Selective Derivatisation of Resorcarenes, 6[‡]

Mannich Reactions with Amino Alcohols

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Keywords: Amino alcohols / Calixarenes / Chirality / Helical structures

The condensation of resorcarenes **1** with various amino alcohols and an excess of formaldehyde was studied. The tetrabenzoxazines **2a**–**e** were found as the only products in the reaction with 6-aminohexan-1-ol, 4-aminobutan-1-ol, and 2-aminoethanol, while 3-aminopropan-1-ol forms the tetraoxazine **3** as the main product. In the case of aminoethanols substituted at the 2-position with alkyl groups, the tetraoxazolidines **4** are the preferred reaction products, while 1-methyl aminoethanol (1-amino-propan-2-ol) yields predominantly the tetrabenzoxazine **2f**. The structures of all these compounds have been confirmed by NMR spectroscopy and additionally by single-crystal X-ray analysis in the case of **2a** and **4b**. In [D_6]DMSO, up to 60% of the corresponding, more polar tetrabenzoxazine structure is detected for compounds **3** and **4**, while the equilibrium is shifted to the less polar tetraoxazine or tetraoxazolidine in $CDCl_3$. Low-temperature NMR spectra show a C_4-symmetrical conformation for the tetraoxazolidines **4** in $CDCl_3$ owing to intramolecular OH···OH···N hydrogen bonds. For chiral residues, two epimeric conformations can be distinguished, one of which is selectively formed for larger substituents at the 2-position.

Introduction

Resorcarenes, readily available in the form of their *rccc*-isomers by acid-catalysed condensation of resorcinol with various aldehydes, are easily substituted at the 2-position of the resorcinol units by mild electrophiles.[1] For instance, the Mannich reaction with formaldehyde and various secondary amines leads to the formation of tertiary amines in high yields.[2] When primary amines are used under similar conditions with a sufficient excess of formaldehyde, benzoxazines **2** are formed in an entirely regioselective reaction.[3,4] This reaction is attractive, since it furnishes potential host molecules with an extended (flexible) cavity and inherent chirality (C_4-symmetry). If a chiral amine ((*R*)- or (*S*)-phenylethylamine) is used, one of the two possible tetrabenzoxazines is formed with high diastereoselectivity,[4] and after methylation of the remaining phenolic hydroxy groups, can be converted into various C_4-symmetrical derivatives.[5] The condensation with formaldehyde may also be extended to various diamines, leading to 1,2- or 1,3-bridged compounds[6] and, in the case of ethylene diamine, also to tetra-bridged dimers of the carcerand type.[7]

As with secondary amines,[2a] the introduction of additional functional groups should be possible using suitably functionalized primary amines, e.g. amino alcohols. However, a different ring-closure reaction was reported in the case of some 2-substituted aminoethanol derivatives[8] which formed five-membered oxazolidine rings instead of the six-membered benzoxazine rings. Our own experiments, on the other hand, showed that a tetrabenzoxazine was formed with ethanolamine itself. These seemingly contradictory observations led us to undertake a more detailed investigation of the Mannich reaction of resorcarenes with various amino alcohols to understand the factors which control the formation of five- or six-membered O/N-acetals.

Results and Discussion

Synthesis and General Structure

All the condensation reactions of resorcarenes **1** were carried out in ethanol at room temperature with various amino alcohols and an excess of formaldehyde, catalysed by a small amount of acetic acid (Scheme 1). The products **2**–**4** were isolated as precipitates and purified by recrystallisation. The final yield was 34–74% and was not optimized.

With linear amino alcohols such as 4-aminobutan-1-ol or 6-aminohexan-1-ol, the C_4-symmetrical tetrabenzoxazines **2d,e** were formed exclusively. This follows unambiguously

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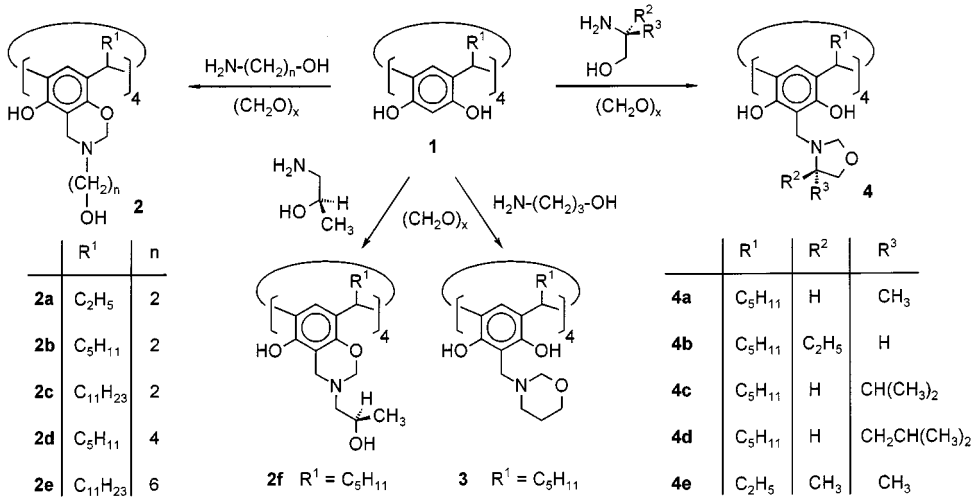

	R^1	n
2a	C_2H_5	2
2b	C_5H_{11}	2
2c	$C_{11}H_{23}$	2
2d	C_5H_{11}	4
2e	$C_{11}H_{23}$	6

	R^1	R^2	R^3
4a	C_5H_{11}	H	CH_3
4b	C_5H_{11}	C_2H_5	H
4c	C_5H_{11}	H	$CH(CH_3)_2$
4d	C_5H_{11}	H	$CH_2CH(CH_3)_2$
4e	C_2H_5	CH_3	CH_3

Scheme 1

from their ^{1}H NMR spectra in $CDCl_3$ (compare Figure 1, b) which show the following signals with the expected intensities in all the examples: One sharp singlet each for the ArOH (7.7 ppm) and for the ArH protons (7.1 ppm), one triplet for the bridge methine protons (4.2 ppm) and one pair of doublets with geminal coupling for the diastereotopic protons of the Ar−CH_2−N groups (3.7 and 3.9 ppm) in the benzoxazine rings. The N−CH_2−O protons, which are also diastereotopic, give rise to a *pseudo*-singlet at (4.9 ppm), while the signals for the aliphatic hydroxy groups are usually hidden in the range of 3−4 ppm.

