Formation of calix[4]arenes with acyloxycarboxylate functions

Bauer, D.; Stipurin, S.; Köckerling, M.; Mamat, C.;

Originally published:

August 2020

Tetrahedron 76(2020), 131395

DOI: https://doi.org/10.1016/j.tet.2020.131395

Perma-Link to Publication Repository of HZDR:

https://www.hzdr.de/publications/Publ-29208

Regioselective *O*-Alkylation of Brominated Calix[4]arenes

David Bauer,[a,b] Sergej Stipurin,[a,b] Martin Köckerling[c] and Constantin Mamat*[a,b]

Abstract: Calix[4]arenes are an exciting class of multifunctional compounds. Their ability to bind small molecules and ions actively make them useful tools for many applications. While looking for a suitable chelating agent, a particular modification of the calix[4]arene lead to an unexpected side reaction. In this work, we will describe the selective formation of the observed acyloxy-acetate derivatives, which can be fine-tuned by controlling the water content of the solvent system. This selective *O*-alkylation reaction is not described in the literature so far. All new compounds were obtained in yields higher than 45% and fully characterized by NMR, MS, and X-ray crystallography. Using the monomeric derivatives of calixarenes and X-ray data, an explanation for the reaction mechanism was postulated. Further, we report on different reaction conditions which were investigated to verify the veracity of our findings. Finally, two additional derivatives of this class were synthesized to support our conclusions.

Introduction

Calix[4]arenes arise from the field of supramolecular chemistry. They consist of four phenolic units linked by a methylene bridge.[1] This arrangement creates a cavity that forms inclusion complexes with small neutral molecules or ions.[2] One major field of application is their use as extraction agents/chelators for nuclear waste treatment,[3] since they interact particularly strongly with heavy group 2 metals.[4] Modification of their backbone modulates the properties of the cavity allowing for an appropriate alignment for the required task. Remarkably, the regioselective alkylation of the phenolic hydroxyl groups provides for an accessible introduction of various moieties to optimize a host-guest interaction. Additionally, the upper rim can be functionalized, e.g., by the introduction of halogen or nitro groups to access multimodal calix[4]arenes.[1] Multimodality is a requirement for the use of these class of molecules e.g. as a carrier system for radiometals in a radiopharmaceutical context.

During our search for suitable ligands for heavy alkaline earth metals, primarily for the radiopharmaceutical-relevant nuclide radium-223 ,[5] we modified various dibromocalix[4]diacetates and found an unexpected and regioselective reaction by using different alkylation agents. In this publication, the synthesis of these compounds is described and the supposed side reaction illuminated. Additionally, varying the reaction conditions allowed control over the ratio between the expected compound and the *O*-alkylated side product.

[a] D. Bauer, S. Stipurin, Prof. Dr. J. Steinbach, Dr. C. Mamat
Institut für Radiopharmazeutische Krebsforschung
Helmholtz-Zentrum Dresden-Rossendorf
Bautzner Landstraße 400, 01328 Dresden (Germany)
E-mail: c.mamat@hzdr.de

[b] D. Bauer, S. Stipurin, Prof. Dr. J. Steinbach, Dr. C. Mamat
Fakultät Chemie und Lebensmittelchemie
TU Dresden, 01062 Dresden (Germany)

[c] Prof. Dr. M. Köckerling
Institut für Chemie-Anorganische Festkörperchemie
Universität Rostock
Albert-Einstein-Straße 3a, 18059 Rostock (Germany)

Supporting information for this article is given via a link at the end of the document

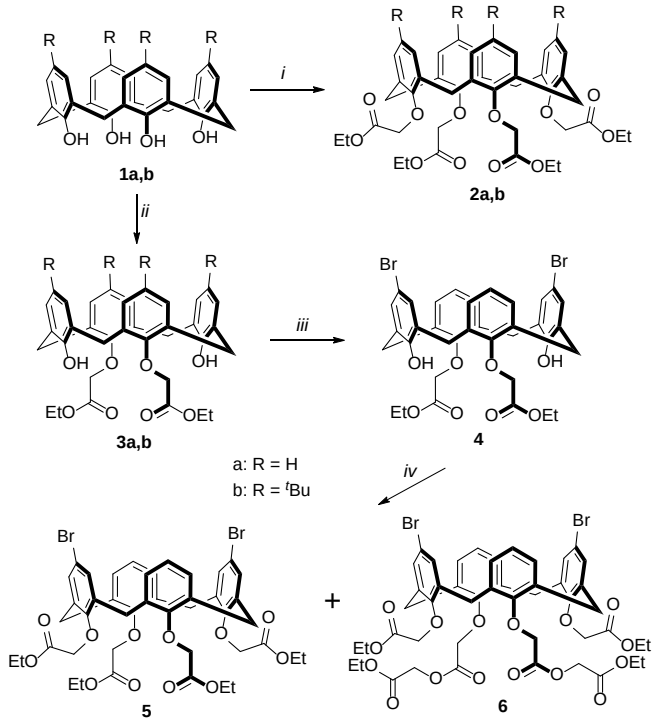
Results and Discussion

We aimed to synthesize a variety of multimodal calix[4]arenes that offer proton-ionizable groups to strongly bind ions of heavy alkaline earth metals, and further bear functional groups (e.g. bromine) at the upper rim for additional modifications. A common method to introduce a simple donor function into the calix backbone is to alkylate the phenolic hydroxyl groups with ethyl bromoacetate, followed by saponification of the ester. Therefore, **1a** and **1b** were reacted with a high excess of ethyl bromoacetate (40 equiv.) under basic conditions. This led to the exhaustedly alkylated products **2a** and **2b** in high yields.[6] A modification of the upper rim, e.g., by bromination, would preferably have to occur at this point. Notably, a straightforward, regioselective mono- or dibromination of **1a** or **2a** is not described in the literature, since the reactivity for all four phenolic units is equal.[1]

