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Substituent Effects on the Conformational Equilibrium of 1,3,5,7-*cis*-Tetraoxadecalin Systems: Force Field Calculations *Versus* Experimental Results.

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Abstract: Conformer populations of a number of 1,3,5,7-*cis*-tetraoxadecalins have been studied by ^{1}H NMR spectroscopy. While the unsubstituted **4** prefers the *proximal* conformation, all 4,8 disubstituted derivatives **5** preferred the *distal* conformation. This was most marked for the di-azidomethyl derivative **5g**. Force field calculations were shown to reproduce only roughly the trends of the conformer equilibria. Changing the solvent from toluene-D_8 to more polar solvents increases the population of the *proximal* conformer.

Introduction

When flexible molecules are involved in biochemistry or material sciences the conformation of their molecular backbones is one of the important factors that determine the properties of such compounds. Since most of the flexible compounds are multiconformational, an understanding of the factors determining conformer equilibria is desired in order to control conformer populations. A long range goal would be to design flexible molecules with defined shape, i.e. compounds whose backbone adopts one or two preferred conformations[1]. An approach toward this goal is to study smaller molecules with high conformational preferences, molecules which could be eventually introduced as building blocks into larger structures in a modular approach.

In this respect biconformational compounds, which populate just two low energy conformations are of interest. To a first approximation their conformer equilibrium is of the simple A $\rightleftharpoons$ B type. By a change of external parameters or by substituent effects it should be possible to control the equilibrium to the point that either conformer A or B is favored. These compounds could be considered as conformational switches: A typical example is given by the system **1** studied by Raban[2]. Compound **1** exists predominantly as the conformer **1a** with axial side chains and an equatorial methyl group. Complexation with metal ions "switches" the conformation to **1b**, in which the methyl group is now axial. Several such systems based on cyclohexane backbones have been reported[3].

Our interest focused on the *cis*-decalin framework, which populates two enantiomeric and therefore isoenergetic conformations[4]. *Cis*-decalin **2** is a typical biconformational structure. Replacement of a CH_2-

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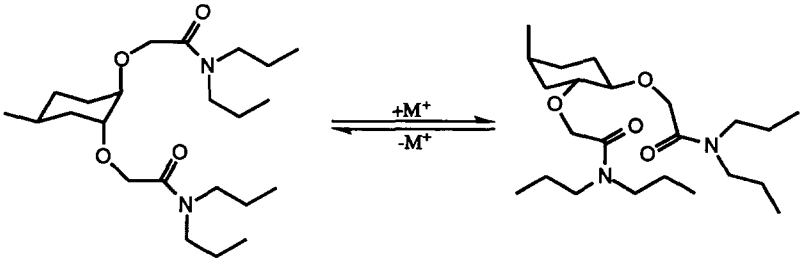


Figure 1. Molecular switching based on the conformer equilibrium of a cyclohexane derivative[2].

group in *cis*-decalin by heteroatoms should generate structures, in which one of the two backbone conformations is favored. For instance, the *cis*-decahydroquinolin **3** adopts the conformation in which the nitrogen occupies an axial arrangement with respect to the cyclohexane ring[5]. This has to do with the smaller size of an NH versus a CH_2-group. Likewise a *cis*-decalin derivative, which had been studied before[6] is the 1,3,5,7- tetraoxadecalin **4**.

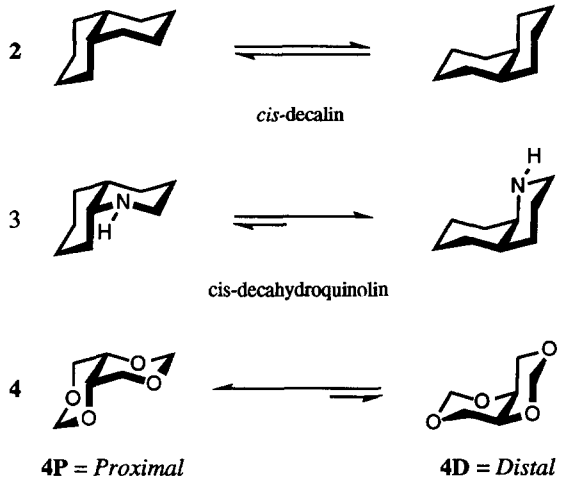


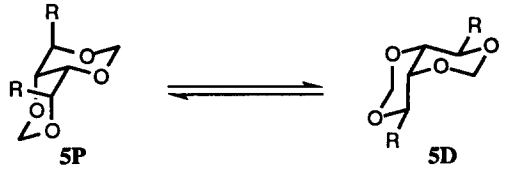
Figure 2. Conformer equilibrium in *cis*-decalin derivatives.

The conformer equilibrium of **4** has been reported to lie to > 90% on the side of the *proximal* conformer. This may have to do with a smaller size of the oxygen versus a CH_2 group (cf. the A - values of 2.18 and 7.50 kJ mol^{-1} respectively[7]), but the major contributor is likely the *gauche* effect[8]. According to this effect a *gauche* arrangement between two vicinal electronegative substituents on a carbon chain is favored with respect to the *anti*-arrangement. The *proximal* conformer **4P** (also called[6] O-inside conformer) has three such O-C-C-O *gauche* arrangements, the *distal* one **4D** (also called[6] H-inside conformer) has three O-C-C-O *anti*-arrangements. The anomeric effect[9] of the O-CH_2-O unit should not effect the conformer equilibrium of **4**, because as far as $n\sigma^*$-delocalization is concerned, this should be equally possible in either conformer **4P** or **4D**.

In this paper we report on studies to influence the conformer equilibrium of **4** by solvent or substituent effects.

Substituent Effects on the Tetraoxadecalin Conformer Equilibrium

Our idea was to counterbalance the preference of **4** to adopt the *proximal* conformer **4P** by substituents in the 4,8-position, vic. **5**. These substituents should be placed in such a manner, that they occupy an axial arrangement in the conformer **5P** and an equatorial one in **5D**. This way the energy of the *proximal* conformer **5P** should be raised such that it reaches or surpasses that of the *distal* conformer **5D**.



