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Ring-chain tautomerism and other versatile behaviour of 1,4-diimino- and 1,2-phenylene derivatives of some *C*-substituted serinols

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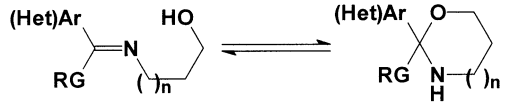
Abstract—The behaviour of the title compounds, obtained from terephthaldicarboxaldehyde or 1,2-phthaldicarboxaldehyde and certain (non)chiral *C*-substituted serinols is discussed in terms of ring (chain)–chain (ring) tautomerism (1,4-phenylene derivatives) or formal intramolecular redox isomerisation (1,2-derivatives).

1. Introduction

The ring-chain tautomerism of the Schiff bases derived from aryl carbonyl compounds and aminoalcohols, as a reversible addition of an hydroxyl group to an imine double bond, is already a very well investigated feature (Scheme 1).[1]



(Het)Ar: (Hetero)Aryl group
RG: **R**ealising **G**roup (Me, Et), optionally H
n = 0, 1

Scheme 1.

According to the literature,[2–7] the general approach in the field indicates a preference for high resolution NMR spectroscopic methods (both in solution and solid state). Starting from the pioneering review of Bergmann[8] and later developments over the years,[9–12] the research has focused on simple Schiff bases originating from aryl carbonyls and monoamino monoalcohols. It was demonstrated that the above equilibria (Scheme 1) can be accurately described by a Linear Free Energy Relationship (LFER) as Hammett–Brown plots ($\log K=\rho\sigma^{+}+\log K_0$ where $K=$ [ring]/[chain] and σ^{+} being the constant for the substituent linked to aryl moiety).[9] Both types of possible saturated O-1–N-3-heterocyclic system (type 1,3-oxazolidines $n=0$ and type 1,3-perhydro oxazines $n=1$, Scheme 1) are the result of clear nucleophilic 5 (and 6) *endo–trig* cyclisations, respectively, but only the latter is favoured according to Baldwin's rules.[13]

Following our initial findings regarding the ring-chain tautomerism exhibited by some simple Schiff bases of *l-p*-nitrophenylserinol[14] and highlighting recently reported data on the double Schiff bases of the epimeric 1,2,3,4-diaminobutanediols,[15–17] we have now dedicated our attention to double Schiff bases derived from an aromatic dicarbonyl compound, such as terephthaldicarboxaldehyde and a variety of *C*-substituted serinols. To the best of our knowledge, both the problem to be solved and the compounds are new ones. Preliminary results are hereafter discussed in the context of 1,2-phthaldicarboxaldehyde reactivity as an attempt to provide a more complete approach.

2. Results and discussion

2.1. Reaction with terephthaldicarboxaldehyde

2.1.1. Synthesis. The compounds under investigation **2–6** (Scheme 2) were prepared from the corresponding serinols **1a–e** (1:2 molar ratio dialdehyde/serinol) by classical methods with good yields.[18]

The *E* configuration of the imine double bond in structures of this type was previously discussed and assigned by us based on NOE-diff. experiments.[14] Indeed, all new compounds **2–6** were unambiguously detected as unique

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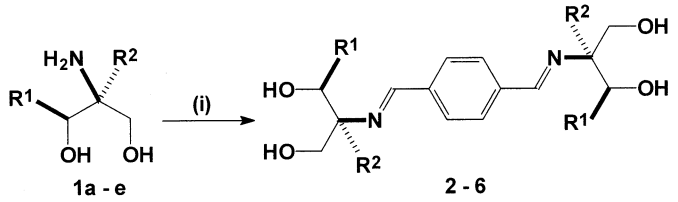


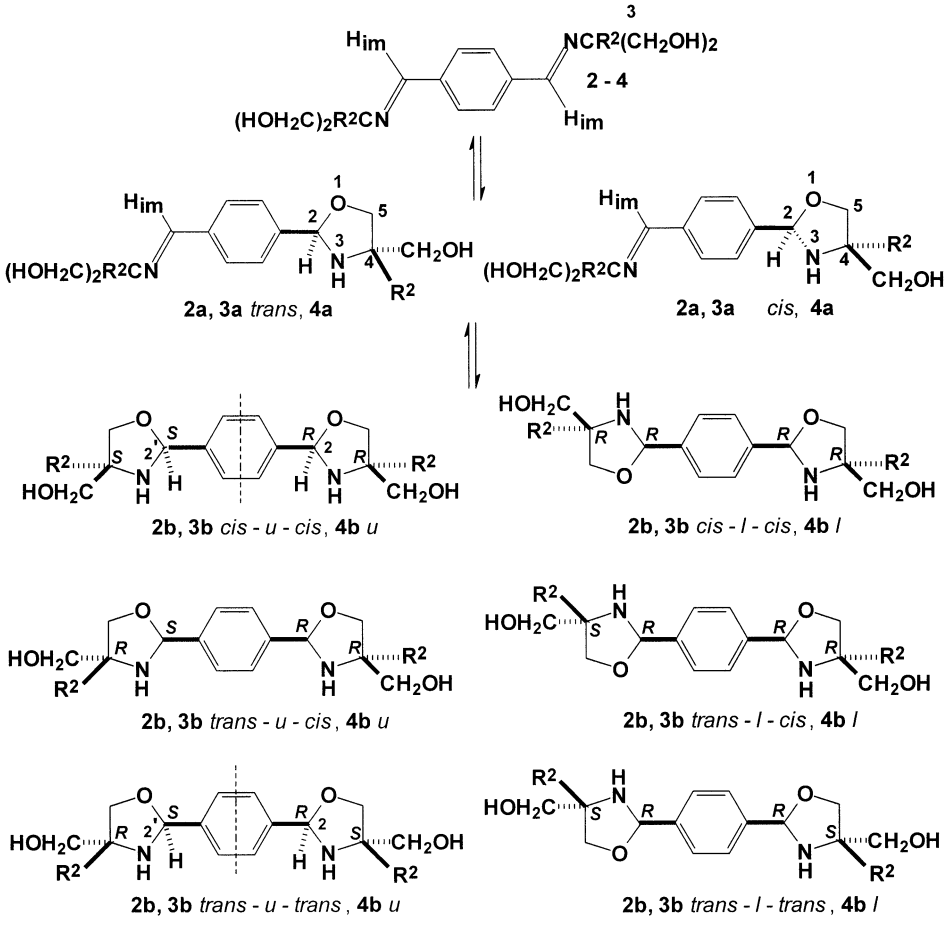
(i): terephthaldicarboxaldehyde (2 : 1 molar ratio **1a - e** : dialdehyde)

Nr.	R^1	R^2	Time (h)	Solvent	Yield (%)
1a → 2	H	Me	10	benzene[a]	92
1b → 3	H	Et	10	benzene[a]	59[b]
1c → 4	H	$-CH_2OH$	8	EtOH	87[b]
1d → 5	Ph	H	8	EtOH	85
1e → 6	*p*-O_2N-C_6H_4-	H	10	*i*-PrOH	74

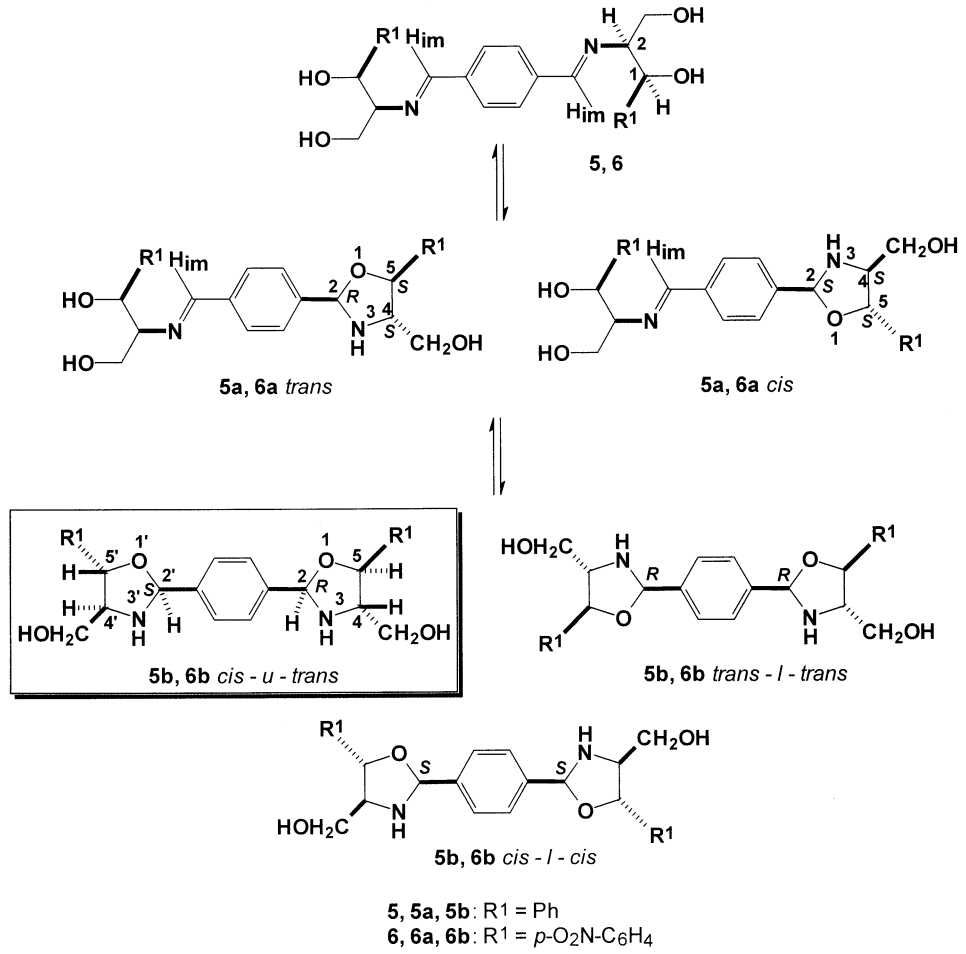
[a] *p*-TsOH as catalyst

[b] isolated as double oxazolidine tautomers **3b**, **4b**, see Discussion and Scheme 3

Scheme 2.



Scheme 3.



