Derivatisation of Pyrogallarenes

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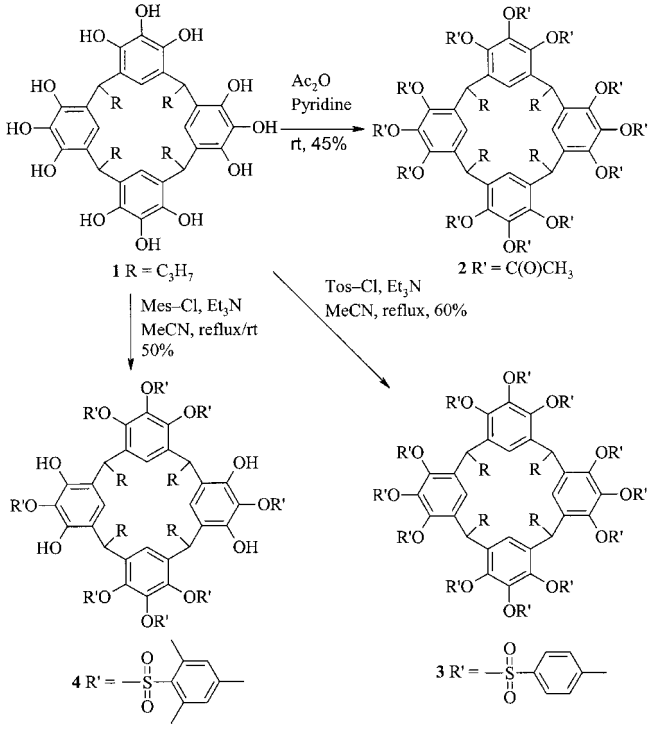
Derivatisation of upper-rim hydroxy groups of pyrogallarenes produced completely acylated and tosylated pyrogallarene derivatives. Mesitylation of pyrogallarene, however, resulted in a regioselective derivatisation of hydroxy groups, i.e. eight OH groups out of 12 were mesitylated. Crystal structures of the synthesised pyrogallarene derivatives indicate that completely substituted pyrogallarenes exist in a distorted crown conformation despite of the lack of stabilising intramolecular hydrogen bonds. In contrast, the partially substituted pyrogallarene adopts a boat conformation and has an open cavity for the inclusion of small guest molecules.

Introduction

Pyrogallarenes such as **1** (Scheme 1) are easily prepared in reasonable yields by acid-catalyzed condensation of pyrogallol with various aldehydes.[1,2] Usually, the synthesis exclusively results in tetrameric bowl-shaped all-*cis* isomers (r-*ccc*), although the tetrameric r-*ctt* (chair conformation) isomer[1] and an example of a cyclic (r-*tctct*) hexamer[2] are also known. Pyrogallarenes and their derivatives have been used for the construction of self-assembled structures like dimeric[2–4] and hexameric[5,6] capsules, as liquid-crystals,[7,8] as potential anti-HIV drugs[9] and in complexation studies.[10,11]

Pyrogallarenes are very similar compounds to resorcinarenes[12] the only difference being an additional hydroxy groups in each 2-position of the aromatic rings, i.e. in between the upper-rim hydroxy groups. Complete[13–19] and regioselective[20–29] derivatisation of hydroxy groups of resorcinarenes are well-studied reactions useful for a selective partial protection of the OH groups.[23] The products are also excellent building blocks for supramolecular assemblies such as capsules and open inclusion complexes.[25] Derivatisation of pyrogallarenes has been studied much less intensively and only one regioselective[30] and a few fully substituted derivatives are known.[7–9,31,32]

In the regioselective tetrasulfonation of resorcinarenes the product formed is usually a complex with Et_3NH^+,[21,23,24] when Et_3N is used as the base promoting the acylation reaction. The regioselectivity of the reaction depends highly on the solvent, which must be acetonitrile or a mixture of acetonitrile with other co-solvents. Also the fast addition of the acid and arylsulfonyl chlorides with vigorous stirring of the reaction mixture is crucial for the purity of the products. The role of the base and the formation of resorcinarene–$Et_3NH^+Cl^-$ complex during the reaction are clearly crucial for the regioselectivity.[23] However, the definite reason for the regioselectivity is still unknown.



Scheme 1. Complete and partial acylation of pyrogallarene **1**.

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Pyrogallarenes are interesting molecules because of their numerous sites for further modifications and the difference in synthetic properties brought by the extra hydroxyl groups at 2-position compared to ordinary resorcinarenes. We started to modify pyrogallarenes by various acylation reactions to see how the additional hydroxy groups affect the course of the synthesis and the nature of the product compared to resorcinarenes. Also, it is interesting to examine potential reactivity differences between the 1,3- and the 2-hydroxy groups of the pyrogallarene scaffold. The aim of the present work was to design, synthesise, and study new pyrogallarene-based receptor molecules suitable for the complexation studies and starting materials for the synthesis of larger host molecules. Herein, we report the synthesis and identification of completely acylated and tosylated pyrogallarenes **2** and **3** and their crystal structures. Also, we have found conditions for the regioselective octasulfonation of pyrogallarene by mesitylenesulfonyl chloride resulting in octasubstituted pyrogallarene **4**.

Results and Discussion

Synthesis and NMR Investigations

The reaction of pyrogallarene **1** with an excess of acetic anhydride gave completely acetylated pyrogallarene **2** in 45% yield (Scheme 1). The reaction was done in pyridine, which acts both as a base and as a solvent. Completely acetylated pyrogallarene **2** can also be synthesised in a tetrahydrofurane (THF)/acetonitrile (MeCN) mixture (3:1, v/v) using acetyl chloride and Et_3N (50% yield).

The ^1H NMR spectrum of **2** in $CDCl_3$ at room temperature exhibits one set of signals for the alkyl chains, two sharp singlets for acetyl groups in the expected 2:1 ratio, a triplet for the methine bridge and one broad singlet for the protons of the four pyrogallol rings indicating a C_{4v} symmetry. The ESI-FTICR mass spectrum shows a major peak at 1247.29 Da corresponding to the $[M + Na]^+$ adduct of **2**.