5P **5D**

a:	$R = CH_3$	**e:**	$R = CH_2O(CH_2)_2OCH_3$
b:	$R = CH_2OH$	**f:**	$R = CH_2OCH_2C_6H_5$
c:	$R = CH_2OCH_3$	**g:**	$R = CH_2N_3$
d:	$R = CH_2\text{-}O(CO)C(CH_3)_3$	**h:**	$R = CH_2NH_2$

Figure 3.

The simple mannitol acetal **5b** has been briefly examined by Stoddart[10] who concluded from NMR studies that the *distal* conformer **5bD** predominates in chloroform solution. Moreover Nørskov[11] studied temperature dependent ^1H NMR spectra of the methyl compound **5a**. He concluded that the *proximal* conformer **5aP** and the *distal* conformer **5aD** are present in a 3.7:1 ratio at room temperature.

Conformer equilibria of various representatives of **5** should be amenable to force field calculations. Recent studies on the parent tetraoxadecalin **4** showed[12] however, that the usual parametrization of the MM3 force field does not adequately reproduce conformer equilibria or bond lengths of the simple tetraoxadecalin and a 2,6-distyryl derivative. For these reasons Fuchs proposed[12] a modified set of parameters, for O-C-C-O units, i. e. those in which the *gauche* effect contributes to the overall stability of the system.

We have carried out force field calculations for several compounds **5** to evaluate the energy of the *proximal* and *distal* conformer both by the MM3 force field implemented in the MACROMODEL program[13] and using the modified parameters suggested by Fuchs[12]. When the side chain R in **5** could adopt several conformations, we picked the arrangement of lowest energy each for the *proximal* and *distal* series. The resulting relative energies of the two conformers were used to calculate the conformer ratio for room temperature assuming a two conformer equilibrium. These results are compiled in table 1.

Change from the original to the modified MM3 parameters raised the energy content calculated for all of the conformers, but it did so in a different manner for the *proximal* and *distal* conformers. Therefore the two sets of parameters resulted in different predictions for the conformer equilibria. The more it was of interest to see, which of these calculations would reproduce the experimental findings better.

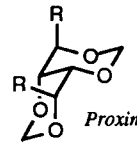
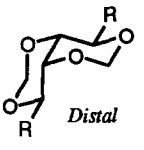
R =	 Proximal		 Distal		Prox./Dist. (%)	
	Orig. Par.	**Corr. Par.**	**Orig. Par.**	**Corr. Par.**	**Orig. Par.**	**Corr. Par.**
H (**4**)	28.08	33.62	49.01	49.06	100/0	100/0
CH_3 (**5a**)	57.69	63.37	60.29	60.32	74/26	22/78
CH_2OH (**5b**)	94.59	100.22	89.80	92.29	13/87	4/96
CH_2OMe (**5c**)	93.91	99.55	93.91	97.76	50/50	33/67
CH_2OPiv (**5d**)	113.50	119.21	110.23	117.94	21/79	38/62
$CH_2O(CH_2)_2OMe$ (**5e**)	144.49	150.51	147.84	151.70	79/21	62/38
CH_2OCH_2Ph (**5f**)	147.22	159.10	158.34	160.97	99/1	68/32
CH_2NH_2 (**5h**)	75.06	80.67	72.18	72.21	24/76	3/97

Table 1. Relative energy calculated (MM3) for the *proximal* and *distal* conformers (kJ/mol) of **4** and **5**. Orig. Par. = Original MM3 parameters. Corr. Par. = Corrected MM3 parameters[12].

The compounds **5c** to **5h** were prepared from the known[14] mannitol derivative **5b** by standard transformations. NMR-spectra of **5** were recorded in toluene-D_8, a rather non polar solvent, in order to approximate the situation of our force field calculations, which pertain to isolated molecules in the gas phase. The ^1H NMR spectra of **5** recorded at room temperature are weighted time averaged spectra over both conformers **5P** and **5D**. Lowering the temperature to -100 °C[11] did not lead to spectra from which the coupling constants of the individual conformers could be derived. Therefore we had to estimate the conformer populations at room temperature based on the averaged coupling constants. Assuming a two conformer equilibrium the conformer ratio n_P/n_D could be derived from the experimental averaged coupling constants J_{exp} if the coupling constants for the individual conformers J_P and J_D are known, according to the equation $J_{exp} = (n_P J_P + n_D J_D)/(n_P + n_D)$.

Figure 4 shows that $J_{1,2} = J_{3,4}$ should be large in the *distal* conformer **5D** and small in the *proximal* conformer **5P**. As in previous studies in this field[11] J_P was taken as 1.2 Hz from the value observed for compound **6**, which exists exclusively as the *proximal* isomer, and J_D was taken as 10.6 Hz, as found for the compound **7**, which exists as a *distal* conformer only. Comparison of the experimental $J_{1,2}$-values for various derivatives of **5** should then give an indication of the conformer population n_P/n_D. However, since the molecules **5** are c_2-symmetric systems, the ^1H-NMR-spectra are not of first order. The total spin system of the four spins of H^1 to H^4 has to be considered. Thus, by simulation of the coupling patterns and the line shapes for each of H^1 and H^2 coupling constants were derived for the compounds **5** studied. These and the derived *proximal/distal* conformer ratios are recorded in table 2. The ratios derived by the force field calculations are included in table 2 for comparison.

