Natural Product Synthesis on Polymeric Supports—Synthesis and Biological Evaluation of an Indolactam Library**

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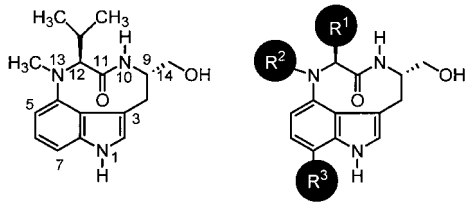
The combinatorial synthesis of molecule libraries on polymeric supports is a powerful approach for the rapid identification of new compounds that are efficient tools for the study of biological phenomena and leads for the development of new drugs.[1] However, its efficiency depends critically on the proper choice of the molecular scaffolds onto which different functional groups are grafted in the process of combinatorial synthesis. The generation of large libraries alone is not sufficient; the underlying basic structure of the individual library members must be biologically relevant. Natural products with proven biological activity offer such relevant molecular frameworks. Therefore, the development of methods for the combinatorial synthesis of compound libraries embodying the molecular architecture of natural products[2] must be of great relevance to combinatorial, bioorganic, and medicinal chemistry. This calls for the development of synthetic techniques and multistep reaction sequences that proceed with high efficiency on a polymeric support. Here we report on a new method for the synthesis of the protein kinase C (PKC) activator indolactam V and the use of this method in the first solid-phase synthesis of indolactam V analogues. The synthesis is amenable to combinatorial variation of substituents (R^1-R^3, see Figure 1), and opens up the opportunity to generate libraries of potential activators and/or inhibitors of PKC.

Protein kinase C plays key roles in signal transduction pathways that regulate numerous cellular responses including gene expression, proliferation, differentiation, apoptosis, and tumor development.[3] It represents a family of at least eleven closely related serine/threonine kinase isoenzymes and is expressed in all cell types. However, the different isoforms often are distributed in a tissue-specific manner.[3] Altered PKC activity has been implicated in many disease states, and modulators of PKC activity may be useful in the treatment of, for example, cancer, asthma, rheumatoid arthritis, complications associated with diabetes, psoriasis, and disorders of the central nervous system.[3c] Therefore, PKC is considered a promising target for the development of new medicinal lead compounds. Selective activators or inhibitors of the different PKC isoenzymes are also likely to be useful in dissecting signaling pathways in different tissues.[4] Members of the PKC family are activated and recruited to the plasma membrane by the second messenger diacyl glycerol (DAG). The function of DAG can be mimicked by (exogenously applied) agents such as phorbol esters. In particular, (−)-indolactam V (**1**), the core structure of tumor-promoting teleocidins,[3, 5] has attracted substantial interest as a key component for investigating the structural requirements for the activation of PKC.[4, 6] As shown in Figure 1 the indolactam core structure displays different substituents in a defined pattern, which allows one to set up a multidimensional library based on a natural product derived template with unique spatial properties.



1 (−)-Indolactam V **2**

Figure 1. The structure of (−)-indolactam V and the general structure of indolactam V analogues to be built up by combinatorial synthesis.

For the design of the library and the synthetic strategy it had to be taken into account that the structure of substituents at C12 and N13 influences the conformation of the nine-membered lactam ring (twist vs. sofa form), determining the ability of the heterocycles to bind PKC (the twist form represents the active conformation of the indolactams).[6b] Furthermore, substituents at C7 mediate membrane binding of the PKC activators, and a free OH group is required at C14 for biological activity.[7] Therefore, indolactam analogues **2** were chosen as promising targets. It was planned to vary substituents R^1-R^3 by means of appropriate reactions, preferably on a solid support, and to link the indolactam core to the polymeric carrier through the primary OH group.

To construct a central enantiomerically pure building block for the combinatorial introduction of residues R^1-R^3 on the solid phase, 4-amino-substituted indole derivative **8** was built up as shown in Scheme 1. *N*-TIPS-protected gramine **3** (TIPS = triisopropylsilyl) was regioselectively lithiated in the 4-position,[8] and an NH_2 group was introduced by treatment of the aryllithium intermediate with trimethylsilylmethyl azide.[9] After protection of the amino group gramine derivative **4** was elaborated to the corresponding substituted tryptophan. To this end, the tertiary amine was N-methylated, followed by fluoride-induced cleavage of the TIPS group. The deprotection was accompanied by elimination of trimethylamine, yielding an *exo*-methylene imine intermediate that was attacked by diallyl phenylacetamidomalonate (**5**) in the sense of a Mannich reaction. The resultant α-alkylated malonic acid diester was deprotected by Pd^0-mediated allyl transfer to morpholine,[10] and the malonic acid formed was decarboxy-

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[**] This research was supported by the Fonds der Chemischen Industrie and the Bayer AG.

