New Supramolecular Host Systems, 11[+]

The Stereoisomeric Diaminobutanediol and Dioxadiazadecalin Systems: Synthesis, Structure, Stereoelectronics, and Conformation − Theory vs. Experiment

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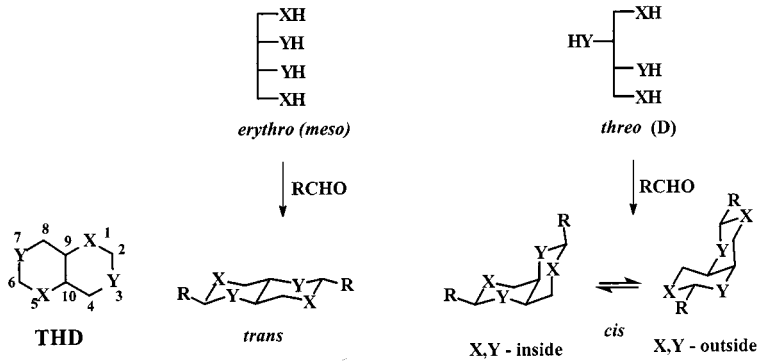
We present new approaches to the (C_2) chiral and *meso* 1,4-diamino-2,3-butanediol (**1**) and 2,3-diamino-1,4-butanediol (**2**) and derivatives. Reactions of these compounds with aldehydes to form the novel 1,5-dioxa-3,7-diazadecalin (DODAD) and 1,5-diaza-3,7-dioxadecalin (DADOD) classes of compounds (**7**, **9**, **11–15**) are also reported. These reactions are diastereospecific, i.e., *erythro (meso)* or *threo* starting compounds lead to *trans* or *cis* products, respectively. The structural, conformational, and stereoelectronic aspects of these systems were probed experimentally and computationally and provided excellent insight into their properties and behaviour. Good agreement was observed between X-ray, NMR, and calculated results of the *N*,*N*′-dibenzyl derivatives of *trans*-DODAD (**14**) and *trans*-DADOD (**15**).

Introduction

We have recently been conceiving and developing new hosts, based on the diastereomeric 1,3,5,7-tetraheterodecalin (THD) systems (Scheme 1), which can be prepared from suitable 1,2,3,4-tetraheterobutanes and aldehydes. Having gained experience with the tetraoxadecalin (X = Y = O)[2] and the tetrazadecalin (X = Y = NH)[3] systems, the preparation and investigation of dioxadiazadecalins (X = O, Y = NH; X = NH, Y = O) for these purposes was compelling, the appropriate starting materials being the positional and diastereoisomeric 1,4;2,3-diaminobutanediols.

Over the past three decades the anticancer drug properties of the 1,2,3,4-diaminobutanediols **1**, **2**, and their derivatives have been examined.[4] For example, the platinum complexes of *threo*-1,4-diamino-2,3-*O*-isopropylidenebutanediol (Scheme 2) showed in vivo and in vitro antitumor activity and desirable properties as good as or better than cisplatin.[5] Complexes of *threo*-2,3-diamino-1,4-butanediol (**2**) were also used as antitumor agents.[6] Recently, in the context of the axisymmetrical nature of human immunodeficency virus (HIV) protease, members of the above C_2-symmetric class of compounds, e.g. *threo*-1,4-diamino-2,3-butanediol, were also proven to be potent and selective inhibitors of the protease.[7] Finding new synthetic strategies and improving existing ones for the preparation of these



Scheme 1. The 1,3,5,7-tetraheterodecalin (**THD**) system in all its diastereomeric forms

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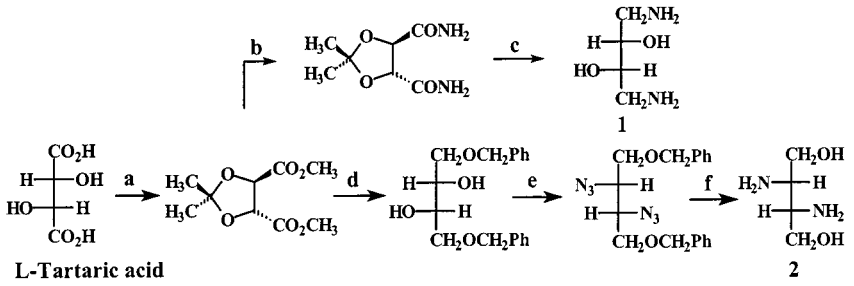


Scheme 2. Synthesis of *threo*-1,4;2,3-diaminobutanediols **1** and **2**: (a) $(CH_3)_2C(OCH_3)_2$, MeOH/PTSA, 75%; (b) NH_3/MeOH, 90%; (c) 1. $LiAlH_4$, dry THF, 95%; 2. HCl, 90% ethanol, 67%; (d) 1. $LiAlH_4$, dry THF, 82%; 2. NaH, $PhCH_2Br$, PTC, THF, 100%; 3. Dowex 50 WX4/H+, ethanol, 99%; (e) 1. Mesyl chloride,Py, 96%; 2. NaN_3, DMF 110°C, 89%; (f) H_2, Pd/C, HCl, 93%.

precursors seemed to us of additional importance to that of securing the desired new bicyclic systems.

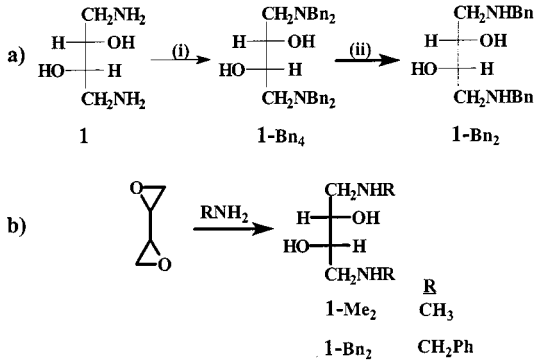
Results and Discussion

Synthesis

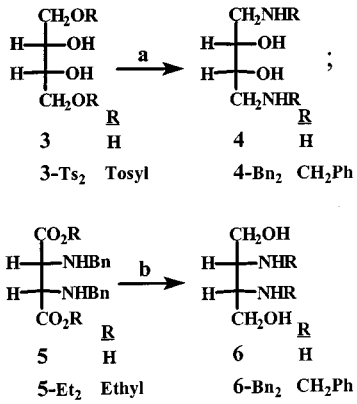
Optically pure L-1,4-diamino-2,3-butanediol (**1**) was prepared (Scheme 2; top) from L-tartaric acid (via L-2,3-*O*-isopropylidenedimethyltartarate, amidation,[8] then LAH reduction[5a] and deprotection). This was also the starting material for optically pure D-2,3-diamino-1,4-butanediol (**2**), based on a series of reactions worked out by Feit et al.[4b] but with certain significant improvements (Scheme 2; bottom). In the last step, hydrogenolysis of the *O*-benzyl group, was problematic, due to the inhibitory effect of amines on the catalytic hydrogenolysis.[9] Benzyl ethers had been cleaved in burdensome procedures, by high-pressure hydrogenolysis using stoichiometric quantities of Pd/C 10% and a large excess of HCl.[10][11] Feit et al.[4b] had obviated this by converting 2,3-diazido-1,4-dibenzyloxybutane to **2** in four costly steps: catalytic hydrogenation of the azide groups, *N*-acetylation, hydrogenolysis of *O*-benzyl groups, and deacetylation. We found, however, that D-2,3-diazido-1,4-dibenzyloxybutane underwent one-pot azide reduction and benzyl hydrogenolysis to D-2,3-diamino-1,4-butanediol, *using a catalytic amount of Pd/C (5−10%) and 1.5 equiv. of HCl, at atmospheric pressure.* This made possible the efficient and economic synthesis of D-2,3-diamino-1,4-butanediol (**2**) and we suggest this as a general approach.

Since the need for *N*-alkyl, especially benzyl, derivatives of **1** and **2** also arose (vide infra), we attempted direct alkylations, but only with partial success. Thus (Scheme 3a), *threo*-1,4-bis(benzylamino)-2,3-butanediol (**1-Bn**$_2$) was obtained from the selective, partial hydrogenolysis of **1-Bn**$_4$, which had been prepared by exhaustive *N*-benzylation of *threo*-1,4-diamino-2,3-butanediol (**1**). We developed, however, a new, general and better approach (Scheme 3b) to the preparation of *N*,*N*′-dialkyl-1,4-diamino-2,3-butanediols, by aminolytic ring opening of *threo*-diepoxybutane, which proceeded regioselectively and smoothly with aqueous amine solutions,[12] to give, e.g. **1-Me**$_2$ or **1-Bn**$_2$ (Scheme 3b).

The basic *meso*-diaminobutanediols **4** and **6** were accessible by known procedures.[4b,8b] The *N*-benzylated derivatives were secured as follows: *meso*-1,4-bis(benzylamino)-2,3-butanediol (**4-Bn**$_2$) was prepared by selective tosylation of the terminal hydroxy groups in erythritol, followed by nucleophilic substitution of erythritol-1,4-ditosylate (**3-Ts**) (Scheme 4). *Meso*-2,3-Bis(benzylamino)-1,4-butanediol (**6-Bn**$_2$) was obtained by esterification of dibenzylaminosuccinic acid (**5**) and reduction of the diethyl ester **5-Et**$_2$ with $LiAlH_4$.[4b] We found that the esterification of **5** in ethanolic HCl is very temperature sensitive and occurs only in a short range around 60°C.