Scheme 4.

diastereomers[†] [e.g. just one signal for imine positions (around 8.35 and 161 ppm in ^{1}H and ^{13}C spectra, respectively) as well as for 1,4-phenylene fragment (around 7.45 and 128 ppm) in a 1:2 ratio]. Despite this incipient diastereoselectivity, revealed by NMR, it is important to point out some features.

Our selection of terephthaldicarboxaldehyde was motivated by the expected interaction (seen as 'activation') between the two imine groups in a **2**–**6** π conjugated system. On the other hand, the corresponding mono Schiff bases of 1,4-terephthaldicarboxaldehyde appear to be unknown structures.

The chosen C-2-substituted serinols **1a**–**c** provide different steric and electronic environments for the involved nucleophiles: the hydroxymethyl groups are enantiotopic in **1a**, **b** but homotopic in **1c** (the very well known TRIS®, tris-(hydroxymethyl)aminomethane).[19] In contrast, the enantiomeric pure 1-aryl serinols **1d**, **e** possess the 1*S*,2*S*-configuration.

2.1.2. Stereochemical aspects of ring tautomers. In a 'classical' approach (Schemes 3 and 4), all the double Schiff bases **2**–**6** give rise to the same stereochemical problem: the ring-chain tautomerism would result in two successive multicomponent equilibria: the first ring closure would yield mono oxazolidine Schiff bases of type **2a**–**6a**, then double oxazolidines of type **2b**–**6b**. In order to simplify discussion, the expected ring stereoisomers are depicted separately in Scheme 3 [(**2**–**4**)→(**2a**–**4a**)→(**2b**–**4b**) and Scheme 4 [(**5**, **6**)→(**5a**, **6a**)→(**5b**, **6b**)].

As shown in Scheme 3, in the case of **2** and **3** eight distinct ring epimers are expected (2+6, if chiral, just one enantiomer is depicted) including two *meso* forms **2b** and **3b** *cis-u-cis* and *trans-u-trans* (descriptors *unlike u* and *like l* refer to the C-2 chiral centers in the oxazolidine moiety; descriptors *cis* and *trans* refer to the disposal of C-4 hydroxymethyl and C-2 phenylene groups with respect to each oxazolidine ring).[20,21] Obviously, for **4** just one diastereomer **4a** and two **4b** (*u* and *l*) are to be considered.

Enantiomerically pure double Schiff bases **5** and **6** (Scheme 4) would give five stereoisomers: two epimers of type **5a** and **6a** but only three of type **5b** and **6b** since the configurations in the oxazolidine ring as 4*S*,5*S* are preserved from the starting materials. In turn, compounds **5** and **6** could rise the supplementary problem of regioselectivity in the ring closure since the nucleophile involved could be

[†] Although this can be assigned as well by simple inspection of Dreiding models, the partial isomerisation of **2**–**6** towards their corresponding (*Z*,*Z*) and (*Z*,*E*) diastereomers was also considered. See later discussion.

Table 1. Equilibrium data between Schiff bases **2–6** (chain form) and their tautomers (ring forms, epimeric oxazolidines) **2a–6a** and **2b–6b**

$$[\mathbf{2-6}] \underset{k_{-a}}{\overset{K_I\ k_a}{\rightleftharpoons}} [\mathbf{2a-6a}] \underset{k_{-b}}{\overset{K_{II}\ k_b}{\rightleftharpoons}} [\mathbf{2b-6b}]$$

Number	Composition (%)						Time (h)	K_I	K_{II}
	Time zero			Equilibrium state					
	Chain form **2–6**	Ring form **2a–6a**	Ring form **2b–6b**	Chain form **2–6**	Ring form **2a–6a**	Ring form **2b–6b**			
2	82 (**2**)	18 (**2a**)	0 (**2b**)	36 (**2**)	47 (**2a**)	17 (**2b**)	5	1.31	0.36
3	13 (**3**)	30 (**3a**)	57 (**3b**)	13 (**3**)	30 (**3a**)	57 (**3b**)	–	2.31	1.90
4	0.25 (**4**)	14 (**4a**)	85.75 (**4b**)	0.25 (**4**)	14 (**4a**)	85.75 (**4b**)	–	56.00	6.13
5	100 (**5**)	0 (**5a**)	0 (**5b**)	70[a] (**5**)	0 (**5a**)	30 (**5b**)	24	–	–
6	95[b] (**6**)	0 (**6a**)	5 (**6b**)	78[b] (**6**)	0 (**6a**)	22 (**6b**)	24	–	–

[a] Assigned as a mixture of diastereomers: 88% (*E*,*E*), 6% (*Z*,*Z*) and 6% (*E*,*Z*) of **5**.
[b] Assigned as a mixture of diastereomers: (*E*,*E*), (*Z*,*Z*) and (*E*,*Z*) of **6** where minor diastereomers (*Z*,*Z*+*E*,*Z* were found less than 5%).

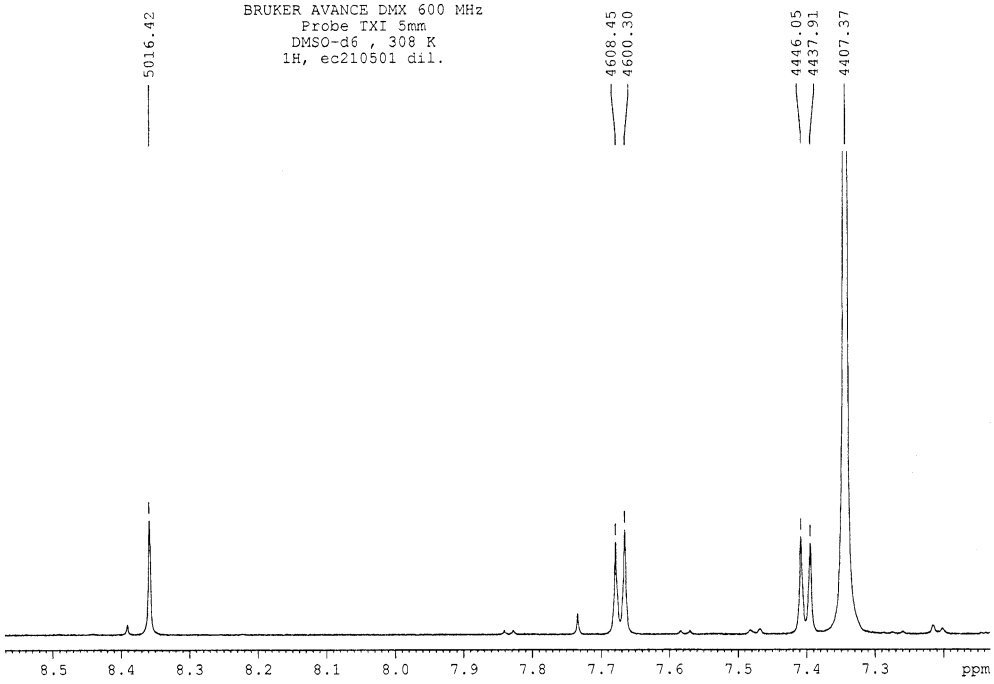


Figure 1. ^{1}H NMR spectrum at the equilibrium between species **4**–**4a**–**4b** (detail in the aromatic zone; 600 MHz, DMSO-d_6, δ in ppm, J in Hz; see Scheme 3), from downfield to upfield: 8.39 (2H, s, H_{im} in **4**), 8.36 (1H, s, H_{im} in **4a**), 7.73 (4H, s, 1,4-phenylene in **4**), 7.67 (2H, d, J=8.2, 1,4-phenylene in **4a**), 7.40 (2H, d, J=8.1, 1,4-phenylene in **4a**), 7.34 (4H, s, 1,4-phenylene in **4b**).

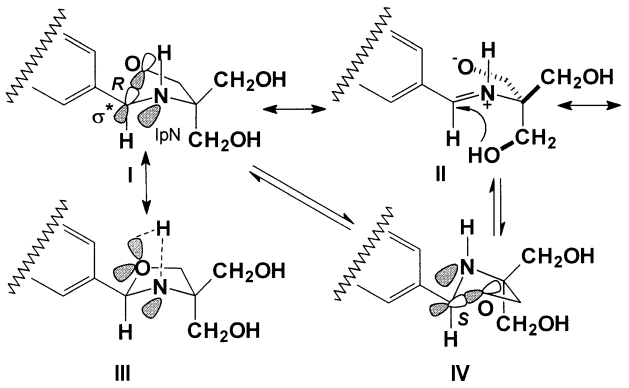
the primary or secondary hydroxyl group. Fortunately, as ^{1}H NMR spectra confirmed, the resulting mono oxazolidines **5a** and **6a** clearly exhibited the presence of a free C-4, -4′ hydroxymethyl group, in complete agreement with our previously reported results concerning the ring-chain tautomerism of mono Schiff bases of (1*S*,2*S*)-*p*-nitrophenylserinol, **1e**.[14] That is, the most acidic hydroxyl group (although the most sterically hindered) is also the most nucleophilic.[11,14]

2.1.3. Results. The evaluation of the equilibria was made by high resolution NMR in solution. An intrinsic drawback of this was that all compounds only exhibited satisfactory solubility in DMSO-d_6; their free evolution was monitored immediately after dissolution, at room temperature. The first display of the ^{1}H NMR spectrum was considered as the *time zero* of our investigation. This was complemented by the IR spectra throughout performed in the solid state (nujol). The results are summarised in Table 1.

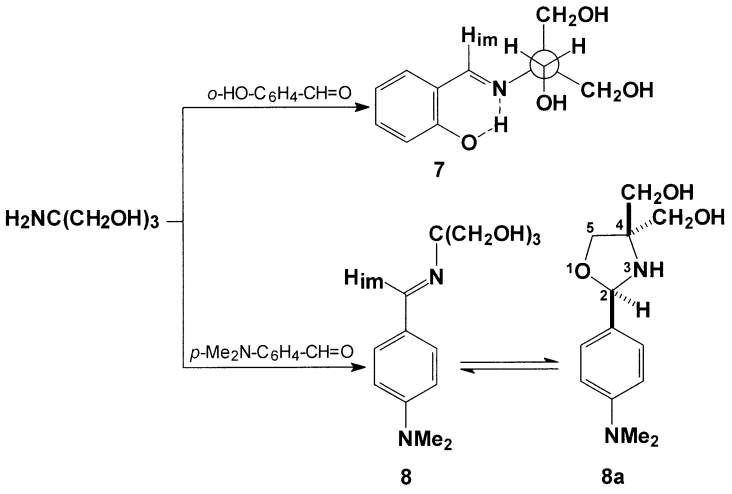
The compositions listed in Table 1 were calculated from ^{1}H NMR (and quantitative ^{13}C NMR whenever possible) spectra by choosing the best separated signals belonging to all observed species. The relevant considered region was the aromatic zone (compounds **2**–**4**) and heterocyclic zone (compounds **5**, **6**). For accurate calculation, correlation between zones was carefully checked.

