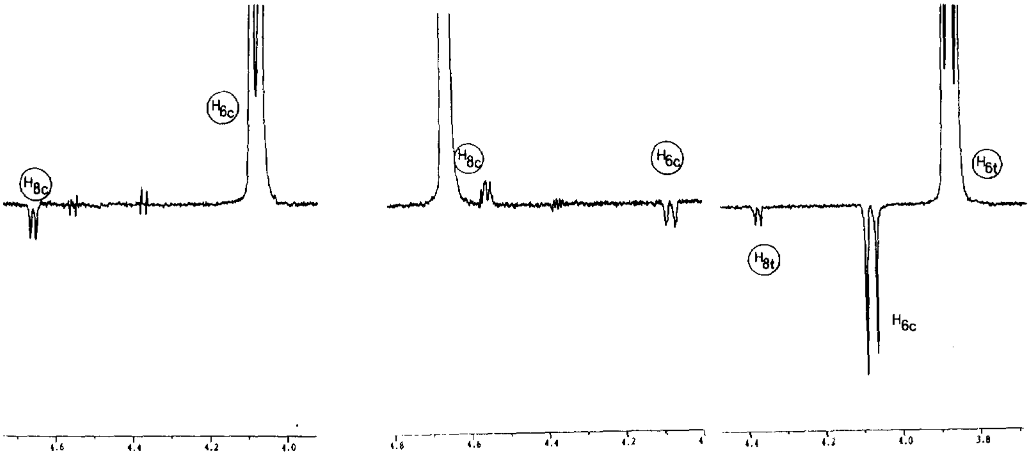
Compound	H_4-H_{5c}	H_{5c}-H_{6c}	H_{5c}-H_{6t}	H_{6c}-H_{6t}
1a*	6.3	1.6	5.7	9.1
1b	6.9	2.2	6.2	8.9
1c	7.3	1.4	5.7	9.1
1d	6.4	-**	-**	8.2
1e	7.3	1.8	6.0	9.2
1f	6.9	2.2	6.0	8.9
1g	7.3	3.1	5.8	9.0
1h	7.1	2.0	6.0	9.2
1i	7.2	1.7	5.9	9.3
1j	7.5	2.0	5.7	9.1
1k	7.4	2.2	5.3	8.9

*Geminal couplings of the C^2 and C^8 methylenes, resp: 4.6 and 5.8Hz. For the same compound derived from *l*-phenylserinol, the *J*-values (Crabb and Coll., op.cit.) as follows: $J_{4\text{-}5c}$:5.5; $J_{5c\text{-}6c}$:1.6; $J_{5c\text{-}6t}$:5.5; $J_{6c\text{-}6t}$:8.1; $J_{2t\text{-}2c}$:4.1; $J_{8t\text{-}8c}$:5.9

**overlapped signals.

The compound **1a** (**R** = H) will be considered first although it does not seem to be the parent compound.There are not significant differences between **1a** and its un-nitrated analogue[25].It is worthy to mention, as reference data, that protons located at C^2 are more deshielded than those linked at C^8. The geminal coupling at C^2 is larger (-4.6Hz) than the same from the un-nitrated analogue (-4.1Hz).There is also a very small difference of the geminal coupling at C^8 (-5.8Hz in **4a**, -5.9Hz in the un-nitrated analogue). The protons H_{2c} and H_{8c} are more deshielded than H_{2t} and H_{8t} due to the overlapping with the lone pair of N^1. All these assignments are in perfect agreement with the presence of the *p*-NPh group, whose influence is stronger on the closer C^2-methylene[25-27].

In successive NOE-diff. experiments, all heterocyclic protons were irradiated showing, besides their *cis* or *trans* location concerning *p*-NPh group, the following steric correlations: protons H_{2c}-H_{8c}, H_{5c}-H_{8c}, H_{5c}-H_{2c}, are too far from each other, in order to exhibit detectable NOE's. In turn, protons located *trans* H_{2t}-H_{8t}-H_4 revealed their vicinity unambiguously. From **Table 1** data one can see that the δ-values are very close between H_4 and H_{2t} , that is, NOE-diff showed no difference between them when double resonance was performed on H_{8t} .This partial overlapping had, unfortunately, its importance, as will be seen later. Inspection of Dreiding models allowed conclusion that the absence of NOE between H_{2c}-H_{5c}-H_{8c} is the consequence of the *cis*-fused ring (with respect to the lone orbital of N^1 and H_{5c} as reference)-subsequently, the configuration of N^1 is ***R***. A slight NOE was also observed between H_{8c}-H_{6c} and H_{8t}-H_{6t} (**Figure 1**).