Scheme 3. Preparation of *N*,*N*′-dialkyl *threo*-1,4-diamino-2,3-butanediols: (a) benzylation of **1**: (i) benzyl bromide/K_2CO_3 aq.; (ii) H_2, Pd/C, HCl. (b) from *threo*-1,2;3,4-diepoxybutane

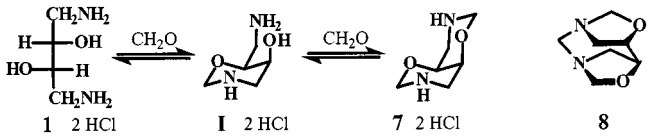


Scheme 4. The preparation of the *N*,*N*′-dibenzyl derivatives of *meso*-diaminobutanediols (**4**, **6**): (a) (i) TsCl/Py, −10°C; (ii) benzylamine. (b) (i) EtOH/HCl, 60°C; (ii) LAH.

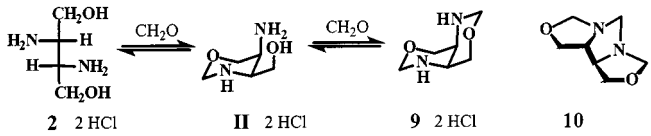
Another goal of this work, was the preparation and study of the hitherto unknown diastereomeric 1,5-dioxa-3,7-diaz-

adecalin (DODAD) and 1,5-diaza-3,7-dioxadecalin (DADOD) systems, by condensation of the starting tetrafunctionalized butanes (e.g. **1**, **2**) with aldehydes. The only known related system was 1,3,5-trioxa-7-aza-*cis*-decalin[13a] and 1,5-dioxa-4,8-diazadecalin.[13b]

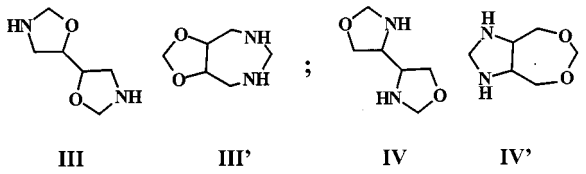
The reaction of **1** and **2** with formaldehyde gave the bicyclic *cis*-1,5-dioxa-3,7-diazadecalin (*cis*-DODAD, **7**) and *cis*-1,5-diaza-3,7-dioxadecalin (*cis*-DADOD, **9**) products, respectively (Schemes 5 and 6). These are formed via the corresponding monocyclic intermediates **I** and **II**; in principle, additional corresponding bi(oxazolidinyl), aminal and/or acetal by-products, viz., **III** or **III′** in the DODAD series and **IV** or **IV′** in the DADOD one (Scheme 7) (and their monocyclic intermediates) are possible, but were not observed. These are pH dependent reactions, the nitrogen atoms being the most reactive centres in these systems.



Scheme 5. Reaction of L-*threo*-1,4-diamino-2,3-butanediol (**1**) with formaldehyde



Scheme 6. Reaction of D-*threo*-2,3-diamino-1,4-butanediol (**2**) with formaldehyde



Scheme 7. Possible alternative reaction products of formaldehyde with **1** (**III**, **III′**) and **2** (**IV**, **IV′**)

Best results for **1** → **7** were obtained in the temperature range of 50−60°C and at pH 5, of the dihydrochloride of **1**, which decreased to pH = 3 during the reaction (this low pH precluded formation of undesired aminal systems). Complete conversion was achieved by using an excess (5 mol-equiv.) of formaldehyde (37% aq.), which gave a **I/7** = 1:4 ratio and concentration of this solution brought about complete conversion of **I** to **7** and ca. 10% by products, in addition to polyoxymethylene (**POM**), formed from an excess of formaldehyde (in a polymerization process known[14] to be initiated inter alia, by ammonium salts). On making the above reaction mixture basic, and extraction with chloroform, *cis*-DODAD (**7**) became the minor product and the tricyclic product (**8**) (Scheme 5) was isolated, which is formally the methylene bridged bi(oxazolidinyl) (**III**) species (Scheme 7).

A similar procedure was used for *cis*-DADOD (**9**) and best results for **2** → **9** were obtained in the temperature range of 50−60°C and at very low pH (< 1). Highest conversion (75%) was achieved by using an excess (3 mol-equiv.) of formaldehyde (37% aq.), which gave a **II/9** ratio of 1:2. Reaction at natural pH of the dihydrochloride of **2** or higher, gave exclusively the tricyclic product (**10**) (Scheme 6), i.e., the methylene bridged bi(oxazolidinyl) (**IV**) (Scheme 7). Also, on adding base to the above reaction mixture and extraction with chloroform, a 1:1 mixture of **9** and **10** was isolated.

Similar attempts to produce the *trans*-DODAD and *trans*-DADOD molecules from the corresponding *meso*-1,4;2,3-diaminobutanediols, were largely unsuccessful.

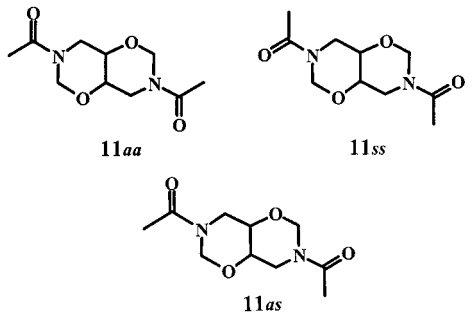
cis-DODAD (and even more so *cis*-DADOD) undergoes hydrolysis in aqueous solution and transacetalation in alcohols, leading to starting materials. *cis*-DODAD could, however, be stored for a long time in the desiccator in presence of **POM**, whose unzipping and release of formaldehyde has a stabilizing effect on *cis*-DODAD. Both *cis*-DODAD and *cis*-DADOD were, therefore, used and probed only as obtained in their crude form, but their *N*,*N′*-substituted (see below) or 2,6-substituted derivatives could be further purified and characterized. The latter have been probed and discussed,[1] in particular the 2,6-aryl-substituted compounds, in the context of their formation via Schiff base intermediates and the ring-chain tautomerism associated with this process.[1a]

In *N*-acylation attempts, acetylation of *cis*-DODAD proceeded smoothly to give 3,7-diacetyl-*cis*-DODAD (**11**); 3,7-dinitroso-*cis*-DODAD (**12**) was prepared by nitrosation of crude *cis*-DODAD followed by crystallization. In contrast to these, no good acylation procedures could be worked out for *cis*-DADOD; the isolated mixtures of diacetyl derivatives were difficult to separate and 1,5-dinitroso-*cis*-DADOD was obtained in low yield.

Using the ^{1}H-NMR C4H$_{ax,eq}$−C10H (^3J) couplings criterion, both **11** and **12** exist predominantly in the N,O-inside form (Scheme 1), similar to *cis*-DODAD itself and its derivatives (vide infra). The ^{1}H- and ^{13}C-NMR spectra of both indicated the occurrence of a relatively slow dynamic process in its solution at room temperature. In the diacetyl compound (**11**) two main dynamic processes are possible, amide rotation and ring inversion, in order of decreasing energies of activation (nitrogen inversion is too fast to be counted).

3,7-diacetyl-*cis*-DODAD exists in three possible conformational isomers related by amide double-bond rotation: two symmetric (**11***aa*, **11***ss*) and one asymmetric rotameric (**11***as*) forms (Scheme 8; *a* and *s* stand for an *anti* or *syn* direction of the carbonyl to the acetal moiety). A variable-temperature ^{1}H-NMR study in [D$_8$]toluene solution showed coalescence to occur at 76°C, the resulting activation free energy, $\Delta G^{\neq}$ = 16.9 kcal mol^{-1}, being typical for amide rotation barriers.[15] All three rotamers were observed and relative populations could be evaluated, using chemical shift and NOE criteria, as follows: **11***aa*/**11***ss*/**11***as* = 2:1:2.

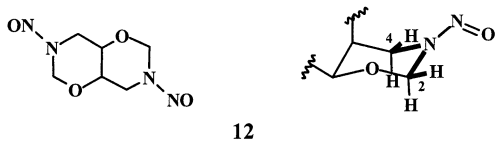
Study of the dinitroso derivative (**12**), relied on the extensive ^{1}H-NMR spectroscopic documentation for determination of the stereochemistry and barriers of rotation in *N*-nitrosamines.[16] The shielding effect of the nitrosamino



Scheme 8. The observed forms of 3,7-diacetyl-*cis*-DODAD (**11**) (*a* = *anti*, *s* = *syn* indicate directionality of C=O with C2)

group on differently oriented vicinal protons is seen in the wide separation (over 2 ppm) of the ^{1}H-NMR signals: $\delta_{4eq} - \delta_{4ax}$ in 3,7-dinitroso-*cis*-DODAD (**12**) is 2.2 ppm, as compared to 0.13 ppm in *cis*-DODAD. It is known that the proton *syn* to the nitroso oxygen (and nearly coplanar with the NNO group), resonates at lower frequency than the one *anti* to the oxygen.[17a] The axial protons are located deeper in the shielding zone of the NNO group and therefore resonate appreciably upfield from the corresponding equatorial ones. Hence, we deal with the **12*aa*** rotamer, accompanied by ca. 15% of other rotamers.

The difference in the geminal (^2J) coupling constant of the α-methylene protons may also serve as a valuable diagnostic tool for configurational assignment[17a] and arises probably from the interaction of the oxygen 2*p* component of the π_{NNO} molecular orbital with the neighboring 2-*syn* C−H bond. In 3,7-dinitroso-*cis*-DODAD (**12**) the ^2J couplings of the α-methylene protons are $^2J(C2H_2) = 10.3$ Hz and $^2J(C4H_2) = 14.8$ Hz, while the long-range coupling $^4J_{ee} = 1.8$ Hz is due to the defined W arrangement of bonds in the HCN(NO)CH moiety (Scheme 9) (in *cis*-DODAD they are 10.4 Hz, 14.5 Hz and 1 Hz, respectively).