Nevertheless, a regioselective alternating dibromination is possible by taking additional steps.[7] Regioselectively alkylated calix[4]arenes **3a** and **3b** were obtained in yields of approx. 90%, when using 2-3 equiv. of ethyl bromoacetate instead of 40 equiv.[6a,8] The regioselective alkylation of **1a** and **1b** (Scheme 1) is provided by intramolecular hydrogen bonds and the resulting gradation of the hydroxyl-pK_a values.[9] The products **3a** and **3b** were obtained in high yields.[8] The alkylated phenolic units in **3a** and **3b** will not undergo the bromination reaction, as reported in the literature.[10] According to that, bromination with elemental bromine leads to a rapid and quantitative formation of compound **4**,[11] which we confirmed. After the selective modification of the upper rim, the two remaining hydroxyl groups of **4** can be easily functionalized using alkylation or acylation reactions. Since the synthesis of compound **5** by alkylation with ethyl bromoacetate is not described in the literature so far, the reaction conditions were chosen according to the preparation of comparable derivatives.[12]

Side Reactions

After the reaction of **4** with an excess of ethyl bromoacetate according to conditions *iv* in Scheme 1, two compounds were isolated. Astonishingly, the desired product **5** gave a yield of only 2%. The main product (40% yield) belongs to an unknown compound class and could not be identified solely by NMR spectroscopy. ESI mass spectrometry revealed an additional mass of 116 u compared to compound **5**, which strongly correlates with two extra ethyl acetate units. However, a crystal structure was required to unambiguously identify the molecular structure of compound **6** (Figure 2).



Scheme 1. Reagents and conditions. *i*) $BrCH_2COOEt$ (40 equiv.), K_2CO_3, KI, ACN, reflux, 2 d; *ii*) $BrCH_2COOEt$ (2 equiv.), K_2CO_3, ACN, reflux, 1 d. *iii*) Br_2, DCM, 30 min. *iv*) $BrCH_2COOEt$ (8 equiv.), NaOH, DMF, 90 °C, 1 d.

Table 1. Conditions for the conversion of the starting material **4** to calix-compounds **5** and **6**.

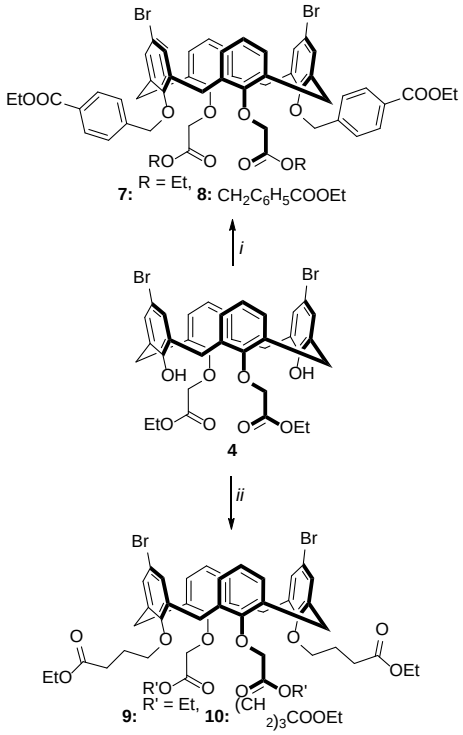
Nr	Solvent	Base	Water	Yield 5	Yield 6
1	DMF	K_2CO_3	-	45%	-
2	DMF	KO^{t}Bu	-	-	-
3	DMF	NaH	-	55%	-
4	DMF	NaOH	-	21%	-
5	THF	K_2CO_3	-	39%	-
6	THF	KO^{t}Bu	-	-	-
7	THF	NaH	-	27%	-
8	THF	NaOH	-	12%	-
9	DMF	K_2CO_3	0.1%	<1%	6%
10	DMF	KO^{t}Bu	0.1%	-	-
11	DMF	NaH	0.1%	2%	28%
12	DMF	NaOH	0.1%	5%	40%

Interestingly, a selective alkylation of the ester moieties attached to the unbrominated phenolic units occurred. The formation of the acyloxyacetate moiety itself is reported.[13] However, there is no reference for the selectivity of this reaction in the literature. The reaction conditions were optimized to produce either product **5** or **6** in high yields. The alkylation of compound **4** was forced by an excess of 8 equiv. ethyl bromoacetate with various bases like K_2CO_3, NaH or KO^{t}Bu. In both anhydrous solvents THF or DMF, the fourfold alkylated product **5** was only isolated; no formation of calix **6** was obtained. However, when no anhydrous DMF was used and traces of water were present, product **6** was formed. All reaction conditions and yields are summarized in Scheme 1.

Worthy of mention is the absence of product formation when using KO^{t}Bu as a base. Compound **5** was obtained in high yields when using anhydrous DMF with NaH or K_2CO_3 as base. Compound **6** was obtained in highest yields using the reaction conditions of entry 12 in Table 1. Since an appropriate protocol to synthesize the acyloxy-acetic acid ethyl ester was found, it had to be investigated whether other alkylating agents react with compound **4** to produce analogs of product **6**.