We will start our analysis with the apparently most simple case, the expected compound **4**. The ^{1}H NMR spectrum in the aromatic region is depicted in Fig. 1.

One may conclude that the reaction between TRIS **1c** and terephthaldicarboxaldehyde (Scheme 2) did not yield, in



Scheme 5.



Scheme 6.

fact, the Schiff base **4** but instead gave directly the double oxazolidine **4b**. That is, no unique structure at time zero could be assigned but already a spontaneous equilibrium state originating from two successive ring openings and not ring closures (e.g. 'ring→chain' **4→4a→4b**). The IR spectrum confirmed this assumption: just a single very weak (almost flat) band was found in the relevant zone at 1643 cm^{-1} to be assigned as $\nu_{C=N}^{sk}$, hence a C_i symmetry of the dominant species as *meso* form **4b** *u*.[‡] Although the oxazolidine O-1–C-2–N-3 system, characterised by a 'classic triplet' of bands in the regions 1149–1185, 1116–1139 and 1080–1114 cm^{-1} was also found (as described by Bergmann since 1953),[8] the multiplicity of signals made our conclusion ambiguous and the stereochemistry of double oxazolidine **4b** (*u* or *l*?) in solution was a remaining question. Both ^{1}H and ^{13}C NMR spectra displayed just one complete set of signals even at the highest power of detection used (600 MHz). In contrast to the solid state, a configuration equilibrium between **4b** *u* and **4b** *l* (ring–ring tautomerism, as we previously described for other double oxazolidines derived from TRIS[22]) was considered the most plausible explanation. This would be consistent with the unexpected great vicinal coupling pattern (doublet) between H-2 and the amine proton, revealed throughout in **4a** and **4b** as $^{3}J_{H\text{-}2\text{–}NH}$=11.3 Hz; hence, τ_1 (lifetime of the involved nuclei in a particular magnetic environment, e.g. a *trans* configuration[14,23]) should be greater than $1/J$=0.088 s in both environments **4b** *u* and *l* (Scheme 3). Keeping in mind this ascertained stereochemistry, the *trans* disposal H-2–N*H* can also be the result of a strong anomeric effect involving a well positioned donor (lpN) overlapping with an excellent acceptor σ^{*}C-2–O-1 as Fuchs[15–17] and Pavia[24] have recently reported for related five and six membered 1,3-oxazanes (Scheme 5).

Thus, the iminium intermediate **II** (Scheme 5) should be responsible for the isomerisation **4b** *u*–**4b** *l* (**I** vs **IV**) since it contains the key activating withdrawing group against the other end of the molecule. Unfortunately, since **4b** was only soluble in DMSO-d_6, no NMR experiment could be carried out at low temperature. Accordingly, in solution, our diagnostic is the complete overlapping of signals belonging to both diastereomers **4b** *u* and *l* and an isomerisation controlled by:

(i) the existence of three statistically equivalent hydroxymethyl groups vs one imine group (S_N1 like mechanism via open chain structure **II**, Scheme 5).
(ii) a strong anomeric effect (also favoured by intramolecular hydrogen bonds as **III**) in both types of oxazolidines **4a** and **4b**.

We were particularly interested in evaluating this behaviour because the literature exclusively reports substituted 1,3-oxazolidines from the reaction of TRIS with carbonyl compounds.[22] However, in 1990 the remarkable stability of the imine derivatives of salicylaldehyde and certain amino alcohols (due to an intramolecular hydrogen bond between *o*-phenolic group and imine nitrogen generating a six membered chelate) was reported by Potapov et al.[25] Extension to ring-chain tautomerism of this concept by us[14] and later by Fuchs[17] demonstrated the absence (or minor occurrence) of ring forms in such type of Schiff bases. This prompted us to prepare the TRIS derivatives **7** and **8** (Scheme 6).

[‡] Valid for a frozen conformation as *anti* with respect to benzyl (C-2, -2′) protons; in Scheme 3 they are depicted as *syn* C_{1V} conformation for reason of simplicity.

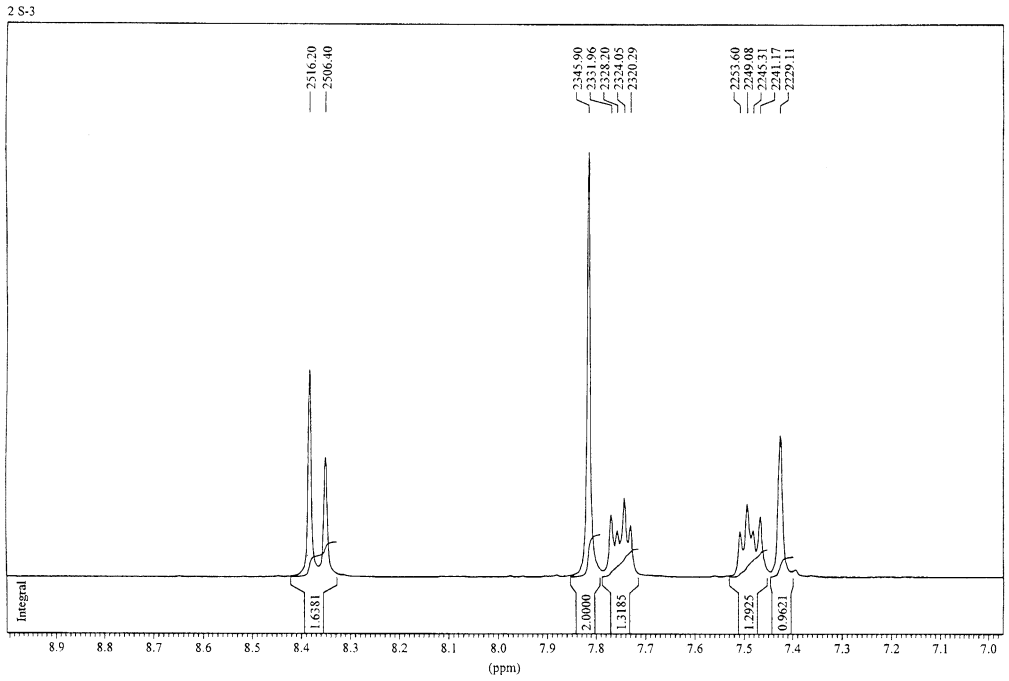


Figure 2. ^{1}H NMR spectrum at the equilibrium state (5 h) starting from the compound **2** (detail in the aromatic zone; 300 MHz, DMSO-d_6, δ in ppm, J in Hz; see Scheme 3), from downfield to upfield: 8.37 (2H, s, H_{im} in **2**), 8.35 (2H, s, H_{im} in both *cis trans* **2a**), 7.81 (4H, s, 1,4-phenylene in **2**), 7.76, 7.75, 7.50 and 7.48 (8H, d, J=7.9–8.3, 1,4-phenylene in both *cis trans* **2a**), 7.43 (4H, s, 1,4-phenylene in **2b**).

The NMR spectra of **7** were identical over time and hence evidenced one authentic *E* imine structure (e.g. H_{im} at 8.57 ppm and the corresponding C_{im} at 164.4 ppm). In turn, even at time zero, in the case of compound **8**, a clean 1:1 mixture of imine **8** (H_{im} at 8.28 and C_{im} at 159.7 ppm) and oxazolidine **8a** (H-2 at 5.44 ppm and C-2 at 101.3 ppm) was detected. No evolution of the composition (**8** vs. **8a**) was observed. Thus, compared with a stabilising intramolecular hydrogen bond (compound **7**, Scheme 6), even one of the strongest donating groups (p-Me_2N, $\sigma^+=-1.70$)[26] was unable to fix the chain form **8** if more than two free hydroxyl groups are present β to the imine double bond. In IR spectra, the $\nu_{C=N}^{sk}$ absorption were easily recognised as typical strong bands (1636 cm^{-1}in **7** and 1607 cm^{-1} in **8a**).

Isomerisations involving the di-imines **2** and **3** were found to be not only more complicate (Table 1) but also very different. The ^{1}H NMR spectrum of **2** is given below as an illustrative example (Fig. 2).

Calculations supported by ^{1}H NMR spectra led us to establish that the process really starts from **2** which is partially converted to an approximately 1:1 mixture of the intermediate epimers (*E-cis* and *E-trans*) of **2a**. No diastereoselectivity was reasonably detected at this first stage. Consequently, in the second step, the singlet located at 7.43 ppm was assigned for all phenylene protons in all **2b** species suggesting the limits of ^{1}H NMR detection rather than a certain diastereoselectivity. Indeed, for a more complete picture of both stages (**2→2a→2b**), we checked the ^{13}C NMR spectra (quantitative experiment). They confirmed the above deductions: no configurational preference was found for the entire isomerisation. Thus, despite overlapping, the compounds **2a** exhibited distinctly their four aromatic quaternary carbons (142.6, 136.7 and 142.4, 136.8 ppm, respectively) as well as the epimers **2b** (almost all detected, as the C-2 carbons located around 90 ppm, seven distinct signals in lieu of ten).

On the other hand **2** was the single case which allowed a kinetic estimation of the isomerisation **2→2a** as a clear 1st order equilibrium (see Section 4). The equilibrium state was established after 5 h ($k_a=2.22\times10^{-3}$ min^{-1}, $k_{-a}=1.69\times10^{-3}$ min^{-1}, $t_{1/2}=177$ min, $r=0.986$, Table 1). Finally, the IR spectrum enabled us to ascertain the compound **2**, as an authentic starting di-imine structure, by its strong relevant absorption at 1631 cm^{-1}.

Surprisingly, as for **4**, it was impossible to detect for the compound **3** (Table 1) any progressive evolution but directly an equilibrium state, presumably because of the increased nucleophilicity of the hydroxyl groups (though the final appearance of ^{1}H and ^{13}C NMR spectra was almost identical with the above discussed **2**).[§] In the IR spectrum, a single relevant band $\nu_{C=N}^{sk}$ was displayed (again very weak) at 1641 cm^{-1} indicating a reverse process as 'ring→chain tautomerism' originating from the dominant *meso* forms **3b** *cis-u-cis* and/or **3b** *trans-u-trans* (C_i symmetry) (Scheme 3).