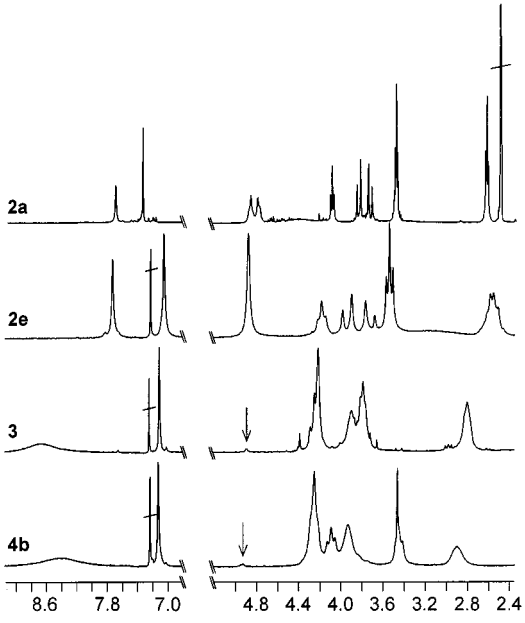

Figure 1. Sections of the ^{1}H NMR spectra of a) **2a** ([D_6]DMSO, 500 MHz); b) **2e** ($CDCl_3$, 200 MHz); c) **3** ($CDCl_3$, 200 MHz); d) **4b** ($CDCl_3$, 200 MHz). The signal assigned to the O/N-acetal of the tetrabenzoxazine is indicated for c,d) by an arrow

In the case of 3-aminopropan-1-ol, two different six-membered rings could be formed by O/N-acetal formation including either the aromatic or the aliphatic hydroxy group. The ^{1}H NMR spectrum in $CDCl_3$ (Figure 1, c), showing a strong upfield shift for the O/N-acetal protons (4.2 ppm) relative to those of **2d,e** and one very broad signal for **two** OH-protons (8.81 ppm) per resorcinol unit, suggests the formation of the tetraoxazine **3**. A singlet at 3.9 ppm assigned to the Ar−CH_2−N protons confirms this structure. In [D_6]DMSO, however, about 50% of the corresponding tetrabenzoxazine structure is present, as estimated from the signal at approximately 4.9 ppm, corresponding to the O/N-acetal in a benzoxazine.

With 2-substituted aminoethanol derivatives, the tetraoxazolidines **4** are formed in all cases. This is corroborated by a broad signal at approximately 9.0 ppm for **two** ArOH protons per resorcinol unit, a *pseudo*-singlet for N−CH_2−O at 4.3 ppm (only in the achiral **4e** are these protons not diastereotopic) and a signal (broad singlet or pair of doublets due to intramolecular OH···N hydrogen bonding) for Ar−CH_2−N. This formation of the tetraoxazolidines **4a−e** is in agreement with the results reported by Mattay and Iwanek.[8] However, critical inspection of the ^{1}H NMR spectra ($CDCl_3$) of compounds **4a−d**, shows an additional very small amount (<4%) of the benzoxazine structure, which can be mainly deduced from the signals for the O/N-acetal protons at 4.9 ppm. This amount of benzoxazine increases again in [D_6]DMSO to 50% for **4a** and **4e**, 40% for **4b**, while 10% and 5% of the corresponding tetrabenzoxazine structures are found for the sterically more crowded **4c** and **4d**, respectively. These spectra in [D_6]DMSO are not as sharp as those in $CDCl_3$, since various compounds which simultaneously contain both structural elements may be present.

The NMR spectra ([D_6]DMSO, Figure 1, a) of the products of the reaction with unsubstituted 2-aminoethanol are entirely consistent with the benzoxazine structure **2a−c**, showing the characteristic signals at 7.7 (ArOH), 4.8/4.9 (N−CH_2−O) and 3.7/3.8 ppm (Ar−CH_2−N). However, in addition to these main signals for the benzoxazine structure, further signals are observed in the less polar $CDCl_3$, indicating the presence of up to 15% of a second species. Among them, especially the ^{1}H NMR signals at 8.8 ppm (seen only

at low temperature) and 4.3 ppm correspond to the oxazolidine structure **4** (with $R^2 = R^3 = H$). Additionally, PFG ^1H-^{13}C HMQC experiments show characteristic cross-peaks for both structures. Similar observations were also made for compound **2f**, obtained by the condensation with an aminoethanol substituted at the 1-position.

The simultaneous observation of both tetrabenzoxazines and tetraoxazolidines, indicates a relatively small energy difference between these two possible structures of the condensation products with ethanolamines. Substituents at the 2-position favour the formation of oxazolidines, while the benzoxazine is predominant in products formed with unsubstituted ethanolamine and 1-methylethanolamine. These structural factors are obviously superimposed by a solvent-dependent equilibrium between benzoxazines and oxazolidines (or oxazine in the case of **3**). DMSO (and to a lesser extent, acetone) favours the benzoxazine structure, while the oxazolidine structure is preferred in $CDCl_3$ or benzene. This can easily be understood by the difference in the polarity of both structures. In the tetraoxazolidines **4** (and in the tetraoxazine **3**) all hydroxy groups are involved in intramolecular hydrogen bonds of the type O−H···O−H···N. Inspection of the X-ray structure of **4b** reveals the "apolar" characteristics of the molecule. The ArOH groups of **2** are also involved in intramolecular O−H···O hydrogen bonds, as shown by the X-ray structure of **2a** and by several other X-ray structures,[3,4] but the aliphatic hydroxyl groups remain "unpaired" and can be much better solvated in DMSO or acetone than in chloroform or benzene.

While the molecular peak is usually found for tetrabenzoxazines **2**, the FD-mass spectra of compounds **3** and **4** gave a weak peak for the molecular ion only in a few examples. In all cases with $R^1 = C_5H_{11}$ (**3, 4a−d**) the same series of peaks were found (*m*/*z* = 688.9, 615.8, 567.7, 494.7, 410.5, 289.5 and 205.3), indicating the complete loss of all amino functions and in addition, even a fragmentation of the resorcarene skeleton.