These results show that for all the compounds **5** studied the *distal* conformer predominates in the equilibrium. Thus, the steric effects of the substituents are marked enough to shift the conformer equilibrium to the *distal* side from the *proximal* preference recorded[6,12] for the unsubstituted tetraoxadecalin **4**. For the

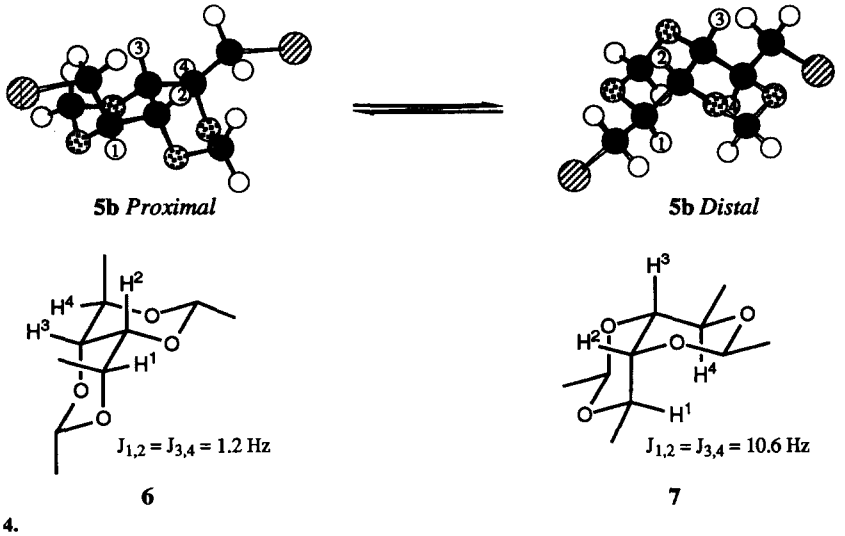


Figure 4.

simple compounds **5a**, **5c**, and **5d** the agreement between calculated and experimental conformer populations is fair, the corrected MM3-parameters leading to smaller discrepancies. In the case of the more extended R-groups in **5e** and **5f**, the agreement between calculations and experiments is poor, and again, the deviations with the modified MM3 parameters are smaller. No calculations were possible for the azido compound **5g** due to a lack of force field parameters. The azido-methyl- substituent in **5g**, however, was the one which led to the largest substituent induced shift of the conformer equilibrium when compared to the unsubstituted tetraoxadecalin **4**.

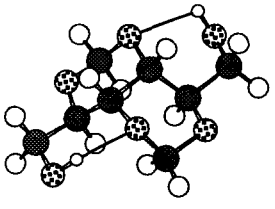
R =	$J_{1,2}$	$J_{2,3}$	$J_{1,3}$	Proxi./Dist. (%)		
				Experim.	Orig. Par.	Corr. Par.
H (**4**)	1.8[12]	---	---	94/6	100/0	100/0
CH_3 (**5a**)	9.2	5.7	-0.6	15/85	74/26	22/78
CH_2OMe (**5c**)	8.6	5.4	-0.5	21/79	50/50	33/67
CH_2OPiv (**5d**)	9.6	5.7	-0.6	11/89	21/79	38/62
$CH_2O(CH_2)_2OMe$ (**5e**)	8.2	4.2	-0.4	25/75	79/21	62/38
CH_2OCH_2Ph (**5f**)	8.3	4.0	-0.6	25/75	99/1	68/32
CH_2N_3 (**5g**)	10.3	6.6	-0.5	3/97	----	----

Table 2. Experimental ^1H NMR coupling constants in toluene-D_8 and conformer populations derived thereof as well as from force field calculations.

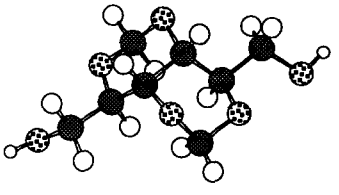
Solvent- and Hydrogen-bonding Effects on the Tetraoxadecalin Conformer Equilibrium

The hydroxymethyl substituent in **5b** and the aminomethyl substituent in **5h** should be capable of forming intramolecular hydrogen bonds to the acetal oxygens[15]. If the strength of such hydrogen bonds is different for the *proximal* and *distal* conformers, intramolecular hydrogen bonding could change the position of the conformer equilibrium. Calculations carried out with the modified MM3-parameters[12] for the hydroxymethyl substituted system **5b** showed that intramolecular hydrogen bonding stabilizes the *distal* conformer by 9.07 kJ mol^{-1}, whereas the *proximal* isomer preferred a non hydrogen bonded conformation.

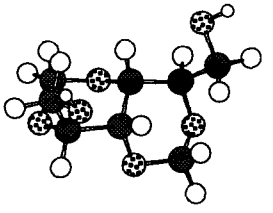
Thus, the formation of intramolecular hydrogen bonds should shift the conformer equilibrium further to the side of the *distal* conformer.



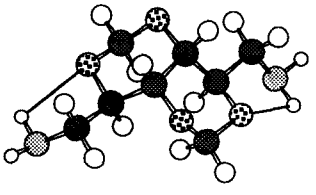
Distal with H bond 92.29 kJ/mol



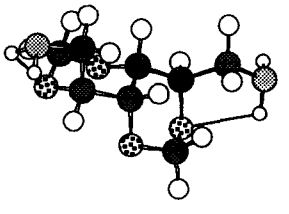
Distal without H bond 101.36 kJ/mol



Proximal 100.22 kJ/mol



Distal with H bond 72.21 kJ/mol
Without H bond 84.18 kJ/mol



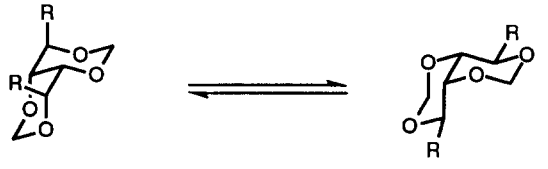
Proximal with H bond 80.67 kJ/mol
Without H bond 89.10 kJ/mol

Figure 5. Minima energy conformations for the diol **5b** and the diamine **5h**. Intramolecular hydrogen bond effect.

For the diamine **5h** calculations suggest intramolecular hydrogen bonding to occur for both the *distal* and the *proximal* conformer. The stabilization due to hydrogen bonding is calculated to be larger for the *distal* conformer. Thus again, hydrogen bonding should shift the conformer equilibrium to the *distal* side according to these calculations. The experimental results for the diamine **5h** in $CDCl_3$ are shown below and may be compared with the data for the methoxymethyl compound **5c** and for the azido compound **5g** in the same solvent. The hydroxymethyl compound **5b** was not soluble enough in either toluene-D_8 or $CDCl_3$.