Regioselective acylation of **1** with acetyl chloride was also studied by varying the solvent mixture (THF/MeCN, 5:1 and 7.5:1, v/v) and the amount of the reagents (4 and 8 equiv.). These reactions gave inseparable mixture of products. NMR, ESI-TOF mass spectrometric studies and TLC analysis showed that mixture of crude products contained several partially acetylated pyrogallarenes. In the case of resorcinarenes, no regioselective reaction takes place with acetyl chloride and acetic anhydride and only the formation of completely acylated product is observed.[23]

Completely tosylated pyrogallarene **3** was synthesised successfully from pyrogallarene **1** (1 equiv. **1**, 18 equiv. TosCl and 18 equiv. Et_3N) in 60% yield (Scheme 1). The ^1H NMR spectrum of **3** in $CDCl_3$ at room temperature again exhibits one set of signals for the alkyl chains, a triplet for the methine bridges, two sets of signals for the tosyl groups (one for the 2-position and the other for the 1- and 3-positions of the pyrogallol ring), and one singlet for the aromatic protons of the pyrogallarene ring indicating again C_{4v} symmetry. The signals of the tosyl groups in the 2-positions are shifted upfield by 0.36 ppm (methyl groups) and 0.96 and 0.39 ppm (aromatic protons), which indicates that they are slightly bent towards the cavity and feel the anisotropy of the aromatic rings surrounding it. The ESI-TOF mass spectrum showed a major peak at 2593.27 Da corresponding to the sodium adduct of **3**.

Reducing the amount of reagents gave a mixture of partially substituted products, which were investigated preliminarily by ^1H NMR spectroscopy and mass spectrometry. An interesting feature was observed in the mass spectra, where partially tosylated pyrogallarenes formed 1:1 adducts with Et_3NH^+, whereas the completely tosylated pyrogallarene gave only sodium and potassium adducts. An isolation of individual products in pure form has not been achieved so far.

Partially substituted pyrogallarene **4** was synthesised in 50% yield. The addition of Et_3N (18 equiv.) to a solution of pyrogallarene **1** in MeCN yielded a white precipitate. After the addition of mesitylenesulfonyl chloride (18 equiv.), the reaction mixture became homogeneous and after a while a white precipitate, which could be assigned to compound **4**, formed (Scheme 1). The ^1H NMR spectrum of the crude product contained a trace of $Et_3NH^+Cl^-$ and the ESI-TOF mass spectrum showed a major peak for the Et_3NH^+ adduct of **4**. After recrystallisation, the ^1H NMR spectrum was free of signals for the Et_3NH^+ salt and the ESI-TOF mass spectrum gave rise to major signals at 2201.77 and 2217.78 Da corresponding to the sodium and potassium adducts of **4**.

The ^1H NMR spectrum (Figure 1) of compound **4** was measured in $[D_6]$DMSO at 393 K because the proton signals of the pyrogallol rings were broad at lower temperatures and, thus, no 2D proton–carbon correlation spectra could be obtained. Increasing the temperature also sharpened the signal of the doublet of doublets corresponding to the methine protons. The splitting of the doublet is due to the coupling with the diastereotopic protons of the neighbouring methylene groups that appear in turn as two well-separated multiplets. Also, the protons of the methylene groups more remote from the methine carbon atoms appear as two well-separated multiplets. In addition, the spectrum of **4** contains six singlets (in a 4:2:2:1:1:2 ratio) for the methyl groups of the mesitylene groups, three singlets for the aromatic protons of the mesitylene groups, one singlet for the free OH groups, and two singlets for the aromatic protons of the pyrogallol rings. This spectrum is in line with isomer **4** as shown in Scheme 1 and indicates a C_{2v}-symmetric conformation. Increasing the temperature to 423 K sharpened signals even more, but the compound started to decompose at this temperature.

The ^1H NMR spectrum of compound **4** in $CDCl_3$ at 333 K (Figure 2, top trace) is very similar to corresponding spectra in $[D_6]$DMSO at 393 K. The protons at the 5-positions of the pyrogallol rings give rise to two broad singlets ($\Delta\delta$ = 0.64 ppm) which again indicate the boat conformation of the pyrogallarene to be realised. Reducing the temperature to 223 K results in the splitting of all signals into

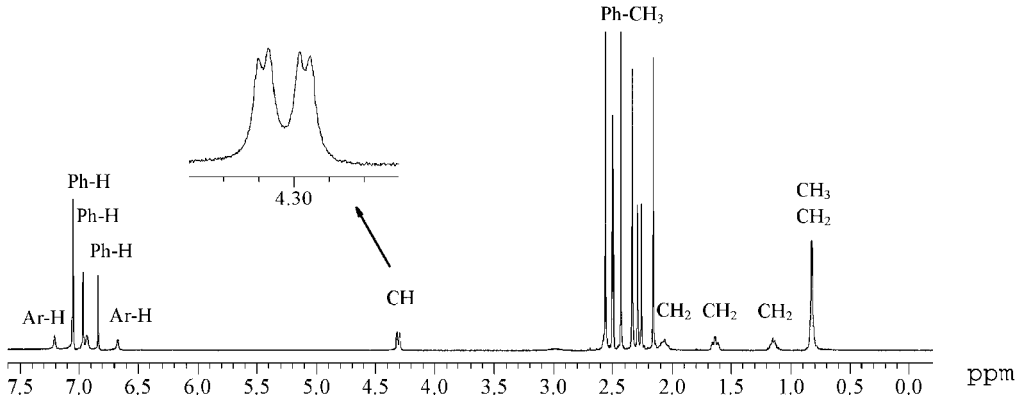


Figure 1. ^{1}H NMR spectra of **4** in [D$_6$]DMSO at 393K. Two singlets for the aromatic protons of pyrogallol rings indicate a C_{2v}-symmetric conformation. The doublet of doublets corresponding to the methine protons of the bridges is also clearly separated.

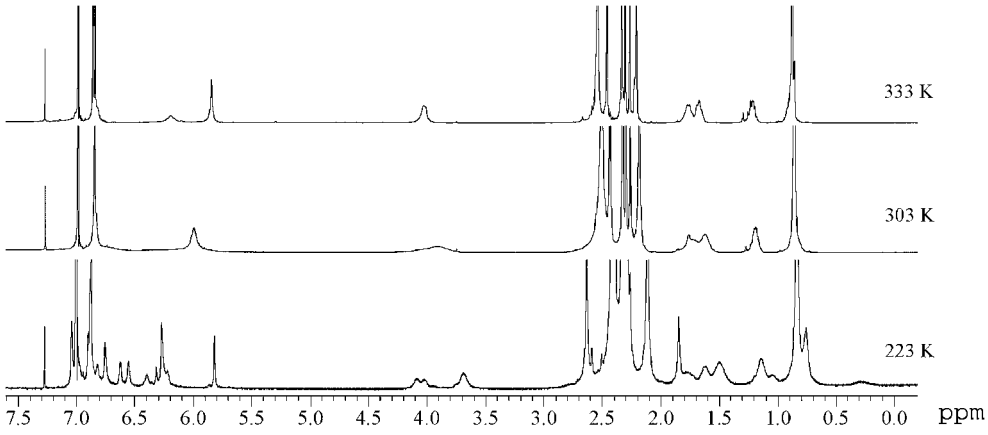


Figure 2. ^{1}H NMR spectra of **4** in $CDCl_3$ at 223, 303, and 333 K. The appearance of several sets of signals at 223 K indicates interconversion between different orientations of the sulfonyl groups.

several sets (Figure 2, bottom trace) and thus indicates the existence of an interconversion of different orientations of sulfonyl groups which becomes slow on the NMR timescale at that temperature.