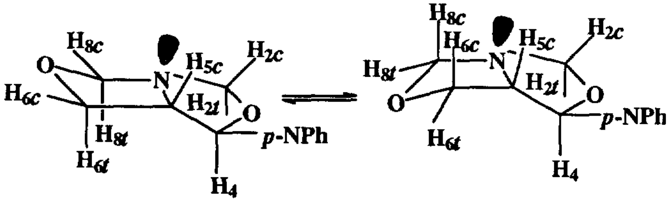


A: NOE on H_{6c} **B**: NOE on H_{8c} **C**: NOE on H_{6t}

Figure 1: Compound **1a** NOE-diff. experiments (**A**, **B**, **C**)

If the spin system H_4-H_{5c}-H_{6c}-H_{6t} is examined from the ^3J-values point of view, H_4-H_{5c} are more *trans*-coupled than H_{5c}-H_{6t} so an equatorial position of the *p*-NPh group is plausible in an envelope conformation (ring *A*). The AMX system (H_{5c}-H_{6t}-H_{6c}) exhibited a *trans*-coupling and a *cis*-coupling (**Table 2**) but, despite these values, one can not assume if H_{5c} is or not "sandwiched" between H_{6c}-H_{6t}[26]. Simple approximation from the Karplus equation gives the following values for dihedral angles: H_{5c}-H_{6t} = 148^0 and H_{5c}-H_{6c} = 62^0 which are not consistent with orientation of H_{5c} between H_{6t}, H_{6c} [along C^6-C^5 axis, although $\Sigma^3J(H_{5c}) < 10$ Hz][26].

According to the observed NOE's in the ***B*** ring, it may be assumed is flipping[28] but without pyramidal inversion of the heterocyclic N^1 [such inversion would lead to a NOE between H_{2c} (H_{8c}) and H_{5c}] (**Scheme 5**):

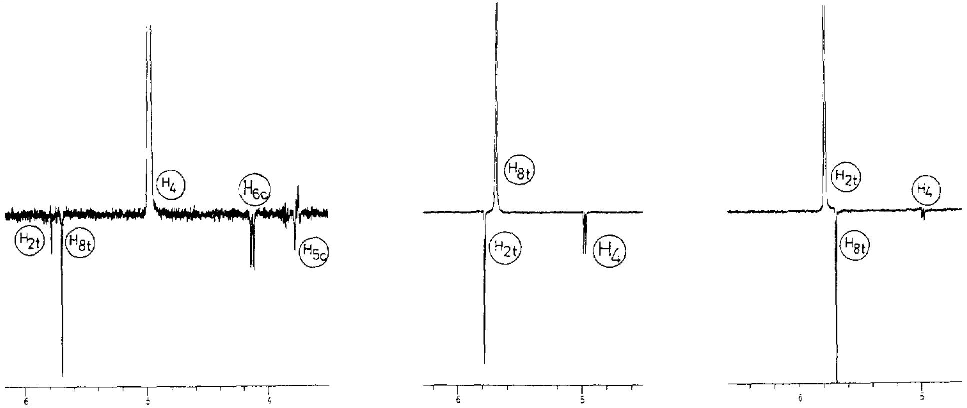


Scheme 5

The following terms of series **1b-i** are sterically different with respect to the whole molecular building:

a) The configurations at N^1, C^2 and C^8 are: ***R***, ***R*** and ***S*** resp., determined by successive NOE-diff. experiments that revealed unambiguously the proximity of protons assigned as *cis* or *trans* (**Table 1**).

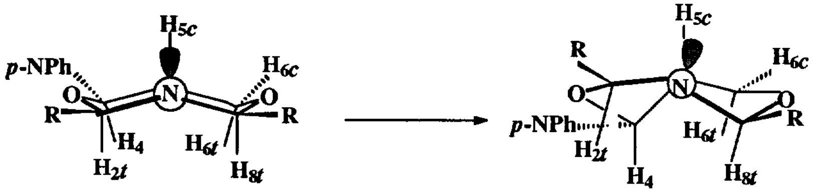
b) The presence of two identical (hetero)aryl substituents linked at C^2 and C^8 was responsible for the assumption that a new element of chirality had appeared. As a typical example, compound **1h** will be discussed (**Figure 2**).