Conformational Studies by Variable-Temperature NMR

The main reason for the regioselective formation of C_4-symmetrical tetrabenzoxazines is the tendency to form the maximum number of intramolecular O−H···O hydrogen bonds, as also supported by semiempirical calculations.[3b] Intramolecular hydrogen bonds also determine the C_4-symmetrical conformation found for resorcarene tetraacetamides[9] and for aminomethylation products with secondary amines.[2c] A similar behaviour may be deduced for the compounds **3** and **4,** and has already been discussed as the reason for the solvent-dependence of the equilibrium between the isomeric structures **2** and **4**.

Such a system of O−H···O−H···N hydrogen bonds represents an additional stereogenic element[10] and should lead to two diastereomeric conformations in the case of the chiral oxazolidine rings **4a−d.** In fact, ^1H and ^{13}C NMR experiments at a lower temperature (−50 °C) show a doubling of signals for compounds **4a−c**. This is clearly seen for the ArH and the diastereotopic $Ar-CH_2-N$ protons, which is in agreement with the postulated formation of a diastereomeric (epimeric) pair of conformers. A 50:50 mixture of both diastereomers is found for **4a** and **4b** (see Figure 2), while for **4c** the ratio is 60:40. In contrast to **4a−c**, compound **4d** shows only one sharp set of signals at low temperatures, which in principle could be interpreted as incidental isochrony (unlikely for various peaks) or as a rapid change of the directionality of the hydrogen bonds (unlikely in comparison to **4a−c**). One has to conclude therefore, that in this case one of the two diastereomers is strongly preferred. The reason must be sought in the different steric requirements of the substituent R^2/R^3. For one of the diastereomers, this substituent at the 2-position must point more into the molecular cavity than for the other one, if the oxazolidine rings are orientated in such a way, that their oxygens point outwards (compare the X-ray structure below). Obviously this inward orientation is possible without hindrance only for the smaller residues Me and Et in **4a** and **4b** (the different R^2/R^3 number stems from the different configuration). The slightly larger *i*Pr in **4c** already disfavours the inward orientation, which is impossible for *i*Bu. Thus only the more outward-oriented diastereomer exists in which the oxazolidine rings are directed counter-clockwise, relative to the cavity side of the molecule. In contrast to **4**, the tetraoxazine **3** shows only a broadening of the signals, even at −55 °C, which suggests a lower energy barrier for the inversion of the O−H···O−H···N hydrogen bonds.

Single-Crystal X-ray Structures

Single crystals suitable for X-ray analysis were obtained for **2a** from acetonitrile/ethanol and for **4b** from chloro-

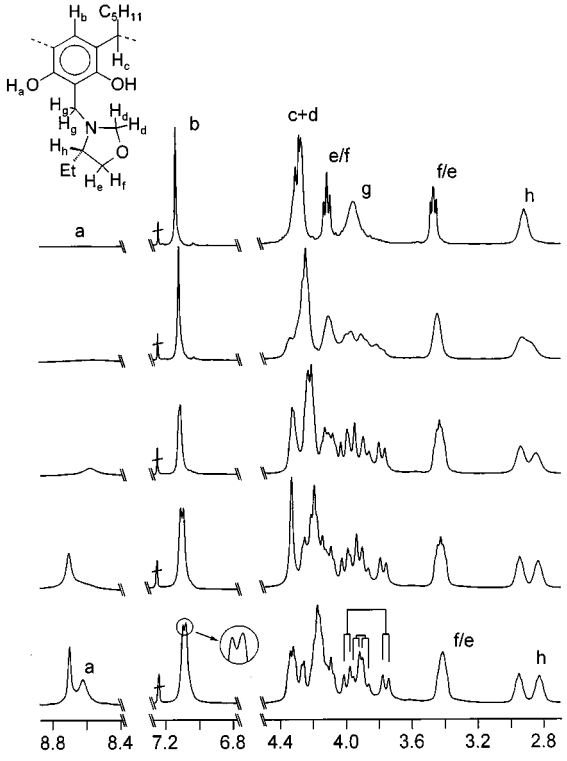

Figure 2. Sections of the ^1H NMR spectra of **4b** at 298, 273, 253, 233 and 223 K. The splitting of the $ArCH_2N$ protons is indicated

form/acetonitrile. Details of the experimental conditions, cell data, structure solution and refinements are shown in Table 1.

Table 1. Crystallographic data for the compounds **2a** and **4b**

	2a	4b
Empirical formula	$C_{52}H_{68}N_4O_{12}\cdot C_2H_5OH\cdot 0.5H_2O$	$C_{72}H_{108}N_4O_{12}\cdot CH_2Cl_2\cdot CH_3CN\cdot 2H_2O$
M_r	991.17	1383.64
Space group	*P*-1	$P3_221$
Crystal system	triclinic	trigonal
T (K)	173.0(1)	293(2)
a (Å)	12.234(7)	22.404(1)
b (Å)	12.288(3)	22.404(1)
c (Å)	17.806(3)	13.706(1)
α (deg)	77.48(2)	90°
β (deg)	73.97(3)	90°
γ (deg)	88.15(3)	120°
V (Å^3)	2511(2)	5957.9(2)
Z	2	3
D_C (g/cm^3)	1.31	1.157
F (000)	1064	2244
μ (mm^{-1})	0.09	0.143
R (%)	7.6	9.78
R_W(%)	20.7	25.11

The molecular structure of **2a** shown in Figure 3 (a) confirms its constitution as a tetrabenzoxazine with a C_4-symmetrical orientation of the oxazine rings at the resorcarene skeleton. These oxazine rings cannot be planar, and for three of them the nitrogen atom points toward the cavity. The hydroxyethyl residues attached to these nitrogen atoms always assume the axial position. All the bond lengths and angles in **2a** are found within the usual range. Four intramolecular hydrogen bonds between the ArOH-groups and the ether oxygen atoms are revealed by O···O distances of 2.69−2.74 Å.