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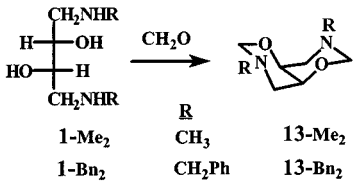
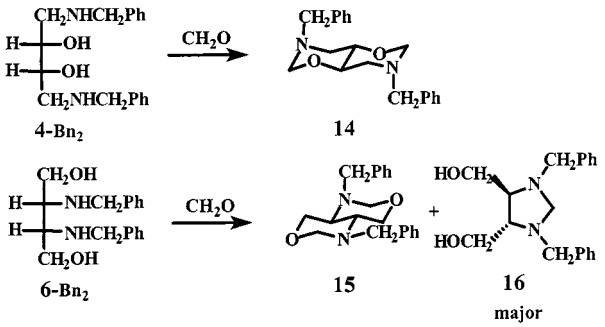
Scheme 9. *N,N′*-Dinitroso-*cis*-DODAD (**12**)

N-Alkylation attempts were largely discouraging in both series. Various methylations of *cis*-DODAD, viz., with methyl iodide, methyl iodide with silver oxide, dimethyl sulfate, use of sodium hydride, were fruitless and benzylation with benzyl bromide and potassium carbonate lead to 3,7-dibenzyl-*cis*-DODAD (**13-Bn$_2$**) in low yield. However, having secured the *N,N′*-dialkylated *threo*-1,4-diamino-2,3-butanediols (**1-R$_2$**) (Scheme 3), we were able to attain the corresponding 3,7-disubstituted *cis*-DODAD systems, among them **13-Bn$_2$**, in good yields by reactions of the former with formaldehyde (Scheme 10).

By the same approach (Scheme 11), *trans*-3,7-dibenzyl-DODAD (**14**), and *trans*-1,5-dibenzyl-DADOD (**15**) were readily isolated from the condensation reactions of formaldehyde with *erythro*-1,4-bis(benzylamino)-2,3-butanediol



Scheme 10. The reaction products of *N,N′*-dibenzyl-L-*threo*-1,4-diamino-2,3-butanediol (**1-Alk$_2$**) with formaldehyde



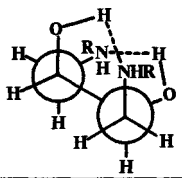
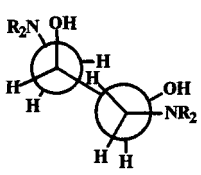
Scheme 11. The reaction products of *N,N′*-dibenzyl-*meso*-diaminobutanediols with formaldehyde

(**4-Bn$_2$**) or with *erythro*-2,3-bis(benzylamino)-1,4-butanediol (**6-Bn$_2$**), respectively. In the latter case, the major product was actually the isomeric imidazolidine (**16**).

Conformational Analysis of Diaminobutanediols

The different behaviour of *N,N′*-substituted *threo*-1,4-diamino-2,3-butanediols in protic and aprotic solutions, as manifested in the ^{1}H-NMR signals of their C1H$_2$−C2H protons (Table 1), is interesting. In aprotic (e.g. $CHCl_3$) solution, two well-separated and differently split AB patterns were registered, evidently due to a fixed conformation. The calculated dihedral angles[18] related to vicinal coupling suggest pseudobicyclic structures stabilized by intramolecular hydrogen bonds (Table 1). In the case of free rotation around the C1−C2 bond, the coupling constants would be averaged to 6 Hz. This is exactly what is observed in D_2O solution of **1-Me$_2$**, where no intramolecular hydrogen bonding can operate.

Table 1. ^{1}H-NMR coupling constants ($^3J_{1,2}$) and derived dihedral angles in the H$_2$C−CH moiety of *N*-substituted *threo*-1,4-diamino-2,3-butanediols (see Scheme 3)

	1-Me$_2$	**1-Bn$_2$**	**1-Bn$_4$**
$^3J_{1,2}$, Hz	1.8; 3.5	2.1; 3.4	5; 6
φ°[a]	67, 42[b] (60, 57)[c]	64, 42[b]	140, 25 [b]
Conformations			

[a] The H$_2$C−CH dihedral angles: [b] calculated by Haasnoot equation;[18] [c] calculated (MM3) lowest energy conformation of **1-Me$_2$**.

Similar observations have been reported[17b] for 2-hydroxymethylcyclohexylamine and 2-aminomethylcyclohexanol, but in our 1,4-diamino-2,3-butanediol cases, there is no structural preorganisation, so the double amine/alcohol hydrogen bond may be the main driving force to attain the pseudobicyclic structures.

MM3 calculations of **1-Me**$_2$ showed that its most stable conformation includes six-membered OH---N and NH---O hydrogen-bonded modes and the C1/C2 hydrogens have dihedral angles of 60°, consistent with the observed vicinal coupling constants (Table 1). In all calculated conformations of **1-Me**$_2$ the *N*-Me group is *anti* to the C1−C2 bond, so replacing the methyl groups with benzyl, should have no significant effect on the conformation of the molecule. The NMR data of **1-Bn**$_2$ (Table 1) indicate indeed that it exists in aprotic solution in a similar conformation. For **1-Bn**$_4$, the calculated structure has the bulky tertiary dibenzylamino groups buttressed against the hydroxyl groups and reinforced by five-membered O−H···N hydrogen bonds (Table 1).

Conformational Analysis of 1,5-Dioxa-3,7-diaza-and 1,5-diaza-3,7-dioxadecalins (DODAD & DADOD)

In the diastereomeric tetraheterodecalin (THD) series (Scheme 1), *cis*-THD exist in two chair conformations, X-inside and X-outside, which, in contrast to the fixed *trans* isomer, may interconvert by conformational ring inversion or by chemical (acid-catalysed) isomerization. The *cis/trans* relative stabilities and the equilibrium distribution between *cis*-THD X-inside and X-outside chair−chair forms depend on a combination of steric and stereoelectronic effects, due to their fragment components, e.g. in the dioxadiazadecalins, C−C−C−C in the centre and C−O(N)−C−C in the flanks, O−C−N units (with their *anomeric effect*) in each ring, O−C−C−O in DODAD and N−C−C−N in DADOD, as well as O−C−C−N in both (with their *gauche effect*).

The well-known *anomeric effect*[19] has been investigated in our group, both experimentally and theoretically, in O−C−O,[20] N−C−N[21] and O−C−N[22] containing systems. In O−C−N [Figure 1(i)] the *anomeric effect* is outstanding, since it has a good N lone-pair donor adjacent and *anti* to an excellent C−O σ* acceptor, to mix into.[13b,22] This is illustrated for the g^+a and g^-a forms of the R−O−C−N lone pair moiety [Figure 1(ii)], including the structural manifestations of this phenomenon, viz., contraction of the N−C bond and elongation of the C−O bond and, an upright *gauche* N−H (dictated by the *anti* N lone pair). The g^-a form is, evidently, the one occurring in the 1,3-oxazane chair and, implicitly in the DODAD [Figure 1(iii)] and DADOD bicyclic systems, with all the above structural implications.

As to the *gauche* effect (i.e. the lessening of the preference of *anti* over *gauche* forms), we have recently reviewed[23] it and studied it in O−C−C−O systems, where we concluded from available experimental and computational results that it is smaller than previously thought. The *gauche* effect in other X−C−C−Y moieties is less well documented, but very recent computational studies made possible the re-evaluation of the *gauche* effect in O−C−C−O,[24a] N−C−C−O,[24] and N−C−C−N.[24a,25] The values were taken in particular from the most recent and detailed paper of Y.-P. Chang et. al.,[24a] namely, results of high-level ab initio [MP2/6-311+G(2d,p)] calculations of 1,2-ethanediol, 1,2-diaminoethane, and 2-aminoethanol in their various conformations (see Figure 2 for selected viable N−C−C−O conformations). Also included was a conformational energy decomposition scheme, which allowed the evaluation of the *intrinsic gauche* effect and of the hydrogen-bonding contributions (MM3 calculations were included as well). Thus, we adopted their[24a] values for the *anti*−*gauche* differences due to the *intrinsic gauche* effect in O−C−C−O ($E_{rel(a-g)}$ = 0.8 kcal mol^{-1}), N−C−C−N, ($E_{rel(a-g)}$ = −0.5 kcal mol^{-1}) and N−C−C−O ($E_{rel(a-g)}$ = 0.4 kcal mol^{-1}), along with that of the intramolecular N−H---O hydrogen bond (0.8 kcal mol^{-1}).

This enabled us to carry out a fragment analysis[26] (Table 2) for the DODAD and DADOD series, following their molecular composition of C−C−C−C (butane), O−C−N

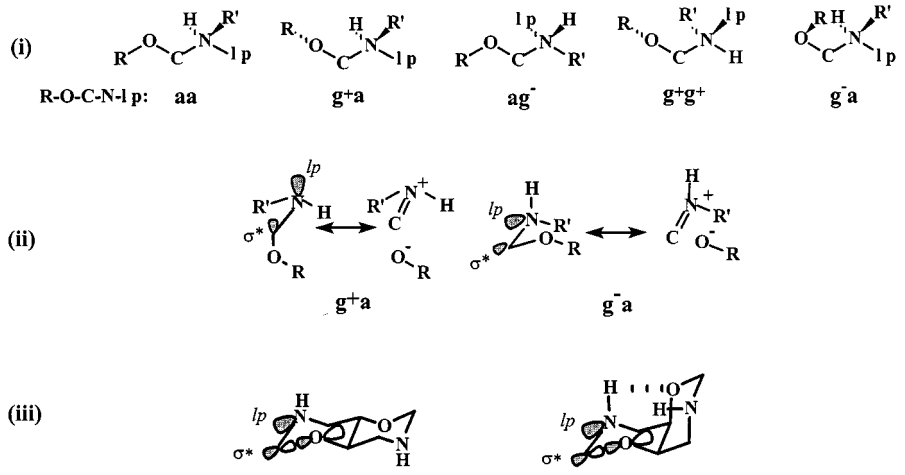


Figure 1. The *anomeric effect*: (i) in the prototypal R−O−C−N−R′ moiety (uniquely defined by the N lone pair and OR termini); (ii) with MO visualization of its geometrical consequences; (iii) in the 1,3-oxazane system of *trans*-and *cis*-DODAD

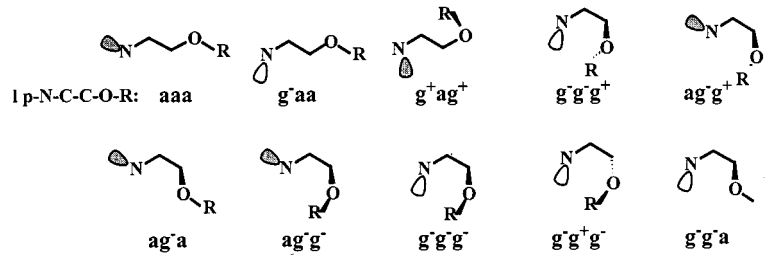


Figure 2. Selected conformations of the N−C−C−O moiety, uniquely defined by the N lone pair and OR termini

(oxymethylamine), O−C−C−O (dioxyethane), N−C−C−N (diaminoethane), and O−C−C−N (1-oxy-2-aminoethane) described above, as well as C−O−C−C (methylethyl ether) ($E_{rel(a-g)}$ = 1.5 kcal mol^{-1})[26a,b] and C−N−C−C (methylethyl amine) ($E_{rel(a-g)}$ = 1.1 kcal mol^{-1})[26a,c] fragments.