A: NOE on H_4 **B**: NOE on H_{8t} C: NOE on H_{2t}

Figure 2: Compound **1h** NOE-diff. experiments (**A**, **B**, **C**)

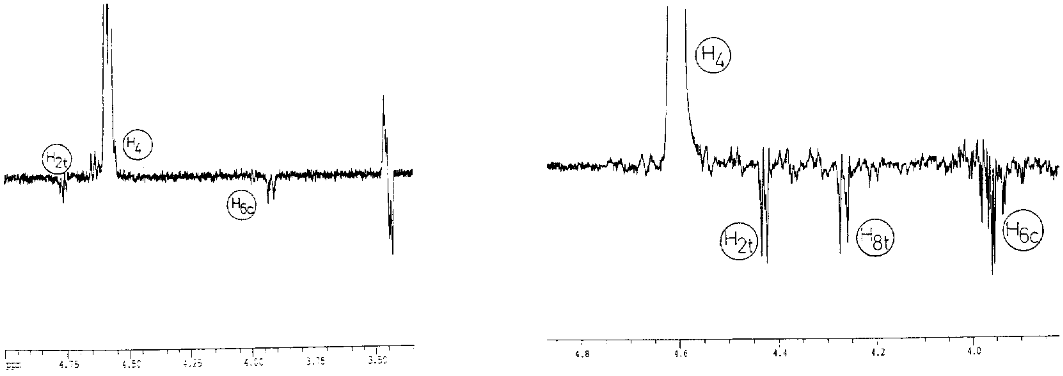
In the so called *endo*-region[25] of the fused-rings (H_4-H_{2t}-H_{8t}) NOE-diff. showed that H_{8t} is closer to H_4 than H_{2t}. This can be explained as an equatorial position of the 3-Py substituent (C^8) and axial of H_{8t} suggesting ring ***B*** as an envelope. To diminish possible non-bonded interactions (e.g. 3-Py *vs.* H_{6c} and H_{5c} and the eclipsed conformation around C^5-N^1 axis) H_{8t} is pushed towards H_4 strong enough for a NOE to be observed (**Scheme 6**). As a result of this supplementary dissymmetry, the new conformation obtained can be assigned by the helicity rule as ***M***. Coupling constants (**Table 2**) are consistent with a real *trans*-disposal H_4-H_{5c} and with an equatorial orientation of the *p*-NPh group attached to the *A* ring. This assumption should be correct because in contrast H_{2t} is axially placed (3-Py at C^2 eq.) and a stronger NOE should be observed on H_{2t} than H_{8t}.



Scheme 6

c) NOE-diff on H_4 put also showes, besides the H_{5c} normal location and *trans*-coupling, the geminal anisochronism of the C^6 diastereotopic methylene. Thus, in **1b-i** series, NOE's (double irradiation **on** H_4) were detected in succession on the more deshielded proton H_6 that was previously and reasonably assigned to be *cis* oriented (H_{6c}) (**Tables 1, 2**). The coupling patterns of the AMX H_{5c}-H_{6c}-H_{6t} system $^3J_{trans}$ (H_{5c}-H_{6t}) $>$ $^3J_{cis}$ (H_{5c}-H_{6c}) agrees with NOE's only if the enhancement at H_{6c} is the result of an indirect NOE, from H_{5c} to H_{6c}. On the other hand, the downfield position of H_{6c} compared with H_{6t} is due to the closer vicinity of the (hetero)aryl groups [eq-*p*-NPh (C^4) and eq-3-Py (C^8)]. Considering the above discussed distortion of the molecule, no NOE was detected between H_{8t}-H_{6t} and H_4-H_{6t} (**Figure 2**).

d) Supplementary data have been issued from the last two terms **1j, k** analysis. According to NOE-diff experiments, there were some different correlations between H_{8t} and H_{2t} *vs*. H_4 found. In compound **1k**, NOE on H_4 gave the same enhancement at H_{8t} and H_{2t} (**Figure 3**) but in the case of compound **1j** only the H_{2t} enhancement was observed.