The hydroxyethyl group (O54) pointing away from the molecular cavity forms an intermolecular hydrogen bond with one of the inward-pointing hydroxyethyl groups of a second molecule. Thus, two resorcarene molecules related by a symmetry centre are arranged as dimers by means of hydrogen bonds between O54···O60A and O60···O54A (2.72 Å). Both resorcarenes form their own cavity, in which an ethanol molecule is included. This ethanol molecule forms a hydrogen bond with a third hydroxyethyl group as can be seen by the O51···O61 distance of 2.72 Å. The remaining fourth hydroxyethyl group of **2a** is hydrogen bonded to the corresponding group of the adjacent dimer (O57···O57B = 2.83 Å), thus creating a one-dimensional network of dimers. The crystal lattice showed one additional peak which was treated as a fractional water molecule (occupancy 0.25, H-atoms were not located). This water molecule is situated at a position outside the cavity (O64···O54 = 2.65 Å). Figure 3 (b) shows the very interesting packing of **2a**·C_2H_5OH·0.5 H_2O.

The X-ray structure of compound **4b** confirms the constitution of a tetraoxazolidine (Figure 4), for which all bond lengths and bond angles are in the usual range. Secondly, it confirms, in principle, the C_4-symmetrical conformation with four intramolecular OH···OH···N hydrogen bonds, as suggested by the NMR spectra. However, since the molecule resides on a twofold crystallographic axis, the resorcarene skeleton actually shows a slightly pinched cone conformation with small differences in the interplanar angles (127.5° and 131.2°) between the resorcinol rings and the best plane through the methine carbon atoms. In contrast to the case in solution, only one direction for OH···OH···N hydrogen bonds is found in the crystal. Since the configuration of the oxazolidine is known to be (*R*), this direction could be established as clockwise around the macrocycle, seen from the cavity side of the molecule. The O···O distances of 2.77 and 2.78 Å and the O···N distances of 2.61 and 2.63 Å are typical for strong hydrogen bonding.

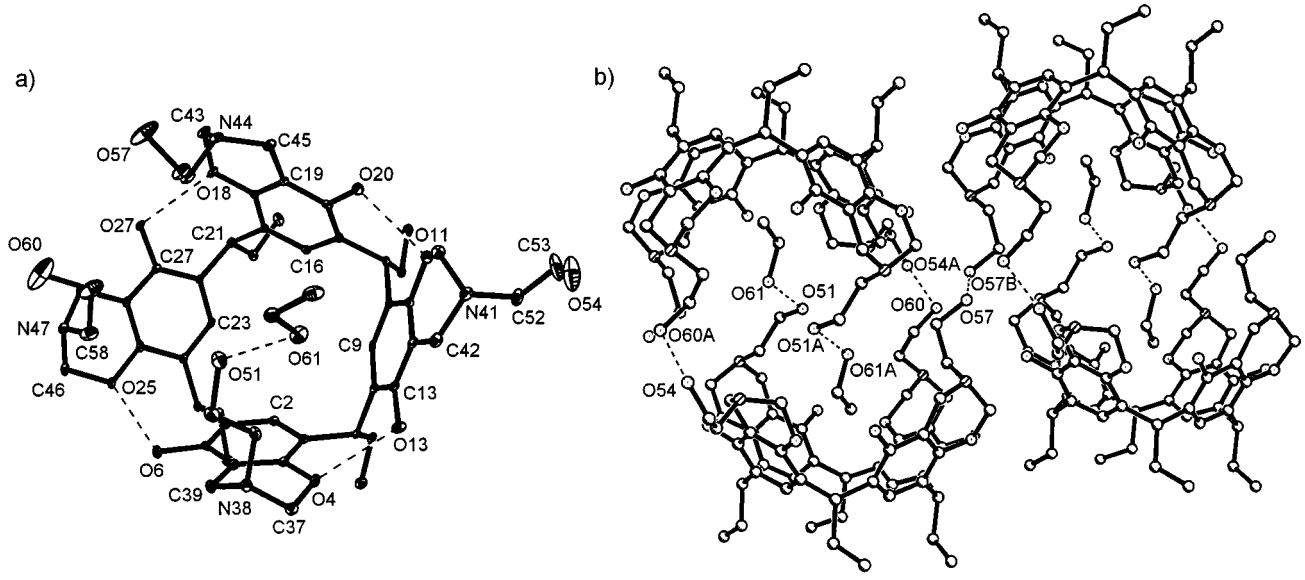

Figure 3. Molecular structure (a) and crystal packing (b) of **2a**·C_2H_5OH·0.5 H_2O. Thermal ellipsoids in a) are drawn at 10% level. The numbering scheme is indicated and hydrogen bonds are marked by dotted lines, while the water molecule and the hydrogen atoms are omitted for clarity

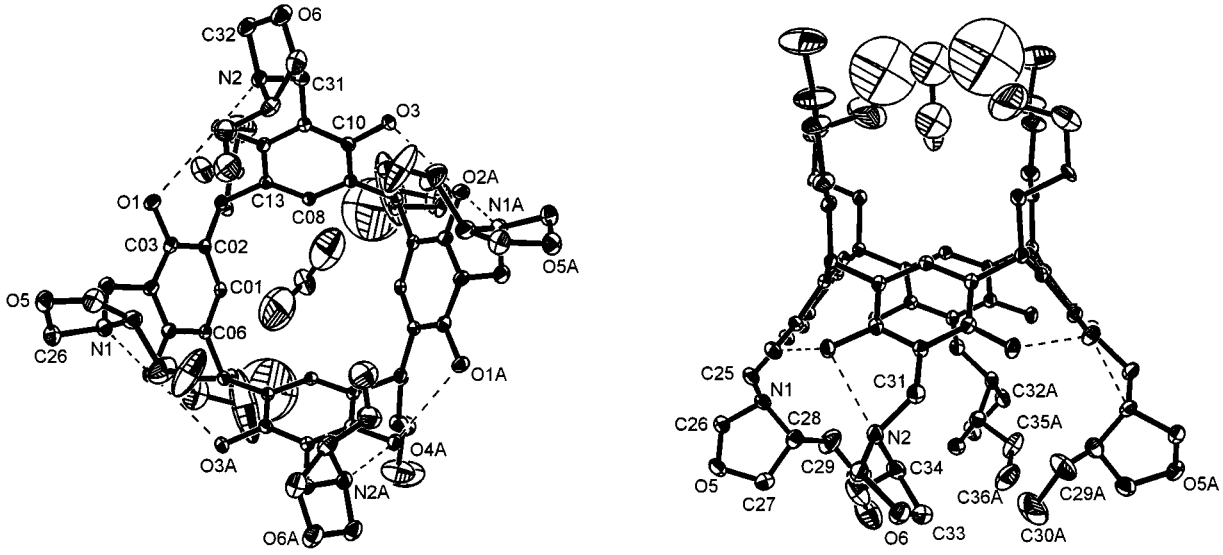

Figure 4. Molecular conformation of **4b**, seen from different directions. Thermal ellipsoids are drawn at the 10% level. The numbering scheme is indicated and hydrogen bonds are marked by dotted lines. The included CH_2Cl_2 is shown only on the left side and the included CH_3CN only on the right side.