The position of the conformer equilibrium of the amine **5h** is inbetween those of the methoxy compound **5c** and the azide **5h**. This does not suggest the operation of a major effect caused by intramolecular hydrogen bonding in **5h**. Also, for the diol **5b**, the calculations suggest a larger stabilization of the *proximal* conformer in the absence of intramolecular hydrogen bonding. However table 3 shows that in methanol, a solvent in which intramolecular hydrogen bonds are not favored, compound **5b** exists predominantly in the *distal* conformation. Thus, the intramolecular hydrogen bonding should not be the factor responsible for the greater

stabilization of the *distal* conformers of these molecules. These results are in line with the fact that the basicity of oxygen atoms in acetals is substantially smaller than that in ethers[16]. Accordingly, hydrogen bond formation is not particularly favorable. Not only intramolecular, but also intermolecular hydrogen bonding may affect the position of the conformer equilibria. A change from the non-hydrogen-bonding solvent



		Proximal/Distal
5c	$R = CH_2OCH_3$	22/78
5h	$R = CH_2NH_2$	13/87
5g	$R = CH_2N_3$	5/95

Figure 6. *Proximal/Distal* conformer ratios derived from ^1H NMRcoupling constants.

toluene-D_8 to the weakly hydrogen bonding solvent $CDCl_3$ lead to small but noticeable effects in the cases of the compounds **5a**, **5c**, **5d**, **5f**, and **5g**, favouring more of the *proximal* conformer in $CDCl_3$, cf. Table 3.

Such effects should be more marked in going to protic solvents such as methanol or water. The data in table 3 shows that these solvents indeed shift the conformer equilibrium further to the *proximal* side. It would, however, be premature to ascribe this effect to hydrogen bonding alone. In fact, since the *proximal* conformer is more polar than the *distal* one[12] a change to more polar solvents should shift the conformer equilibrium to the *proximal* side. If this would be the main factor contributing to the solvent effect of the conformer equilibrium, a plot of ln P/D versus E_T should be linear (cf. figure 7).

In this context, the large difference in the conformer equilibrium for the diamine **5h** when going from methanol-D_4 to D_2O is surprising. This difference corresponds to an additional stabilization of the *proximal* conformer by 6 kJ mol^{-1}. It could be speculated that the *proximal* conformer is set up to form an internally hydronium ion bridged structure (figure 8) which would not be possible with methanol as solvent.

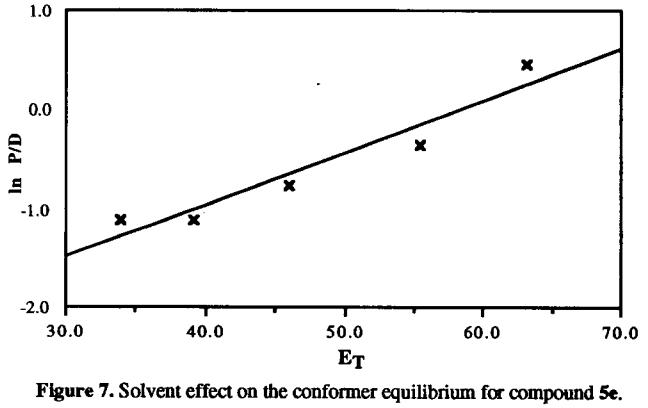


Figure 7. Solvent effect on the conformer equilibrium for compound **5e**.

Whatever the reason behind this effect, the diamine **5h** shows a major change in conformer population on going from $CDCl_3$ to D_2O as solvent.

The purpose of this study was to reveal factors by which the conformer population of a bi-conformational system, such as the tetraoxadecalin **4**, can be shifted to either side. We noted that by placing different substituents in the 4,8-position the conformer

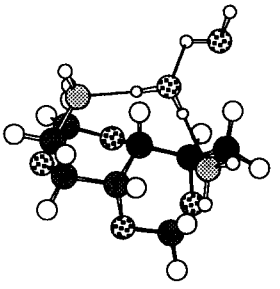
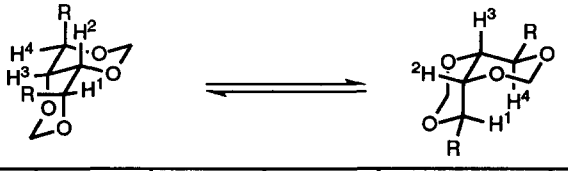


Figure 8. Stabilization of the *proximal* conformation due to intermolecular hydrogen bond formation.

equilibrium can be shifted to the *distal* side. Likewise by adjusting the polarity of the solvent the position of the conformer equilibrium can be fined-tuned due to differential solvation of the conformers.



R =	$J_{1,2}$	$J_{2,3}$	$J_{1,3}$	Prox/Dist (%)	Solvent
CH_3 (**5a**)	9.2	5.7	-0.6	15/85	Toluene-D_8
	6.5	4.0	-0.6	44/56	$CDCl_3$
	6.1	4.0	-0.7	48/52	Methanol-D_4
CH_2OH (**5b**)	7.7	4.9	-0.5	31/69	Methanol-D_4
	6.7	4.3	-0.4	41/59	Acetone-D_6
	5.1	3.2	-0.7	59/41	D_2O
CH_2OMe (**5c**)	8.6	5.4	-0.5	21/79	Toluene-D_8
	8.5	5.3	-0.5	22/78	$CDCl_3$
	7.3	4.7	-0.5	35/65	Methanol-D_4
CH_2OPiv (**5d**)	9.6	5.7	-0.6	11/89	Toluene-D_8
	8.5	5.2	-0.6	22/78	$CDCl_3$
$CH_2O(CH_2)_2OMe$ (**5e**)	8.2	4.2	-0.4	25/75	Toluene-D_8
	8.2	5.2	-0.6	25/75	$CDCl_3$
	7.6	4.8	-0.5	32/68	CD_3CN
	6.7	4.4	-0.5	41/59	Methanol-D_4
	4.9	2.8	-1.0	61/39	D_2O
CH_2OCH_2Ph (**5f**)	8.3	4.0	-0.6	25/75	Toluene-D_8
	7.3	4.6	-0.9	35/65	$CDCl_3$
CH_2N_3 (**5g**)	10.3	6.6	-0.5	3/97	Toluene-D_8
	10.1	6.1	-0.5	5/95	$CDCl_3$
	9.5	5.8	-0.6	12/88	Methanol-D_4
CH_2NH_2 (**5h**)	9.4	5.7	-0.5	13/87	$CDCl_3$
	8.4	5.2	-0.5	23/77	Methanol-D_4
	3.4	2.1	-1.1	77/23	D_2O

Table 3. Solvent effect on the conformational equilibrium.