A: NOE on H_4 (compound **1j**)

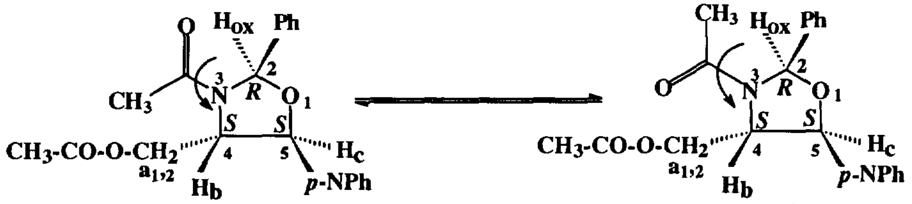
B: NOE on H_4 (compound **1k**)

Figure 3: NOE-diff. experiments of the compounds **1j, k**

Thus, the chiral conformation (**Scheme 3**) remains unclear. A change in the substitution with (aryl)alkyl groups at C^2 and C^8, NOE-diff. in the H_4-H_5-H_6 zone, gave the same assignments as in the above case : NOE on H_4 was observed this time at the more shielded proton (**Figure 3A**) but was also involved in the small vicinal coupling, $^3J_{cis}$ (H_{5c}-H_{6c}). This was assigned again to H_{6c} that is now more shielded than H_{6t} (*viceversa* as in **1a-k** series).

e) Certain details have also been available concerning the side chains, linked at C^2 and C^8. The standard difference $\Delta\delta(H_{2t}$-$H_{8t})$ (where H_{2t} is more deshielded than H_{8t}, as a normal assumption) is 0.19ppm (compound **1a**) (**Table 1**). In **1b-i** series, this difference decreases to about 0.09ppm but *ortho*-substitution gave very different $\Delta\delta$-values: 0.02ppm (**1c**) and 0.18ppm (**1d**). This may be due to the specific anisotropy of the *o*-substituted aromatic rings and not to any rotational preference which, even in these cases, exists in normal free rotation around the σ-bonds at C^2 and C^8. It was unexpected by easily to determine this behaviour. Thus, from both regioisomers **1d**, **1e** (the most apt to ring cleavage) only the *ortho*-substituted **1d** could be recrystallized from alcoholic media.On the contrary, compound **1e**, by the same treatment, was rapidly and quantitatively converted to its starting Schiff base (**3b**-type).Thus, the steric hindrance promoted by the *o*-nitro substituent against the nucleophilic attack from any direction is consistent with equal populations of rotamers of type **1d**.

The key compound, diacetyloxazolidine **4b**, was much more difficult to elucidate than a simple inspection of the structure would suggest. To resume all steps of its NMR-analysis, combined experiments were performed (**Scheme 7, Figure 4A-E**).



4b-*Z* **4b-*E***

Scheme 7

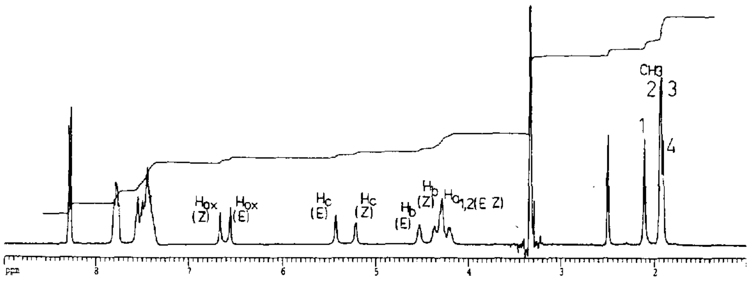


Figure 4A: 1D-^{1}H-NMR spectrum of the compound **4b** (298K, DMSO-d_6)

From the 1D-^{1}H-NMR spectrum (298 K) (**Figure 4A**) one can see no iminic proton but two sets of signals (7-4ppm) to suggest a mixture **4b** as two equal populations of epimers, about the C^2-chiral center (2*R*,4*S*,5*S* + 2*S*,4*S*,5*S*).Considering the already discussed ring-chain tautomerism, singlets located at 6.65ppm and 6.56ppm were assigned to H_{ox} and those of H_c at 5.42 and 5.21ppm. We note here, as a surprising fact, the absence of the *trans*-vicinal coupling H_c-H_b. Four methyl groups (peaks 1-4) were normally found upfield. The same spectrum performed at 333K (**Figure 4B**) revealed just one set of signals, suggesting a dynamic process: isomerisation towards the most thermodynamic stable epimer of **4b** but, more plausible, a free rotation around N^3-C amidic bond.