The OH···N hydrogen bonds require an orientation of the oxazolidine rings which is roughly perpendicular (105.4 and 118.3°, respectively) to the corresponding resorcinol rings. The oxazolidine oxygens point away from the cavity, while the stereogenic centres are orientated towards the cavity with the axial ethyl groups extending at its periphery. The nearly closed cavity of each resorcarene **4b** is occupied by a molecule of dichloromethane, while a further molecule of acetonitrile is located on the twofold axis and embedded between the four pentyl chains of the resorcarene skeleton.

In the crystal lattice, the molecules of **4b** are arranged around threefold screw axes running along the *c*-axis of the unit cell (Figure 5). This leads to a counter-clockwise helical arrangement (*M*) in which the pentyl chains of the resorcarene point towards and the oxazolidine residues away from the screw axis. Each helix is surrounded by six independent helices with the same directionality. There are two additional threefold screw axes parallel to the c-axis within the unit cell which are symmetry-related by twofold axes. The molecules are also arranged around these screw axes with the same (*M*)-helicity. Here, one of the oxazolidine rings is near the axis and the pentyl chains of the resorcarene are orientated clockwise or counter-clockwise

In summary this means that the given configuration of the oxazolidine rings leads to one direction of the OH···OH···N hydrogen bonds and to one of two possible helical arrangements of the molecules **4b** in the crystal lattice. Of the two helical space groups, the one favoured by the molecule is dependent on its chirality.

Conclusion

The aminomethylation of resorcarene **1** with various amino alcohols in all cases led to the formation of four O/N-acetal rings. Whether the tetrabenzoxazines **2**, the tetraoxazines **3**, or tetraoxazolidines **4** were formed, depended primarily on the structure of the amino alcohol. However, the relative energies of the isomeric products with five- or six-membered rings are obviously rather similar and both structural elements could be observed simultaneously for 2- and 3-amino alcohols. More polar solvents such as DMSO shift the equilibrium towards the more polar benzoxazines **2** in which the aliphatic hydroxyl groups cannot form intramolecular hydrogen bonds. Compounds **3** or **4** with four intramolecular OH···OH···N hydrogen bonds are favoured by less polar solvents such as $CDCl_3$. The molecular structure and conformation assigned on the basis of ^1H and ^{13}C NMR spectra were confirmed for the tetrabenzoxazine **2a** and the tetraoxazolidine **4b** by single-crystal X-ray analysis.

Experimental Section

General Remarks: Resorcarenes **1**[1] were synthesised as described previously. Melting points were determined with a MEL TEMP2 capillary melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Bruker AC200 (200 MHz), Bruker AM400 (400 MHz) and Bruker DRX500 (500 MHz) spectrometers. FD mass spectra were recorded with a Finnigan MAT 90 (5 kV/10 mA/min) and the FAB mass spectra with a Kratos MS 80 with DART data system.

General Procedure for the Synthesis of Compounds 2−4: To a solution of the resorcarene **1** (1.3 mmol), formaldehyde (35%, 1.5 mL, 17.5 mmol) and glacial acetic acid (0.05 mL) in ethanol (10 mL) was added a solution of amino alcohol (5.4 mmol) in ethanol (5 mL). After 24−48 h at room temperature, the precipitate (which formed eventually only after adding some drops of water) was filtered off and recrystallised from chloroform/methanol (**2d−e**, **3** and **4**) or ethanol (**2a−c,f**). The product thus obtained was usually already pure.

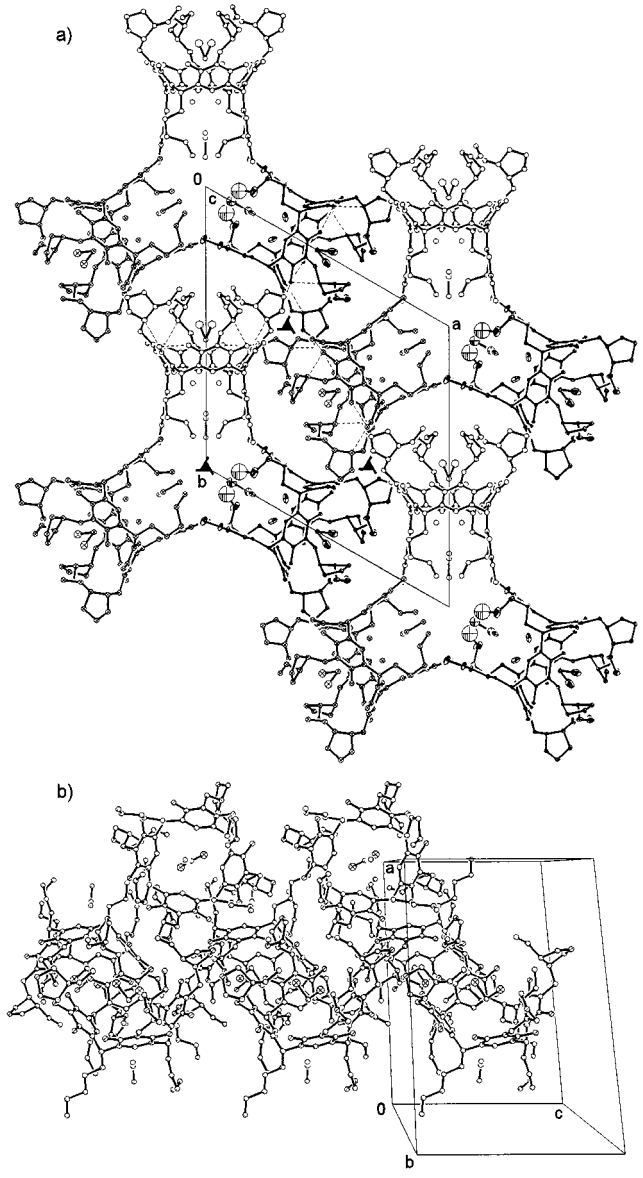

Figure 5. Crystal packing of **4b**: a) The four (*M*)-helices along the c-edges of the unit cell. Molecules at different levels are graphically distinguished (thermal ellipsoids for the lower, cross hatched atoms for the middle and open circles for the higher level). Threefold screw axes are indicated by black triangles. b) Eight molecules of the helix arranged around a threefold screw axis within the unit cell, seen perpendicular to this axis