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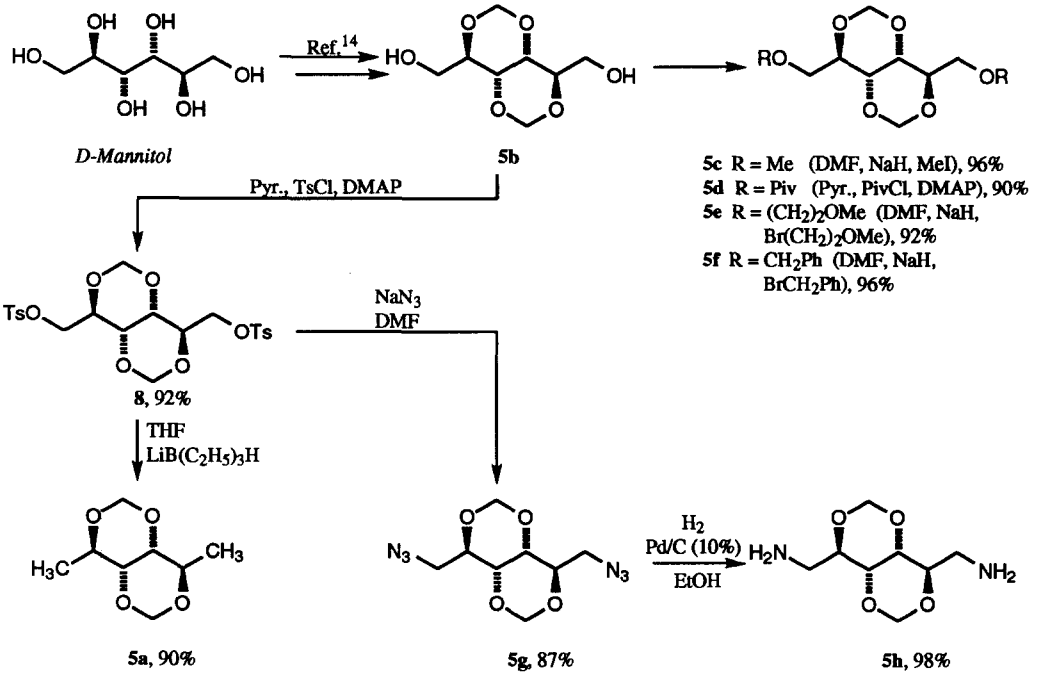
Synthetic aspects

The ether derivatives were prepared by treatment of diol **5b**[14] with sodium hydride in DMF, followed by quenching with the corresponding halide. The dimethyl derivative **5a** was prepared by reduction of the corresponding ditosylate **8** with superhydride. The diazide **5g** was prepared by treating the ditosylate **8** with sodium azide. Reduction of this compound with hydrogen catalyzed by palladium/carbon (10%) afforded the corresponding diamine **5h**, in good yield. The characterization of this compound was made by the preparation of the di-boc derivative.



Scheme 1.

Experimental

^1H NMR and ^{13}C NMR were recorded on a Bruker AC-300 spectrometer at, respectively, 300 MHz or 75 MHz in $CDCl_3$. ^1H chemical shifts are expressed in δ (ppm) referenced to internal tetramethylsilane. ^{13}C chemical shifts are reported in δ (ppm) measured relatively to the center resonance of $^{13}CDCl_3$. Melting points were measured on a Buchi capillary melting point apparatus and are uncorreted. Elemental analyses were obtained on a Heraus CHN-Rapid. Analytical TLC was performed on Merck $60F_{254}$ aluminum plates, and compounds were visualized by U.V. irradiation (254 nm), after spraying with 5% w/v dodecamolybdophosphoric acid in ethanol or with iodine. Flash chromatography (FC) was performed on ICN SiliTech 32-63, 60A silica gel. ^1H NMR spectra were simulated with the program CALM 2.0[17]. Solvents and reagents were purified as described in ref.[18].

4,8-Di-(methoxymethyl)-1,3,5,7-*cis*-tetraoxadecalin (5c). To a solution of **5b** (0.20 g, 0.97 mmol) in

dry DMF (1.5 ml) under argon and in an ice bath was added sodium hydride (0.11 g, 3.88 mmol, 2.0 eq). After stirring for 1 h, methyl iodide (0.36 ml, 5.84 mmol, 3.0 eq) was added. After 3 h at room temperature, the mixture was poured into 3 ml of water and extracted with dichloromethane (3 x 3 ml). The combined organic phases were dried over magnesium sulfate, filtered and evaporated. The residue was purified by flash chromatography (eluent: petrol ether/ethyl acetate; 85/15) affording the title compound as a white crystalline solid (0.22 g, 96%). M.p. 61-62°C, ^{1}H δ 4.866 (2H, AB d, *J* -6.3 Hz, one of 2-H and one of 6-H); 4.824 (2H, AB d, *J* = -6.3 Hz, one of 2-H and one of 6-H); 4.205 (2H, m, *J* = 6.3, 2.2, 8.5 Hz, -0.5, 4-H and 8-H); 3.998 (2H, m, *J* = 8.5, 5.3, -0.5 Hz, 9-H and 10-H); 3.671 (2H, ABX dd, *J* = -10.5, 2.2 Hz, 1/2 of 2 x $C\underline{H}_2OMe$); 3.535 (2H, ABX dd, *J* = -10.5, 6.3 Hz, 1/2 of 2 x $C\underline{H}_2OMe$); 3.356 (6H, s, 2 x $\underline{Me}O$), ^{13}C δ 88.4 (C-2 and C-6); 72.2 (C-4 and C-8); 72.0 (C-9 and C-10); 66.6 (2 x $\underline{C}H_2OMe$); 59.4 (2 x $\underline{C}H_3OCH_2$). Found: C, 51.24; H, 7.82. $C_{10}H_{18}O_6$, 234.25, requires: C, 51.27; H, 7.75%.