The behaviour of chiral di-imines **5** and **6** evidence, besides other unexpected aspects, the occurrence of a certain stereoselectivity. NMR spectra performed on the mixtures at equilibrium indicated very similar shapes for **5** and **6**.

[§] Evidence of the same anomeric effect in oxazolidines **2a**, **2b**, **3a** and **3b** as compared with **4a** and **4b** remained obscure since the NH group displayed its usual shape as a broad singlet although some splitting as a doublet of H-2 (7–11 Hz) was occasionally observed.

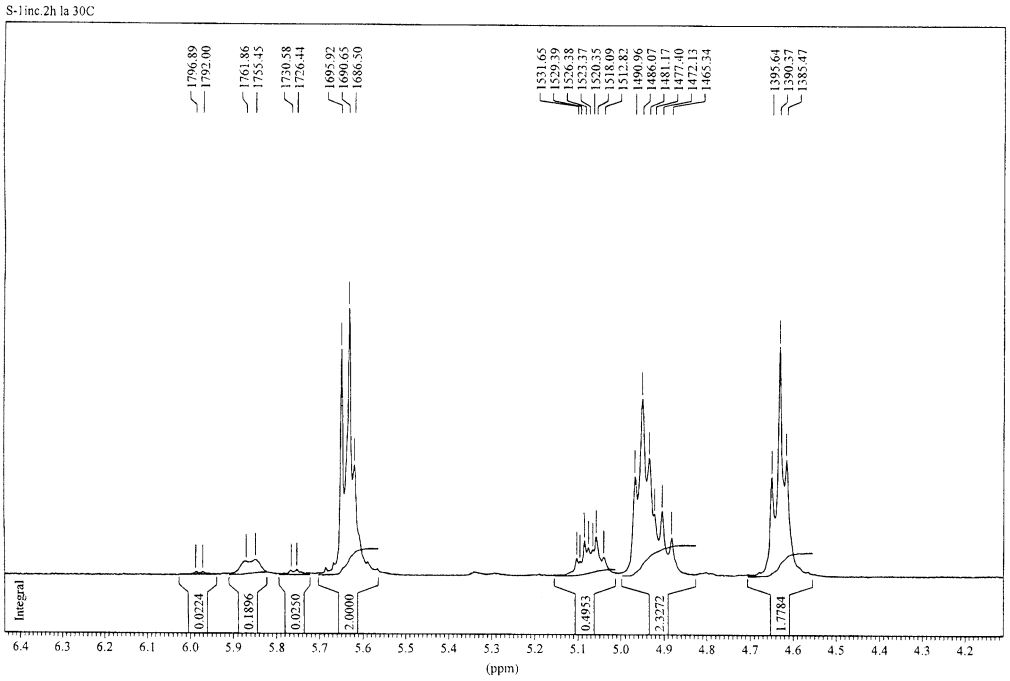


Figure 3. ^{1}H NMR spectrum at the equilibrium state (24 h) starting from the compound **6** (detail in the heterocyclic zone; 300 MHz, DMSO-d_6, δ in ppm, J in Hz; see Scheme 4), from downfield to upfield: 5.98 (1H, d, 4.9, H-2 in **6a** *cis*); 5.86 (1H, d, J=6.4, H-2′ in **6b**); 5.76 (1H, d, J=4.2, H-2 in **6a** *trans*); 5.64 (2H, d, J=5.3, O*H* in **6**); 5.63 (1H, d, J=4.2, H-2 in **6b**); 5.08 (1H, dd, J=4.9, 10.9, CH_2OH in **6b**), 5.07 (1H, dd, J=5.6, 10.9, CH_2OH in **6b**), 4.95 (2H, dd as t, J=4.9, benzyl C*H* in **6**), 4.92 (1H, d, J=5.3, H-5′ in **6b**), 4.90 (1H, d, J=6.8, H-5 in **6b**), 4.63 (2H, dd as t, J=5.1, CH_2OH in **6**).

They were also very consistent with the same spectra of simplest Schiff base of **1e** and benzaldehyde.[14] Moreover, for **6**, even the composition at equilibrium (as 78% chain form **6** vs. 22% ring form **6b**, see Table 1) was identical with that of its above mentioned mono Schiff base as *E*-2-benzylideneamino derivative of **1e**.[14]

We will consider the mixture at equilibrium as resulted from the isomerisation of **6**; its ^{1}H NMR spectrum is depicted in Fig. 3.

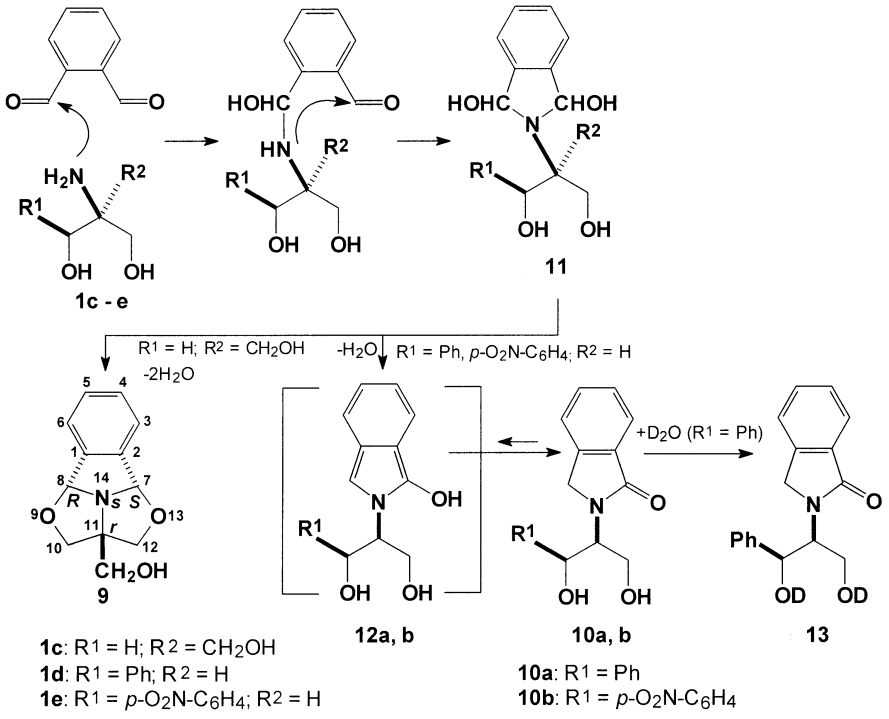
The equal intensity of signals belonging to epimers **6b** suggested two distinct oxazolidine environments as confirmed by ^{13}C NMR spectrum (quantitative experiment) which also showed an equal intensity of relevant peaks: C-2, -2′ (92.9 and 92.1 ppm), C-5, -5′ (79.9 and 78.9 ppm) and C-4, -4′ (69.5 and 67.8 ppm). Next, in the aromatic region, two different environments were evidenced again for the two *p*-nitrophenyl fragments as four distinct tertiary carbons (126.8, 126.5, 123.6 and 123.4 ppm). Finally, two types of tertiary carbon were found for the 1,4-phenylene moiety. No new imine carbon was detected other than the signal belonging to starting **6**. These data demonstrate, in our opinion, the evolution of the equilibrium towards the dominant diastereomer **6b** *cis-u-trans* (Scheme 4) issued from a statistically favoured succession of ring closures as *cis*(*trans*) followed by *trans*(*cis*) of the discrete intermediates **6a** *trans*(*cis*). The latter were under the limit of detection, at equilibrium, at least in ^{13}C NMR spectra. That is, in ^{1}H NMR spectrum discussed above (Fig. 3), one could assign the two doublets located at about 5.98 and 5.76 ppm as belonging to H-2 in **6a** *cis* and *trans* species but we avoided a more conclusive interpretation.

The following observations were also of interest:

Although very similar, only the isomerisation of **5** provides the possibility of epimerisation at the benzyl carbon during ring closure (that is, the benzyl chiral center (Scheme 4) is epimerisable in all **5**, **5a** and **5b** species).[12] Based on our ^{1}H NMR data, we found no evidence that the initial 1*S*,2*S* configuration of the starting **5** would change since, in ring form **5b**, despite partially overlapping, protons H-5, -5′ are split as a doublet with a *trans* stereospecific coupling as 4.9–5.0 Hz (hence indicating an *S* configuration of the C-5, -5′ position).

The absence of the intermediates **5a** and **6a** is plausible by the increased acidity (as autocatalysis) of the secondary hydroxyl group in **5** and **6** as compared with **2** and **3**. In terms of chemical shifts, this group was located at 5.24 ppm in **5** and 5.64 ppm in **6** whereas in **2** and **3** hydroxyl groups were sufficiently upfield (4.59 ppm in **2** and 4.78 ppm in **3**). Accordingly, as anticipated, the secondary hydroxyl is the only nucleophile involved in ring closure.

Compared with the simple *E*-2-benzylideneamino derivative of **1e**,[14] the equilibrium state is reached about four times more quickly (24 h vs. 105 h) for **5** and **6**, to demonstrate the expected activation of an imine double against the other one. However, although in a large series of (hetero)-arylideneamino derivatives of **1e** we previously reported the equilibration time of only *E* diastereomers,[14] the same was not valid for **5** and **6**. Thus (see Table 1) careful inspection of the ^{1}H NMR spectrum in the aromatic region of **5** at equilibrium indicated the presence of the minor diastereomers of **5** (H_{im} at 8.217 and 8.213 ppm and the



Scheme 7.

corresponding 1,4-phenylene signals at 7.82 and 7.79 ppm in a clean 1:2 ratio, respectively; in turn, in the ^{13}C NMR spectrum, only the imine and benzyl carbons were distinct (160.3 and 78.6 ppm, respectively). Similar behaviour was exhibited by **6** when its minor diastereomers were detected even at time zero to coexist with the epimer **6b**. Obviously this last detail indicates a more delicate approach. Without extrapolating, this enables us to assume that the minor diastereomers of **5** and **6** (not detected in the series **2**–**4**) originate from a not total but almost complete diastereoselective ring opening of the discrete intermediates **5a** and **6a**.