The regioselective substitution of pyrogallarenes is an interesting phenomenon. In octasulfonylated pyrogallarene **4** opposite pyrogallol units are pairwise identical; in the first pair, all six hydroxy groups are sulfonylated and in the second pair, the two hydroxy groups in the 2-positions are substituted while the four hydroxy groups in the 1- and 3-positions remain unchanged. Furthermore, the partially substituted product was formed despite of the use of an excess of sulfonating reagent.

Since the only difference between the tosyl and mesitylsulfonyl groups is the presence of two additional methyl groups in the latter substituent, there are two potential rationalisations for the findings discussed above: The first one invokes the precipitation of the octasulfonylated product which prohibits further substitution. However, since **4** is also formed as the major product, when the synthesis is carried out in a larger amount of solvent where no precipitation is observed, this reason appears to be unlikely. Perhaps more convincingly, the second explanation is based on the steric demand of the mesityl sulfonyl groups which blocks the access to the last four phenolic oxygen atoms due to the presence of the additional methyl groups.

X-ray Crystal Structures

In the solid state dodecaacetylated pyrogallarene **2** and dodecatosylated pyrogallarene **3** assume distorted crown conformations (Figures 3 and 4) although there are no possibilities for intramolecular hydrogen bonds, which are usually required to stabilise the crown conformation. The distortion of the crown conformation is described by the dihedral angles between opposite pyrogallol rings, which are 14.9° and 137.0° for **2** and 46.9° and 134.1° for **3**, and the respective distances between opposing ring centers, 5.46 and 7.81 Å for **2** and 6.12 Å and 7.69 Å for **3**. In a typical, nearly symmetrical crown conformation the respective values are 68–71° and 6.7–6.9 Å[33].

The molecules of acetylated pyrogallarene **2** form self-included dimeric assemblies, where one of the acetyl methyl groups of both pyrogallarenes is situated in the cavity of another pyrogallarene by C–H···π interactions (Figure 3). The reason why the conformation of the core pyrogallarene is closer to a crown than a boat conformation is probably

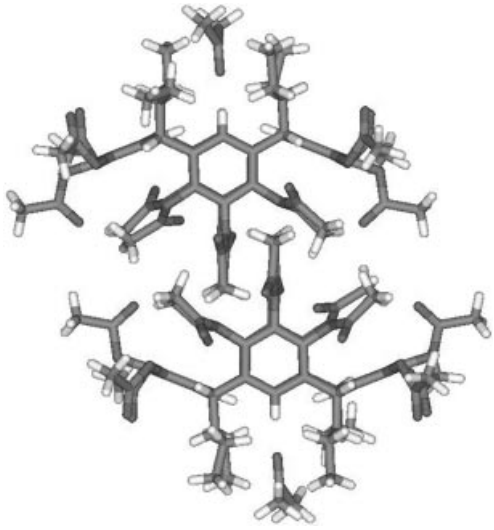


Figure 3. X-ray crystal structure of completely acetylated pyrogallarene **2** forming self-assembled dimers. Acetone molecules are included between the lower-rim alkyl chains.

the self-inclusion and the weak interactions causing the inclusion, which simultaneously stabilise the crown-like conformation. In the case of **3**, neither self-inclusion nor inclusion of any guest molecule is observed since the tosyl groups attached to the 2-positions are pointing towards the cavity, thus filling it completely (Figure 4). This is also the reason for a less pinched crown conformation: bulky substituents require more space in the cavity.

Both crystal structures contain molecules of solvent acetone, which fill the interstice in the crystal. In both cases one of the acetone molecules is located between the four hydrophobic alkyl chains of the lower rim of the pyrogallarene. Similar findings of the location of solvent or anion at the lower rim have been reported earlier for numerous resorcinarene crystal structures.[34–37] The carbonyl oxygen atom of the acetone is pointing towards the interior of the alkyl chain cage and is connected to alkyl chains and the hydrogen atoms in 5-position of the aromatic ring via C–H···O hydrogen bonds of lengths between 3.50 and 4.10 Å.

The octasulfonylated pyrogallarene **4** crystallises in a boat conformation (Figure 5) although the compound has four unsubstituted hydroxy groups capable of forming hydrogen bonds. The pyrogallol rings containing two unsubstituted hydroxy groups are parallel (0.0° dihedral angle and 4.93 Å centroid–centroid distance) while completely sulfonylated rings are nearly coplanar and bent towards the lower rim of the pyrogallarene core (220.7° dihedral angle between the pyrogallol rings). The boat conformation is probably due to the bulkiness of the mesitylene substituens which force the free hydroxy groups into a position too far away from the adjacent pyrogallol oxygen atoms for hydrogen bonding. Instead, two intramolecular hydrogen bonds are formed to sulfonyl oxygen atoms [S=O···O distance 2.840(5) Å].

In contrast to the structures of **2** and **3**, the pyrogallarene **4** has an open cavity for inclusion of small guest molecules. The cavity of **4** indeed contains two THF molecules, which