4,8-Di-(pivaloyloxymethyl)-1,3,5,7-*cis*-tetraoxadecalin (5d). To a solution of **5b** (0.15 g, 0.73 mmol) and a catalytic amount of DMAP (1 mg) in dry pyridine (1.0 ml) under argon and in an ice bath, was added pivaloyl chloride (0.22 ml, 1.75 mmol, 1.2 eq). The mixture was stirred for 3 h at room temperature and was poured into 5 ml of water, with stirring. A white solid precipitated which was further purified by crystallization from ethanol/water, to afford 0.25 g (90%) of the title compound. M.p. 102-103°C, ^{1}H δ 4.847 (2H, AB d, *J* = -6.5, one of 2-H and one of 6-H); 4.793 (2H, AB d, *J* = -6.5 Hz, one of 2-H and one of 6-H); 4.380 (2H, ABX dd, *J* = -12.1, 3.3 Hz, 1/2 of 2 x $C\underline{H}_2OPiv$); 4.283 (2H, m, *J* = 6.5, 3.3, 8.5 Hz, -0.6, 4-H and 8-H); 4.150 (2H, ABX dd, *J* = -12.1, 6.5 Hz, 1/2 of 2 x $C\underline{H}_2OPiv$); 3.955 (2H, m, *J* = 8.5, 5.2, -0.6 Hz, 9-H and 10-H); 1.161 (18H, s, 2 x $C(C\underline{H}_3)_3$), ^{13}C δ 178.3 ($\underline{C}$=O); 88.3 (C-2 and C-6); 71.0 (C-4 and C-8); 66.7 (C-9 and C-10); 63.0 (2 x $\underline{C}H_2OPiv$); 38.8 ($\underline{C}(CH_3)_3$); 27.1 ($C(\underline{C}H_3)_3$). Found: C, 57.61; H, 8.18. $C_{18}H_{30}O_8$, 374.43, requires: C, 57.74; H, 8.08%.

4,8-Di-(methoxy-ethoxymethyl)-1,3,5,7-*cis*-tetraoxadecalin (5e). To a solution of **5b** (0.20 g, 0.97 mmol) in dry DMF (1.5 ml) under argon and in an ice bath was added sodium hydride (0.084 g, 2.91 mmol, 1.5 eq). The mixture was stirred for 1 h and 2-methoxybromoethane (0.27 ml, 2.91 mmol, 1.5 eq) was added. After 3 h at room temperature, the mixture was poured into 3 ml of water and extracted with dichloromethane (3 x 3 ml). The combined organic phases were dried over magnesium sulfate, filtered and evaporated. The residue was purified by flash chromatography (eluent: ethyl acetate) affording the title compound as a colorless oil (0.29 g, 92%). ^{1}H δ 4.879 (2H, AB d, *J* = -6.6 Hz, one of 2-H and one of 6-H); 4.829 (2H, AB d, *J* = -6.6 Hz, one of 2-H and one of 6-H); 4.253 (2H, m, *J* = 6.5, 3.0, 8.2 Hz, -0.6, 4-H and 8-H); 3.982 (2H, m, *J* = 8.2, 5.2, -0.6 Hz, 9-H and 10-H); 3.828 (2H, ABX dd, *J* = -10.9, 3.0 Hz, 1/2 of 2 x $C\underline{H}_2O(CH_2)_2OMe$); 3.631 (2H, ABX dd, *J* = -10.9, 6.5 Hz, 1/2 of 2 x $C\underline{H}_2O(CH_2)_2OMe$); 3.629 (4H, q, *J* = 4.1 Hz, 2 x $CH_2O\underline{C}H_2CH_2OMe$); 3.526 (4H, q, *J* = 4.1 Hz, 2 x $CH_2OCH_2\underline{C}H_2OMe$); 3.344 (6H, s, 2 x $CH_2O(CH_2)_2O\underline{C}H_3$), ^{13}C δ 88.4 (C-2 and C-6); 72.6 (C-4 and C-8); 71.8 (C-9 and C-10); 71.0 (2 x $CH_2O\underline{C}H_2CH_2OMe$); 70.9 (2 x $CH_2OCH_2\underline{C}H_2OMe$); 66.8 (2 x $\underline{C}H_2O(CH_2)_2OMe$); 58.9 (2 x $\underline{C}H_3O(CH_2)_2O$. Found: C, 51.99; H, 7.96. $C_{14}H_{26}O_8$, 322.36 requires: C, 52.16; H, 8.13.

4,8-Di-(benzyloxymethyl)-1,3,5,7-*cis*-tetraoxadecalin (5f). To a solution of **5b** (0.20 g, 0.97 mmol) in dry DMF (1.5 ml) under argon and in an ice bath was added sodium hydride (0.084 g, 2.91 mmol, 1.5 eq). The mixture was stirred for 1 h and benzyl bromide (0.35 ml, 2.91 mmol, 1.5 eq) was added. After 3 h at room temperature, the mixture was poured into 3 ml of water and extracted with dichloromethane (3 x 3 ml). The combined organic phases were dried over magnesium sulfate, filtered and evaporated. The residue was purified by flash chromatography (eluent: petrol ether/ethyl acetate; 85/15) affording the title compound as a

colorless oil (0.36 g, 96%). ^{1}H δ 7.333 (10H, s, Ar); 4.910 (4H, s, 2-H and 6-H); 4.590 (4H, s, 2 x PhC$\underline{H}_2$O); 4.238 (2H, m, *J* = 6.0, 3.3, 7.3, -0.9 Hz, 4-H and 8-H); 4.052 (2H, m, *J* = 7.3, 4.6, -0.9 Hz, 9-H and 10-H); 3.806 (2H, ABX dd, *J* = -10.7, 3.3 Hz, 1/2 of 2 x C$\underline{H}_2$OCH$_2$Ph); 3.673 (2H, ABX dd, *J* = -10.7, 6.0 Hz, 1/2 of 2 x C$\underline{H}_2$OCH$_2$Ph), ^{13}C δ 137.6 (Ar); 128.3 (Ar); 127.7 (Ar); 127.6 (Ar); 88.5 (C-2 and C-6); 73.6 (C-4 and C-8); 72.8 (C-9 and C-10); 69.5 (2 x CH$_2$O$\underline{C}$H$_2$Ph); 67.1 (2 x $\underline{C}$H$_2$OCH$_2$Ph). Found: C, 68.21; H, 6.64. $C_{22}H_{26}O_6$, 386.44, requires: C, 68.38; H, 6.78%.