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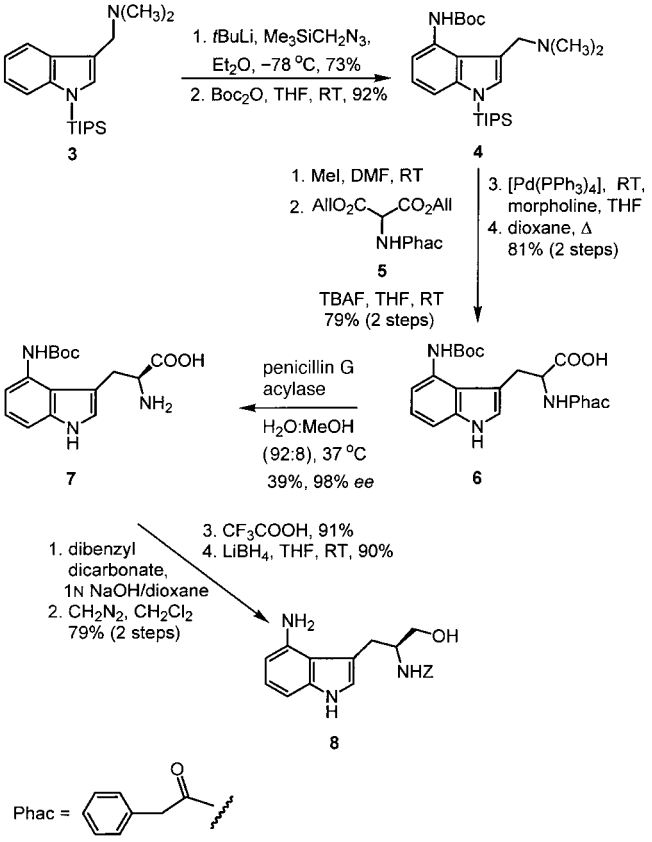
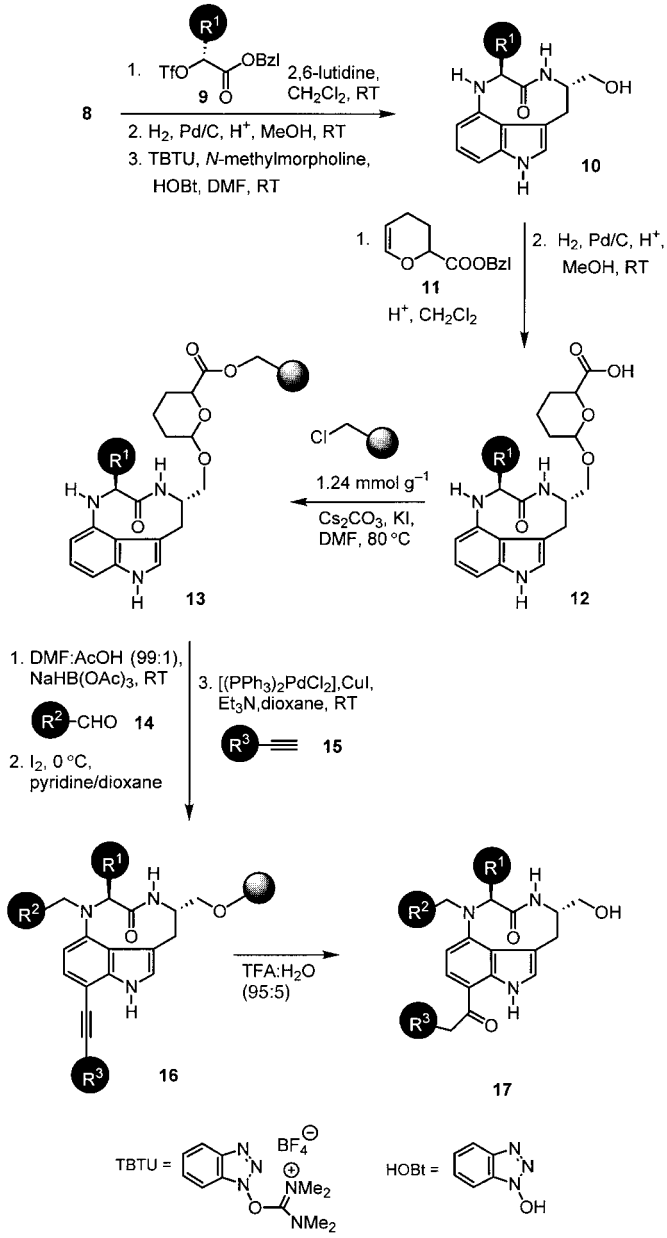