Tetrabenzoxazine 2a: 0.78 g (64%); m.p. 196 °C. − ^{1}H NMR (500 MHz, [D$_6$]DMSO, 30 °C): δ = 7.67 (s, 4 H, ArOH), 7.32 (s, 4 H, ArH), 4.86 (br d, 4 H, OCH_2N), 4.80 (br d, 4 H, OCH_2N), 4.09 (t, *J* = 6.7 Hz, 4 H, $RCHAr_2$), 3.84 (d, *J* = 17.0 Hz, 4 H, $ArCH_2N$), 3.73 (d, *J* = 17.0 Hz, 4 H, $ArCH_2N$), 3.48 (t, *J* = 6.2 Hz, 8 H, OCH_2R), 2.63 (t, *J* = 6.2 Hz, 8 H, NCH_2R), 2.21 (q, *J* = 7.3 Hz, 8 H, CH_2), 0.82 (t, 7.3 Hz, 12 H, CH_3). − ^{13}C NMR (127 MHz, $CDCl_3$, 30 °C): 149.06, 148.02, 123.53, 123.01, 122.36, 107.73, 83.24, 59.46, 53.56, 46.24, 34.63, 26.16, 12.31; − $C_{52}H_{68}N_4O_{12}·H_2O$: C 64.52, H 7.61, N 5.57 Found C 64.42, H 7.75, N 5.62; MS (FAB/NBA) *m*/*z* 941.0 [M$^+$, 941.1].

Tetrabenzoxazine 2b: 0.89 g (62%); m.p. 172 °C. − ^{1}H NMR (500 MHz, [D$_6$]DMSO, 30 °C): δ = 7.65 (s, 4 H, ArOH), 7.25 (s, 4 H, ArH), 4.84 (br d, 4 H, OCH_2N), 4.78 (br d, 4 H, OCH_2N), 4.19 (t, *J* = 7.2 Hz, 4 H, $RCHAr_2$), 3.83 (d, *J* = 17.0 Hz, 4 H, $ArCH_2N$), 3.73 (d, *J* = 17.0 Hz, 4 H, $ArCH_2N$), 3.48 (t, *J* = 6.2 Hz, 8 H, OCH_2R), 2.63 (t, *J* = 6.0 Hz, 8 H, NCH_2R), 2.13 (m, 8 H, CH_2), 1.20 (m, 24 H, CH_2), 0.84 (t, *J* = 7.0 Hz, 12 H, CH_3); − $C_{52}H_{68}N_4O_{12}·H_2O$: C 69.29, H 8.36, N 5.05 Found C 69.13, H 8.27, N 5.14; MS (FD) *m*/*z* 1109.4 [M$^+$, 1109.5]

Tetrabenzoxazine 2c: 1.37 g (73%); m.p. 138 °C. − ^{1}H NMR (200 MHz, [D$_6$]DMSO, 30 °C): δ = 7.63 (s, 4 H, ArOH), 7.30 (s, 4 H, ArH), 4.83 (s, 8 H, OCH_2N), 4.10 (s, 4 H, $RCHAr_2$), 3.82 (br s, 8 H, $ArCH_2N$), 3.50 (s, 8 H, OCH_2R), 2.64 (s, 8 H, NCH_2R), 2.24 (s, 8 H, CH_2), 1.20 (m, 96 H, CH_2), 0.84 (s, 12 H, CH_3); − $C_{52}H_{68}N_4O_{12}·H_2O$: C 73.09, H 9.76, N 3.87 Found C 73.21, H 9.72, N 3.98; MS (FD) *m*/*z* 1445.9 [M$^+$, 1446.1]

Tetrabenzoxazine 2d: 0.63 g (40%); m.p. 96 °C. − ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ = 7.63 (s, 4 H, ArOH), 7.08 (s, 4 H, ArH), 4.84 (s, 8 H, OCH_2N), 4.14 (t, *J* = 7.6 Hz, 4 H, $RCHAr_2$), 3.90 (d, *J* = 17.3 Hz, 4 H, $ArCH_2N$), 3.71 (d, *J* = 17.3 Hz, 4 H, $ArCH_2N$), 3.50 (t, *J* = 6.0 Hz, 8 H, OCH_2R), 2.60 (m, 8 H, CH_2), 2.10 (m, 8 H, CH_2), 1.30 (m, 24 H, CH_2), 0.84 (t, *J* = 7.1, 12 H, CH_3). − ^{13}C NMR (127 MHz, $CDCl_3$, 30 °C): δ = 152.01, 149.65, 124.34, 123.63, 121.19, 108.18, 82.90, 62.43, 51.31, 45.95, 33.56, 33.05, 32.07, 31.35, 24.86, 22.64, 14.09; MS (FD) *m*/*z* 1222.4 [M$^+$, 1221.7].

Tetrabenzoxazine 2e: 1.18 g (69%); m.p. 78 °C. − ^{1}H NMR (200 MHz, $CDCl_3$, 30 °C): δ = 7.74 (s, 4 H, ArOH), 7.06 (s, 4 H, ArH), 4.88 (s, 8 H, OCH_2N), 4.18 (br t, 4 H, $RCHAr_2$), 3.94 (d, *J* = 17.3 Hz, 4 H, $ArCH_2N$), 3.73 (d, *J* = 17.3 Hz, 4 H, $ArCH_2N$), 3.55 (t, *J* = 6.1 Hz, 8 H, OCH_2R), 2.57 (m, 8 H, CH_2), 2.15 (s, 8 H, CH_2), 1.49 (br s, 8 H, CH_2), 1.24 (br s, 96 H, CH_2), 0.86 (br s, 24 H, CH_3); − $C_{104}H_{172}N_4O_{12}$: C 74.78, H 10.38, N 3.35 Found C 74.91, H 10.34 N 3.26; MS (FD) *m*/*z* 1670.9 [M$^+$, 1670.5].