Investigations of the side reaction with different substrates

Since water is required to form the acyloxyacetate moiety, it is obvious that saponification seems to be the first step of the reaction mechanism. However, it has to be clarified why this reaction selectively takes place on the unbrominated phenolic units, and if a specific alkylation agent determines the outcome of the reaction. To further elaborate on and verify this type of reaction, additional alkyl bromides were used as substrates. As shown in Scheme 2, compound **4** was reacted with ethyl 4-bromobutyrate and ethyl 4-(bromomethyl)benzoate under the conditions according to entry 12 in Table 1.



Scheme 2. Alkylation of compound **4** with different substrates. Reaction conditions: *i*) $BrCH_2C_6H_4COOEt$, NaOH, DMF (+ 0.1% water), 90°C; *ii*) $Br(CH_2)_3COOEt$, NaOH, DMF (+ 0.1% water), 90°C.

An established protocol was used in the work-up of both reactions, and all compounds were isolated and analyzed. When using ethyl 4-(bromomethyl)benzoate both compounds **7** and **8** were isolated in yields of 13% and 52%, respectively. In contrast, when using ethyl 4-bromobutyrate, compound **9** was not observed. Instead, product **10** was isolated in a yield of 47%. These findings prove that the formation of the acyloxy ester reproducibly takes place on the unbrominated phenolic units exclusively.
These promising results lead to the assumption that this reaction is promoted by the structure of compound **4**, and is influenced to a lesser degree by the alkylation agent.

Evaluation of the crystal structures

An essential step in the identification of compound **6** was the elucidation of its crystal structure. Crystals of both calix[4]arenes **2b** and **6** were grown using slow evaporation from a solvent mixture of dichloromethane and methanol, and analyzed by single crystal X-ray crystallography. Both NMR and mass spectra confirmed the results.
Almost rectangular relations exist between the phenyl rings in crystals of **2b**. Two of them are inclined by 2.6° (almost parallel) and the other two by 92.5°. One of the ^{t}Bu groups of **2b** shown in Figure 1 is disordered. This has been modeled by a split refinement. Bond lengths and angles are within expected ranges.

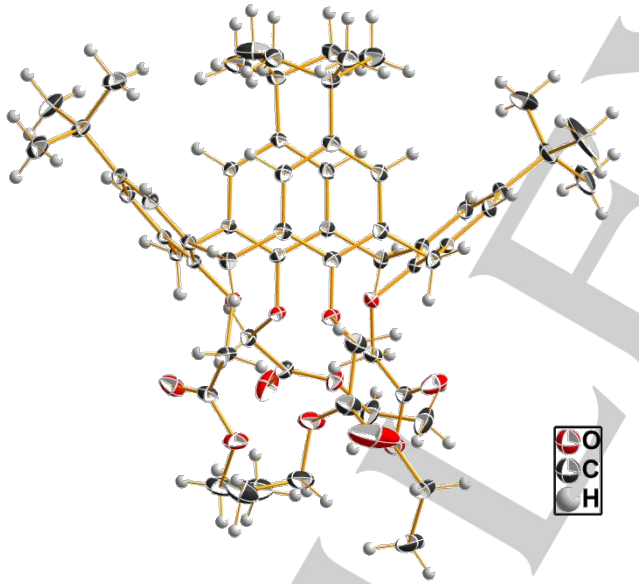


Figure 1. Molecular structure of **2b**, without showing the co-crystallized solvent molecules (only one of the two disordered ^{t}Bu groups is shown).

The structure of **6** is composed of two symmetry-independent molecules **6A** and **6B**. These two conformers (ratio 1:1) are not superimposable and differ significantly as visible in Figure 2. In both conformers **6A** and **6B** also in the calixarene **2b**, the four methylene-bridged phenyl rings are not arranged symmetrically. They form a cage with the shape of a bucket or trapezoid prism. Thereby, two different groups of opposite phenyl rings exist; one with almost parallel phenyl rings (angles between the mean planes through all carbon atoms of the opposite phenyl rings: 13.6° and 24.2°), and one set with two strongly tilted phenyl rings (105.2° and 120.8°). The two conformers differ in which phenolic rings are facing each other: the brominated ones (**6A**) or the unbrominated ones (**6B**).

Calixarenes are known for their pseudopolymorphisms,[14] where the different crystal types (isomers) are the result of interaction with solvent molecules. For compound **6**, true polymorphism was observed. This fact was supported by ^{1}H NMR spectra of this compound recorded at 25°C and -26°C in $CDCl_3$ (see SI). At temperatures below -20°C, most of the proton signals started to split, revealing the existence of the two conformers **6A** and **6B**. The same behavior might be anticipated for compound **2b**, but will not be observed due to its symmetry.
However, the conformer **6A** is peculiar. We assume that due to intramolecular interactions between the bromines (van der Waals force), the phenolic rings are strongly inclined. This pinch in the upper rim leads to a significantly enlarged cavity at the lower rim. Since the NMR study supports it, this might also apply for compound **6** in solution. The **6A**-conformation might possess a catalytic site, which could be the reason why the ester moieties of the unbrominated phenyl rings readily undergo alkylation.
To confirm that this arrangement is necessary for the observed reaction, additional experiments were performed.