Scheme 1. Enantioselective synthesis of the 4-amino-substituted tryptophan derivative **8**—a formal total synthesis of (−)-indolactam V (**1**). All = allyl; Boc = *tert*-butyloxycarbonyl; RT = room temperature; TBAF = tetrabutylammonium fluoride; Z = benzyloxycarbonyl.

lated to give 4-aminotryptophan derivative **6** in high yield. To construct enantiomerically pure indolactam analogues the phenylacetamide group of the N-acylated derivative of racemic amino acid **6** was subjected to enantioselective hydrolysis with penicillin G acylase.[11] The enzymatic hydrolysis proceeded to 50% conversion, and from the reaction mixture the desired L-amino acid **7** was obtained in 39% yield (maximum yield 50%) and with an enantiomeric excess of more than 98%.[12] In addition, the remaining D-amino acid phenylacetamide was isolated as the methyl ester in 40% yield (two steps; maximum yield 50%) and with greater than 98% *ee*. Thus, both enantiomers of 4-*N*-Boc-tryptophan are accessible by this method in a straightforward and efficient manner. L-Amino acid **7** was then converted into selectively masked amino alcohol **8** in 65% overall yield by protecting-group manipulation and reduction of the intermediately formed methyl ester to the alcohol. 4-Aminoindole derivative **8** has previously been built up as an advanced intermediate in a synthesis of (−)-indolactam V.[13] Thus the reaction sequence depicted in Scheme 1 represents a novel formal total synthesis of this PKC activator.

Amino alcohol **8** was employed as the central intermediate in the solid-phase synthesis of indolactam V analogues. The second stereocenter characteristic of the indolactam nucleus was introduced by alkylation of the aromatic amine with different α-hydroxy acid ester triflates **9**. Subsequent hydrogenolytic removal of the Z protecting group and the benzyl ester functionality followed by amide formation yielded nine-membered lactams **10** in high yields (Scheme 2). Direct attachment of indole-derived alcohols **10** to a polystyrene support equipped with a tetrahydropyran (THP) linker[14a] was unexpectedly inefficient. This problem could, however,



Scheme 2. Solid-phase synthesis of indolactam V analogues **17**. Bzl = benzyl; Tf = trifluoromethanesulfonyl; TFA = trifluoroacetic acid.

be circumvented by acetal formation with prelinker **11**[14b] followed by hydrogenolysis of the benzyl ester group and coupling of the resulting linker/substrate conjugates **12** to chloromethylated polystyrene beads by nucleophilic esterification. Thereby resins **13** were obtained typically with loading levels of about 0.9 – 1 mmol g^{-1},[15] corresponding to coupling yields of 73 – 81% (Table 1).

Resin-linked indole derivatives **13** were then subjected to a four-step sequence to introduce substituents R^2 and R^3 and cleave the desired indolactam V analogues from the solid support (Scheme 2). In initial experiments the reaction

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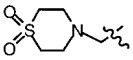
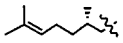
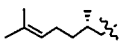
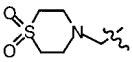
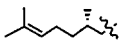
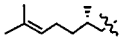
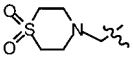
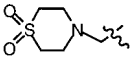
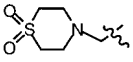
Table 1. Results of the synthesis of resin bound indole derivatives **13**.

	8→**10**		**10**→**12**		**12**→**13**	
R^1	compd	yield [%]	compd	yield [%]	compd	yield [%]
CH_3	**10a**	76	**12a**	25	**13a**	81
*i*Pr	**10b**	67	**12b**	50	**13b**	73
CH_2Ph	**10c**	65	**12c**	68	**13c**	77