Table 2. Relative energies (kcal mol^{-1}) of the DODAD and DADOD diastereomers as obtained by fragment analysis

	cis				*trans*	
DODAD	N,O-inside		N,O-outside			
C-C-C-C	a	0.0	g	0.9	a	0.0
O-C-C-O	g	0.0	a	0.8	a	0.8
O-C-C-N	2×g	0.0	2×a	0.8	2×a	0.8
C-O-C-C	2×a	0.0	2×g	3.0	2×a	0.0
NH···O	2×(-0.8)	-1.6		0.0		0.0
E_{rel}	0.0		6.2		3.2	
	cis				*trans*	
DADOD	N,O-inside		N,O-outside			
C-C-C-C	a	0.0	g	0.9	a	0.0
N-C-C-N	g	0.5	a	0.0	a	0.0
O-C-C-N	2×g	0.0	2×a	0.8	2×a	0.8
C-N-C-C	2×a	0.0	2×g	2.2	2×a	0.0
NH···O	2×(-1.6)	-1.6		0.0		0.0
E_{rel}	0.0		5.0		1.9	

In both the DODAD and DADOD series of diastereomers, the C−O−C−N−C fragments are *intra*annular and conformationally constant, except that conformers having an N lone pair antiperiplanar to the adjacent C−O bond (N−H axial) gain special stability, due to delocalisation of the N lone pair into the adjacent σ^*_{C-O} orbital [e.g. Figure 1(iii)]. Therefore, Table 2 presents the fragment analysis of and comparison between the (N−H) diaxial forms in each series.

In contrast, all the C−C−C−C, O−C−C−O, O−C−C−N, N−C−C−N, C−O−C−C, and C−N−C−C fragments are *inter*annular and vary with each, *trans*-, *cis*-N,O-inside and *cis*-N,O-outside form. Finally, intramolecular hydrogen bonding of N−H---O type is possible only in the *cis*-N,O-inside isomer [Figure 1(iii)]. The quantification of all these contributions within the same frame of reference[24a] and the summation of these differences (Table 2), lead to the final estimation of relative stabilities of the DODAD and DADOD diastereomers.

The results of the fragment analysis agree well in order, if not in magnitude, with those of molecular mechanics calculations, using the MM3(92) force field,[27] given in Table 3. In the case of DODAD, which contains an O−C−C−O unit, we used MM3-GE,[23] that is, MM3(92) reparametrized for the *gauche effect* in O−C−C−O containing systems (we have not yet done the same for N−C−C−N and O−C−C−N systems). In these calculations, the *cis*-N,O-outside conformations were found 10 to 12 kcal mol^{-1} less stable than their inside counterparts (and were, therefore, not included in the display) and axial N−H bonds were clearly preferred. Also, among the two most stable conformations, *cis*-DADOD was calculated to be slightly (0.4 kcal mol^{-1}) more stable than *cis*-DODAD in the O,N-inside forms. The discrepancy in the magnitude of the (*cis*-N,O-outside vs. *cis*-N,O-inside vs. *trans*) energy differences could be understood after having appreciated the substantial disparity between the ab initio and MM3 calculated[24a] *anti-gauche* differences for the N−C−C−N and N−C−C−O basic units.

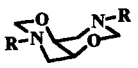
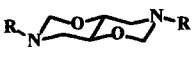
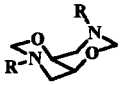
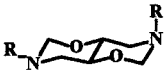
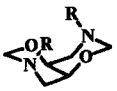
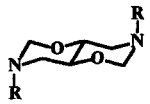
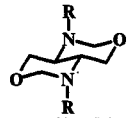
Table 3. Various conformations of *cis*-O,N-inside and *trans*-DODAD and DADOD, and their relative energies (kcal mol^{-1}) as calculated by MM3-GE[a]

cis-DODAD	*trans*-DODAD	*cis*-DADOD	*trans*-DADOD
O,N-inside		N,O-inside	
0.64	7.47	3.74	7.99
1.53	7.73	0.43	8.34
0.00[b]	7.90	0.00[b]	8.37

[a] The O,N-*outside* were omitted since they are all higher by 10−12 kcal/mol then their O,N-*inside* counterparts. − [b] DADOD is slightly (0.4 kcal/mol) more stable than DODAD in the O,N-*inside* form.

We had observed (X-ray diffraction) all axial N−H bonds in 2,6-dinitrophenyl-*cis*-DODAD and -*cis*-DA-

Table 4. Selected conformations of 3,7-dimethyl-*trans*- and -*cis*-DODAD (**13**), as well as 1,5-dibenzyl-*trans*-DADOD (**15**) and their MM3-GE relative energies (kcal mol^{-1}) and dipole moments

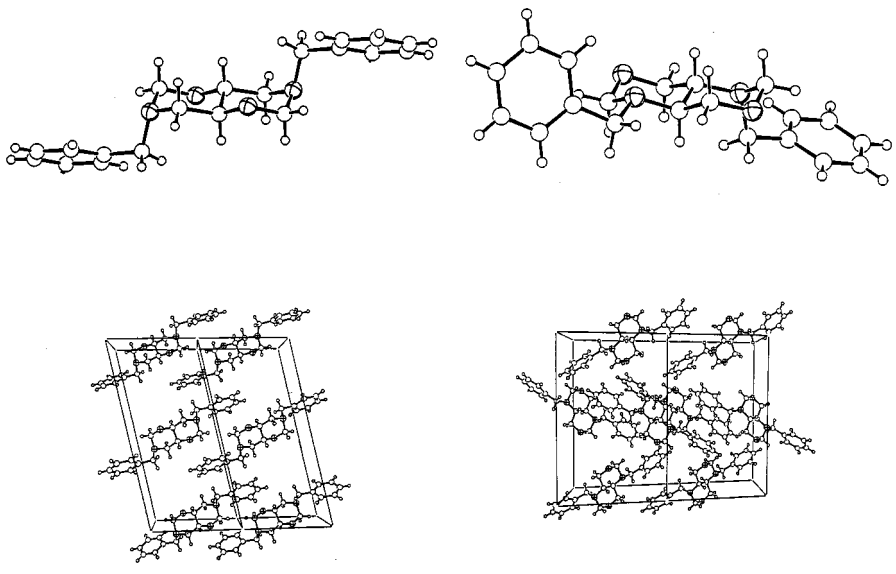
3,7-di(R)-DODAD		3,7-di(R)-DADOD
cis-O,N-inside (**13**)	*trans*	*trans* (**15**)
R = Me		R = CH_2Ph
		
0.44 (3.0 D)	0.17 (0.0 D)	0.52 (0.0 D)
		
0.17 (2.5 D)	0.09 (1.0 D)	0.00 (1.2 D)
		
0.00 (1.8 D)	0.00 (0.0 D)	0.30 (0.0 D)

DOD[1] and interpreted it as a result of the strong N−C−O *anomeric* effect, reinforced by intramolecular N−H---O hydrogen bonding. Notwithstanding the fact that MM3[27] had been parametrized for the *anomeric effect* in O−C−O systems *but not beyond that*, our calculations reproduced the axial positioning of the amine hydrogens. This is most probably due to the strong effect of the intramolecular N−H---O bonding mentioned above, along with dipole−dipole interactions and the alleviation of steric interactions.

The effect of the relative orientation of the lone pair and *N*-substituents on the geminal coupling constants in tetrahydro-1,3-oxazines has been thoroughly studied.[28] The geminal coupling constant of the methylene protons at C2 changes from 7.5 Hz for equatorial to 10.5 Hz for axial N−R. Using this effect for conformational analysis of DODAD and DADOD systems in solution (Table 5), we could assert that 3,7-dimethyl-*cis*-DODAD exists predominantly with diaxial *N*-Me groups and this preference increases with decreasing solvent polarity (Table 5). All *cis*-DODAD systems examined in (polar and nonpolar) solution are by far more stable in the inside form. MM3-GE[23][27] calculations of 3,7-dimethyl-*cis*-and *trans*-DODAD (Table 4) indeed revealed high preference of the N,O-inside form and, interestingly, slight preference of the *N*-Me diaxial conformations in both the *cis* and *trans* series, in good accord with the experimental (NMR) results.