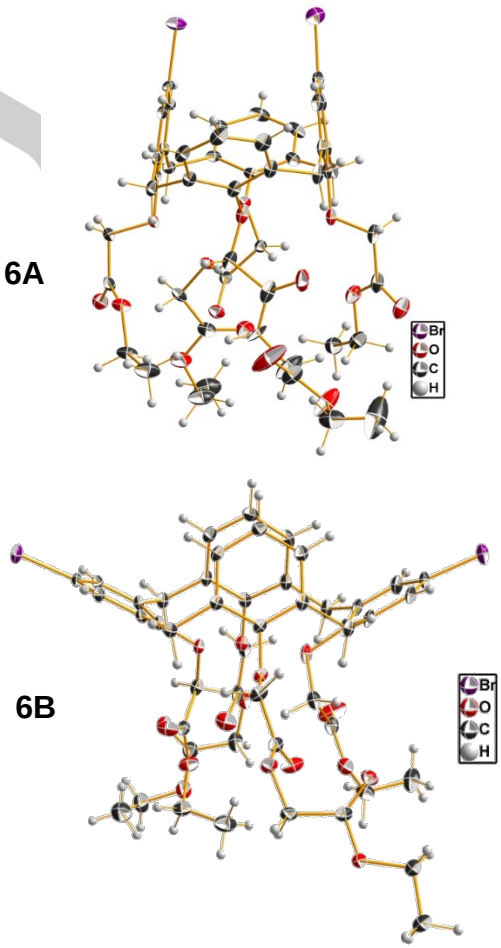


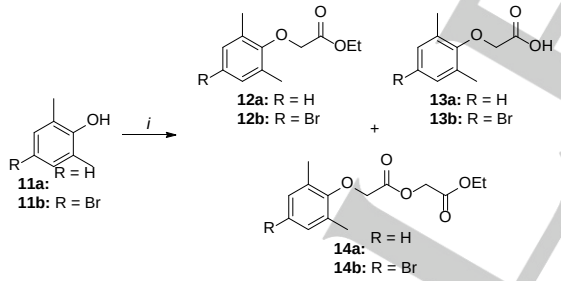
Figure 2. Molecular structure of the two symmetry-independent conformers **6A** and **6B** in crystals of **6**.

Table 2. Crystal data and structure refinement for compounds **2b** and **6**.

Compound	**2b**	**6**
Formula	$C_{60}H_{80}O_{12}\cdot 0.35(CH_3OH)$	$C_{48}H_{50}Br_2O_{16}$
Formula weight (g·mol^{-1})	1004.61	1024.70
Temperature (K)	123	123
Crystal system	triclinic	triclinic
Space group	$P\bar{1}$	$P\bar{1}$
Unit cell dimensions:		
a (Å)	12.1337(7)	15.7713(8)
b (Å)	14.8610(8)	15.9458(8)
c (Å)	16.966(1)	19.448(1)
α (°)	102.438(2)	96.369(2)
β (°)	102.204(2)	101.698(2)
γ (°)	95.184(2)	99.172(3)
Volume (Å^3), *Z*	2890.2(3), 2	4675.8(4), 4
Data/restraints/param.	18500/21/708	18388/0/1189
Measured reflections	157057	200461
θ_{max} (°)	31.09	26.0
GoF on F^2	1.03	1.06
R1 [$I > 2\sigma(I)$][a]	0.051	0.053
wR2 (all data)[b]	0.139	0.139
Larg. diff. peak/hole (e·Å^3)	0.77/-0.69	1.94/-1.06

Alkylation of a simplified, "monomeric" system

The results from the crystallographic analysis led to the assumption that this reaction relies strongly on a holistic influence of the calix[4]arene backbone. It appears not to depend on the difference of the strength of the electron withdrawing effect between the brominated and unbrominated phenolic units. To support this theory, 2,6-dimethylphenol **11a** and 4-bromo-2,6-dimethylphenol **11b** were reacted under the above-mentioned conditions (Scheme 3). These two compounds serve as models for the monomeric phenolic units of compound **4**.



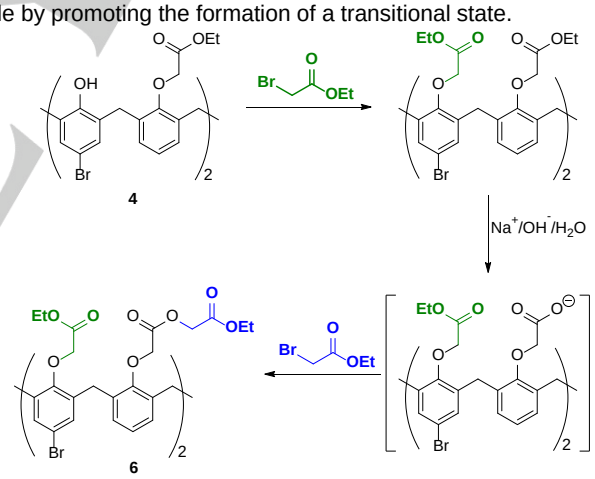
Scheme 3. Alkylation of the monomeric compounds **11a,b**. Reaction conditions: *i*) $BrCH_2COOEt$, NaOH, DMF (+ 0.1% water), 90°C.

Resultantly, compounds **11a** and **11b** delivered the expected alkylated products **12a** and **12b** in yields of 57% and 46%, respectively. Furthermore, both saponified products **13a** and **13b** were isolated in yields of 21% and 24%. However, the acyloxyacetic acid ethyl esters **14a** and **14b** were not obtained. Thus, it must be concluded that the observed reaction is not exclusively dependent on the esters themselves, but rather on the arrangement of the phenolic rings in the rigid calix[4]arene backbone of compound **4**. Based on this investigation, we formulated a mechanism that could explain the observed results of these various reactions.

Proposed mechanism

The formation of the acyloxyacetic acid ethyl ester **6** as well as of compound **8** and **10** was rather astonishing, since the reaction selectively took place on only two opposing ester moieties and is not solely controlled by the functionalization of the attached phenolic units. It is likely that, after the fourfold alkylation of compound **4**, traces of water caused a selectively saponification at the esters connected to the unbrominated phenolic units. Subsequently, the resulting carboxylate groups were alkylated, due to the excess of either ethyl bromoacetate or its analogs. In general, *O*-alkylations of carboxylates with haloalkanes are reported in the literature.[15] The proposed mechanism for this selective reaction is illustrated in Scheme 4.