It is recognised that electronic factors dominate steric requirements regarding the stereochemistry of double oxazolidine **5b** and **6b**. Indeed, there is no preference for a local disposal (*cis* or *trans*) of the two (C-2, -2′ vs -5, -5′) aromatic fragments with respect to each oxazolidine ring in **5b** and **6b** in total agreement with the same stereochemistry of simple epimeric mono oxazolidines derived from **1e** and a large series of (hetero)aryl aledehydes.[14]

In the solid state, the compounds **5** and **6** were typical Schiff bases as proved by the strong IR absorption of $\nu_{C=N}{}^{sk}$ (1643 and 1647 cm^{-1}, respectively).

2.2. Reactions with 1,2-phthaldicarboxaldehyde

The idea to perform reactions with 1,2-phthaldicarboxaldehyde was inspired by Broadbent's[27] and Shipchandler's[28] earlier works as well as our data regarding the unusual isoindoline derivatives obtained by treatment of the above dicarbonyl compound with 5-aminoketals of *l-p*-nitropenylserinol.[29] Although preliminary inspection of Drieding models suggested that it had been possible to construct two oxazolidine rings linked in a 1,2-phenylene moiety starting from the serinols **1a**–**e**, the results revealed different behaviour. The chemistry is depicted in Scheme 7.

Treatment of 1,2-phthaldicarboxaldehyde with **1c** (equimolar ratio or even excess of the later) in methanol, at room temperature (or reflux) afforded in good yield the tetraheterocycle **9** (in context, a masked *N*-substituted isoindoline). In the same conditions, 1-aryl serinols **1d** and **1e** yielded *N*-substituted isoindoline-1-ones **10a** and **10b**. Due to their similarity, we postulated that compounds **9** and **10** could have a common intermediate, assigned as the 1,3-dihydroxyindoline of type **11**. Indeed, formation of **11** is plausible (as a variant of classical Knorr–Paal synthesis of *N*-substituted chiral pyrroles).[27] It can be seen in a double role as follows:

(a) As a source of stable benzylic carbocations to promote the ring closure as two successive etherifications (S_N1 like mechanism) in reaction with the three hydroxymethyl groups of **1c**, to give **9**. The latter, together with its C-11 methyl and ethyl analogues (starting from **1a** and **1b**), are known compounds, previously reported by Shipchandler.[28] However, their intimate formation remained obscure as did their stereochemistry. In our investigation, only compound **9** was prepared and explored by means of combined NMR experiments (ROESY). They confirmed the *trans* disposal of the aromatic ring vs. C-11 hydroxymethyl group and the lone pair at N-14, in order to preserve the tent shape of the basic heterobicycle skeleton. Its 7*S**,8*R**,11*r*,14*s* configuration (*meso* form), assigned by us, is totally different than that of other disubstituted 1-aza-3,7-dioxabicyclo[3.3.0]octanes bearing (hetero)aromatic rings linked at C-2, -8 (*all cis*).[30,31]

(b) The evolution towards *N*-substituted isoindoline-1-ones **10a** and **10b** of the same intermediate **11** could be explained by the weaker reactivity (e.g. due to steric hindrance) of the secondary hydroxyl group in 1-aryl serinols **1d**, **e** as compared with **1a**–**c**. Hence, the key step of the reaction should consist, this time, in a 1–4 dehydration to generate the 2-hydroxy pyrrole derivatives **12a** and **12b** as tautomers of the more stable and isolated **10a** and **10b**. Thus, Shipchandler's previous assumptions[28] regarding a related processes (as a 1,4 shift hydride and a prototropic transfer) to yield alkyl 1,3-oxazolines starting from simple β-aminoalcohols was ruled out. In fact, if the global synthesis of compounds **10a** and **10b** is deliberately considered only from a redox point of view, one might better suppose a preliminary Canizzaro type reaction involving the 1,2-phthaldicarboxaldehyde (as a masked 1,4-dialdehyde) to provide the corresponding 2-hydroxymethyl benzoic acid (or its γ-lactone). However, the specific conditions required (temperature and rhodium phosphine complex, as reported by Bergens in 1990[32]) are essentially different to ours.

The identity of the new chiral compounds **10a** and **10b** was fully confirmed by means of combined NMR methods: the >N–C=O moiety was assigned as amide based on typical chemical shift of the carbonyl in ^{13}C NMR spectrum (around 168 ppm); the heterocyclic methylene exhibited its unusual great vicinal coupling as about 18 Hz. Finally, the double deuteriation of **10a** enabled us to unambiguously assign the two types of free hydroxyl group (completely absent in the ^{1}H NMR spectrum of **13**, Scheme 7).

3. Conclusion

The isomerisations of the reaction products resulting from 1,4-dicarboxaldehyde and certain *C*-substituted serinols can be seen either as 'chain→ring' or 'ring→chain' equilibrations involving (*E*,*E*)-double Schiff bases, double 1,3-oxazolidines (with dominant *u* configuration at C-2) via *cis*–*trans* mono oxazolidine Schiff bases. Diastereoselectivity is rather poor in the double oxazolidine series. Equilibrations are fast (or spontaneous) as a result of activation between the two imine groups and the number of free hydroxymethyl groups. The products from the reaction between *C*-substituted serinols and 1,2-phthaldicarboxaldehyde are of type isoindoline in nature, depending on the nucleophilicity of the hydroxymethyl groups.

4. Experimental

4.1. General

Melting points are uncorrected. NMR spectra were recorded on VARIAN® GEMINI 300 instrument operating at 300 and 75 MHz for ^{1}H and ^{13}C nuclei and/or Brucker® AM300 and 600 instrument operating at 300 (600) and 75 (150) MHz for ^{1}H and ^{13}C nuclei, respectively. No $SiMe_4$ was added; chemical shifts were measured against the solvent peak. ^{13}C NMR spectra (quantitative experiments) were performed on VARIAN GEMINI 300 instrument by using min. 150 mg/sample and $D1=10$ s. All spectra were measured in anhydrous commercially available DMSO-d_6 at room temperature. For the resulting epimers, after equilibration, only distinct and/or characteristic peaks are listed. All chemical shifts as δ values are given throughout in ppm; all coupling patterns as *J* values are given throughout in Hz.

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 FT/IR-615 Jasco® instrument. Only relevant absorption are listed (throughout in cm^{-1} as very weak (vw), weak (w), medium (m) or (s) strong). Specific rotations were performed on Jasco® DIP-1000 Instrument. The compound **9** was prepared according to literature.[27,28]

4.2. General procedure for the preparation of the compounds 2 and 3b

2-Alkyl serinols **1a**, **b** as a 0.60 M suspension in bezene (*p*-TsOH as catalyst) and terephthaldicarboxaldehyde (2:1 molar ratio, respectively) were refluxed in a Dean–Stark trap for 8–10 h (until no further water separated, TLC monitoring, eluent benzene/acetone 3:1 v/v, double visualisation: UV 254 nm and I_2 bath). The solvent was completely removed under vacuum and the residue was crystallised from an appropriate solvent to yield the title compounds **2** and **3b**. Scale-up of the synthesis: starting from 1.00–5.00 g **1a**, **b**.

4.3. Kinetic monitoring of the chain→ring tautomerism for the compounds (2)→(2a)→(2b)

The following values were used: (time in min)/(% **2**; % **2a**; % **2b**): (12)/(82; 18; 0); 38/(73; 24; 3); (63)/(63; 31; 6); (102)/(55; 37; 8); 151/(48; 41; 11); (177)/(45; 44; 11); (307)/(38; 46; 16).

4.3.1. (*E*,*E*)-1,4-Bis-*N*-(1,3-dihydroxy-2-methylpropane-2-yl)-phenylene diimine (2). (92%) white crystalline powder, mp 113–114°C (Et_2O) [Found: C, 62.0; H, 8.2; N, 8.7. $C_{16}H_{24}N_2O_4$ requires C, 62.30; H, 7.84; N, 9.12%; N (after Kjeldahl) 9.0%]; R_f (75% benzene/acetone) 0.75; ν_{max} (Nujol) 1631 (s, $\nu_{C=N}{}^{sk}$), 1461 (s) cm^{-1}. δ_H (300 MHz DMSO-d_6) 8.37 (2H, s, C*H*=N), 7.81 (4H, s, C*H*= 1,4-phenylene), 4.59 (4H, dd as t, $J=5.5$, 5.5 Hz, O*H*), 3.51 (4H, dd, $J=5.2$, 10.6 Hz, CH_aH_bOH), 3.41 (4H, dd, $J=5.8$, 10.8 Hz, CH_aH_bOH), 1.17 (6H, s, *Me*); δ_C (75 MHz DMSO-d_6): 157.6 (2C, *C*H=N), 138.3 (2C, C-q arom.), 127.9 (4C, *C*H= arom.), 65.7 (4C, CH_2OH), 65.0 (2C, C-q), 18.4 (2C, *Me*).

4.3.2. 2-(*E*)-[4-(4-Hydroxymethyl-4-methyl-1,3-oxazolidine-2-yl)-benzylideneamino]-2-methylpropane-1,3-diol (2a). (Both epimers **2a** *cis* and **2a** *trans* as detected by NMR in solution after equilibration as 47%, Scheme 3, Fig. 2, Table 1). δ_H (300 MHz DMSO-d_6) 8.35 (2H, s, C*H*=N), 7.76 (2H, d, $J=7.9$ Hz, C*H*= arom.), 7.75 (2H, d, $J=7.9$ Hz, C*H*= arom.), 7.50 (2H, d, $J=8.3$ Hz, C*H*= arom.), 7.48 (2H, d, $J=7.9$ Hz, C*H*= arom.), 5.41 (1H, s, H-2), 5.39 (1H, s, H-2), 5.00 (2H, bs, O*H*), 4.57 (4H, bs, O*H*), 3.78 (2H, d, $J=7.7$ Hz, H-5), 3.77 (2H, d, $J=7.7$ Hz, H-5), 3.60–3.25 (12H, m, CH_aH_bOH), 2.80 (2H, bs, N*H*), 1.116 (3H, s,

Me), 1.163 (3H, s, *Me*), 1.154 (3H, s, *Me*), 1.151 (3H, s, *Me*); δ_C (75 MHz DMSO-d_6) 142.6 (1C, C-q arom.), 142.4 (1C, C-q arom.), 136.8 (1C, C-q arom.), 136.7 (1C, C-q arom.), 128.2 (2C, *C*H═ arom.), 128.0 (2C, *C*H═ arom.), 127.7 (2C, *C*H═ arom.), 127.5 (2C, *C*H═ arom.), 91.7 (1C, C-2), 91.6 (1C, C-2), 72.5 (1C, C-5), 72.2 (1C, C-5), 65.7 (4C, *C*H_2OH), 64.96 (2C, *C*H_2OH), 64.7 (2C, C-q), 63.3 (2C, C-4), 22.3 (1C, *Me*), 22.2 (1C, *Me*), 18.1 (2C, *Me*).