An even more detailed and enlightening analysis was possible for the *N,N′*-dibenzyl-*trans*-DODAD and DADOD (**14**, **15**) compounds. According to NMR ^2J criteria, 3,7-dibenzyl-*trans*-DODAD (**14**) exists in solution ($CDCl_3$) mostly as the diaxial conformer (^2J = 10 Hz). At the same time, 1,5-dibenzyl-*trans*-DADOD (**15**) exhibits ^2J = 9.2 Hz, which indicates some equatorial character of the *N*-substituent. (Table 5). MM3-GE calculations (Table 4 last column) showed indeed that while, similarly to 3,7-dimethyl-*trans*-DODAD, the diaxial form of the 3,7-dibenzyl derivative (**14**) is the most stable one, 1,5-dibenzyl-*trans*-DADOD (**15**) slightly prefers the axial/equatorial conformation.

For a decisive answer, we were able to secure single crystals of both *N,N′*-dibenzyl derivatives and to subject them to X-ray diffraction analysis. The observed structures confirmed that we deal with diaxial *N,N′*-dibenzyl-*trans*-DODAD (**14**) and axial-equatorial *N,N′*-dibenzyl-*trans*-DADOD (**15**) (Figure 3), as concluded from NMR ^2J criteria (Table 5) and from the molecular mechanics calculation (Table 4). The structural parameters (Table 6) substantiate the existence of strong N−C−O *anomeric* effects in the *N*-axially substituted rings, namely, short N−C bonds and long C−O bonds. Careful comparison of the X-ray and calculated structures shows that the MM3 forcefield,[27] which



14 **15**

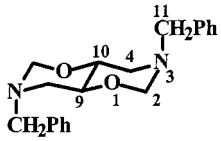
Figure 3. ORTEP drawings of 3,7-dibenzyl-*trans*-DODAD (**14**) and 1,5-dibenzyl-*trans*-DADOD (**15**). Molecular packing of **14** is projected down the *b*-axis (frames of two, and content of three, unit cells are shown) and of **15** down the *a*-axis (two unit cells)

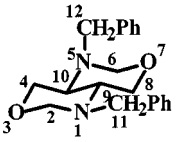
has not been parametrized for the N−C−O *anomeric* effect, does not reproduce these geometrical features (Table 6; italics). Clearly, MM3 needs additional parametrization, to be able to reproduce faithfully large systems endowed with such stereoelectronic effects.

Table 5. NMR spectral data of DODAD and DADOD systems

		δ, ppm					J, Hz	
Compound	solvent	H_{2e}	H_{2a}	H_{4e}	H_{4a}	H_9	2a2e	4a4e
7	$CDCl_3$	4.63	4.32	3.08	2.95	3.61	10.4	14.5
9	$CDCl_3$	4.58	4.22	-	-	2.72	10.6	-
13-Me$_2$	$CDCl_3$	4.51	4.03	3.08	2.79	3.44	9.3	13.9
	C_6D_6						10.0	14.3
13-Bn$_2$	$CDCl_3$	4.56	4.28	3.15	3.07	3.50	10.4	14.5
14	$CDCl_3$	4.44	4.30	3.10	2.80	3.56	10.0	12.5
15	$CDCl_3$	4.34	3.98	4.17	3.51	3.06	9.2	10.5

Table 6. Observed (X-ray) vs. calculated (MM3) selected structural parameters of *trans*-3,7-dibenzyl-DODAD (**14**) *trans*-1,5-dibenzyl-DADOD (**15**)[a]





14	X-Ray	MM3 [b]	**15**	X-Ray	MM3
O1-C2	1.425(4)	1.423	N1-C2	*1.448(5)*	*1.465*
O1-C9	1.412(3)	1.421	N1-C9	1.465(4)	1.471
C2-N3	*1.428(4)*	*1.461*	N1-C11	1.463(5)	1.466
N3-C4	1.464(4)	1.464	C2-O3	1.398(5)	1.418
N3-C11	1.459(4)	1.462	O3-C4	1.418(5)	1.419
C9-C10	1.500(4)	1.520	C9-C10	1.522(5)	1.533
O1-C2-N3	*114°*	*111°*	N5-C6	*1.428(5)*	*1.459*
			N5-C10	1.467(4)	1.465
			N5-C12	1.471(4)	1.464
			C6-O7	1.424(5)	1.418
			O7-O8	1.412(4)	1.421
			N1-C2-O3	*112°*	*111°*
			N5-C6-O7	*114°*	*110°*

[a] See formulae and numbering in Scheme 11. − [b] MM3 reparametrized for the gauche effect in OCCO systems.

Conclusions

New and improved approaches to the chiral and *meso* 1,4-diamino-2,3-butanediol (**1**) and 2,3-diamino-1,4-butanediol (**2**) and derivatives have been developed. Their diastereospecific reactions with aldehydes provided the novel 1,5-dioxa-3,7-diazadecalin (DODAD) and 1,5-diaza-3,7-dioxadecalin (DADOD) classes of compounds (**7**, **9**, **11**−**15**). Thorough understanding of the structural, conformational, and stereoelectronic properties of these systems was achieved from experimental and computational probes. Good agreement was observed between X-ray, NMR, and calculated results of the *N*,*N*′-dibenzyl derivatives of *trans*-DODAD (**14**) and *trans*-DADOD (**15**). We anticipate significant use of these findings and of the insight gained, both in the area of C_2-dissymetric drug design and in the supramolecular field (functionalized derivatives of **7** already showed good heavy-ion complexation[29])

Experimental Section

General: Melting points were recorded on a capillary melting-point apparatus and are uncorrected. − The NMR spectra were obtained on a AC 200, AMX 360, or ARX 500 Bruker spectrometer. All ^1H chemical shifts are in ppm and δ values are relative to TMS as internal standard. ^{13}C chemical shifts are reported in ppm relative to $CDCl_3$ (centre of triplet δ = 77.0) except for those taken in D_2O which are reported in ppm relative to TMS salt as internal standard. − Mass spectra (DEI-MS, DCI-MS, and FAB) were recorded on a VG Autospec 250 mass-spectrometer. − Elemental analysis were performed at the Microanalytical Laboratory of the Hebrew University, Jerusalem. − IR spectra were measured on a Nicolet 205 FTIR instrument in potassium bromide pellets (solids), sodium chloride cells (solutions), or sodium chloride pellets (neat). UV spectra were taken on a Unikon 931 spectrophotometer.

L-1,4-Diamino-2,3-butanediol (1): Prepared from L-2,3-*O*-isopropylidenedimethyl tartarate[8a] by amidation with methanolic ammonia,[8b] then reduction with lithium aluminium hydride[5a] and finally the solution of acetonide 3.6 g (22.5 mmol) in ethanol (90%) 60 mL, saturated with HCl was refluxed for 1 h and then left at room temperature overnight. Filtration gave a white dihydrochloride salt 2.9 g (67%), m.p. 210°C. − ^1H NMR (D_2O): δ = 3.94 (dd, *J* = 4.0, 7.0 H_2), 3.16 (m, 2 H_1); − ^{13}C NMR (D_2O): δ = 71 (d, C_2), 45 (t, C_1). − $C_4H_{14}Cl_2N_2O_2$ (193.07).

1,5-Dioxa-3,7-diazadecalin (*cis*-DODAD) (7): To L-1,4-diamino-2,3-butanediol dihydrochloride (**1**:2HCl) (0.40 g, 2 mmol) in 10 mL of water, formaldehyde (37% aq.) (0.8 mL, 10 mmol) was added at room temperature. The reaction mixture was heated at 60°C for 2 h. According to NMR, **7** was the major product (72%). ^1H NMR (D_2O, pH = 3): δ = 5.16 (d, ^2J = 9.3, 1 H_{2eq}), 4.74 (d, ^2J = 9.3, 1 H_{2ax}), 4.31 (brs, 1 H_9), 3.69 (m, 2 H_4); − ^{13}C NMR (D_2O, pH = 3): δ = 78 (t, C_2), 70 (d, C_9), 48 (t, C_4). − The minor product (18%) at these reaction conditions was **5-hydroxy-6-aminometyltetrahydro-1,3-oxazine (I):** ^1H NMR (D_2O, pH = 3): δ = 5.16 (d, ^2J = 9.3, 1 H_{2eq}), 4.74 (d, ^2J = 9.3, 1 H_{2ax}), 4.20 (m, $^3J_{6,7}$ = 5, $^3J_{4,5}$ = 1.7, 2 $H_{5,6}$), 3.57 (d, $^3J_{4,5}$ = 1.7, 2 H_4), 3.33 (d, $^3J_{6,7}$ = 5, 2 H_7); − ^{13}C NMR (D_2O, pH = 3): δ = 78 (t, C_2), 77 (d, C_6), 64 (d, C_5), 51 (t, C_4), 43 (t, C_7). − Adding base (sodium carbonate) to the reaction mixture and extraction with chloroform gave **7**. H NMR ($CDCl_3$): δ = 4.63 (dd, $^2J_{2,2'}$ = 10.4, $^4J_{2,4}$ = 1, H_2), 4.32 (d, $^2J_{2',2}$ = 10.4, $H_{2'}$), 3.08 (ddd, $^2J_{4,4'}$ = 14.5, $^3J_{4,9}$ = 1.5, $^4J_{2,4}$ = 1, H_4), 2.95 (dd, $^2J_{4',4}$ = 14.5, $^3J_{4',9}$ = 2, $H_{4'}$), 3.38 (dd, $^3J_{9,4'}$ = 2, $^3J_{9,4}$ = 1.5, H_9); − ^{13}C NMR ($CDCl_3$): δ = 79.2 (t, C_2), 70.1 (d, C_9), 49.3 (t, C_4). − $C_6H_{12}N_2O_2$ (144.17). Since ultimate purification was practically impossible, elemental analysis was performed on its derivatives.