Interestingly, after the work-up of the *O*-alkylation reactions free carboxylates were not observed. This is in contrast to the results of the reactions with the monomeric compounds **11a** and **11b**. Moreover, the introduced acyloxyacetic acid ethyl esters of compound **6** are stable under these conditions, and did not undergo saponification. The aforementioned leads to the consideration that the mechanism may well be of a holistic nature. The pinched conformation of the brominated rings is attributable to the van der Waals-effect. This is accompanied by the opening of the cavity at the lower rim, which could perform auto-catalytic functionality. The hydrolysis of the ester and the alkylation likely take place simultaneously. Since the reaction depends on the specific base (Table 1), it is likely that sodium ions play a central role by promoting the formation of a transitional state.



Scheme 4. Suggested mechanism for the formation of compound **6**. The last two steps of this reaction likely occur simultaneously than separate.

Conclusions

During our investigation, we found that reacting the calix[4]arene derivative **4** with ethyl bromoacetate caused an unexpected regioselective side reaction, leading to the acyloxyacetic acid ethyl ester **6**, which is a newly described compound.

Various reaction conditions were tested to control the yield-ratio between the expected and novel products. Finally, reproducible protocols were established to for the synthesis of the desired compounds.

In accordance with this protocol, compound **4** was reacted with two additional alkylating agents to produce two novel compounds. When using the monomeric phenolic units 2,6-dimethylphenol **11a** and 4-bromo-2,6-dimethylphenol **11b** instead of the calix[4]arene **4** the *O*-alkylation was not viable.

From the data derived from the crystal structure of compound **6**, and the observed products of the *O*-alkylations, we therefore suggest a holistic mechanism involving the formation of a transition state containing the brominated calix, a sodium ion, a water molecule, and the ester. This arrangement requires a specivic chemical environment, which is provided by the enlarged cavity formed through the pinching of the brominated phenolic units. The final step is a selective saponification for which trace water is required. The reaction works best when using a sodium-containing base. Therefore, sodium may play a central role in coordinating and orienting the reaction partners.

Experimental Section

General

All chemicals were purchased from commercial suppliers and used without further purification, unless otherwise specified. Anhydrous THF and DMF was purchased from Acros and deuterated solvents were purchased from deutero GmbH. Compounds **2a**, **2b**,[6a] **3a** and **3b**[8c] were prepared according to the literature. Spectra of compounds **12a** and **13a** are in accordance with those, previously published.[16] ^{1}H and ^{13}C NMR spectra were recorded on an Agilent DD2–600 MHz NMR spectrometer with ProbeOne at 298 K. Chemical shifts of the spectra were reported in parts per million (ppm) using TMS as internal standard. Mass spectrometric (MS) data were obtained on a Xevo TQ-S mass spectrometer (Waters) by using electrospray ionization (ESI). The melting points were determined on a Galen III melting point apparatus (Cambridge Instruments & Leica) and are uncorrected. Microanalyses were carried out with an LECO CHNS 932 elemental analyzer.Diffraction data were collected with a Bruker Nonius Apex Kappa-II CCD diffractometer, using graphite-monochromated MoK_α radiation (λ = 0.71073 Å) and the measurement was performed at –150°C. The structure was solved by direct methodsand refined against F^2 by full-matrix least-squares using the program suites from G. M. Sheldrick.[17] All non-hydrogen atoms were refined anisotropically; all hydrogen atoms were placed on geometrically calculated positions and refined by using riding models. CCDC 1904616 and 1906961 contain the supplementary crystallographic data for compounds **2b** and **4**.[18] Preparative column chromatography was carried out with silica gel 60 (Merck, particle size 0.040–0.063 mm), petroleum ether (Fisher Scientific, bp 40–60 °C, analytical reagent grade), and ethyl acetate (Fisher Scientific, HPLC grade).

Syntheses

5,17-Dibromo-25,27-bis((ethoxycarbonyl)methoxy)-26,28-dihydroxycalix[4]arene (4)

25,27-Bis((ethoxycarbonyl)methoxy)-26,28-dihydroxycalix[4]aren (**3a**, 3.0 g, 5.03 mmol) was dissolved in dichloromethane (100 mL) and a solution of elemental bromine (2.03 g, 12.70 mmol) in dichloromethane (10 mL) was slowly added at rt. After stirring for 30 min, the reaction was quenched by adding an aqueous solution of $Na_2S_2O_5$ (approx. 15 mL) until the color of the solution disappeared. Next, the organic layer was washed with water (20 mL) and dried over Na_2SO_4 to yield compound **4** as a colorless solid (3.79 g, >99%) after removal of the solvent. R_f = 0.7 (petroleum ether/ethyl acetate 1:2); m.p. 246–248°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (t, ^3J = 7.2 Hz, 6H, CH_3), 3.33 (d, ^2J = 13.2 Hz, 4H, CH_2), 4.33 (q, ^3J = 7.2 Hz, 4H, OCH_2), 4.43 (d, ^2J = 13.2 Hz, 4H, CH_2), 4.70 (s, 4H, CH_2C=O), 6.81 (t, ^3J = 7.5 Hz, 2H, ArH), 6.93 (d, ^3J = 7.5 Hz, 4H, ArH), 7.15 (s, 4H, ArH), 7.73 ppm (s, 2H, OH); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.3 (CH_3), 31.4 (CH_2), 61.6 (OCH_2), 72.5 ($\underline{C}H_2C$=O), 110.8 (C_q), 126.0 (p-CH), 129.6 (m-CH), 130.3 (C_q), 131.0 (m-CH), 132.7 (C_q), 152.2 (C_q), 152.6 (C_q), 168.9 ppm (C=O); MS (ESI+): *m/z* (%): 779 (11) [M^++Na,^{81}Br], 777 (23) [M^++Na,$^{79/81}$Br], 775 (12) [M^++Na,^{79}Br], 757 (52) [M^++Na,^{81}Br], 755 (100) [M^++H,$^{79/81}$Br], 753 (50) [M^++H,^{79}Br]; elemental analysis calcd (%) for $C_{36}H_{34}Br_2O_8$: C 57.31, H 4.54; found: C 57.58, H 4.44.