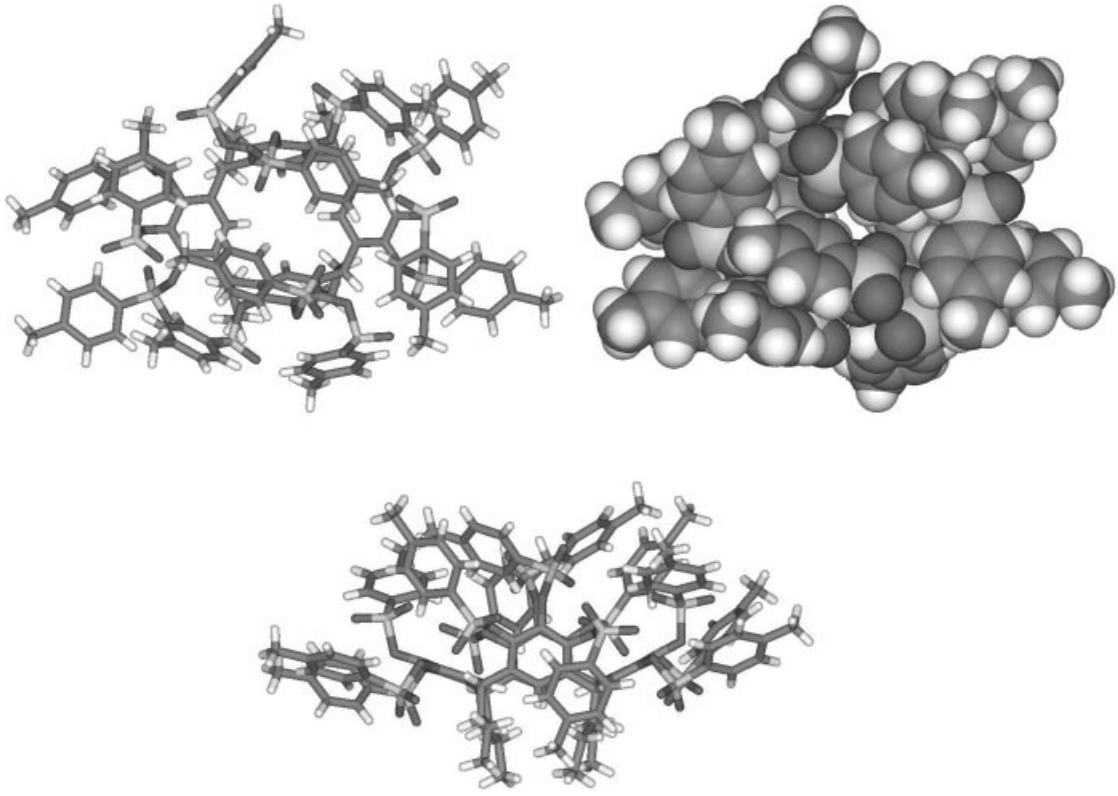


Figure 4. Side (bottom) and top (left) views of the X-ray crystal structure of fully tosylated pyrogallarene **3**. The top view is also shown as a VDW presentation (right) showing the blocked cavity. For clarity, the acetone molecules are omitted.

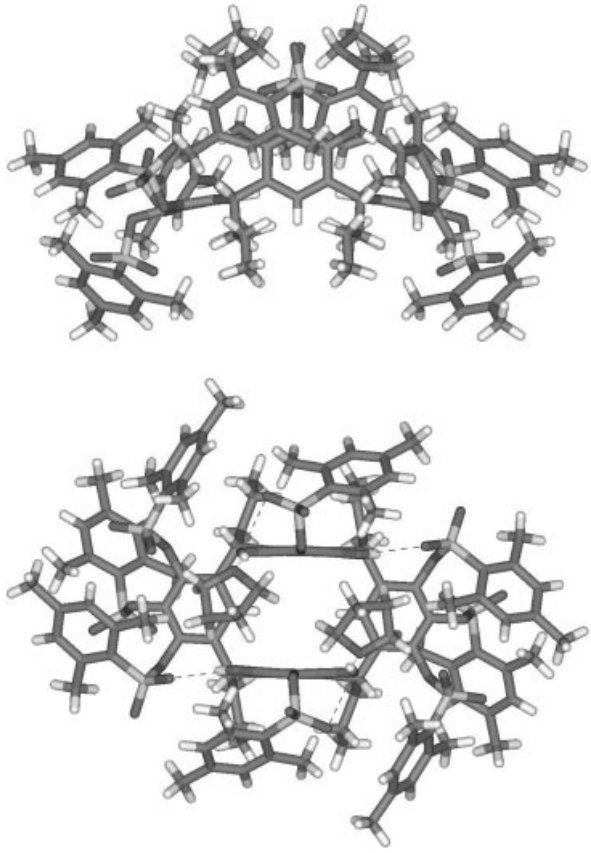


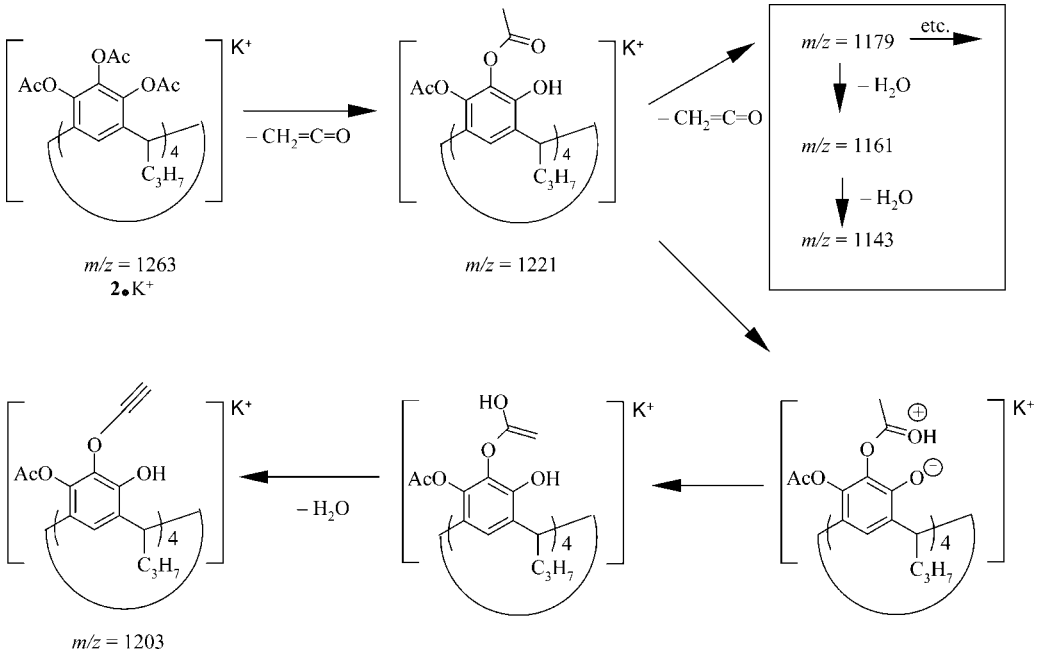
Figure 5. X-ray crystal structure of partially substituted pyrogallarene **4**. Side view (top) and top view (bottom).

are hydrogen-bonded to two of the unsubstituted hydroxy groups of pyrogallarene [O···O distance 2.712(5) Å]. Other THF molecules fill the interstice in the crystal lattice and one disordered THF molecule is included between the lower-rim alkyl chains of **4** like the acetone molecules in the structures of **2** and **3**, with the electronegative oxygen atom pointing towards the cavity.

FT-ICR Mass Spectrometric Analysis and Fragmentation Pattern

All compounds under study here can easily be ionised and transferred intact into the gas phase by electrospray ionisation (ESI). The ESI source was coupled to a Fourier-transform ion-cyclotron-resonance (FT-ICR) mass spectrometer. The exact masses of the sodium and potassium adducts match those calculated within ca. 10 ppm and the isotope patterns obtained by experiment agree well with those simulated on the basis of natural abundances. Although methanol was used as the spray solvent, signals for the protonated compounds were hardly observed. All mass spectra are very clean and do not indicate the presence of major impurities in the samples. For an investigation of the fragmentation behaviour in the gas phase, a small amount of KCl was added to the sample solutions in order to increase the intensity of the potassium adduct.