3,3′-Methylene-5,5′-bi(oxazolidinyl) (8): Obtained according to the method described for **7**, but extraction of the reaction mixture (pH = 3) with chloroform was done in the presence of Amberlite® (IR-4B, weakly basic) overnight. Evaporation of chloroform gave exclusively **8** which was purified by column chromatography

(MeOH washed SiO_2, EtOAc). Yield 0.09 g (30%). − ^{1}H NMR ($CDCl_3$): δ = 4.70 (d, $^2J_2$ = 9.2, H_2), 4.63 (dd, $^2J_2$ = 9.2, $^4J_{2,4}$ = 1.7, H_2), 4.23 (m, H_5), 4.14 (s, H_6), 3.35 (dm, $^2J_4$ = 15, H_4), 3.13 (dd, $^2J_4$ = 15, $^4J_{4,2}$ = 1.7, H_4); − ^{13}C NMR ($CDCl_3$): δ = 83.0 (t, C_2), 80.0 (t, C_6), 71.3 (d, C_5), 49.4 (t, C_4). − FAB MS; *m/z*: 157.0 $[MH]^+$. − EI-MS; *m/z* (%): 157 (23.9) $[M]^+$, 156 (61.2), 127 (26.4), 114 (21.9), 98 (100), 86 (45.5), 85 (77.5), 84 (37.2), 72 (39.7), 57 (80). − $C_7H_{12}N_2O_2$ (156.0): calcd. C 53.82, H 7.75, N 17.94; found C 53.64, H 8.04, N 17.81.

D-2,3-Diamino-1,4-butanediol (2): To a solution of D-2,3-diazido-1,4-dibenzyloxybutane [prepared by Feit's procedure[2b] from L-1,4-dibenzyloxy-2,3-butanediol (Aldrich)] (3.52 g, 10 mmol) in 30 mL of ethanol, Pd/C (10%) (0.352 g) was added, followed by slow addition of conc. HCl (3 mL, 30 mmol). The resulting solution was stirred under hydrogen at atmospheric pressure for 48 hours. The catalyst was filtered out and evaporation provided D-2,3-diamino-1,4-butanediol dihydrochloride (**2** · 2 HCl) (1.8 g, 93%). − ^{1}H NMR (D_2O): δ = 4.00 (m, 2 H_1), 3.86 (m, H_2); − ^{13}C NMR (D_2O): δ = 61.4 (t, C_1), 54.6 (d, C_2). − $C_4H_{14}Cl_2N_2O_2$ (193.07).

3,7-Dioxa-1,5-diazadecalin (*cis*-DADOD, 1,5-diaza-3,7-dioxadecalin, **9):** D-2,3-diamino-1,4-butanediol dihydrochloride (**2** · 2 HCl) (0.35 g, 1.8 mmol) in 10 mL HCl (0.8 M) was treated with formaldehyde (37% aq.) (0.5 mL, 6 mmol) by dropwise addition at room temperature. The reaction mixture was heated at 60°C for 4 h. According to NMR spectrscopy, **9** was the major product (75%). − ^{1}H NMR (D_2O, pH = 0): δ = 5.14 (d, ^2J = 9.5, H_2), 4.7 (d, ^2J = 9.5, H_2), 4.22 (d, ^2J = 14, H_4), 4.11 (d, ^2J = 14, H_4), 4.10 (br. s, H_9). − ^{13}C NMR (D_2O, pH = 0): δ = 79.0 (t, C_2), 69.8 (t, C_4), 50.9 (d, C_9). − **5-Amino-4-hydroxymethyl-1,3-oxazane (II)** was obtained as a by-product (30%) under these reaction conditions. − ^{1}H NMR (D_2O, pH = 0): δ = 5.13 (d, ^2J = 9.5, H_2), 4.7 (d, ^2J = 9.5, H_2), 3.92 (m), other signals overlap. − ^{13}C NMR (D_2O, pH = 0): δ = 79.1 (t, C_2), 71.1 (t, C_6), 62.1 (t, CH_2OH), 56.7 (d, C_5), 49.7 (d, C_4). Adding base (sodium carbonate) to the reaction mixture and extraction with chloroform gave **9** and **10** in a 1:1 ratio. − **3,7-Dioxa-1,5-diazadecalin (*cis*-DADOD**, 1,5-diaza-3,7-dioxadecalin, **9):** ^{1}H NMR ($CDCl_3$): δ = 4.58 (d, ^2J = 10.6, H_2), 4.22 (d, ^2J = 10.6, H_2), 3.88 (d, $^2J \approx 8$, H_4); 3.81 (d, $^2J \approx 8$, H_4); 2.72 (s, H_9); − ^{13}C NMR (CD_3Cl): δ = 79.2 (t, C_2), 71.0 (t, C_4), 49.8 (d, C_9). − FAB MS; *m/z*: 145.1 $[MH]^+$. $C_6H_{12}N_2O_2$ (144.17).

3,3′-Methylene-4,4′-bi(oxazolidinyl) (10): ^{1}H NMR ($CDCl_3$): δ = 4.49 (d, ^2J = 6, H_2), 4.3 (d, ^2J = 6, H_2); 3.92 (s, H_6), 3.86 (dd, ^2J = 8.3, ^3J = 7.0, H_5); 3.77 (dd, ^2J = 8.3, ^3J = 4.3, H_5), 3.57 (dd, ^3J = 7.0, 4.3, H_4); − ^{13}C NMR (CD_3CN): δ = 86.2(t, C_2), 76.0(t, C_6) (hidden in $CDCl_3$), 69.9(t, C_5), 68.2(d, C_4). − EI MS; *m/z* (%): 156.2 (7) $[M]^{+\cdot}$, 85.1 (100). − HREIMS: calcd for $C_7H_{12}N_2O_2$ $[M]^{+\cdot}$ 156.0899, observed *m/z* = 156.0907.

3,7-Diacetyl-*cis*-DODAD (11): The crude *cis*-DODAD hydrochloride (**7** · 2 HCl) (prepared from **1** (1 mmol) was dissolved in pyridine (5 mL) / acetic anhydride (15 mL) mixture and heated at 50−60°C overnight. The excess of acetic anhydride was removed in vacuo and the residue was dissolved in CH_2Cl_2, washed with H_2O, and dried with $MgSO_4$. The solvent was evaporated to give the crude product **11** which was purified by flash chromatography (SiO_2, CH_2Cl_2/MeOH, 96:4). − Yield 0.18 g (64%). NOE (OCMe) measurements and chemical shifts (below) show a composition of **11***aa* (40%), **11***ss* (20%), and **11***as* (40%). ^{1}H NMR ($CDCl_3$): δ = 6.02 (dd, ^2J = 10.2, ^4J = 2.2) (*ss* and *as*), 5.30 (dd, ^2J = 11, ^4J = 2), 5.28 (dd, ^2J = 11, ^4J = 2) (*aa*), 4.84 (ddd, ^2J = 14.5, ^3J = 1.4, ^4J = 2) (*aa*), 4.80 (ddd, ^2J = 14.1, ^3J = 1.4, ^4J = 2) (*as*), 4.66 (m), 4.62 (d, ^2J = 11) (*aa*), 4.10 (d, ^2J = 10.2) (*ss* and *as*), 3.97 (dd, ^2J = 14.5, ^4J = 2.2) (*ss* and *as*), 3.64−3.71 (m) (*as*), 3.71 (s) (*aa*), 3.66 (s) (*ss*), 3.47 (d, ^2J = 14.5) (*ss* and *as*), 2.96 (dd, ^2J = 14, ^3J = 1.5) (*aa* and *as*), 2.17 (s) (*aa* and *as*), 2.12 (s) (*ss*), 2.10 (s) (*as*). − ^{13}C NMR ($CDCl_3$): δ = 170.5, 170.3, 169.9, 169.7 (s), 77.2 (t), 72.7 (t), 71.9(d), 71.3(d), 70.9 (d), 49.4 (t), 44.7 (t), 21.3 (q), 21.0 (q). − UV: λmax = 199 nm (acetonitrile). − DEI MS; *m/z* (%): 228 (45.4) $[M^{+\cdot}]$, 168 (19.6), 141 (56.5), 128 (61.8), 111 (42.6), 98 (37.6), 85 (91.3), 72 (100). − $C_{10}H_{16}N_2O_4$ (228.25): calcd. C 52.61, H 7.07, N 12.28; found C 52.20, H 7.30, N 12.10.

VT-NMR measurements of conformational equilibria of **11** were taken at 360 MHz. The temperature was checked using an ethylene glycol solution.[30]

3,7-Dinitroso-*cis*-DODAD (12): To a cold solution (0−5°C) of crude *cis*-DODAD (**7**) (1.5 mmol) and $NaNO_2$ (0.22 g) in water, concentrated HCl (0.3 mL) was added. The reaction mixture was stirred for 1 h, and allowed to stand overnight in the refrigerator. NaOH was added to neutralize the HCl and the product was extracted with $CHCl_3$. The solvent was removed in vacuo to give solid product **12** (0.30 g, 99%), m.p. 197°C (CH_3CN/H_2O). − ^{1}H NMR ($CDCl_3$): δ = 6.11 (dd, $^2J_{2,2'}$ = 10.3, $^4J_{2,4}$ = 1.8, H_2), 5.23 (d, $^2J_{2',2}$ = 10.3,$H_{2'}$), 5.21 (dd, $^2J_{4,4'}$ = 14.8, $^4J_{4,2}$ = 1.8, H_4), 4.01 (brs, H_9), 3.01 (dd, $^2J_{4,4'}$ = 14.8, $^3J_{4',9}$ = 2.7, $H_{4'}$) (in addition there are low (ca. 15%) signals at 6.16 (dd), 5.34 (d), 5.06 (dd), 4.04 (d)); − ^{13}C NMR ($CDCl_3$): δ = 79.1 (t, C_2), 71.8 (d, C_9), 41.6 (t, C_4). − IR: $\tilde{\nu}$ = 2850 cm^{-1} (med.), 1450 (strong), 1360 (strong), 1051 (strong). − EI MS; *m/z* (%): 202 (100) $[M^{+\cdot}]$, 149 (34), 142 (28), 114 (38), 113 (25), 101 (53, $M^{+\cdot}/2$). − $C_6H_{10}N_4O_4$ (202.07): calcd. C 35.63, H 4.99, N 27.72; found C 35.85, H 5.00, N 27.43.