Tetrabenzoxazine 2f: 0.52 g (34%); m.p. 134 °C. − ^{1}H NMR (200 MHz, [D$_6$]DMSO, 30 °C): δ = 7.67 (s, 4 H, ArOH), 7.30 (s, 4 H, ArH), 4.89 (s, 8 H, OCH_2N), 4.08 (s, 4 H, $RCHAr_2$), 3.81 (br s, 8 H, $ArCH_2N$), 3.76 (s, 8 H, $OCHR_2$), 2.69 (s, 8 H, NCH_2R), 2.21 (s, 8 H, CH_2), 1.30 (br s, 24 H, CH_2), 1.19 (s, 12 H, CH_3), 0.87 (s, 12 H, CH_3); − $C_{52}H_{68}N_4O_{12}·H_2O$: C 70.07, H 8.65, N 4.81 Found C 70.14, H 8.54, N 4.72; MS (FD) *m*/*z* 1165.3 [M$^+$, 1165.6]

Tetraoxazine 3: 0.84 g (56%); m.p. 147 °C. − ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C): δ = 8.81 (br s, 8 H, ArOH), 7.11 (s, 4 H, ArH), 4.24 (t, *J* = 7.9 Hz, 4 H, $RCHAr_2$), 4.21 (s, 8 H, OCH_2N), 3.91 (s, 8 H, $ArCH_2N$), 3.78 (s, 8 H, RCH_2O), 2.81 (s, 8 H, RCH_2N), 2.16 (s, 8 H, CH_2), 1.72 (s, 8 H, CH_2), 1.40−1.20 (m, 24 H, CH_2), 0.87 (t, *J* = 6.3 Hz, 12 H, CH_3). − ^{13}C NMR (127 MHz, $CDCl_3$, 30 °C): δ = 151.08, 124.14, 122.28, 107.29, 83.99, 67.61, 49.68, 49.02, 33.58, 33.41, 32.02, 27.86, 22.89, 22.71, 14.13.

Tetraoxazolidine 4a: 0.62 g (41%); m.p. 130 °C; $[\alpha]_D^{20}$ = −10.23. − ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ = 9.04 (br s, 4 H, ArOH), 7.18 (s, 4 H, ArH), 4.43 (d, *J* = 5.2 Hz, 4 H, OCH_2N), 4.35−4.25 (m, 8 H, OCH_2N + $RCHAr_2$), 4.11 (t, *J* = 7.7 Hz, 4 H, RCH_2O), 4.02 (d, *J* = 14.7 Hz, 4 H, $ArCH_2N$), 3.91 (d, *J* = 14.6 Hz, 4 H, $ArCH_2N$), 3.40 (dd, *J* = 8.1 Hz, *J* = 5.7 Hz, 4 H, RCH_2O), 3.10 (m, 4 H, $NCHR_2$), 2.20 (s, 8 H, CH_2), 1.41−1.28 (m, 24 H, CH_2), 1.14 (d, *J* = 6.5 Hz, 12 H, CH_3), 0.91 (t, *J* = 7.1 Hz, 12 H, CH_3). − ^{13}C NMR (127 MHz, $CDCl_3$, 30 °C): δ = 150.95, 123.74, 122.30, 108.34, 85.32, 71.41, 58.23, 50.88, 33.54, 33.25, 31.87, 27.75, 22.64, 17.82, 14.05. − ^{13}C NMR (127 MHz, $CDCl_3$, −30 °C): δ = 150.35, 149.70, 124.19, 123.52, 121.94, 108.09, 84.94, 84.72, 70.83, 58.16, 57.68, 51.51, 50.97, 33.06, 31.90, 27.78, 22.67, 18.27, 14.22.

Tetraoxazolidine 4b: 1.17 g (74%); m.p. 133 °C; $[\alpha]_D^{20} = 5.79$. − ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ = 7.16 (s, 4 H, ArH), 4.35−4.25 (m, 12 H, OCH_2N and $RCHAr_2$), 4.12 (t, J = 7.7 Hz, 4 H, RCH_2O), 3.97 (br s, 8 H, $ArCH_2N$), 3.48 (dd, J = 8.1 Hz, J = 5.9 Hz, 4 H, RCH_2O), 2.94 (br s, 4 H, $NCHR_2$), 2.18 (s, 8 H, CH_2), 1.64 (m, 4 H, CH_2), 1.45 (m, 4 H, CH_2), 1.40−1.28 (m, 24 H, CH_2), 0.89 (t, J = 7.6 Hz, 12 H, CH_3). − ^{13}C NMR (127 MHz, $CDCl_3$, 55 °C): δ = 151.31, 150.93, 124.50, 124.23, 122.57, 108.85, 85.65, 69.94, 65.35, 51.83, 33.80, 33.46, 31.95, 27.84, 25.71, 22.70, 14.01, 10.50. − ^{13}C NMR (127 MHz, $CDCl_3$, −60 °C): δ = 151.53, 151.34, 149.68, 149.63, 124.30, 124.21, 123.56, 123.31, 121.64, 108.46, 108.19, 84.65, 84.53, 69.31, 64.67, 64.42, 52.35, 51.86, 33.04, 32.06, 31.96, 27.97, 27.85, 26.12, 25.73, 22.85, 22.82, 14.40, 10.77, 10.70; − $C_{72}H_{108}N_4O_{12}$: C 70.79, H 8.91, N 4.59 Found C 70.61, H 8.86, N 4.61.