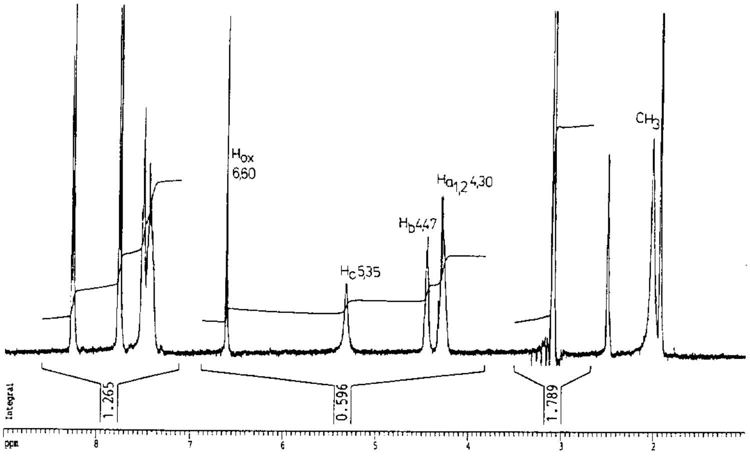


Figure 4B: 1D-^{1}H-NMR-spectrum of the compound **4b** (333K, DMSO-d_6)

This latter hypothesis was also supported by the ASIS experiment (**Figure 4C**): it exhibited no expected simplifying but the shape of signals showed an intermediate speed interchange (vicinity of coalescence) between unequal populations of rotameric diastereomers **4b-*E*-*Z*** (**Scheme 7**).

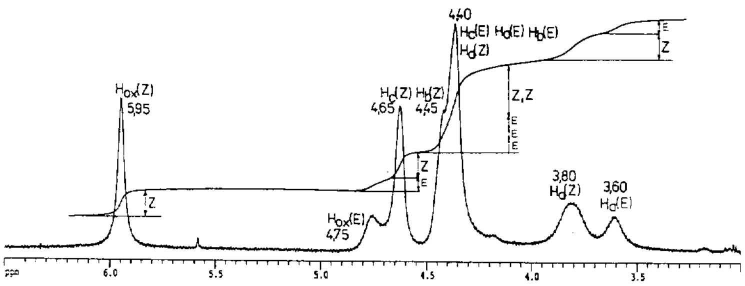


Figure 4C: 1D-^{1}H-NMR-spectrum of the compound **4b** (298K, C_6D_6)

The complete analysis was difficult to accomplish because of the overlapping involving protons H_b and $H_{a1,2}$. To attempt pertinent assignment between diastereomers (designed by *E-Z* descriptors, according to Stewart and Siddall[29]) the field anisotropy shape of the amidic group was considered to assume that proton H_{ox} should be more deshielded in the Z-diastereomer. The next correlations (**Figure 4A, C**) were made based on 2D-(H, H)-COSY experiment (**Figure 4D**).

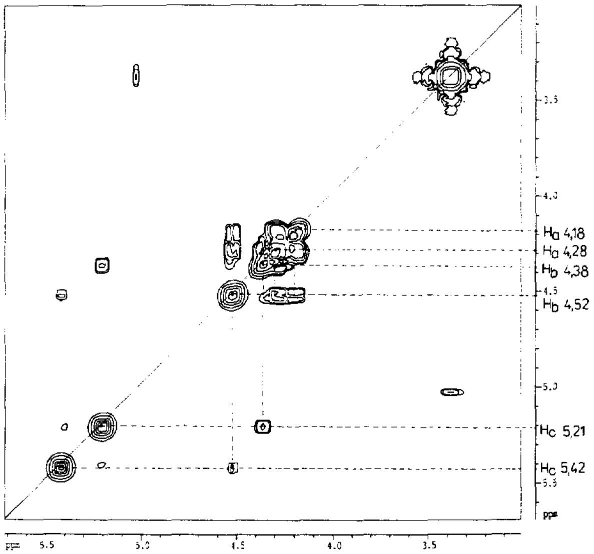


Figure 4D: 2D-(H, H)-COSY experiment of the compound **4b** (298K DMSO-d_6)

The two distinct structures were also easily detected by 2D-(C, H)-HETCOR experiment (not depicted). Finally, the purpose of these investigations was accomplished by NOE experiments at 333K (**Figure 4E**) : NOE on H_c was observed at H_{ox} to prove their *cis*-disposal and, subsequently, the C^2 ***R*** configuration.