5,17-Dibromo-25,26,27,28-tetra((ethoxycarbonyl)methoxy)calix[4]arene (5)

Calix[4]arene (**4**, 250 mg, 0.33 mmol) was dissolved in anhydrous DMF (10 mL), NaH (132 mg, 3.31 mmol, 60% in mineral oil) and ethyl bromoacetate (443 mg, 2.65 mmol) were added and the resulting mixture was stirred at 90°C overnight. After cooling to rt, the solvent was removed. The crude product was dissolved in dichloromethane (20 mL) and washed with 10% HCl (2 x 20 mL) and water (2 x 20 mL). The organic layer was dried over Na_2SO_4, the solvent was removed and the crude product was purified via column chromatography (first column: DCM/MeOH 0 → 4%, second column: petroleum ether/ethyl acetate 5:1 → 2:1) to give **5** as a colorless solid (169 mg, 55%). R_f = 0.51 (petroleum ether/ethyl acetate 2:1); m.p. 136°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (t, ^3J = 7.2 Hz, 12H, CH_3), 3.20 (d, ^2J = 13.7 Hz, 4H, CH_2), 4.20 (q, ^3J = 7.2 Hz, 8H, OCH_2), 4.67 (s, 4H, CH_2C=O), 4.72 (s, 4H, CH_2C=O), 4.84 (d, ^2J = 13.7 Hz, 4H, CH_2), 6.64 (s, 6H, ArH), 6.85 ppm (s, 4H, ArH); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 14.3 (m, CH_3), 31.4 (CH_2), 60.7 (OCH_2), 60.8 (OCH_2), 71.4 ($\underline{C}H_2C$=O), 71.5 ($\underline{C}H_2C$=O), 115.8 (C_q), 123.5 (p-CH), 128.9 (m-CH), 131.3 (m-CH), 133.8 (C_q), 137.1 (C_q), 155.3 (C_q), 155.7 (C_q), 170.0 (C=O), 170.1 ppm (C=O); MS (ESI +): *m/z* = 951 [M^++Na; ^{81}Br], 949 [M^++Na; $^{79/81}$Br], 947 [M^++Na; ^{79}Br]; elemental analysis calcd (%) for $C_{44}H_{46}Br_2O_{12}$: C 57.03, H 5.00; found: C 56.96, H 5.10.

5,17-Dibromo-25,27-bis(((ethoxycarbonyl)methoxycarbonyl)methoxy)-26,28-bis((ethoxycarbonyl)methoxy)calix[4]arene (6)

Calix[4]arene (**4**, 250 mg, 0.33 mmol) was dissolved in DMF (10 mL), NaOH (132 mg, 3.31 mmol), a few drops of water and ethyl bromoacetate (443 mg, 2.65 mmol) were added and the resulting mixture was stirred at 90°C overnight. After cooling to rt, the solvent was removed. The crude product was dissolved in dichloromethane (20 mL) and washed with 10% HCl (2 x 20 mL) and water (2 x 20 mL). The organic layer was dried over Na_2SO_4, the solvent was removed and the crude product was purified via column chromatography (first column: DCM/MeOH 0 → 4%, second column: petroleum ether/ethyl acetate 5:1 → 2:1) to give **5** as a colorless solid (138 mg, 40%). R_f = 0.34 (petroleum ether/ethyl acetate 2:1); m.p. 117–118°C; ^{1}H NMR (400 MHz, CD_3CN): δ = 1.18–1.32 (m, 12H, CH_3), 3.26 (d, ^2J = 13.7 Hz, 4H, CH_2), 4.11–4.25 (m, 8H, OCH_2), 4.59 (s, 4H, CH_2C=O), 4.66 (s, 4H, CH_2C=O), 4.77 (d, ^2J = 13.7 Hz, 4H, CH_2), 4.95 (s, 4H, CH_2C=O), 6.66 (s, 4H, ArH), 6.86 (t, ^3J = 7.5 Hz, 2H, ArH), 7.50 ppm (d, ^3J = 7.5 Hz, 4H, ArH); ^{13}C NMR (101 MHz, CD_3CN): δ = 14.4 (CH_3), 14.5 (CH_3), 31.8 (CH_2), 61.7 ($\underline{C}H_2C$=O), 61.8 (OCH_2), 62.2 (OCH_2), 71.7 ($\underline{C}H_2C$=O), 72.4 ($\underline{C}H_2C$=O), 116.1 (C_q), 124.4 (p-CH), 130.2 (m-CH), 131.6 (m-CH), 135.9 (C_q), 137.7 (C_q), 155.5 (C_q), 157.0 (C_q), 168.6, 170.4, 170.8 ppm (3 x C=O); MS (ESI+): *m/z* = 1045 [M^++H; ^{81}Br], 1043 [M^++H, $^{79/81}$Br], 1041 [M^++H; ^{79}Br], 1067 [M^++Na, ^{81}Br], 1065 [M^++Na, $^{79/81}$Br], 1063 [M^++Na; ^{79}Br]; elemental analysis calcd (%) for $C_{48}H_{50}Br_2O_{16}$: C 55.29, H 4.83; found: C 55.16, H 4.90.