4,8-Di-(tosyloxymethyl)-1,3,5,7-*cis*-tetraoxadecalin (8). To a solution of **5b** (0.50 g, 2.43 mmol) and a catalytic amount of DMAP (2 mg) in dry pyridine (2.5 ml) under argon and in an ice bath, was added solid tosyl chloride (1.11, 5.82 mmol, 1.2 eq). The mixture was stirred for 4 h at room temperature and was poured into 10 ml of water, with stirring. A white solid precipitated which was further purified by crystallization from ethanol/petrol ether, to afford 1.15 g (92%) of the title compound. M.p. 154-155°C, ^{1}H δ 7.773 (4H, d, *J* = 8.5 Hz, Ar); 7.339 (4H, d, *J* = 8.5 Hz, Ar); 4.753 (2H, AB d, *J* = -6.6 Hz, one of 2-H and one of 6-H); 4.699 (2H, AB d, *J* = -6.6 Hz, one of 2-H and one of 6-H); 4.303 (2H, ABX dd, *J* = -13.5, 3.3 Hz, 1/2 of 2 x C$\underline{H}_2$OTs); 4.282 (2H, m, *J* = 7.6, 3.3, 9.4, -0.5 Hz, 4-H and 8-H); 4.095 (2H, ABX dd, *J* = -13.5, 7.6 Hz, 1/2 of 2 x C$\underline{H}_2$Ts); 3.910 (2H, m, *J* = 9.4, 5.7, -0.5 Hz, 9-H and 10-H); 2.430 (6H, s, 2 x C$\underline{H}_3$Ph), ^{13}C δ 145.2 (Ar); 132.6 (Ar); 129.9 (Ar); 128.0 (Ar); 88.2 (C-2 and C-6); 70.6 (C-4 and C-8); 68.6 (C-9 and C-10); 65.8 (2 x $\underline{C}$H$_2$Ts); 21.6 (H$_3\underline{C}$Ph). Found: C, 51.48; H, 5.15. $C_{22}H_{26}O_8S_2$, 514.56, requires: C, 51.35; H, 5.09%.

4,8-Di-(azidomethyl)-1,3,5,7-*cis*-tetraoxadecalin (5g). To a solution of **8** (0.38 g, 0.74 mmol) in 2 ml of dry DMF under an argon atmosphere, was added 0.48 g (7.4 mmol, 5.0 eq) of sodium azide and the mixture was heated to 80°C during 6 h. The mixture was than cooled, poured into 6 ml of water and extracted with dichloromethane (3 x 5 ml). The combined organic phases were dried over magnesium sulfate, filtered and evaporated. The residue was purified by flash chromatography (eluent: petrol ether/ethyl acetate, 80/20), affording the title compound as a white crystalline solid (0.16 g, 87%). M.p. 100-103°C (decomp.), ^{1}H δ 4.853 (2H, AB d, *J* = -6.3 Hz, one of 2-H and one of 6-H); 4.828 (2H, AB d, *J* = -6.3 Hz, one of 2-H and one of 6-H); 4.268 (2H, m, *J* = 6.8, 2.8, 10.1, -0.5 Hz, 4-H and 8-H); 4.089 (2H, m, *J* = 10.1, 6.1, -0.5 Hz, 9-H and 10-H); 3.577 (2H, ABX dd, *J* = -13.3, 2.8 Hz, 1/2 of 2 x C$\underline{H}_2$N$_3$); 3.471 (2H, ABX dd, *J* = -13.3, 6.8 Hz, 1/2 of 2 x C$\underline{H}_2$N$_3$), ^{13}C δ 88.4 (C-2 and C-6); 71.8 (C-4 and C-8); 66.9 (C-9 and C-10); 51.9 (2 x $\underline{C}$H$_2$N$_3$). Found: C, 37.44; H, 4.87; N, 32.76. $C_8H_{12}N_6O_4$, 256.22, requires: C, 37.50; H, 4.72; N, 32.80%.

4,8-Di-(aminomethyl)-1,3,5,7-*cis*-tetraoxadecalin (5h). To a solution of **5g** (0.40 g, 1.56 mmol) in anhydrous ethanol (10 ml) was added 75.5 mg of Pd/C (10%). The mixture was than stirred for 5 h under hydrogen (1 atm). Filtration of the catalyst and solvent evaporation afforded the title compound as a colorless oil (0.31 g, 98%). ^{1}H δ 4.868 (2H, AB d, *J* = -6.6 Hz, one of 2-H and one of 6-H); 4.772 (2H, AB d, *J* = -6.6 Hz, one of 2-H and one of 6-H); 4.078 (2H, m, *J* = 7.6, 3.3, 9.4, -0.5 Hz, 4-H and 8-H); 3.949 (2H, m, *J* = 9.4, 5.7, -0.5 Hz, 9-H and 10-H); 3.045 (2H, ABX dd, *J* = -13.5, 3.3 Hz, 1/2 of 2 x C$\underline{H}_2$NH$_2$); 2.880 (2H, ABX dd, *J* = -13.5, 7.6 Hz, 1/2 of 2 x C$\underline{H}_2$NH$_2$); 1.523 (4H, br, 2 x N$\underline{H}_2$), ^{13}C δ 88.0 (C-2 and C-6); 74.1 (C-4 and C-8); 67.6 (C-9 and C-10); 43.0 (2 x $\underline{C}$H$_2$NH$_2$). The di-boc derivative was prepared as follows: To a solution of **5h** (0.20 g, 1.00 mmol), triethylamine (0.40 ml, 2.80 mmol, 1.4 eq) and a catalytic amount of DMAP (1 mg) in dry dichloromethane (2.5 ml) under argon and at room temperature, was added di-(*t*-butyl)-dicarbonate (0.60 ml, 2.80 mmol, 1.4 eq). The mixture was stirred for 4 h, poured into 5 ml of water and extracted with dichloromethane (3 x 4 ml). The combined organic phases were dried over magnesium sulfate, filtered and evaporated. The residue was purified by flash chromatography (eluent: petrol ether/ethyl acetate; 7/3) affording the di-boc derivative (0.34 g, 85%) as a white crystalline solid. M.p. 147-148°C, ^{1}H δ 4.881