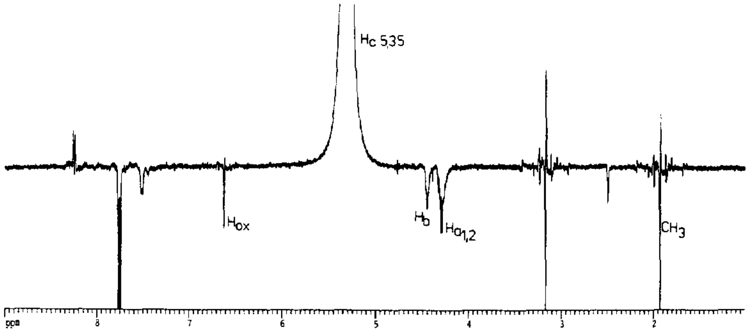


Figure 4E: Compound **4b**, NOE-diff. experiment on H_c (333K, DMSO-d_6)

At room temp., the NOE between H_{ox}-H_c was not observed, presumably due to the already anticipated distortion of the N-acetyloxazolidine ring (**Scheme 4**) caused by the sp^2 hybridisation of the amidic N^3. It is worth mentioning, however, that the same result is given by the ASIS experiment.Thus, one can note a general shielding of the signals ($\Delta\delta$ DMSO-d_6 - C_6D_6 ppm) as follows: H_c: + 0.56 (*Z*) and +1.02 (*E*); H_b: + 0.07 (*Z*) and - 0.02 (*E*); H_{ox}: +0.70 (*Z*) and +1.79 (*E*) (**Figure 4A, C**).This suggests that protons located on the same side of the medium plane of the heterocycle (e.g. H_c and H_{ox}) are the most influenced due to the shielding induced by the aromatic solvent.^{13}C-NMR spectra (298 and 333K) were in complete agreement with all of the above assignments.

CONCLUSIONS

To summarise the above data, enantiomerically pure 1-aza-4-(4-nitrophenyl)-2,8-(un)substituted-3,7-dioxabicyclo[3.3.0]octanes are intrinsic versatile all enough compounds to be valid building-blocks for more complex polychiral structures. Under thermodynamic control, large series of type **1** are available, especially if the configuration of the starting *l*-*p*-nitrophenylserinol (1*R*,2*R* or 1*S*,2*S*) is *a priori* a discriminating factor towards the required products.

EXPERIMENTAL

NMR spectra were performed on Brucker AM 400 spectrometer (with an Aspect 3000 computer) operating at 400MHz for ^{1}H and 100MHz for ^{13}C. No $SiMe_4$ was added; chemical shifts were measured against the solvent peak. Melting points are not corrected. Specific rotations were determined on Polamat K. Z. Jena instrument. Compounds **1c-d**, **f-k** have not been previously reported.

Synthesis-general procedure:

21.2g (0.1mole) (1*S*,2*S*)-*p*-Nitrophenylserinol and 0.22-0.25mole of the appropriate aldehyde (about 1g *p*-Ts-OH acid as catalyst) are suspended in 200ml anhydrous benzene and refluxed in a Dean-Stark trap, for continuous removal of water, with vigorous stirring (in the case of compound **1e** about 10% (v/v) DMSO is added for complete dissolution). The reaction can not be accurately monitored by the total amount of water separated but by means of TLC: plates made of glass with usual MERCK silicagel; eluent ligroin:acetone 3:1 v/v: visualisation in I_2-bath. The process is considered complete when the starting aminodiol is still present in small traces (as well as the intermediate Schiff base) or constant concentration.The following procedures should be carried out in anhydrous conditions: filtering off the unreacted materials, neutralizing the filtrate with 10-

15% excess of solid and anh. Na_2CO_3 and finally filtering off all the byproduct salts.The organic solution is concentrated *in vacuo* on a steam bath and the oily residue is crystallized from an appropriate alcohol. Crystallization takes 24-48h and the crude product needs recrystallization from min. amount of the same alcohol.

Syntheses of compounds **1a, b** have been described elsewhere[13]. Compound, yield (%), reaction time (h), m.p.(^{0}C) (solvent), $[\alpha]_D^{20}$ and elemental analysis, are listed below. NMR data are listed in **Tables 1, 2**.