5,17-Dibromo-25,27-bis((ethoxycarbonyl)methoxy)-26,28-bis((ethoxycarbonyl)benzyloxy)calix[4]arene (7) and 5,17-dibromo-25,27-bis(((ethoxycarbonyl)benzyloxycarbonyl)methoxy)-26,28-bis((ethoxycarbonyl)benzyloxy)calix[4]arene (8)

Calix[4]arene (**4**, 250 mg, 0.33 mmol) was dissolved in DMF (10 mL), NaOH (132 mg, 3.31 mmol), a few drops of water and ethyl 4-(bromomethyl)benzoate (2.03 g, 2.65 mmol) were added and the resulting mixture was stirred at 90°C overnight. After cooling to rt, the solvent was removed. The crude product was dissolved in dichloromethane (20 mL) and washed with 10% HCl (2 x 20 mL) and water (2 x 20 mL). The organic layer was dried over Na_2SO_4, the solvent was removed and the crude product was purified via column chromatography (first column: DCM/MeOH 0 → 4%, second column: petroleum ether/ethyl acetate 5:1 → 2:1) to give **7** (46 mg, 13%) and **8** (232 mg, 52%) both as a colorless solids. Compound **7**: R_f = 0.75 (petroleum ether:ethyl acetate 2:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.24 (t, ^3J = 7.2 Hz, 6H, CH_3), 1.40 (t, ^3J = 7.1 Hz, 6H, CH_3), 3.04 (d, ^2J = 13.7 Hz, 4H, CH_2), 4.15 (q, ^3J = 7.2 Hz, 4H, OCH_2), 4.36-4.41 (m, 8H, CH_2+OCH_2), 4.44 (s, 4H, CH_2C=O), 5.14 (s, 4H, CH_2C=O), 6.60-6.67 (m, 6H, ArH), 6.78 (s, 4H, ArH), 7.50 (d, ^3J = 8.2 Hz, 4H, ArH), 7.99 ppm (d, ^3J = 8.2 Hz, 4H, ArH); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 14.3, 14.5 (2 x CH_3), 31.3 (CH_2), 60.8, 61.1 (2 x OCH_2), 71.0, 76.5 (2 x $\underline{C}H_2C$=O), 115.7 (C_q), 123.5 (*p*-CH), 129.0 (*m*-CH), 129.5 (CH_{Ar}), 129.7 (CH_{Ar}), 130.3 (), 131.2 (*m*-CH), 133.9, 137.4, 142.2, 154.5, 155.5 (5 x C_q), 166.6, 169.7 ppm (2 x C=O); MS (ESI+): *m*/*z* (%): 1080 (47) [M^++H,^{81}Br], 1078 (95) [M^++H,$^{79/81}$Br], 1076 (48) [M^++H,^{79}Br]; elemental analysis calcd (%) for $C_{56}H_{53}Br_2O_{12}$: C 62.40, H 4.96; found: C 62.58, H 4.81; Compound **8**: R_f = 0.49 (petroleum ether:ethyl acetate 2:1)^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34-1.42 (m, 12H, CH_3), 3.02 (d, ^2J = 13.4 Hz, 4H, CH_2), 4.33-4.41 (m, 12H, CH_2O + CH_2), 4.58 (s, 4H, CH_2C=O), 4.98 (s, 4H, CH_2C=O), 5.06 (s, 4H, CH_2C=O), 6.66-6.73 (m, 8H, ArH), 7.25 (d, ^3J = 8.1 Hz, 4H, ArH), 7.45 (d, ^3J = 8.1 Hz, 4H, ArH), 7.93–8.00 ppm (m, 8H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.4, 14.5 (2 x CH_3), 31.3 (CH_2Ar), 61.2, 65.8, 70.9, 76.6 (4 x CH_2), 115.9 (C_q), 123.7 (*p*-CH), 127.8 (CH_{Ar}), 129.2 (*m*-CH), 129.5 (CH_{Ar}), 129.6 (CH_{Ar}), 129.9 (CH_{Ar}), 130.4 (C_q), 130.6 (C_q), 131.2 (*m*-CH), 154.2 (C_q), 155.6 (C_q), 166.2, 166.4, 169.4 ppm (3 x C=O); MS (ESI+): *m*/*z* (%): 1049 (47) [M^++H,^{81}Br], 1047 (95) [M^++H,$^{79/81}$Br], 1045 (47) [M^++H,^{79}Br]; elemental analysis calcd (%) for $C_{72}H_{66}Br_2O_{16}$: C 64.20, H 4.94; found: C 64.28, H 4.90.

5,17-Dibromo-25,27-bis(((ethoxycarbonyl)butoxycarbonyl)methoxy)-26,28-bis((ethoxycarbonyl)butoxy)calix[4]arene (10)