4.3.3. 1,4-Bis(4-hydroxymethyl-4-methyl-1,3-oxazolidine-2-yl)-benzene (2b). (All six epimers as detected by NMR in solution after equilibration as 17%, Scheme 3, Fig. 2, Table 1). δ_H (300 MHz DMSO-d_6), 7.43 (4H, s, C*H*═ 1,4-phenylene), 5.43 (2H, s, H-2), 4.83 (2H, bs, O*H*), 1.138 (3H, s, *Me*), 1.134 (3H, s, *Me*), 1.127 (3H, s, *Me*), 1.124 (3H, s, *Me*); δ_C (75 MHz DMSO-d_6) 140.5, 140.3 and 140.2 (C-q in 1,4-phenylene fragment), 126.6, 126.5, 126.3, 126.0 and 125.7 (*C*H═ in 1,4-phenylene fragment), 91.4, 91.3, 91.0, 90.75 and 90.67 (C-2), 22.5 and 22.0 (*Me*).

4.3.4. (*E*,*E*)-1,4-Bis-*N*-(2-ethyl-1,3-dihydroxypropane-2-yl)-phenylene diimine (3). (As detected by NMR in solution after equilibration 13%, Scheme 3, Table 1). δ_H (300 MHz DMSO-d_6) 8.40 (2H, s, C*H*═N), 7.81 (4H, s, C*H*═ 1,4-phenylene), 4.78 (4H, dd as t, J=5.5 Hz, O*H*), 3.60–3.30 (8H, m, CH_aH_bOH), 1.70–1.45 (4H, m, CH_2CH$_3$), 0.95–0.75 (6H, m, *Me*); δ_C (75 MHz DMSO-d_6) 157.8 (2C, *C*H═N), 138.5 (2C, C-q arom.), 127.8 (4C, *C*H═ 1,4-phenylene), 66.0 (4C, *C*H_2OH), 65.9 (2C, C-q), 24.7 (2C, *C*H_2CH$_3$), 7.4 (2C, *Me*).

4.3.5. 2-(*E*)-[4-(4-Ethyl-4-hydroxymethyl-1,3-oxazolidine-2-yl)-benzylideneamino]-2-ethylpropane-1,3-diol (3a). (Both epimers **3a** *cis* and **3a** *trans*, as detected by NMR in solution after equilibration as 30%, Scheme 3, Table 1). δ_H (300 MHz DMSO-d_6) 8.36 (2H, s, C*H*═N), 7.75 (2H, d, J=8.2 Hz, C*H*═ arom.), 7.74 (2H, d, J=8.2 Hz, C*H*═ arom), 7.50 (2H, d, J=8.1 Hz, C*H*═ arom.), 7.49 (2H, d, J=8.1 Hz, C*H*═ arom.), 5.42 (1H, s, H-2), 5.37 (1H, s, H-2), 4.93 (4H, dd as t, J=5.2, 5.2 Hz, O*H*), 4.57 (2H, dd as t, J=5.2, 5.2 Hz, O*H*), 3.77 (1H, d, J=7.6 Hz, H-5), 3.76 (1H, d, J=7.7 Hz, H-5), 3.70 (1H, d, J=7.9 Hz, H-5), 3.69 (1H, d, J=7.9 Hz, H-5), 3.60–3.30 (12H, m, CH_aH_bOH), 2.80 (2H, bs, N*H*), 1.70–1.45 (8H, m, CH_2CH$_3$), 0.95–0.75 (12H, m, *Me*). δ_C (75 MHz DMSO-d_6) 142.6 (1C, C-q arom.), 142.4 (1C, C-q arom.), 138.8 (1C, C-q arom.), 136.7 (1C, C-q arom.), 127.6 (2C, *C*H═ arom.), 127.5 (2C, *C*H═ arom.), 126.4 (2C, *C*H═ arom.), 126.3 (2C, *C*H═ arom.), 66.0 (4C, *C*H_2OH), 65.9 (2C, *C*H_2OH), 63.2 (2C, C-4), 62.8 (2C, C-q).

4.3.6. 1,4-Bis(4-ethyl-4-hydroxymethyl-1,3-oxazolidine-2-yl)-benzene (3b). (59%) white crystalline powder, mp 114–115°C (*i*-PrOH). [Found: C, 64.5; H 8.6; N, 8.0. $C_{18}H_{28}N_2O_4$ requires C, 64.24; H 8.39; N, 8.36%. N (after Kjeldahl): 8.2%]; R_f (75% benzene/acetone) 0.75; ν_{max} (Nujol) 1641 (vw, $\nu_{C=N}^{sk}$), 1152 (w), 1112 (w) 1080 (s, ν_{N-C-O}) cm^{-1}; δ_H (300 MHz DMSO-d_6) 7.48 (4H, s, C*H*═ 1,4-phenylene), 5.35 (2H, d, J=11.7 Hz, H-2), 4.54 (2H, dd as t, J=5.4, 5.4 Hz, O*H*), 3.60–3.30 (8H, m, H-5, CH_aH_bOH), 1.70–1.45 (4H, m, CH_2CH$_3$), 0.95–0.75 (6H, m, *Me*); δ_C (75 MHz DMSO-d_6) 140.5, 140.4, 140.30, 140.25 (C-q in 1,4-phenylene fragment), 126.2 (4C, *C*H═ arom.), 91.3 (2C, C-2), 71.9 and 71.6 (2C, C-5), 63.0 (2C, C-4), 27.4 and 27.3 (2C, *C*H_2CH$_3$), 8.41 and 8.34 (2C, *Me*).

4.4. General procedure for the preparation of the compounds 4b, 5 and 6

1-Aryl serinols **1d**, **e** as a 0.45 M suspension in ethanol (for **1c** as 0.70 M suspension in isopropanol) and terephthaldicarboxaldehyde (2:1 molar ratio, respectively) were refluxed for 8–10 h (TLC monitoring, eluent benzene/acetone 3:1 v/v, double visualisation: UV 254 nm and I_2 bath). The solvent was removed under vacuum and the residue was crystallised from an appropriate solvent to yield the title compounds **4b**, **5** and **6**. Scale-up of the synthesis: starting from 1–5.00 g **1c**–**e**.

4.4.1. (*E*,*E*)-1,4-Bis-*N*-(1,3-dihydroxy-2-hydroxymethylpropane-2-yl)-phenylene diimine (4). This compound was detected by means of NMR in small traces only as 0.25% (Scheme 3, Fig. 1, Table 1).

4.4.2. 2-(*E*)-[4-(4,4-Bis-hydroxymethyl-1,3-oxazolidine-2-yl)-benzylideneamino]-2-hydroxymethylpropane-1,3-diol (4a). (As detected by NMR in solution after equilibration as 14%, Scheme 3, Fig. 1, Table 1). δ_H (600 MHz DMSO-d_6) 8.36 (1H, s, C*H*═N), 7.67 (2H, d, J=8.2 Hz, C*H*═ arom.), 7.40 (2H, d, J=8.1 Hz, C*H*═ arom.), 5.31 (1H, d, J=11.1 Hz, H-2), 3.63 (1H, d, J=6.5 Hz, H-5), 3.59 (1H, d, J=7.6 Hz, H-5), 3.39 (5H, dd, J=5.2, 11.1 Hz, CH_aH_bOH), 3.33 (5H, dd, J=4.9, 11.7 Hz, –CH_aH_bOH), 2.67 (1H, d, J=11.3 Hz, N*H*);

4.4.3. 1,4-Bis(4,4-bis-hydroxymethyl-1,3-oxazolidine-2-yl)-benzene (4b). (87%) white crystalline powder, mp 138–139°C (MeOH); [Found: C, 56.1; H, 6.9; N, 7.9. $C_{16}H_{24}N_2O_6$ requires C, 56.44; H, 7.11; N, 8.26%; N (after Kjeldahl): 8.1%]; R_f (75% benzene/acetone) 0.50; ν_{max} (Nujol) 1643 (vw, $\nu_{C=N}^{sk}$), 1498 (m, $\nu_{C=C}^{sk}$), 1165 (w), 1128 (w), 1083 (s, ν_{N-C-O}) cm^{-1}; δ_H (600 MHz DMSO-d_6) 7.34 (4H, s, C*H*═ 1,4-phenylene), 5.27 (2H, d, J=11.2 Hz, H-2), 4.72 (2H, dd as t, J=5.5, 5.5 Hz, O*H*), 4.59 (2H, dd as t, J=5.5, 5.5 Hz, O*H*), 3.62 (2H, d, J=7.8 Hz, H-5), 3.58 (2H, J=7.9 Hz, H-5); 3.35 (4H, d, J=4.4 Hz, CH_aH_bOH), 3.34 (4H, d, J=4.2 Hz, CH$_a$$H_b$OH), 2.63 (2H, d, J=11.3 Hz, N*H*); δ_C (150 MHz DMSO-d_6) 141.2 (2C, C-q arom.), 126.9 (4C, *C*H═ arom.), 92.2 (2C, C-2), 69.8 (2C, C-5), 68.1 (2C, C-4), 64.0 (2C, *C*H_2OH), 63.2 (2C, *C*H_2OH).