sequence was established for compounds **17/1**–**17/4** (Table 2). To this end, N13 of the indolactam nucleus was N-alkylated by reductive amination with aldehydes **14** and $NaHB(OAc)_3$ to yield the corresponding immobilized tertiary amines. Subsequently, C7 of the aromatic nucleus was regioselectively iodinated by treatment with iodine in pyridine/dioxane at 0 °C.[16] The resulting aryl iodides were subjected to Sonogashira coupling with acetylenes **15** on the polymeric support[17] to give immobilized alkynes **16**. Finally, the multiply substituted indole derivatives were released from the polymeric carrier by cleavage of the acetal linker with aqueous trifluoroacetic acid. Under these conditions the alkynyl groups attached to C7 unexpectedly were hydrated to give the corresponding ketones **17**.[18] By means of this four-step sequence indolactam analogues **17/1**–**17/4** were obtained in yields ranging from 40 to 50%, that is, with high overall efficiency (average yield per step: 80–84%). With an efficient solid-phase sequence in hand we then constructed a library of indolactam analogues (Table 2). In particular, resin-bound indole derivative **13c** served as starting material which was derivatized with a series of different aldehydes and alkynes in parallel syntheses[19] according to the protocol described above. The results given in Table 2 demonstrate that differently substituted aldehydes and alkynes carrying additional functional groups can be applied successfully in the developed solid-phase sequence. With three α-hydroxy acid triflates, seven aldehydes, and eight alkynes, a library of 31 indolactam analogues was synthesized in overall yields ranging from 65 to 10% (average yield per step 90 to 57%).

Table 2. Results of the solid phase synthesis of indolactam V analogues **17**.[a]

Compd	R^1	R^2	R^3	Yield [%]
17/1	CH_2Ph	*n*Bu	*n*Pr	40
17/2	CH_2Ph	*n*Bu	Ph	50
17/3	CH_3	*i*Pr	*n*Pr	43
17/4	CH_3	*i*Pr	Ph	47
17/5	*i*Pr	CH_3	*n*Pr	20
17/6	CH_2Ph		CH_2Ph	13
17/7	CH_2Ph			17
17/8	CH_2Ph		*t*Bu	21
17/9	CH_2Ph			52
17/10	CH_2Ph		Ph	20
17/11	CH_2Ph		$CH_2N(CH_3)_2$	33
17/12	CH_2Ph		CH_2Ph	10
17/13	CH_2Ph			30
17/14	CH_2Ph		Ph	11
17/15	CH_2Ph		$CH_2N(CH_3)_2$	20
17/16	CH_2Ph	$CH_2CH(CH_3)Ph$	CH_2Ph	12
17/17	CH_2Ph	$CH_2CH(CH_3)Ph$		14
17/18	CH_2Ph	$CH_2CH(CH_3)Ph$	*t*Bu	15
17/19	CH_2Ph	$CH_2CH(CH_3)Ph$	CH_2CH_2OH	17
17/20	CH_2Ph	$CH_2CH(CH_3)Ph$		56
17/21	CH_2Ph	$CH_2CH(CH_3)Ph$	$CH_2N(CH_3)_2$	65
17/22	CH_2Ph	*n*Bu	CH_2Ph	20
17/23	CH_2Ph	*n*Bu		22
17/24	CH_2Ph	*n*Bu	*t*Bu	15
17/25	CH_2Ph	*n*Bu		49
17/26	CH_2Ph	*n*Bu	$CH_2N(CH_3)_2$	53
17/27	CH_2Ph	CH_2CH_2Ph	CH_2Ph	18
17/28	CH_2Ph	CH_2CH_2Ph		16
17/29	CH_2Ph	CH_2CH_2Ph		53
17/30	CH_2Ph	CH_2CH_2Ph	Ph	17
17/31	CH_2Ph	CH_2CH_2Ph	$CH_2N(CH_3)_2$	51

[a] The yields given are based on the total reaction sequence **13**→**17**.

To investigate if the indolactam analogues formed by the route described above are indeed PKC activators, eleven selected members of the compound libraries were subjected to a cell-based assay system. In this assay Swiss 3T3 fibroblasts are treated with PKC modulators. Activation of PKC causes the phosphorylation of the major PKC substrate, MARCKS (myristoylated alanine-rich C kinase substrate).[20] The unphosphorylated 80-kDa MARCKS protein is attached to membranes through its N-terminal myristoylated domain and the unphosphorylated phosphorylation domain in the middle of the protein (Figure 2A). MARCKS is a specific PKC substrate.[21] After activation of PKC, MARCKS becomes phosphorylated in the phosphorylation domain, resulting in rapid and extensive translocation of MARCKS from the membrane to the cytosol. Thus analysis of subcellular MARCKS localization (membrane-bound vs. cytosolic) allows one to determine the activation of PKC. Confluent and quiescent cultures of Swiss 3T3 cells were exposed for 30 min to a saturating concentration of phorbol dibutyrate (PDB, 200 nM) for maximal activation of PKC. The cells were homogenized and the extracts separated into cytosolic and membrane fractions.