Tetraoxazolidine 4c: 0.84 g (51%); m.p. 145 °C; $[\alpha]_D^{20} = -11.32$. − ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ = 7.17 (s, 4 H, ArH), 4.30 (t, J = 7.8 Hz, 4 H, $RCHAr_2$), 4.26 (d, J = 5.6 Hz, 4 H, OCH_2N), 4.21 (br d, 4 H, OCH_2N), 4.08 (dd, J = 8.3 Hz, J = 7.5 Hz, 4 H, RCH_2O), 3.86 (br s, 8 H, $ArCH_2N$), 3.56 (dd, J = 8.4 Hz, J = 6.5 Hz, 4 H, RCH_2O), 2.76 (q, J = 6.9 Hz, 4 H, $NCHR_2$), 2.18 (s, 8 H, CH_2), 1.76 (m, J 6.8, 4 H, CHR_3), 1.42−1.29 (m, 24 H, CH_2), 0.97 (d, J = 6.7 Hz, 12 H, CH_3), 0.91 (t, J = 6.3 Hz, 24 H, CH_3). − ^{13}C NMR (127 MHz, $CDCl_3$, 30 °C): δ = 151.07, 124.24, 124.00, 122.31, 108.64, 85.75, 70.28, 68.00, 52.98, 33.62, 33.29, 31.93, 30.57, 27.79, 22.70, 19.87, 18.50, 14.09. − ^{13}C NMR (127 MHz, $CDCl_3$, −30 °C): δ = 151.63, 151.52, 149.93, 149.82, 124.36, 124.27, 123.49, 123.40, 121.93, 121.83, 108.77, 108.58, 85.25, 84.93, 70.06, 69.84, 53.42, 33.19, 33.06, 33.01, 31.91, 30.76, 30.50, 27.83, 27.77, 22.73, 19.91, 18.50, 18.29, 14.28; MS (FD) *m*/*z* 1278.7 [M^+, 1277.8].

Tetraoxazolidine 4d: 1.00 g (58%); m.p. 137 °C; $[\alpha]_D^{20} = 2.69$. − ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ = 8.84 (br s, 8 H, ArOH), 7.15 (s, 4 H, ArH), 4.29 (m, 12 H, NCH_2O and $RCHAr_2$), 4.14 (t, J = 7.2 Hz, 4 H, RCH_2O), 3.99 (br s, 4 H, $ArCH_2N$), 3.87 (br s, 4 H, $ArCH_2N$), 3.41 (br s, 4 H, RCH_2O), 3.07 (s, 4 H, $NCHR_2$), 2.15 (m, 8 H, CH_2), 1.54 (m, 8 H, CH_2), 1.40−1.20 (m, 32 H, CH_2), 0.90 (t, J = 7.1 Hz, 12 H, CH_3), 0.83 (d, J = 6.2 Hz, 12 H, CH_3), 0.79 (d, J = 6.2 Hz, 12 H, CH_3). − ^{13}C NMR (127 MHz, $CDCl_3$, 55 °C): δ = 151.57, 150.61, 124.67, 124.16, 122.50, 109.10, 85.47, 70.60, 62.02, 51.72, 42.60, 33.81, 33.59, 32.09, 27.93, 25.48, 22.70, 22.58, 14.04. − ^{13}C NMR (127 MHz, $CDCl_3$, −60 °C): δ = 151.27, 149.56, 124.38, 123.57, 121.59, 108.82, 84.45, 69.89, 60.84, 58.29, 51.99, 42.39, 33.13, 32.15, 28.09, 24.73, 22.90, 22.82, 21.95, 18.18, 14.38; MS (FD) *m*/*z* 1333.6 [M^+, 1333.9].

Tetraoxazolidine 4e: 0.51 g (37%); m.p. 180 °C (dec.). − ^{1}H NMR (500 MHz, $CDCl_3$, 30 °C): δ = 7.13 (s, 4 H, ArH), 4.35 (s, 8 H, NCH_2O), 4.19 (t, J = 7.6 Hz, 4 H, $RCHAr_2$), 3.91 (s, 8 H, $ArCH_2N$), 3.76 (s, 8 H, OCH_2R), 2.22 (t, 8 H, 7.1 Hz, CH_2), 1.23 (s, 24 H, CH_3), 0.93 (t, J = 7.1 Hz, 12 H, CH_3). − ^{13}C NMR (127 MHz, $CDCl_3$, 30 °C): δ = 151.52, 124.49, 122.64, 108.72, 85.81, 79.46, 60.71, 43.91, 35.96, 27.26, 22.07, 13.27; − $C_{60}H_{84}N_4O_{12}$: C 68.42, H 8.04, N 5.32 Found C 68.53, H 8.13, N 5.24; MS (FD) *m*/*z* 1053.2 [M^+, 1053.4].

X-ray Crystallographic Study: Crystallisation of **2a** from acetonitrile/ethanol gave single crystals suitable for X-ray analysis. The data were collected with an Enraf−Nonius CAD4 diffractometer using graphite monochromated Mo-K_α radiation [λ(Mo-K_α) = 0.71073] at −93 °C. *Lp* correction was performed, but no absorption correction was done. The structure was solved by direct methods (SHELXS86) and refined on F^2 (SHELXL97)[11] using WinGX[12] as an integrated system, in which solution and refinement programmes are available. The hydrogen atoms were calculated to their idealised positions with isotropic temperature factors (1.2 or 1.5 times the C temperature factors) and were refined as riding atoms.

Crystals of compound **4b** were obtained by crystallisation from CH_2Cl_2:CH_3CN (2:1). A crystal of dimensions 0.64 × 0.25 × 0.2 mm^3 was sealed in a Lindemann-glass capillary. Measurements were performed by a Bruker AXS computer-controlled four-circle diffractometer, equipped with a CCD area-detector. The intensities were measured on the same apparatus: Mo-K_α radiation (X-ray generator with a rotating anode: 0.5 × 5 mm^2 focus, 50 kV, 120 mA). The structure was solved (direct methods) and refined (full-matrix, refinement on F^2, weighting with a function according to the counting statistics) using the programmes of G. M. Sheldrick. Full crystallographic details and tables of coordinates, temperature factors and bond lengths and angles are given for both compounds in the supporting information.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-144173 and CCDC-144174. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) +44−1223/336−033; E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgments

This work was supported by the Deutsche Forschungsgemeinschaft and the Academy of Finland. We are grateful to Mr. Reijo Kauppinen (Jyväskylä) for help with NMR spectroscopy and Prof. Jouni Pursiainen (Oulu) for the help with MS spectroscopy.

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Received May 12, 2000
[O00236]