Upon activation of mass-selected, monoisotopic **2**·K^+ by collisions with argon (collision-induced decay, CID; Figure 6, top trace), the parent ion showed a series of up to eight losses of ketene, CH_2=C=O, which can be traced back to 1,2-elimination reactions within the acetyl groups (Scheme 2). After the first ketene loss, a consecutive loss of a water molecule (Δm = 18.015 Da) is observed. Such water losses are also observed from fragment ions stemming from consecutive ketene losses throughout the series. It is unlikely that the expulsion of water involves the phenolic OH group formed during the 1,2-elimination of ketene, because the C–O bond to the aromatic ring is rather strong and



Scheme 2. Fragmentation mechanisms of mass-selected **2**·K^+. All reactions are exemplarily shown for one of the four pyrogallol rings in the pyrogallarene ion. They can occur at only one of these rings or consecutively at others as well.

because there is no second hydrogen atom available in the phenol intermediate. Therefore, we suggest the mechanism in Scheme 2 to rationalise the water losses. It invokes an enolisation step within the acetyl group adjacent to the free phenolic OH group followed by the 1,2-elimination of water yielding an ethynyl ether moiety. Since no water loss is observed from the parent ion, the free phenolic OH group is likely involved in this reaction as indicated in Scheme 2.

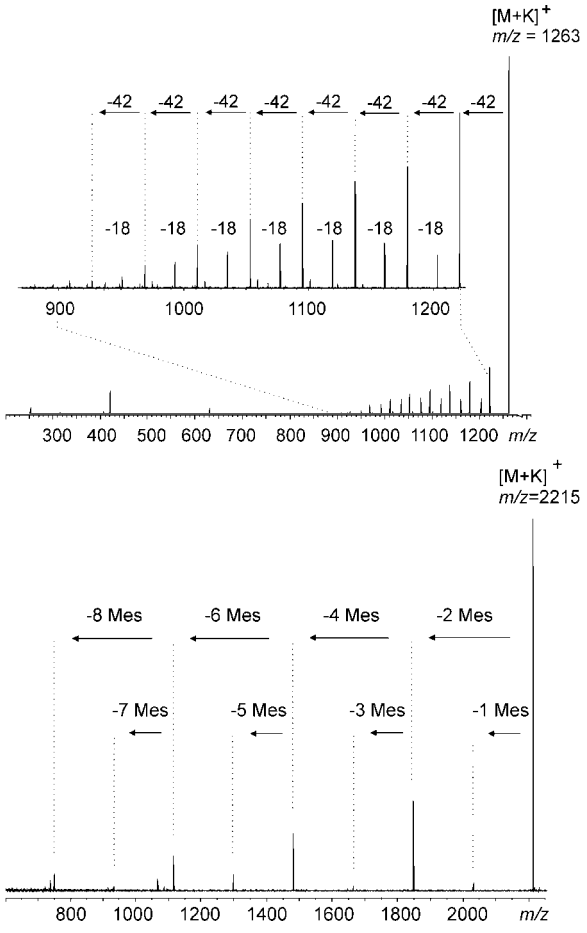


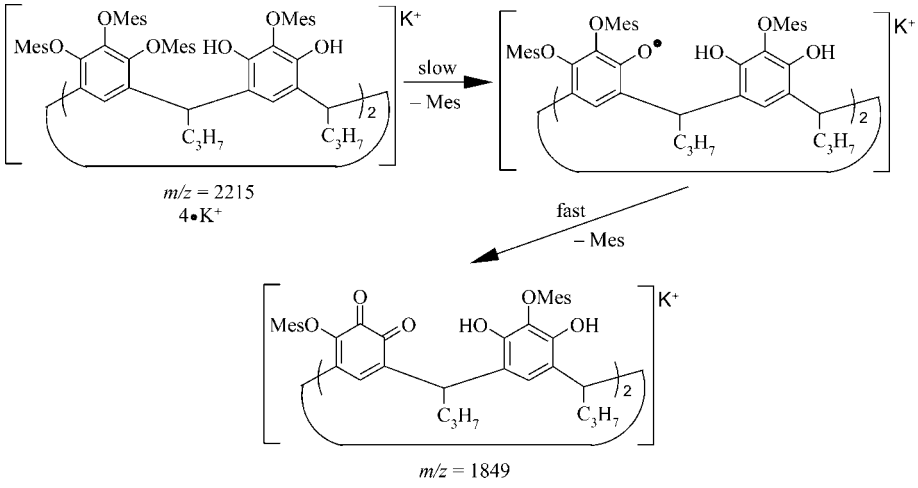
Figure 6. Collision-induced decay (CID) mass spectra of mass-selected **2**·K^+ (top) and **4**·K^+ (bottom). Fragmentations are induced by collisions with Ar as the collision gas.

The K^+ adduct of the octasulfonylated pyrogallarene **4**·K^+ reveals a completely different fragmentation pattern due to the absence of hydrogen atoms in the α-position relative to the sulfonyl group (Figure 6, bottom trace). The first intense fragment corresponds to the loss of two mesitylsulfonyl substituents, while the expulsion of only one of them occurs only with low abundance. Rather than invoking the formation of a covalent bond between the two neutral sulfonyl fragments, this fragmentation behaviour can be attributed to the mechanism shown in Scheme 3. Loss of the first mesitylsulfonyl group leads to an oxygen-centered radical which induces the loss of a second substituent. The second step in this process is energetically favourable, because a quinoidal system can be formed, in which all electrons are paired again. Consequently, the first step is likely rather slow compared to the second one so that the intermediate formed upon the loss of the first sulfonyl group is observed in the spectrum only with low intensity due to the high rate of the consecutive fragmentation steps. Another pairwise loss of sulfonyl groups is observed among the consecutive fragments. The expulsion of the fifth sulfonyl group is already quite pronounced, because the parent ion bears only two triply substituted rings, from which the pairwise loss of substituents can be expected.

These tandem mass spectra provide some insight into very different, sometimes quite complex fragmentation patterns for the three compounds under study here. When more derivatives become available in the future, the CID spectra may even provide a means to distinguish different isomers by their fragmentation reactions.

Conclusions

Pyrogallarenes were acylated and sulfonylated according to the procedures known for resorcinarenes. The acylation and tosylation of pyrogallarene **1** resulted in completely substituted pyrogallarenes **2** and **3**, when an excess of the



Scheme 3. Fragmentation mechanisms of mass-selected **4**·K^+.

acylation or sulfonylation reagent was used. Changing the solvent and reducing the amount of the reagents resulted in mixtures of incompletely functionalised products in both cases. Further studies for the separation of these mixtures are currently under way.

When mesitylenesulfonyl chloride was used, partially substituted pyrogallarene **4** with eight substituents was obtained as a product, even though excess of sulfonylating agent was used. The location of eight substituents in **4** is interesting: two opposite pyrogallol subunits of the pyrogallarene bear three mesitylenesulfonyl groups and the other two only one substituent in the central 2-position. The exact reason why exactly this regioisomer is formed is still unclear, although one might invoke steric factors of the mesitylene groups as an explanation.