The levels of MARCKS protein in these fractions were determined by Western blot analyses using an antiserum raised against recombinant GST-MARCKS protein (GST = glutathione S transferase). This antiserum detects a single band corresponding to MARCKS.[20] In quiescent cells, only small amounts of MARCKS were detected in the cytoplasmic fraction (Figure 2B; control), while the majority of this

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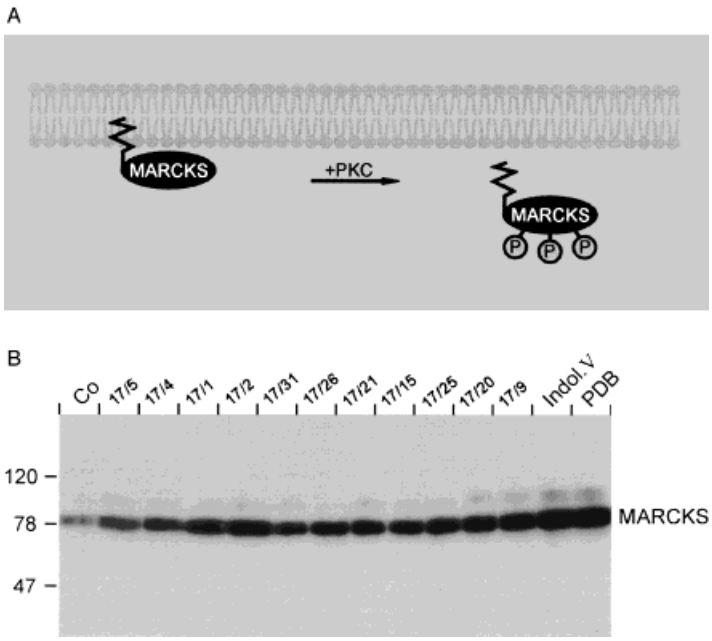

Figure 2. Activation of PKC induces translocation of MARCKS. A) The PKC substrate MARCKS is membrane-bound in its unphosphorylated state. Phosphorylation by PKC causes a rapid and extensive translocation of MARCKS from the membrane to the cytosolic fraction. B) Quiescent Swiss 3T3 cells remained untreated (control) or were treated for 30 min with the substances depicted (200 nM). The cells were washed and homogenized, and the resulting extracts were fractionated by high-speed centrifugation. Cytoplasmic proteins were separated by sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE) and analyzed by Western blotting employing a polyclonal MARCKS antiserum and enhanced chemiluminescence. The positions of protein markers (in kDa) are shown on the left. Co = control; Indol.V = indolactam V.

protein was found in association with the membrane (data not shown). We then utilized this system to examine the potency of eleven members of our library of indolactam derivatives (200 nM) to activate PKC in 3T3 fibroblasts and to promote MARCKS translocation. All substances tested caused a striking translocation of MARCKS to various degrees (Figure 2B). Scanning of autoradiographs revealed a MARCKS translocation induced by the indolactam V derivatives by three- to fivefold, which was slightly less efficient than with indolactam V itself and with the phorbol ester PDB (both sevenfold, Figure 2B). Preincubation of the Swiss 3T3 cells with 2.5 μM GF109203X, a specific PKC inhibitor,[20] completely abrogated the MARCKS translocation (data not shown). Phosphorylation of MARCKS by PKC is a prerequisite for MARCKS translocation.[20a] Thus, these results demonstrate that the indolactam V analogues are potent PKC activators.

MARCKS is a specific PKC substrate for all conventional and novel PKC isoforms in vitro and in fibroblasts.[21] Our data concerning the differently pronounced activation of PKC in Swiss 3T3 cells by different indolactam analogues maybe explained by the varying potency of these indolactam analogues for binding to and activating PKC in general. This possibility might open new routes for the establishment of structure – function relationships. Alternatively, the individual indolactam analogues tested may bind the individual members of the PKC family with different efficiency. In this context it should be noted that the murine Swiss 3T3 fibroblasts used in this study express mainly the conventional PKC isoform α, the novel isoforms δ and ε, and the atypical isoform ζ.[22]

Received: February 15, 1999
Revised version: July 5, 1999 [Z13032IE]
German version: *Angew. Chem.* **1999**, *111*, 3083 – 3087

Keywords: alkaloids · combinatorial chemistry · drug research · signal transduction · total synthesis