(1*R*,2*R*,4*S*,5*S*,8*S*)-1-Aza-2,8-di(2-chlorophenyl)-4-(4-nitrophenyl)-3,7-dioxabicyclo[3.3.0]octane 1c; 40: 18; 128-9 (BuOH); -29.8 (1% $CHCl_3$). Anal. calcd. for $C_{23}H_{18}Cl_2N_2O_4$: C 60.39%, H 3.93%, Cl 15.36%, N 6.12%. Found: C 60.50%, H 4.14%, Cl 15.50%, N 6.20%

(1*R*,2*R*,4*S*,5*S*,8*S*)-1-Aza-2,8-di(2-nitrophenyl)-4-(4-nitrophenyl)-3,7-dioxabicyclo[3.3.0]octane 1d; 66; 16; 159-60 (EtOH); -39.5 (1% $CHCl_3$). Anal. calcd. for $C_{23}H_{18}N_4O_8$: C 57.74%, H 3.76%, N 11.71%. Found: C 57.50%, H 4.00%, N 12.00%

(1*R*,2*R*,4*S*,5*S*,8*S*)-1-Aza-2,4,8-tris(4-nitrophenyl)-3,7-dioxabicyclo[3.3.0]octane 1e; 11; 38; 161-2 (EtOH at room temp.); -44,5 (0.5% AcOEt). Anal. calcd. for $C_{23}H_{18}N_4O_8$: C 57.74%, H 3.76%, N 11.71%. Found: C 58.00%, H 3.98%, N 11.80%

(1*R*,2*R*,4*S*,5*S*,8*S*)-1-Aza-2,8-di(2-naphthyl)-4-(4-nitrophenyl)-3,7-dioxabicyclo[3.3.0]octane 1f; 48; 114-6 (BuOH); -90,5 (1% $CHCl_3$). Anal. calcd. for $C_{31}H_{24}N_2O_4$: C 76.23%, H 4.91%, N 5.73%. Found: C 76.00%, H 4.66%, N 5.75%.

(1*R*,2*R*,4*S*,5*S*,8*S*)-1-Aza-4-(4-nitrophenyl)-3,7-dioxa-2,8-di(2-pyridin-1-yl)-bicyclo[3.3.0]octane 1g; 22; 48; 109-9.5 (*i*PrOH); -29.5 (0.5% MeOH). Anal. calcd. for $C_{21}H_{18}N_4O_4$: C 64.61%, H 4.51%, N 14.35%. Found: C 64.50%, H 4.40%, N 14.30%.

(1*R*,2*R*,4*S*,5*S*,8*S*)-1-Aza-4-(4-nitrophenyl)-3,7-dioxa-2,8-di(3-pyridin-1-yl)-bicyclo[3.3.0]octane 1h; 67; 16; 109-10 (*i*PrOH); -32.8 (0.5% MeOH). Anal. calcd. for $C_{21}H_{18}N_4O_4$: C 64.61%, H 4.51%, N 14.35%. Found: C 64.90%, H 4.45%, N 14.40%.

(1*R*,2*R*,4*S*,5*S*,8*S*)-1-Aza-4-(4-nitrophenyl)-3,7-dioxa-2,8-di(4-pyridin-1-yl)-bicyclo[3.3.0]octane 1i; 62; 48; 149-51 (*i*PrOH); -29.2 (0.5% MeOH). Anal. calcd. for $C_{21}H_{18}N_4O_4$: C 64.61%, H 4.51%, N 14.35%. Found : C 64.80%, H 4.11%, N 14.25%.

(1*R*,2*R*,4*S*,5*S*,8*S*)-1-Aza-2,8-dibenzyl-4-(4-nitrophenyl)-3,7-dioxabicyclo[3.3.0]octane 1j; 50; 3; 127-8 (Et_2O); -13.10 (1% $CHCl_3$). Anal. calcd. for $C_{25}H_{24}N_2O_4$: C 72.11%, H 5.77%, N 6.73%. Found: C 72.00%, H 6.15%, N 6.75%

(1*R*,2*R*,4*S*,5*S*,8*S*)-1-Aza-2,8-diisopropyl-4-(4-nitrophenyl)-3,7-dioxabicyclo[3.3.0]octane 1k; 63; 8;

85-6 (EtOH); -26.6 (1% $CHCl_3$). Anal. calcd. for $C_{17}H_{24}N_2O_4$: C 63.75%, H 7.50%, N 8.75%. Found: C 63.50%, H 7.70%, N 8.50%.