Dodecasubstituted pyrogallarenes **2** and **3** adopt a distorted crown conformation in solution and in the solid state despite of the lack of stabilising intramolecular hydrogen bonds, while **4**, still capable of forming intramolecular hydrogen bonds, adopts a C_{2v}-symmetrical boat conformation both in solution and in the solid state.

In the ESI-FT-ICR mass spectra of the potassium adducts of **2**, **3**, and **4** different fragmentation reactions are observed. While **2**·K^+ decomposes in a series of ketene losses from the acetyl groups, **3** and **4** exhibit pairwise losses of tosyl or mesitylsulfonyl groups, respectively.

In summary, we have characterised the products of the syntheses reported here in the solid state, in solution, and in the gas phase. These results already show that pyrogallarenes behave quite differently compared to the resorcinarenes. Only mesitylation gave an easy to isolate, partially substituted product. Nevertheless, this reaction provides a valuable intermediate for further functionalisations, after which the mesitylsulfonyl groups could be cleaved off, thus providing regioselective access to other pyrogallarene derivatives.

Experimental Section

General Remarks: ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or [D_6]DMSO solution with a Bruker Avance DRX 500 spectrometer (500.13 MHz for ^{1}H and 125.77 MHz for ^{13}C). ^{1}H and ^{13}C assignments were mainly based on HMQC and HMBC 2D correlation spectra. All signals are expressed as δ values in ppm using the residual solvent signal as an internal standard. Routine mass spectra were obtained with a Micromass LCT ESI-TOF mass spectrometer and elemental analyses were carried out with a Varior ELIII elemental analyzer. Melting points were determined with a Mettler Toledo FP62 capillary melting point apparatus and are uncorrected.

Dodecaacetylated Pyrogallarene 2: Acetic anhydride (10.0 mL, 0.11 mmol) was added to a solution of pyrogallarene **1** (500 mg, 0.69 mmol) in pyridine (65 mL). The reaction mixture was stirred at room temperature for 4 d and the solvent was removed under vacuum. The white precipitate was thoroughly washed with water, crystallised from acetone, and dried in a vacuum. Yield 0.38 g (45%); m.p. 286 °C. ^{1}H NMR (500 MHz, 333 K, $CDCl_3$): δ = 0.94 (t, $^3J_{H,H}$ = 7.2 Hz, 12 H, CH_2CH_3), 1.36 (sept, $^3J_{H,H}$ = 7.6 Hz, 8 H, CH_2CH_3), 1.90 (q, $^3J_{H,H}$ = 7.2 Hz, 8 H, $CHCH_2$), 2.09 (s, 12 H, $COCH_3$), 2.19 (s, 24 H, $COCH_3$), 4.20(t, $^3J_{H,H}$ = 7.4 Hz, 4 H, $CHCH_2$), 6.78 (br. s, 4 H, Ar-*H*) ppm. ^{13}C NMR: δ = 13.7 (CH_2CH_3), 19.8 ($COCH_3$), 19.9 ($COCH_3$), 20.8 (CH_2CH_3), 36.6 ($CHCH_2$), 36.8 ($CHCH_2$), 122.7 (*Ar*), 134.3 (*Ar*-CH), 136.1 (*Ar*-CO), 140.4 (*Ar*-CO), 166.6 (*C*O), 167.1 (*C*O) ppm. $C_{64}H_{72}O_{24}$·H_2O (1243.29): calcd. C 61.83, H 6.00; found C 61.90, H 5.90. ESI-TOF-MS: *m*/*z* = 1247.3 [M + Na]$^+$.

Dodecatosylated Pyrogallarene 3: Et_3N (3.45 mL, 25.0 mmol) was added to a solution of pyrogallarene **1** (1.00 g, 1.39 mmol) in boiling MeCN (65 mL). A white precipitate formed and the reaction mixture was stirred for 15 min. A solution of tosyl chloride (4.77 g, 25.0 mmol) in MeCN (15 mL) was added to the solution and the precipitate dissolved. After a while, compound **3** started to precipitate. The reaction mixture was refluxed under N_2 for 5 h and then stirred at room temperature for 4 d. The resulting white precipitate was filtered, thoroughly washed with water and dried under vacuum. Yield 2.15 g (60%); m.p. 275 °C. ^{1}H NMR (500 MHz, 303 K, $CDCl_3$): δ = 0.98 (t, $^3J_{H,H}$ = 7.3 Hz, 12 H, CH_2CH_3), 1.17 (m, $^3J_{H,H}$ = 7.9 Hz, 8 H, CH_2CH_3), 1.99 (m, $^3J_{H,H}$ = 7.6 Hz, 8 H, $CHCH_2$), 2.05 (s, 12 H, Tos-CH_3), 2.41 (s, 24 H, Tos-CH_3), 5.14 (t, $^3J_{H,H}$ = 7.5 Hz, 4 H, $CHCH_2$), 6.81 (br. s, 8 H, Tos-*H*), 6.89 (d, $^3J_{H,H}$ = 6.5 Hz, 8 H, Tos-*H*), 7.20 (d, $^3J_{H,H}$ = 8.5 Hz, 16 H, Tos-*H*), 7.85 (d, $^3J_{H,H}$ = 8.0 Hz, 16 H, Tos-*H*), 7.90 (s, 4 H, Ar-*H*) ppm. ^{13}C NMR: δ = 14.4 (CH_2CH_3), 20.7 (CH_2CH_3), 21.4 (Tos-CH_3), 21.6 (Tos-CH_3), 36.7 ($CHCH_2$), 38.6 ($CHCH_2$), 124.0 (*Ar*), 127.3 (*Tos*), 129.2 (*Tos*), 129.5 (*Tos*), 129.6 (*Tos*), 132.3 (*Tos*-SO_2), 132.6 (*Tos*-SO_2), 137.3 (*Ar*-CH), 140.3 (*Ar*-SO_2), 144.6 (*Tos*-CH_3), 144.8 (*Tos*-CH_3) ppm. $C_{124}H_{120}O_{36}S_{12}$·$H_2O$ (2589.11): calcd. C 56.74, H 4.84; found C 56.60, H 4.58. ESI-TOF-MS: *m*/*z* = 2593.27 [M + Na]$^+$.