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Guest-Controlled Formation of a Hydrogen-Bonded Molecular Capsule**

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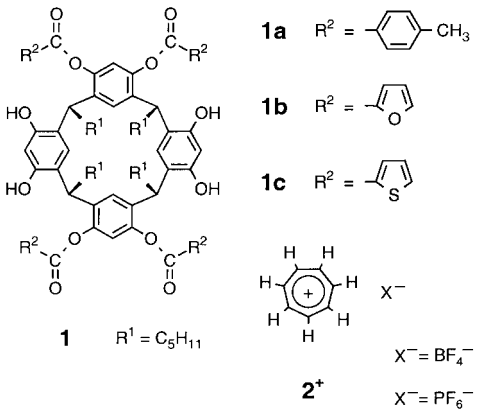
Several concave, self-complementary molecules[1] have been shown to form self-assembled dimeric capsules held together by multiple hydrogen bonds in which various guests can be reversibly entrapped. The encapsulation of a suitable guest is usually necessary for the dimerization, since an empty or incompletely filled cavity would be thermodynamically disadvantageous.[2] Herein we describe a novel type of dimeric hydrogen-bonded molecular capsules whose formation can be strictly controlled by the amount of guest available for the encapsulation.

C_{2v}-symmetrical tetraesters **1** are easily prepared by regioselective acylation of resorcarenes with various acid chlorides.[3] These molecules contain four phenolic hydroxy groups and four ester carbonyl groups as potential hydrogen-bond donors and acceptors and should be able, according to molecular models, to dimerize through eight CO···HO hydrogen bonds forming a closed π-basic cavity. The tropylium cation $\mathbf{2}^+$ as π acceptor was considered to be an appropriate guest and template for such an assembly.



^{1}H NMR spectra of tetraesters **1a–c** ($CDCl_3$, 293 K) are sharp and contain one triplet for the methine protons of the bridges and four singlets for the protons of the resorcinol rings[4] (Figure 1a). Surprisingly, in the case of **1a** and **1b** the proton exchange between hydroxy groups and water (always present in traces) occurs with such a rate that no signals are observed for the corresponding protons. This indicates that the hydroxy groups are not involved in strong CO···HO hydrogen bonds, but are available for the solvation by water in $CDCl_3$.

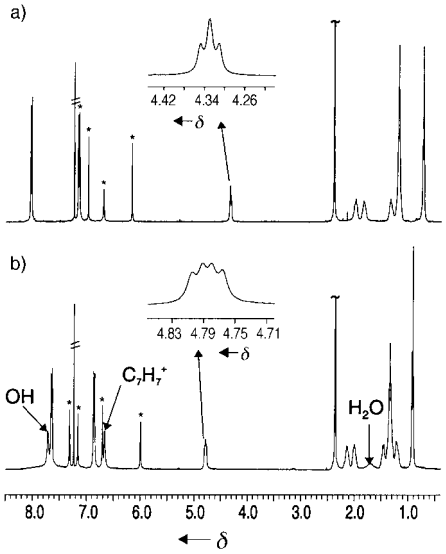


Figure 1. ^{1}H NMR spectra (400 MHz, $CDCl_3$, 293 K, $c(\mathbf{1a}) = 10^{-2}$ M) of: a) tetraester **1a**; b) $(\mathbf{1a}C_7H_7^+\mathbf{1a})PF_6^-$. The signals for the protons of resorcinol rings are marked with an asterisk.

Compounds **1** solubilize tropylium salts $\mathbf{2}^+X^-$ in CH_2Cl_2 or $CHCl_3$. The intensive orange-red color of such solutions ($\lambda_{max} = 463$ nm, CH_2Cl_2) is caused by the formation of charge-transfer complexes with $C_7H_7^+$.[5] The complexation with $C_7H_7^+PF_6^-$ also drastically changes the ^{1}H NMR spectra of resorcarenes **1a–c** ($CDCl_3$, 293 K). Especially remarkable is the down field shift for the signal of the bridges ($\Delta\delta = 0.45$) and the change of its multiplicity (Figure 1b).[6] Furthermore, the proton exchange between hydroxy groups of **1a**,**b** and water becomes slow on the NMR time scale, suggesting the formation of strong hydrogen bonds.

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[**] This work was supported by the Deutsche Forschungsgemeinschaft. We thank Mr. H. Kolshorn (Universität Mainz) for the 2D NMR measurements.

  1433-7851/99/3819-2906 $ 17.50+.50/0