(2H, br, 2 x NH); 4.823 (2H, AB d, J = -6.5 Hz, one of 2-H and one of 6-H); 4.742 (2H, AB d, J = -6.5 Hz, one of 2-H and one of 6-H); 4.085 (2H, m, J = 7.3, 3.0, 8.8, -0.7 Hz, 4-H and 8-H); 3.851 (2H, m, J = 8.8, 5.0, -0.7 Hz, 9-H and 10-H); 3.582 (2H, m, J = -12.0, 3.0 Hz, 1/2 of 2 x CH_2NH_2); 2.880 (2H, m, J = -12.0, 7.3 Hz, 1/2 of 2 x CH_2NH_2); 1.382 (18H, s, (2 x $CH_3)_3CO$), ^{13}C δ 155.9 (2 x C=O); 88.2 (C-2 and C-6); 79.7 (2 x $(CH_3)_3CO$); 71.9 (C-4 and C-8); 67.7 (C-9 and C-10); 41.5 (2 x CH_2NHBoc). Found: C, 53.25; H, 7.63; N, 6.78. $C_{18}H_{32}N_2O_8$, 404.46, requires: C, 53.45; H, 7.92; N, 6.93%.

4,8-Dimethyl-1,3,5,7-*cis*-tetraoxadecalin (5a). To a solution of **8** (0.20 g, 0.39 mmol) in dry THF (4 ml) under argon was added, at room temperature, a 1M solution of lithium-triethylborhydride (superhydride) (1.25 ml, 1.25 mmol, 1.6eq). The mixture was stirred under reflux during 6 h, cooled, poured into 5 ml of water and extracted with dichloromethane (3 x 5 ml). The combined organic phases were dried over magnesium sulfate, filtered and evaporated. The residue was purified by flash chromatography (eluent: petrol ether/ethyl acetate; 1/1) affording the title compound (61 mg, 90%). The NMR data corresponded to that given in ref.[11].

References and notes

1 Hoffmann, R. W., *Angew. Chem. Int. Ed. Engl.*, **1992**, *31*, 1124.

2 Raban, M.; Burch, D. L.; Hortelano, E. R.; Durocher, D., *J. Org. Chem.*, **1994**, *59*, 1283.

3 a) Hegetschweiler, K.; Kradolfer, T.; Gramlich, V.; Hancock, R. D., *Chem. Eur. J.*, **1995**, *1*, 74; b)Ghisletta, M.; Jalett, H.-P.; Gerfin, T.; Gramlich, V.; Hegetschweiler, K., *Helv. Chim. Acta*, **1992**, *75*, 2233.

4 Gerig. J. T.; Roberts, J. D., *J. Am. Chem. Soc.*, **1966**, *88*, 2791.

5 Booth, H.; Bostock, A. H., *J. Chem. Soc. Perkin II*, **1972**, 615.

6 Lemieux, R. U.; Howard, J., *Can. J. Chem.*, **1963**, *41*, 393.

7 Nasipuri, D., *Stereochemistry of Organic Compounds. Principles and Applications*, John Wiley & Sons, New Delhi, **1991**, 252.

8 a) Wolfe, S., *Acc. Chem. Res.*, **1972**, *5*, 102; b) Juaristi, E., *J. Chem. Ed.*, **1979**, *56*, 438.

9 a) Salzner U., *J. Org. Chem.*, **1995**, *60*, 986; b) Perrin, C. L.; Armstrong, K. B.; Fabian, M. A., *J. Am. Chem. Soc.*, **1994**, *116*, 715.

10 Burden, I. J.; Stoddart, J. F., *J. Chem. Soc. Perkin I*, **1975**, 666. For other publications on this subject see: a) Haskins, W. T.; Hann, R. M.; Hudson, C. S., *J. Am. Chem. Soc.*, **1943**, *65*, 67; b) Bernstein, J.; Green, B. S.; Rejtö, M., *J. Am. Chem. Soc.*, **1980**, *102*, 323; c) Senderowitz, H.; Linden, A.; Golender, L.; Abramson, S.; Fuchs, B., *Tetrahedron*, **1994**, *50*, 9691.

11 Nørskov, L.; Jensen, R. B.; Schroll, G., *Acta Chem. Scand.*, **1983**, *37 B*, 133.

12 Senderowitz, H.; Golender, L.; Fuchs, B., *Tetrahedron*, **1994**, *50*, 9707.

13 Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C., *J. Comp. Chem.*, **1990**, *11*, 440.

14 a) Haworth, W. N.; Wiggins, L. F., *J. Chem. Soc. C*, **1944**, 58; b) Brigl, P.; Grüner, H., *Chem. Ber.*, **1932**, 641.

15 a) Hoffmann, R. W.; Weidmann, U., *Chem. Ber.*, **1985**, *118*, 3980; b) Jäger, V.; Buß, V., *Liebigs Ann. Chem.*, **1980**, 101; c) Jäger, V.; Schohe, R., *Tetrahedron*, **1984**, *40*, 2210.

16 a) Kankaanperä, A., *Acta Chem. Scand.*, **1969**, *23*, 1723; b) Kankaanperä, A., *Acta Chem. Scand.*, **1969**, *23*, 1728; c) Kankaanperä, A.; Lahti, M., *Acta Chem. Scand.*, **1969**, *23*, 2465; d) Kagiya, T.; Sumida, Y.; Inoue, T., *Bull. Chem. Soc. Jap.*, **1968**, *41*, 767.

17 CALM is a program for iterative analysis of high resolution NMR-spectra for IBM-PC and compatibles. CALM is based on LAOCOON-type algorithm. This program can be obtained from Brucker, at the address IP 128.32.144.132 in the directory /pub/nmr/ms-dos/calm.zip, by anonymous FTP.

18 Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R., *Purification of Laboratory Chemicals*, 2nd Edition, Pergamon Press, **1980**.

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