Octasulfonylated Pyrogallarene 4: Et_3N (2.44 mL, 17.5 mmol) was added to a solution of pyrogallarene **1** (700 mg, 0.97 mmol) in boiling MeCN (45 mL) under N_2. A white precipitate formed and the reaction mixture was stirred for 15 min. A solution of mesitylsulfonyl chloride (3.82 g, 17.5 mmol) in MeCN (10 mL) was added to the reaction solution and the precipitate dissolved. After a while, compound **4** started to precipitate. The reaction mixture was refluxed under N_2 for 5 h and then stirred at room temperature for 4 d. A white precipitate was filtered off, thoroughly washed with water and crystallised from THF. Yield 1.16 g (50%); m.p. >300 °C. ^{1}H (500 MHz, 393 K, $CDCl_3$): δ = 0.82 (m, 14 H, CH_2CH_3, CH_2CH_3), 1.15 (m, 4 H, CH_2CH_3), 1.63 (m, 4 H, $CHCH_2$), 2.06 (m, 4 H, $CHCH_2$) 2.16 (s, 12 H, Mes-CH_3), 2.26 (s, 6 H, Mes-CH_3), 2.29(s, 6 H, Mes-CH_3), 2.33 (s, 12 H, Mes-CH_3), 2.43 (s, 12 H, Mes-CH_3), 2.56 (s, 24 H, Mes-CH_3), 4.31 (dd, ^3J = 3.0, $^3J_{H,H}$ = 11.5 Hz, 4 H, $CHCH_2$), 6.67 (s, 2 H, *Ar*), 6.84 (s, 4 H, Mes-*H*), 6.96 (s, 4 H, Mes-*H*), 7.05 (s, 8 H, Mes-*H*), 7.20 (s, 2 H, *Ar*) ppm. ^{13}C NMR δ = 13.2 (CH_2CH_3), 20.0 (Mes-CH_3), 20.1 (Mes-CH_3), 20.2 (CH_2CH_3), 21.5 (Mes-CH_3), 21.8 (Mes-CH_3) 21.9 (Mes-CH_3), 35.9 ($CHCH_2$), 36.8 ($CHCH_2$), 119.4 (*Ar*-O), 123.8 (*Ar*), 124.5 (*Ar*), 130.0 (*Mes*-SO_2), 130.9 (*Mes*), 131.0 (*Mes*), 131.0 (*Mes*), 131.8 (*Mes*-SO_2), 132.4 (*Mes*-SO_2), 138.3 (*Ar*-SO_2), 138.5 (*Mes*-CH_3), 139.2 (*Mes*-CH_3), 139.3 (*Ar*-CH), 134.0 (*Mes*-CH_3), 142.8 (*Mes*-CH_3), 143.2 (*Mes*-CH_3), 146.9 (*Mes*-SO_2) ppm. $C_{124}H_{120}O_{36}S_{12}$·$H_2O$ (2196.78): calcd. C 61.47, H 5.92; found C 61.40, H 5.88. ESI-TOF-MS: *m*/*z* = 2217.79 [M + K]$^+$.

X-ray Crystallographic Study: The data for **2**, **3**, and **4** were recorded with a Nonius Kappa CCD using graphite-monochromatised Mo-K_α radiation (λ = 0.71073 Å) and a temperature of 173.0 ± 0.1 K. The CCD data were processed with Denzo-SMN v0.95.373.[38] All structures were solved by direct methods (SHELXS-97)[39] and refinemed, based on F^2, by full-matrix least-

Table 1. Crystallographic data for substituted pyrogallarenes **2**–**4**.

	2	**3**	**4**
Empirical formula	$C_{64}H_{74}O_{24}\cdot 2.5(CH_3)_2CO$	$C_{124}H_{120}O_{36}S_{12}\cdot 2.5(CH_3)_2CO$	$C_{112}H_{128}O_{28}S_8\cdot 6.5(CH_2)_4O$
Formula mass	1370.41	2716.11	2647.30
Crystal size [mm]	0.05×0.15×0.5	0.1×0.2×0.3	0.2×0.2×0.4
Crystal system	triclinic	orthorhombic	monoclinic
Space group	$P\bar{1}$ (No. 2)	$P2_12_12_1$ (No. 19)	$C2/c$ (No. 15)
a [Å]	14.3989(8)	18.3932(4)	32.9675(5)
b [Å]	17.033(1)	26.2232(7)	16.0140(4)
c [Å]	17.680(1)	27.7855(5)	28.8852(7)
α [°]	106.518(3)	90	90
β [°]	93.644(4)	90	104.410(1)
γ [°]	92.285(4)	90	90
Volume [Å^3]	4141.1(5)	1331.2(1)	14769.9(6)
Z	2	4	4
$D_{calcd.}$ [Mg·m^{-3}]	1.099	1.346	1.191
μ [mm^{-1}]	0.084	0.276	0.192
$F(000)$	1456	5696	5648
θ range [°]	2.93–22.72	1.07–24.71	1.28–24.70
Reflections collected/unique/R_{int}	18136/11090/0.070	54181/22737/0.114	45430/12507/0.077
Reflections used in refinement[a]/parameters	5318/936	12070/1640	8821/906
Goodness-of-fit on F^2	1.015	1.012	1.118
R/R_w	0.126/0.393	0.073/0.184	0.076/0.243
Largest difference peak/hole	0.774/–0.564	0.817/–0.643	0.842/–0.472

[a] $I > 2\sigma(I)$.

squares techniques (SHELXL-97).[40] No absorption corrections were applied. The hydrogen atoms were calculated to their idealised positions with isotropic temperature factors (1.2 or 1.5 times the C temperature factor) and refined as riding atoms. Three acetone molecules in the structure of **2** and two in the structure of **3** were refined isotropically. The oxygen atoms of the three acetone molecules in the structure of **2** are disordered over two positions with site occupation factors of 0.25:0.25. The methyl group C40 at the lower rim of compound **4** is disordered over two positions (occupancies 0.67:0.33). Other X-ray data are presented in Table 1. CCDC-258945 to -258947 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

FT-ICR Mass Spectrometry: ESI mass spectra and MS/MS spectra were recorded with a Bruker APEX IV Fourier-transform ion cyclotron resonance (FT-ICR) mass spectrometer with an Apollo electrospray ion source equipped with an off-axis 70° spray needle. Typically, methanol (if necessary with a small amount of $CHCl_3$ to improve solubility) served as the spray solvent and ca. 100 μM solutions of the analytes were used. Analyte solutions were introduced into the ion source with a syringe pump (Cole-Parmers Instruments, Series 74900) at flow rates of ca. 2–3 μL/min. Ion transfer into the first of three differential pump stages in the ion source occurred through a glass capillary with 0.5 mm inner diameter and nickel coatings at both ends. Ionisation parameters were adjusted as follows: capillary voltage: +4.6 to +4.9 kV; endplate voltage: +4.0 to +4.3 kV; capexit voltage: –300 to –350 V; skimmer voltages: –8 to –12 V; temperature of drying gas: 150 to 200 °C. The pressure of drying gas was kept in a medium range (ca. 10 psi), while the pressure of nebulizer gas was set to ca. 15 psi. Over a large range of parameter settings, the protonated compounds were only observed with vanishing intensities, while the alkali metal adducts were abundant. The ions were accumulated in the instrument's hexapole for 1.8–2.5 s, introduced into the FT-ICR cell which was operated at pressures below 10^{-10} mbar, and detected by a standard activation and detection sequence. For each measurement, 16–128 scans were averaged to improve the signal-to-noise ratio. For MS/MS experiments, the whole isotope pattern of the ion of interest was isolated by applying correlated sweeps, followed by shots to remove the higher isotopes. After isolation, argon was introduced into the ICR cell through a pulsed valve at a pressure of ca. 10^{-8} mbar. The ions were accelerated by a standard excitation protocol and detected after a pumping delay of 2 s. A sequence of several different spectra was recorded at different excitation pulse attenuations in order to obtain at least a rough and qualitative idea of the effects of different collision energies.