1,5-Dinitroso-*cis*-DADOD: Prepared as described for **12,** from crude *cis*-DADOD (**9**). − Yield: 90 mg, (30%); − m.p. 229°C (dec.) ($EtOH/H_2O$). − ^{1}H NMR ($CDCl_3$): δ = 6.02 (d, ^2J = 11.0, H_2), 5.33 (d, ^2J = 11.0, H_2) 5.2 (bm, H_9), 4.0 (m, H_4), 3.85 (m, H_4); − ^{13}C NMR ($CDCl_3$): δ = 77.5 (C_2), 61.4 (C_4), 42.3 (C_9). − EI MS; *m/z*: 202.1 $[M]^{+\cdot}$, 172.1 [M − NO], 142.1 [M − 2 NO]. − HRCIMS: calcd for $C_6H_{11}N_4O_4$ $[MH]^+$ 203.1018, observed *m/z* 203.1018.

General Procedure for the Preparation of *threo*-1,4-Diamino-2,3-butanediols: *threo*-1,2,3,4-Diepoxybutane (0.4 mL, 5 mmol) was added dropwise with good stirring to a cold (0−5°C) aq. solution of primary amine (25−30%) (10 mL). The reaction mixture was stirred overnight at room temperature. ***threo*-1,4-Bis(methylamino)-2,3-butanediol (1-Me$_2$)** was prepared from methylamine.[12] Evaporation gave solid product (0.74 g, quantitative yield); m.p. 142°C (*i*PrOH), 144°C (MeOH)[12]. − ^{1}H NMR ($CDCl_3$): δ = 3.84 (dd, ^3J = 3.5, 2, H_2), 3.07 (dd, ^2J = 12, ^3J = 3.5, H_1), 2.65 (dd, ^2J = 12, ^3J = 2, H_1), 2.42 (s, CH_3); ^{1}H NMR (D_2O): δ = 3.61 (m, H_2), 3.57 (m, 2 H_1), 2.27 (s, CH_3); − ^{13}C NMR (D_2O): δ = 73.7 (d, C_2), 55.3 (t, C_1), 37.3 (q, CH_3). − DEI MS; *m/z* (%): 104 (40) [M − $CH_2NHCH_3]^{+\cdot}$, 86 (63), 74 (23), 57 (17), 45 (24), 44 (100); DCI MS: 149.1 (25) $[MH]^+$, 118.1 (100), 104.1 (20), 86.1 (20). − HRCIMS: calcd for $C_6H_{17}N_2O_2$ $[MH]^+$ 149.1290, observed *m/z* 149.1301.

***threo*-1,4-Bis(benzylamino)-2,3-butanediol (1-Bn$_2$):** Prepared from benzylamine. The solid product was filtered in vacuo, thoroughly washed with water and dried in a vacuum desicator o.n. − Yield 1.5 g (quant.), m.p. 107°C (CH_3CN). − ^{1}H NMR ($CDCl_3$): δ = 7.28 (m, Ph), 3.83 (dd, ^3J = 3.5, 2.2, H_2), 3.82 (d, ^2J = 13, CH_2Ph), 3.72 (d, ^2J = 13, CH_2Ph), 3.08 (dd, ^2J = 12, ^3J = 3.5, H_1), 2.72 (dd, ^2J = 12, ^3J = 2.2, H_1); − ^{13}C NMR ($CDCl_3$): δ = 139.8 (s, Ph), 129.1, 128.9, 127.8 (d, Ph),73.2 (d, C_2), 54.3 (t), 53.5 (t). − FAB MS; *m/z*: 301 $[MH]^+$. − $C_{18}H_{24}N_2O_2$ (300.40): calcd. C 71.97, H 8.05, N 9.33; found C 72.20, H 7.94, N 9.25.

L-1,4-Bis(dibenzylamino)-2,3-butanediol (1-Bn$_4$): To a refluxing ethanol/ water (1:1) (20 mL) solution of L-1,4-diamino-2,3-butanediol (**1**) (1 mmol) and K_2CO_3, benzyl bromide (0.5 mL, 4 mmol) was added and after reflux for 1 hour the solution was stirred overnight. Filtration of water-insoluble solids gave tetrabenzyl **1-Bn$_4$** (0.23 g, 48%), m.p. 120°C. − ^{1}H NMR ($CDCl_3$): δ = 7.27 (m, 2 Ph), 4.39 (brs, O*H*), 3.76 (d, ^2J = 13.3, CH_2Ph), 3.61 (dd, ^3J = 6.3, 5.1, H_2), 3.44 (d, ^2J = 13.3, CH_2Ph), 2.65 (dd, ^2J = 13.2, ^3J = 6.3, H_1), 2.52 (dd, ^2J = 13.2, ^3J = 5.1, H_1); − ^{13}C NMR ($CDCl_3$): δ = 139.1 (s, Ph), 129.9, 129.1, 128.0 (d, Ph), 70.2 (d, C_2), 59.7(t), 57.2 (t). − FAB-MS; *m/z*: 481.3 [M$^+$]. $C_{32}H_{36}N_2O_2$ (480.65).

The extraction of filtrate with $CHCl_3$ gave **1-Bn$_4$** and other benzylated products (0.24 g, 51%). The crude benzylated products were hydrogenolyzed (30 ψ, Pd/C (5%), HCl, MeOH) for 2 h. Filtration of catalyst, evaporation of solvent, treatment with aq. NaOH, and extraction with $CHCl_3$ gave 1,4-bis(benzylamino)-2,3-butanediol (**1-Bn$_2$**) (0.08 g, 27% from **1**).

Erythritol-1,4-ditosylate (**3-Ts$_2$**): To a cooled (−10°C) solution of *meso*-erythritol (2.2 g, 18 mmol) in dry pyridine (40 mL) freshly recrystallysed tosyl chloride (7.0 g, 37 mmol) in CH_2Cl_2 was added dropwise at such a rate that the temperature did not exceed 5°C at the start, then 10°C. After an additional one hour, the cooling bath was removed and the resulting green-yellow solution was stirred overnight. The reaction mixture was poured onto ice/HCl, extracted with CH_2Cl_2, and dried with $MgSO_4$. The crude product was used without further purification. Yield 3.13 g (63%).

***meso*-1,4-Bis(benzylamino)-2,3-butanediol (4-Bn$_2$):** Prepared in the reaction of **3-Ts$_2$** (0.5 g, 1.16 mmol) with benzylamine (aq. 30%) (4.6 mL, 13 mmol) at 0°C for half an hour and then at room temperature for an additional two hours. − Yield 0.1 g (30%), m.p. 160°C. − ^{1}H NMR (CD_3OD): δ = 7.52 (m, Ph), 3.99 (d, ^2J = 13, C*H*HPh), 3.84 d (^2J = 13, CH*H*Ph), 3.75 (dd, ^3J = 7.6, 3.5, H_2), 3.02 (dd, ^2J = 12, ^3J = 3.5, H_1), 2.(dd, ^2J = 12, ^3J = 7.6, H_1); − ^{13}C NMR (CD_3OD): 140.5 (s, Ph), 129.9, 128.7 (d, Ph), 73.6 (d, C_2), 54.7 (t), 53.2 (t). − CI MS; *m/z* (%): 301 (100) [MH]$^+$, 194 (28) [M − C_7H_8N]$^+$, 91 (88) [C_7H_7]$^+$. $C_{18}H_{24}N_2O_2$ (300.18).

***meso*-2,3-Bis(benzylamino)-1,4-butanediol (6-Bn$_2$):** Prepared by Feit's method,[4b] m.p. 76°C (EtOH). − ^{1}H NMR ($CDCl_3$): δ = 7.28 (m, Ph), 3.7 (m, CH_2Ph and 2 H_1), 2.69 dd (^3J = 2.8, H_2); − ^{13}C NMR (50.3 MHz, $CDCl_3$): 139 s, 128 d, 128 d, 127 d (Ph); 63 t, 60 t, 52 (d, C_2). − DCI MS; *m/z* (%): 301 (100) [MH]$^+$, 283 (10) [M − OH]$^+$, 194 (18) [M − C_7H_8N]$^+$, 150 (27) [M/2]$^+$, 91 (29) [C_7H_7]$^+$. − $C_{18}H_{24}N_2O_2$ (300.18).

General Procedure for the Preparation of *N,N′*-Disubstituted Dioxadiazadecalins (13): To an aqueous solution of diaminobutanediols (1 mmol) formadehyde (aq. 37% or paraformaldehyde) (2 mmol) was added and the solution was heated in an ultrasonic bath for 2 h. The reaction solutions were extracted with $CHCl_3$.

***cis*-3,7-Dimethyl-DODAD (13-Me$_2$**): Prepared from *threo*-1,4-bis(methylamino)-2,3-butanediol (**1-Me$_2$**). Yield (oil): 0.15 g, (90%). − ^{1}H NMR ($CDCl_3$): δ = 4.51 (dd, ^2J = 9.3, ^4J = 2, H_{2eq}), 4.03 (d, ^2J = 9.3, H_{2ax}), 3.44 (dd, ^3J = 2.4, ^3J = 1, H_9), 3.08 (ddd, ^2J = 13.9, ^4J = 2, ^3J = 1, H_{4eq}), 2.79 (dd, ^2J = 13.9, ^3J = 2.4, H_{4ax}), 2.55 (s, NCH_3). − ^{13}C NMR ($CDCl_3$): δ = 85.7 (t, C_2), 71.6 (d, C_9), 56.0 (t, C_4), 41.5 (q, NCH_3). − FAB MS; *m/z*: 173 [MH]$^+$; CI MS; *m/z* (%): 173.1 (100) [MH]$^+$, 142.1 (14), 111.1 (20), 99.1 (44), 83.0 (17), 71.1 (36). − HRCIMS: calcd for $C_8H_{17}N_2O_2$ [MH]$^+$ 173.1290, observed *m/z* = 172.1310.