Synthesis of compound 4b:

20.00g (0.066mole) (1*S*,2*S*)-*E*-2-(benzylideneamino)-1-(4-nitrophenyl)-propane-1,3-diol is dissolved in 50ml acetic anhydride (54g, 0.53mole) and kept at room temp. for about one week until no more Shiff base is detected by TLC (eluent ligroin : acetone 3:1 v/v; visualisation on I_2 bath). The solution is poured into 500g ice and 150ml aq. NH_3 (25%). After 12h the solid is filtered of to yield about 26g of crude product. After two recrystallizations from the min. amt. of MeOH 15g of pure product is obtained as white powder crystals (yield 59%).

(2*R*,4*S*,5*S*)-4-Acetoxymethyl-3-acetyl-5-(4-nitrophenyl)-1,3-oxazolidine 4b: m.p. = 94-6^{0}C; $[\alpha]_D^{20}$ = - 21.10 (1% MeOH). Anal. calcd. for $C_{20}H_{20}N_2O_6$: C 62.50%, H 5.20%, N 7.29%. Found: C 62.35%, H 4.90%, N 7.15%. **^{1}H-NMR (DMSO-d_6 298K):** 8.40-7.30 (2×9H, both *E-Z* diastereomers); 2.20-1.80 (4×3H, CH_3, both *E-Z* diastereomers). **4b-*E***: 6.56 (1H, s, H_{ox}); 5.42 (1H, s, H_c); 4.52 (1H, s, H_b); 4.28-4.18 (2H, m, $H_{a1,2}$); **4b-*Z***: 6.65 (1H, s, H_{ox}); 5.21 (1H, s, H_c); 4.38 (1H, s, H_b); 4.28-4.18 (2H, m, $H_{a1,2}$). **^{1}H-NMR (DMSO-d_6 333K):**8.30-7.30 (9H); 6.60 (1H, s, H_{ox}); 5.35 (1H, H_c); 4.47 (1H, d, H_b); 4.30 (2H, m, $H_{ai,2}$); 2.20-1.90 (6H, CH_3). **^{1}H-NMR (C_6D_6 298K):** 5.95 (1H, H_{ox}, **4b-*Z***); 4.75 (1H, H_{ox}, **4b-*E***); 4.65 (1H, H_c **4b-*Z***); 4.45 (1H, H_b, **4b-*Z***); 4.40 (4H, H_c **4b-*E***, H_b **4b-*E***, $H_{a1(2)}$ **4b-*Z***, $H_{a1(2)}$ **4b-*E***); 3.80 (1H, $H_{a1(2)}$ **4b-*Z***); 3.60 (1H, $H_{a1(2)}$ **4b-*E***). **^{13}C-NMR (DMSO-d_6 298K APT experiment, both *E-Z* diastereomers):** 20.15, 21.83, 22.48 (4×CH_3, 1 peak overlapped); 60.93, 61.43 (2C, C^b); 62.03, 63.28 (2C, C^a); 78.67, 79.79 (2C, C^c); 88.53, 89.40 (2C, C^{ox}); 123.47-128.80 (12C, 3peaks overlapped); 138.03, 138.64 (2C, *ipso*-C, phenyl); 145.87, 146.24 (2C, *ipso*-C, *p*-NPh); 168.71, 169.23 (2C, *C*O-N); 169.81 (2C, *C*O-O- overlapped). **^{13}C-NMR (DMSO-d_6, 333K APT experiment):** 20.03 (1C, CH_3-CO-O); 22.07 (1C, CH_3-CO-N); 61.30p (1C, C^b); 123.39-128.15 (6C, 2 peaks overlapped); 146.10 (1C, *ipso*-C, phenyl); 147.29 (1C, *ipso*-C, *p*-NPh); 168.89 (1C, *C*O-N); 169.64 (1C, *C*O-O); signals belonging to C^a, C^c, C^{ox} were not detected at 333K presumably due to the coincidence between the environments interchange frequency and the applied sweep frequency. **HETCOR** experiment (DMSO-d_6, 298K): **4b-*E***: 6.56 and 88.53 (H_{ox}-C^{ox}); 5.42 and 79.79 (H_c-C^c); 4.52 and 61.43 (H_b-C^b); **4b-*Z***: 6.65 and 89.40 (H_{ox}-C^{ox}); 5.21 and 78.67 (H_c-C^c); 4.38 and 60.93 (H_b-C^b).

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