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[1] T. Gerkensmeier, C. Agena, W. Iwanek, R. Fröhlich, S. Kotila, C. Näther, J. Mattay, *Z. Naturforsch. B* **2001**, *56*, 1063–1073.
[2] M. Luostarinen, A. Åhman, M. Nissinen, K. Rissanen, *Supramol. Chem.* **2004**, *16*, 505–515.
[3] A. Shivanyuk, J. Friese, S. Doering, J. Rebek, Jr., *J. Org. Chem.* **2003**, *68*, 6489–6496.
[4] M. Luostarinen, A. Åhman, M. Nissinen, K. Rissanen, unpublished results.
[5] T. Gerkensmeier, W. Iwanek, C. Agena, R. Frölich, S. Kotila, C. Näther, J. Mattay, *Eur. J. Org. Chem.* **1999**, *9*, 2257–2262.
[6] J. L. Atwood, L. J. Barbour, A. Jerga, *Supramol. Chem.* **2001**, *1*, 131–134.
[7] M. Ricco, E. Dalcanale, *J. Phys. Chem.* **1994**, *98*, 9002–9008.
[8] G. Cometti, E. Dalcanale, A. Du Vosel, A.-M. Levelut, *J. Chem. Soc. Chem. Commun.* **1990**, 163–165.

[9] S. Harris, WO02/44121, **2002**.
[10] K. Kobayashi, Y. Asakawa, Y. Kato, Y. Aoyama, *J. Am. Chem. Soc.* **1992**, *114*, 10307–10313.
[11] T. Fujimoto, R. Yanagihara, K. Kobayashi, Y. Aoyama, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2113–2124.
[12] P. Timmerman, W. Verboom, D. N. Reinhoudt, *Tetrahedron* **1996**, *52*, 2663–2704.
[13] P. D. Beer, E. L. Tite, *Tetrahedron Lett.* **1988**, *29*, 2349–2352.
[14] L. Abis, E. Dalcanale, A. Du Vosel, S. Spera, *J. Org. Chem.* **1988**, *53*, 5475–5479.
[15] P. D. Beer, E. L. Tite, *J. Chem. Soc. Dalton Trans.* **1990**, *8*, 2543–2550.
[16] P. D. Beer, E. L. Tite, A. Ibbotson, *J. Chem. Soc. Chem. Commun.* **1990**, *24*, 1874–1876.
[17] G. Rumboldt, V. Böhmer, B. Botta, E. F. Paulus, *J. Org. Chem.* **1998**, *63*, 9618–9619.
[18] Y. Yamakawa, M. Ueda, R. Nagahata, K. Takeuchi, M. Asia, *J. Chem. Soc., Perkin Trans. 1* **1998**, *24*, 4135–4239.
[19] O. Haba, K. Haga, M. Ueda, O. Morikava, H. Konishi, *Chem. Mater.* **1999**, *11*. 427–432.
[20] D. J. Cram, L. M. Tunstad, C. B. Knobler, *J. Org. Chem.* **1992**, *57*, 528–535.
[21] O. V. Lukin, V. V. Pirozhenko, A. N. Shivanyuk, *Tetrahedron Lett.* **1995**, *36*, 7725–7728.
[22] H. Konishi, T. Takamura, H. Ohkubo, K. Kobayashi, O. Morikava, *Chem. Lett.* **1996**, *8*, 685–686.
[23] A. Shivanyuk, E. F. Paulus, V. Böhmer, W. Vogt, *J. Org. Chem.* **1998**, *63*, 6448–6449.
[24] O. Lukin, A. Shivanyuk, V. Pirozhenko, I. Tsympal, V. Kalchenko, *J. Org. Chem.* **1998**, *63*, 9510–9516.
[25] A. Shivanyuk, E. F. Paulus, V. Böhmer, *Angew. Chem.* **1999**, *111*, 3091–3094; *Angew. Chem. Int. Ed.* **1999**, *38*, 2906–2909.
[26] J. O. Green, J.-H. Baird, B. C. Gibb, *Org. Lett.* **2000**, *2*, 3845–3848.
[27] A. Shivanyuk, E. F. Paulus, K. Rissanen, E. Kolehmainen, V. Böhmer, *Chem. Eur. J.* **2001**, *7*, 1944–1951.
[28] C. Agena, C. Wolff, J. Mattay, *Eur. J. Org. Chem.* **2001**, *15*, 2977–2981.
[29] D. J. Eisler, R. J. Puddephat, *Can. J. Chem.* **2004**, *82*, 185–194.
[30] D. Conevey, B. Costello, EP 1367044 A1, **2003**.
[31] E. T. van Velzen, J. Engbersen, D. N. Reinhoudt, *Synthesis* **1995**, *8*, 989–997.
[32] P. Beer, A. Smythe, E. Tite, *J. Organomet. Chem.* **1989**, *376*, C11–C14.
[33] D. Falábu, A. Shivanyuk, M. Nissinen, K. Rissanen, *Org. Lett.* **2002**, *4*, 3019–3022.
[34] H. Mansikkamäki, M. Nissinen, C. A. Schalley, K. Rissanen, *New J. Chem.* **2003**, *27*, 88–97.
[35] M. Nissinen, K. Rissanen, *Supramol. Chem.* **2003**, *15*, 581–590.
[36] M. Mäkinen, P. Vainiotalo, M. Nissinen, K. Rissanen, *J. Am. Soc. Mass. Spectrom.* **2002**, *14*, 143–151.
[37] H. Mansikkamäki, M. Nissinen, K. Rissanen, *Chem. Commun.* **2002**, 1902–1903.
[38] Z. Otwinowski, W. Minor, *Processing of X-ray Diffraction Data Collected in Oscillation Mode*, in: *Methods in Enzymology*, vol. 276 ("Macromolecular Crystallography, Part A") (Eds.: C. W. Carter, Jr., R. M. Sweet), Academic Press, New York, **1997**, pp. 307–326.
[39] G. M. Sheldrick, *Acta Crystallogr. A* **1990**, *46*, 467–473.
[40] G. M. Sheldrick, *A program for crystal structure refinement*, University of Göttingen, Germany, **1997**.

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