4.4.4. (*E*,*E*)-1,4-Bis-*N*-[(1*S*,2*S*)-1-phenyl-1,3-propanediol-2-yl]-phenylene diimine (5). (85%) white crystalline powder, mp 122–123°C (MeOH); [Found: C, 71.9; H, 6.9; N, 6.1. $C_{26}H_{28}N_2O_4$ requires: C 72.18, H, 6.52, N 6.50%; N (after Kjeldahl): 6.5%]; R_f (75% benzene/acetone) 0.65; $[\alpha]_D^{20}$=+9.6 (*c* 1.0, MeOH); ν_{max} (Nujol) 1643 (m, $\nu_{C=N}^{sk}$), 1599 (w), 1567 (w), 1508 (s), 1462 (s, $\nu_{C=C}^{sk}$) cm^{-1}; δ_H (300 MHz DMSO-d_6) 8.24 (2H, s, C*H*═N), 7.85 (4H, s, C*H*═ 1,4-phenylene), 7.40–7.25 (10H, m, C*H*═ arom.), 5.24 (2H, d, J=6.0 Hz, O*H*), 4.73 (2H, s, benzyl C*H*), 4.51 (2H, d, J=3.0 Hz, CH$_2$O*H*), 3.42 (6H, s, >C*H*–, CH_aH_bOH); δ_C (75 MHz DMSO-d_6) 161.0 (2C, *C*H═N), 143.6 (2C, C-q arom.), 137.9 (2C, C-q

arom.), 128.2 (4C, *C*H= arom.), 127.8 (4C, *C*H= arom.), 126.9 (4C, *C*H= arom.), 126.3 (2C, *C*H= arom.), 78.7 (2C, benzyl *C*H), 73.2 (2C, >*C*H–), 61.8 (2C, *C*H_2OH).

4.4.5. (2*R*,2′*S*,4*S*,4′*S*,5*S*,5′*S*)-1-(4-Hydroxymethyl-5-phenyl-1,3-oxazolidine-2-yl)-4-(4′-hydroxymethyl-5′-phenyl-1′,3′-oxazolidine-2′-yl)-benzene (5b). (As detected by NMR in solution after equilibration as 30%, Scheme 4, Table 1). δ_H (300 MHz DMSO-d_6) 7.64 (2H, d, *J*=8.3 Hz, C*H*= 1,4-phenylene), 7.60 (2H, d, *J*=8.7 Hz, C*H*= 1,4-phenylene), 7.45–7.19 (10H, m, C*H*= arom.), 5.81 (1H, s, H-2′), 5.61 (1H, s, H-2), 5.02 (1H, dd as t, *J*=5.5, 5.5 Hz, CH_2OH), 4.94 (1H, dd as t, *J*=5.5, 5.5 Hz, CH_2OH), 4.74 (1H, d, *J*=4.9 Hz, H-4′), 4.72 (1H, d, *J*=4.9 Hz, H-4), 3.62 (4H, m, –CH_aH_bOH), 3.18 (2H, bs, N*H*); δ_C (75 MHz DMSO-d_6) 142.4 (1C, C-q arom.), 142.1 (1C, C-q arom.), 136.4 (1C, C-q arom.), 136.2 (1C, C-q arom.), 92.6 and 91.6 (2C, C-2, -2′), 80.7 and 79.6 (2C, C-4, -4′), 69.5 and 67.7 (2C, *C*H_2OH), 61.2 and 58.8 (2C, C-5, -5′).

4.4.6. (*E*,*E*)-1,4-Bis-*N*-[(1*S*,2*S*)-1-(4-nitrophenyl)-1,3-propanediol-2-yl)-phenylene diimine (6). (74%) yellowish crystalline powder, mp 162–163°C (MeOH); [Found: C, 59.6; H, 4.8; N, 11.0. $C_{26}H_{26}N_4O_8$ requires C, 59.74; H, 5.01; N, 10.76%]; R_f (75% benzene/acetone) 0.70; $[\alpha]_D^{20}$=+15.7 (*c* 1.0, MeOH); ν_{max} (Nujol) 1647 (s, $\nu_{C=N}^{sk}$) cm^{-1}. δ_H (300 MHz DMSO-d_6) 8.20 (2H, s, C*H*=N), 8.18 (4H, d, *J*=8.7 Hz, C*H*= arom.), 7.80 (4H, s, C*H*= 1,4-phenylene), 7.64 (4H, d, *J*=8.3 Hz, C*H*= arom.), 5.64 (2H, d, *J*=5.3 Hz, O*H*), 4.95 (2H, dd as t, *J*=4.9, 4.9 Hz, benzyl C*H*), 4.63 (2H, dd as t, *J*=5.1, 5.1 Hz, CH_2OH), 3.64 (2H, dd, *J*=5.8, 11.1 Hz, CH_aH_bOH), 3.56 (2H, dd, *J*=4.5, 10.4 Hz, –CH_aH_bOH), 3.45 (2H, m, H-4, -4′); δ_C (75 MHz DMSO-d_6) 161.5 (2C, *C*H=N), 151.6 (2C, C-q arom.), 146.4 (2C, C-q arom.), 137.9 (2C, C-q arom.), 128.2 (4C, *C*H= arom.), 128.0 (4C, *C*H= arom.), 122.9 (4C, *C*H= arom.), 77.7 (2C, benzyl *C*H), 72.4 (2C, >*C*H–), 61.6 (2C, *C*H_2OH).

4.4.7. (2*R*,2′*S*,4*S*,4′*S*,5*S*,5′*S*)-1-[4-Hydroxymethyl-5-(4-nitrophenyl)-1,3-oxazolidine-2-yl]-4-(4′-hydroxymethyl-5′-(4′-nitrophenyl)-1′,3′-oxazolidine-2′-yl)-benzene (6b). (As detected by NMR in solution after equilibration as 22%, Scheme 4, Fig. 3, Table 1). δ_H (300 MHz DMSO-d_6) 8.26 (4H, m, C*H*= arom.), 7.75–7.57 (8H, m, C*H*= arom.), 5.86 (1H, d, *J*=6.4 Hz, H-2′), 5.63 (1H, d, *J*=4.2 Hz, H-2), 5.08 (1H, dd, *J*=4.9, 10.9 Hz, CH_2OH), 5.07 (1H, dd, *J*=5.6, 10.9 Hz, CH_2OH), 4.92 (1H, d, *J*=5.3 Hz, H-5′), 4.90 (1H, d, *J*=6.8 Hz, H-5), 3.68–3.52 (4H, m, CH_aH_bOH), 3.50–3.42 (2H, m, H-4, -4′), 3.20 (2H, bs, N*H*); δ_C (75 MHz DMSO-d_6 as quantitative carbon, QC NMR experiment) 150.4 (1C, C-q arom.), 150.3 (1C, C-q arom.), 142.0 (1C, C-q arom.), 141.5 (1C, C-q arom.), 136.3 (1C, C-q arom.), 136.2 (1C, C-q arom.),127.2 (2C, *C*H= arom.), 127.1 (2C, *C*H= arom.), 126.8 (2C, *C*H= arom.), 126.5 (2C, *C*H= arom.), 123.6 (2C, *C*H= arom.), 123.4 (2C, *C*H= arom.), 92.9 and 92.1 (2C, C-2, -2′), 79.9 and 78.9 (2C, C-5, -5′), 69.5 and 67.8 (2C, C-4, -4′), 61.6 and 59.0 (2C, *C*H_2OH).

4.4.8. 2-(*E*)-(2-Hydroxybenzylideneamino)-2-hydroxymethylpropane-1,3-diol (7). TRIS® (2.00 g, 16.5 mmol) and salicylaldehyde (1.90 mL, 2.22 g, 18.2 mmol) in toluene (50 mL) were refluxed in a Dean–Stark trap for 12 h to complete removal of water (TLC monitoring, eluent benzene/methanol 3:1 v/v, double visualisation: UV 254 nm and I_2 bath). The reaction mixture, as a fine yellow suspension, was cooled at room temperature, filtered off and the crude product was washed with ether (about 50 mL, to complete removal of unreacted salicylaldehyde), then recrystallised from hot toluene to *yield the title compound* **7** (3.00 g, 88%) as a yellow crystalline powder, mp 164–166°C (toluene); [Found: C, 59.0; H, 6.7; N, 6.4. $C_{11}H_{15}NO_4$ requires C, 58.64; H, 6.71; N, 6.24%]; R_f (75% benzene/methanol) 0.70; ν_{max} (Nujol) 1636 (s, $\nu_{C=N}^{sk}$), 1607 (m), 1556 (w), 1536 (s) cm^{-1}. δ_H (300 MHz DMSO-d_6) 9.50 (1H, bs, O*H* phenol); 8.57 (1H, s, C*H*=N–), 7.41 (1H, d, *J*=7.0 Hz, C*H*= arom.), 7.29 (1H, dd as t, *J*=7.2, 7.2 Hz, C*H*= arom.), 6.79 (2H, dd as t, *J*=4.2, 4.2 Hz, C*H*= arom.), 4.82 (3H, bs, O*H*), 3.51 (6H, s, CH_2OH); δ_C (75 MHz DMSO-d_6) 164.4 (1C, *C*H=N), 163.5 (1C, C-q arom.), 132.4 (1C, *C*H= arom.), 132.2 (1C, *C*H= arom.), 118.4 (1C, C-q arom.), 117.5 (1C, *C*H= arom.), 117.0 (1C, *C*H= arom.), 67.0 (1C, C-q), 61.3 (3C, *C*H_2OH).

4.4.9. 2-(*E*)-(4-Dimethylaminobenzylideneamino)-2-hydroxymethylpropane-1,3-diol (8). TRIS® (1.00 g, 8.25 mmol) and *p*-dimethylaminobenzaldehyde (1.23 g, 8.25 mmol) in toluene (25 mL) were refluxed in a Dean–Stark trap for 12 h to complete removal of water (TLC monitoring, eluent methanol/dichloromethane 2:1 v/v, double visualisation UV 254 nm and I_2 bath). The reaction mixture, as a fine suspension, was filtered hot and the insoluble deposited TRIS was washed with hot toluene. The combined toluene solution was cooled at room temperature and filtered to give 1.00 g crude product. The latter was dissolved in boiling toluene and filtered hot, to remove the traces of unreacted TRIS, then cooled at 0°C. The deposited solid was filtered off and washed with cooled ether to yield the title compound **8** (0.30 g, 15%) as a yellow crystalline powder, mp 146–148°C (toluene); [Found: C, 62.2; H, 8.3; N, 10.8. $C_{13}H_{20}N_2O_3$ requires C 61, 86; H, 7.99; N, 11.15%]; R_f (50% dichloromethane/methanol) 0.70; ν_{max} (Nujol) 1607 (s, $\nu_{C=N}^{sk}$), 1528 (s, $\nu_{C=C}^{sk}$) cm^{-1}; δ_H (300 MHz DMSO-d_6) 8.28 (1H, s, C*H*=N), 7.60 (2H, d, *J*=7.5 Hz, C*H*= arom.), 6.76 (2H, d, *J*=7.5 Hz, C*H*= arom.), 4.55 (3H, bs, O*H*), 3.48 (6H, s, CH_2OH), 3.28 (6H, s, *Me*); δ_C (75 MHz DMSO-d_6) 159.7 (1C, *C*H=N), 129.2 (2C, *C*H= arom.), 126.1 (1C, C-q arom.), 124.2 (1C, C-q arom.), 111.4 (2C, *C*H= arom.), 63.3 (3C, *C*H_2OH), 61.1 (1C, C-q), 40.1 (2C, *Me*).