***cis*-3,7-Dibenzyl-DODAD (13-Bn$_2$**): Prepared from *threo*-1,4-bis(benzylamino)-2,3-butanediol (**1-Bn$_2$**). Yield (pale oil): 0.30 g, (92%). − ^{1}H NMR ($CDCl_3$): δ = 7.33 (m, Ph), 4.56 (dd, $^2J_{2',2}$ = 10.4, $^4J_{2,4eq}$ = 1.3, H_2), 4.28 (d, $^2J_{2',2}$ = 10.4, $H_{2'}$), 4.31 (d, ^2J = 13.2, C*H*HPh), 4.19 (d, ^2J = 13.2, CH*H*Ph), 3.50 (s, H_9), 3.15 (d, ^2J = 14.5, H_{4eq}), 3.07 (d, ^2J = 14.5, ^3J = 2, H_{4ax}). − ^{13}C NMR ($CDCl_3$): δ = 129.3, 128.3, 127.1 (d, Ph), 83.0 (t, C_2), 72.7 (d, C_9), 57.7 (t, C_4), 53.5 (t, *C*H_2Ph). − DEI MS; *m/z* (%) 324.3 (2) [M]$^{+\cdot}$, 294.3 (8), 233.2 (6), 187.2 (7), 176.2 (26), 175.2 (32), 174.2 (24), 162.0 (7) [M/2], 146.2 (12), 120.2 (26), 91.0 (100). − HRCIMS: calcd for $C_{20}H_{25}N_2O_2$ [MH]$^+$ 325.1916, observed *m/z* 325.1917.

***trans*-3,7-Dibenzyl-DODAD (14):** Prepared from *meso*-1,4-bis(benzylamino)-2,3-butanediol (**4-Bn$_2$**). Yield: 0.31 g, (95%); m.p. 107°C (petroleum ether). − ^{1}H NMR ($CDCl_3$): δ = 7.30 (m, Ph), 4.44 (dd, ^2J = 10, ^4J = 1.5, H_{2eq}), 4.30 (d, ^2J = 10, H_{2ax}), 3.96 (d, ^2J = 13.4, C*H*HPh), 3.87 (d, ^2J = 13.4, CH*H*Ph), 3.56 (m, H_9), 3.10 (ddd, ^2J = 12.5, ^3J = 2.2, ^4J = 1.5, H_{4eq}), 2.80 (m, ^2J = 12.5, ^3J = 10.3, H_{4ax}) (non-equiv. magn.). − ^{13}C NMR ($CDCl_3$): 138.9 (s, Ph), 129.5, 129.1, 128.0 (d, Ph), 85.0 (d, C_2), 74.1 (d, C_9), 57.6 (t, C_4), 53.7 (t, *C*H_2Ph). − DCI MS; *m/z* (%): 325.2 (100) [MH]$^+$, 134.1 (46) [C_8H_8NO], 91.0 (23) [C_7H_7]. − $C_{20}H_{24}N_2O_2$ (324.42).

***trans*-1,5-Dibenzyl-DADOD (15)** and aminal **16** (1:4.5) were obtained from *meso*-2,3-bis(benzylamino)-1,4-butanediol (**6-Bn$_2$**). Separation by column chromatography (SiO_2 (methanol washed), petroleum ether/EtOAc, gradient) gave compound **15,** yield: 6 mg (2%), m.p. 108°C (petroleum ether). − TLC (SiO_2:petroleum ether/EtOAc, 1:1) R_f = 0.7. − ^{1}H NMR ($CDCl_3$): δ = 7.30 (m, Ph), 4.34 (d, ^2J = 9.2, H_2), 4.17 (dd, ^2J = 10.5, ^3J = 3.5, H_{4eq}), 3.98 (d, ^2J = 9.2, H_2), 3.89 (d, ^2J = 14, C*H*HPh), 3.48 (d, ^2J = 14, CH*H*Ph), 3.51 (m, ^2J = 10.5, ^3J = 10, H_{4ax}), 3.06 (m, ^3J = 3.5, 10, H_9) (non equiv. magn.). − ^{13}C NMR ($CDCl_3$): δ = 139.0 (s, Ph), 129.1, 127.9 (d, Ph), 85.5 (t, C_2), 70.4 (t, C_4), 58.7 (d, C_9), 52.3 (t, CH_2Ph). DCI MS; *m/z* (%): 325.2 (100) [MH]$^+$, 233.1 (21) [M − C_7H_7], 162.1 (12) [M/2], 91.0 (35) [C_7H_7]. − $C_{20}H_{24}N_2O_2$ (324.42). − **1,3-Dibenzyl-4,5-dihydroxyethylimidazolidine (16):** Isolated (35%) at higher polarity. Yield (oil): 0.123 g, (44%). TLC (SiO_2:petroleum ether/EtOAc, 1:1) R_f = 0.2. − ^{1}H NMR ($CDCl_3$): δ = 7.25 (m, Ph), 3.90 (d, ^2J = 13, C*H*HPh), 3.44 (d, ^2J = 13, CH*H*Ph), 3.81 (d, ^2J = 4.2, H_2), 3.8 (brs, O*H*), 3.73 (dd, ^2J = 11.4, ^3J = 6.2, −C*H*HOH), 3.64 (d, ^2J = 11.4, −CH*H*OH), 2.99 (brs, ^3J = 6.2, H_4), 2.89 (d, ^2J = 4.2, H_2); − ^{13}C NMR ($CDCl_3$): δ = 138 (s, Ph), 129.2, 129.0, 127.9 (d, Ph), 76.5 (t, C_2), 66 (d, C_4), 60 (t), 58 (t). DCI MS; *m/z* (%): 313.2 [MH]$^+$, 295.2 (25) [M − OH], 281.2 (47) [M − CH_3O], 91.0 (32) [C_7H_7]. − $C_{19}H_{24}N_2O_2$ (312.41).

***cis*-3,7-Dibenzyl-DODAD (13-Bn$_2$**): To the refluxing ethanol/water (1:1) (20 mL) solution of *cis*-DODAD (**7**) (1 mmol) and K_2CO_3, benzylbromide (0.25 mL, 2 mmol) was added and the solution was refluxed for 1.5 h. Extraction with $CHCl_3$ gave after drying with K_2CO_3 and evaporation a pale oil (0.09 g, 28%). The crude **13-Bn$_2$** was purified by column chromatography [SiO_2 (methanol washed), petroleum ether/EtOAc, gradient]. − Yield: 48 mg (15%).

Crystal Structure Determination: The X-ray diffraction measurements were carried out at ca. 295 K on an automated CAD4 diffractometer equipped with a graphite monochromator, using Mo-*Kα* (λ = 0.7107 Å) radiation. Diffraction data were measured to $2\theta_{max}$ = 50° with a constant scan rate of 4° min^{-1}. Intensity data were collected using the ω−2θ scan mode. Possible deterioration of the analyzed crystal was tested by detecting periodically the intensities of three reference reflections from different zones of the reciprocal space, and was found to be negligible during the experiment. No corrections for absorption or secondary extinction effects were applied. The structure was solved by direct methods (SHELXS-86[31]), and refined by full-matrix least-squares (SHELXL-97[32]). Non-hydrogen atoms were treated anisotropically. The hydrogen atoms were located in calculated positions.

trans-3,7-dibenzyl-DODAD (**14**) and *trans*-1,5-dibenzyl-DADOD (**15**) showed centrosymmetric crystal packing. In the case of the diaxial **14** (C_i symmetry) the molecule is in the centre of the unit cell. It is noteworthy that in the crystal there is *inter*molecular hydrogen bonding of CH (benzylic)−Ph (π) type.

14: $C_{20}H_{24}N_2O_2$, formula weight 324.42, monoclinic, space group $P2_1/c$, a = 8.541(2), b = 5.782(1), c = 18.094(5) Å, β = 102.77(2)°, V = 871.4(4) Å^3, Z = 2, D_{calc} = 1.236 g/cm^{-3}, F(000) = 348, μ(Mo-$K\alpha$) = 0.80 cm^{-1}, 1323 unique reflections, R = 0.052 for 941 observations with $F_0 > 4\sigma(F_0)$ and R = 0.075 for 1323 unique data; at convergence, S = 1.07 and $|\Delta\rho| \leq 0.19$ e Å^{-3}. The molecular units are located in the crystal on centres of inversion at (1/2, 0, 0).

15: $C_{20}H_{24}N_2O_2$, formula weight 324.42, monoclinic, space group $P2_1/n$, a = 9.614(3), b = 17.057(3), c = 10.954(3) Å, β = 102.73(3)°, V = 1752.2(8) Å^3, Z = 4, D_{calc} = 1.230 g/cm^{-3}, F(000) = 696, μ(Mo-$K\alpha$) = 0.80 cm^{-1}, 2557 unique, R = 0.061 for 1600 observations with $F_0 > 4\sigma(F_0)$ and R = 0.099 for all 2557 unique data; at convergence, S = 0.97 and $|\Delta\rho| \leq 0.17$ e Å^{-3}. One of the phenyl rings was found to be partially disordered in the crystal structure.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited at the Cambridge Data Centre. Deposition numbers: CCDC 113786 (**14**) and CCDC 113787 (**15**). Copies of the data can be obtained free of charge on application to Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; Fax: internat. +44−1223/336−033; E-mail: deposit@ccdc.cam.ac.uk; WWW.

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