4.4.10. 4,4-Bis(hydroxymethyl)-2-(4-dimethylaminophenyl)-1,3-oxazolidine (8a). (As detected by NMR in solution after equilibration as 50%, Scheme 6). ν_{max} (Nujol) 1185 (m), 1127 (m) and 1087 (m, ν_{N-C-O}) cm^{-1}; δ_H (300 MHz DMSO-d_6) 7.28 (2H, d, *J*=8.7 Hz, *C*H= arom.), 6.73 (2H, d, *J*=9.0 Hz, *C*H= arom.), 5.44 (1H, s, H-2), 4.92 (1H, bs, O*H*), 4.50 (1H, bs, O*H*), 4.20 (2H, d, *J*=8.5 Hz, H-5), 3.78 (2H, d, *J*=8.5 Hz, H-5), 3.28 (6H, s, *Me*), 3.01 (2H, d, *J*=10.1 Hz, CH_aH_bOH), 2.92 (2H, d, *J*=9.1 Hz, CH_aH_bOH), 2.60 (1H, bs, N*H*); δ_C (75 MHz DMSO-d_6) 127.0 (2C, *C*H= arom.), 126.1 (1C, C-q arom.), 124.2 (1C, C-q arom.), 111.3 (2C, *C*H= arom.), 101.3 (1C, C-2), 82.6 (1C, C-4), 71.0 (1C, C-5), 63.3 (2C, *C*H_2OH), 40.0 (2C, *Me*).

4.4.11. (7*S,8*R**,11*r*,14*s*)-14-Aza-11-hydroxymethyl-9,13-dioxatetracyclo[6.5.1.0^{2,7}.0^{11,14}]-tetradeca-2,4,6-triene (9).** (80%) white crystalline powder, mp 123–125°C (methanol) (lit. 123–125°C[27,28]); ν_{max} (Nujol) 1367 (s, $\nu_{>N-}$), 1153 (m), 1136 (m) 1108 (m, ν_{N-C-O}) cm^{-1}; δ_H (300 MHz DMSO-d_6) 7.44 (2H, ddd, *J*=2.5, 3.5, 8.0 Hz, C*H*= arom.), 7.43 (2H, ddd, *J*=3.4, 8.0, 10.0 Hz, C*H*= arom.), 5.73 (2H, s, H-7, -8), 4.99 (1H, t, *J*=5.3 Hz, O*H*), 3.98 (2H, d, *J*=8.6 Hz, H-10, -12), 3.67 (2H, d, *J*=8.6 Hz, H-10, -12), 3.53 (2H, d, *J*=4.6 Hz, CH_2OH); δ_C (75 MHz DMSO-d_6 as quantitative carbon, QC NMR experiment) 139.0 (2C, C-q arom.), 129.8 (2C, *C*H= arom.), 124.0 (2C, *C*H= arom.), 98.2 (2C, C-7, -8), 73.3 (1C, C-11), 72.6 (2C, C-10, -12), 63.6 (1C, *C*H_2OH).

4.5. General procedure for the preparation of the compounds 10a and 10b

1-Aryl serinols **1d**, **e** (as a 0.15 M suspension in methanol) and the corresponding equimolar amount of 1,2-phthaldicarboxaldehyde were stirred at reflux for 4 h (TLC monitoring benzene/acetone 3:1 v/v, double visualisation: UV 254 nm and I_2 bath). The reaction mixture, as a clear solution, was evaporated in vacuo to give, in each case, an oily residue. Starting from **1d**, the oily residue was crystallised from dichloromethane/ligroine 1:1 v/v to yield the title compound **10a**. Starting from **1e**, the oily residue was purified by column chromatography (eluent ligroine/THF 1:1 v/v) to yield the title compound **10b**. Scale up of the synthesis: starting from 0.50–1.00 g **1d**, **e**.

4.5.1. *N*-[(1*S*,2*S*)-1-Phenylpropane-1,3-diol-2-yl)-isoindoline-1-one (10a). (60%) white crystalline powder, mp 154–156°C (dichloromethane/ligroine 1:1 v/v); [Found: C, 72.3; H, 6.1; N, 4.6. $C_{17}H_{17}NO_3$ requires C, 72.05; H, 6.05; N, 4.96%]; R_f (75% benzene/acetone) 0.55; ν_{max} (Nujol) 1651 (s, $\nu_{N-C=O}$), 1458 (s) cm^{-1}; $[\alpha]_D^{20}$=+11.0 (*c* 1.0, MeOH); δ_H (300 MHz DMSO-d_6) 7.78 (1H, d, *J*=7.5 Hz, C*H*= arom.), 7.76 (1H, m, C*H*= arom.), 7.72 (1H, d, *J*=7.5 Hz, C*H*= arom.), 7.62 (1H, dd as t, *J*=6.8, 6.8 Hz, C*H*= arom.), 7.50 (2H, dd as t, *J*=7.0, 7.0 Hz, C*H*= arom.), 7.45 (2H, dd as t, *J*=7.3, 7.3 Hz, C*H*= arom.), 7.38 (1H, m, C*H*= arom.), 5.80 (1H, d, *J*=4.5 Hz, O*H*), 5.13 (1H, dd as t, *J*=5.1, 5.1 Hz, CH_2O*H*), 4.97 (1H, dd as t, *J*=5.5, 5.5 Hz, benzyl C*H*), 4.79 (1H, d, *J*=18.1 Hz, heterocyclic CH_aH$_b$), 4.70 (1H, d, *J*=18.1 Hz, heterocyclic CH$_a$$H_b$), 4.59 (1H, ddd as q, *J*=6.0, 6.0, 6.0 Hz, >C*H*–), 3.79 (1H, d, *J*=5.7 Hz, CH_aH$_b$OH), 3.77 (1H, d, *J*=5.3 Hz, CH$_a$$H_b$OH); δ_C (75 MHz DMSO-d_6) 168.4 [1C, >N–*C*(=O)–], 143.7 (1C, C-q arom.), 142.8 (1C, C-q arom.), 132.8 (1C, C-q arom.), 131.3 (1C, *C*H= arom.), 128.3 (2C, *C*H= arom.), 127.9 (1C, *C*H= arom.), 127.4 (1C, CH= arom.), 126.6 (2C, *C*H= arom.), 123.5 (1C, *C*H= arom.), 122.9 (1C, *C*H= arom.), 71.3 (1C, benzyl *C*H), 59.9 (1C, heterocyclic *C*H_2), 59.3 (1C, >*C*H–), 48.5 (1C, –*C*H_2OH).

4.5.2. *N*-[(1*S*,2*S*)-1-(4-Nitrophenyl)-propane-1,3-diol-2-yl]-isoindoline-1-one (10b). (33%) yellowish powder; mp 168–170°C; [Found: C, 62.0; H, 4.8; N, 8.2. $C_{17}H_{16}N_2O_5$ requires C, 62.17; H, 4.91; N, 8.57%]; R_f (50% ligroine/THF) 0.65; $[\alpha]_D^{20}$=+9.1 (*c* 1.0 MeOH); ν_{max} (Nujol) 1653 (s, $\nu_{N-C=O}$), 1459 (s) cm^{-1}; δ_H (300 MHz DMSO-d_6) 8.14 (2H, d, *J*=7.9 Hz, C*H*= arom.), 7.64 (2H, d, *J*=8.3 Hz, C*H*= arom.), 7.65–7.56 (4H, m, C*H*= arom.), 6.06 (1H, d, *J*=4.5 Hz, O*H*), 5.19 (1H, dd as t, *J*=4.3, 4.3 Hz, CH_2O*H*), 4.97 (1H, dd as t, *J*=5.3, 5.3 Hz, benzyl C*H*), 4.72 (1H, d, *J*=17.9 Hz, heterocyclic CH_aH$_b$), 4.57 (1H, d, *J*=18.0 Hz, heterocyclic CH$_a$$H_b$), 4.56 (1H, s, >C*H*–), 3.79 (1H, dd, *J*=5.7, 10.6 Hz, CH_aH$_b$OH), 3.77 (1H, dd, *J*=5.7, 11.4 Hz, CH$_a$$H_b$OH); δ_C (75 MHz DMSO-d_6) 168.3 [1C, >N–*C*(=O)–], 151.9 (1C, C-q arom), 146.8 (1C, C-q arom.), 142.8 (1C, C-q arom.), 132.3 (1C, C-q arom.), 131.4 (1C, *C*H= arom.), 127.9 (1C, *C*H= arom.), 127.7 (2C, *C*H= arom.), 123.5 (1C, *C*H= arom.), 123.4 (2C, CH= arom.), 123.0 (1C, *C*H= arom.), 71.2 (1C, benzyl *C*H), 60.0 (1C, heterocyclic *C*H_2), 58.7 (1C, >*C*H–), 48.7 (1C, *C*H_2OH). *CARE*! The compound partially decomposes on column chromatography; it is also sensitive to moisture (see yield).

4.5.3. *N*-[(1*S*,2*S*)-1,3-Bis-deuterioxy-1-phenylpropane-2-yl)-isoindoline-1-one (13). This compound was obtained directly in the NMR standard tube by adding one drop of D_2O in the DMSO-d_6 solution of **10a**. δ_H (300 MHz DMSO-d_6) (only modified coupling patterns with respect to **10a** are listed): 4.93 (1H, d, *J*=6.0 Hz, benzyl C*H*), 4.61 (1H, d, *J*=18.1 Hz, heterocyclic CH_aH$_b$), 4.52 (1H, d, *J*=18.1 Hz, heterocyclic CH$_a$$H_b$), 4.42 (1H, ddd as q, *J*=6.0, 6.0, 6.0 Hz, >C*H*–), 3.59 (2H, d, *J*=6.0 Hz, –CH_aH$_b$OH).

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