Calix[4]arene (**4**, 250 mg, 0.33 mmol) was dissolved in DMF (10 mL), NaOH (132 mg, 3.31 mmol), a few drops of water and ethyl bromobutanoate (559 mg, 2.65 mmol) were added and the resulting mixture was stirred at 90°C overnight. After cooling to rt, the solvent was removed. The crude product was dissolved in dichloromethane (20 mL) and washed with 10% HCl (2 x 20 mL) and water (2 x 20 mL). The organic layer was dried over Na_2SO_4, the solvent was removed and the crude product was purified via column chromatography (first column: DCM/MeOH 0 → 4%, second column: petroleum ether/ethyl acetate 5:1 → 2:1) to give **10** as a colorless solid (180 mg, 47%). R_f = 0.65 (DCM:MeOH 16:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.36-1.41 (m, 12H, CH_3), 3.02 (d, ^2J = 13.7 Hz, 4H, CH_2), 4.34-4.41 (m, 12H, CH_2+OCH_2), 4.59 (s, 4H, CH_2C=O), 4.98 (s, 4H, CH_2C=O), 5.07 (s, 4H, CH_2C=O), 6.67 (s, 4H, ArH), 6.69-6.75 (m, 6H, ArH), 7.26 (d, ^3J = 8.2 Hz, 4H, ArH), 7.45 (d, ^3J = 8.2 Hz, 4H, ArH) 7.94-8.00 ppm (m, 8H, ArH); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 14.4, 14.5 (2 x CH_3), 31.3 (CH_2), 61.2 (OCH_2), 65.8, 70.9, 76.6 (3 x $\underline{C}H_2C$=O), 115.9 (C_q), 123.7 (CH_{Ar}), 127.8 (CH_{Ar}), 129.2 (CH_{Ar}), 129.6 (CH_{Ar}), 129.9 (CH_{Ar}), 130.4 (C_q), 130.6 (C_q), 131.1 (CH_{Ar}), 134.2, 136.9, 140.2, 142.0, 154.2, 155.6 (6 x C_q), 166.2, 166.4, 169.4 ppm (3 x C=O); MS (ESI+): *m*/*z* (%): 1156 (20) [M^++H; ^{81}Br], 1054 (100) [M^++H,$^{79/81}$Br], 1052 (49) [M^++H,^{79}Br]; elemental analysis calcd (%) for $C_{56}H_{66}Br_2O_{16}$: C 58.24, H 5.76; found: C 58.50, H 5.79.

Ethyl 2-(2,6-dimethylphenoxy)acetate (12a) and 2-(2,6-dimethyl phenoxy)acetic acid (13a)

2,6-Dimethylphenol (**11a**, 300 mg, 2.46 mmol) was dissolved in DMF (15 mL), NaOH (491 mg, 12.3 mmol), a few drops of water and ethyl bromobutanoate (1.64 g, 9.8 mmol) were added and the resulting mixture was stirred at 90°C overnight. After cooling to rt, the solvent was removed. The crude product was dissolved in dichloromethane (40 mL) and washed with 10% HCl (2 x 40 mL) and water (2 x 40 mL). The organic layer was dried over Na_2SO_4, the solvent was removed and the crude product was purified via column chromatography (petroleum ether/ethyl acetate 5:1 → 1:1) to give **12a** (291 mg, 57%) and **13a** (93 mg, 21%) both as a colorless oil. NMR and MS data are in accordance with the previously published. [16]

Ethyl 2-(4-bromo-2,6-dimethylphenoxy)acetate (12b) and 2-(4-bromo-2,6-dimethylphenoxy)acetic acid (13b)

4-Bromo-2,6-dimethylphenol (**11b**, 500 mg, 2.49 mmol) was dissolved in DMF (15 mL), NaOH (497 mg, 12.4 mmol), a few drops of water and ethyl bromobutanoate (1.66 g, 9.95 mmol) were added and the resulting mixture was stirred at 90°C overnight. After cooling to rt, the solvent was removed. The crude product was dissolved in dichloromethane (40 mL) and washed with 10% HCl (2 x 40 mL) and water (2 x 40 mL). The organic layer was dried over Na_2SO_4, the solvent was removed and the crude product was purified via column chromatography (petroleum ether/ethyl acetate 5:1 → 1:1) to give **12b** (328 mg, 46%) and **13b** (154mg, 24%) both as colorless oil. Compound **12b**: R_f = 0.65 (DCM:MeOH 16:1); ^{1}H NMR (400 MHz, $CDCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$): 1.31 (t, ^3J = Hz, 3H, CH_3), 2.26 (s, 6H, $ArCH_3$), 4.28 (q, ^3J = Hz, 2H, CH_2), 7.11 ppm (s, 2H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.3 (CH_3), 16.2 ($ArCH_3$), 61.4, 69.2 (2 x CH_2), 117.1 (C_q), 131.6 (CH_{Ar}), 133.0 (CH_{Ar}), 154.6 (C_q), 168.8 ppm (C=O); MS (ESI+): *m*/*z* (%): 108 (20) [M^+], 107 (60) [M^+−H], 91 (100) [$C_7H_7^+$]; elemental analysis calcd (%) for $C_{12}H_{15}BrO_3$: C 50.19, H 5.27; found: C 50.00, H 5.29. Compound **13b**: R_f = 0.1 (DCM:MeOH 16:1); ^{1}H NMR (400 MHz, $CDCl_3$): 2.26 (s, 6H, CH_3), 4.42 (s, 2H, CH_2), 7.15 ppm (s, 2H, ArH); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 16.3 (CH_3), 68.5 (CH_2), 117.7 (C_q), 131.9 (CH_{Ar}), 132.9 (CH_{Ar}), 153.9 (C_q), 172.2 ppm (C=O); MS (ESI+): *m*/*z* (%): 108 (20) [M^+], 107 (60) [M^+−H], 91 (100) [$C_7H_7^+$]; elemental analysis calcd (%) for $C_{10}H_{11}BrO_3$: C 46.36, H 4.28; found: C 46.34, H 4.20.

Acknowledgements

This work is part of the master thesis of Sergej Stipurin (TU Dresden, Faculty of Chemistry and Food Chemistry).

Keywords: calix[4]arenes • esterification • *O*-alkylation • complexation • selective bromination

[1] a) C. D. Gutsche, B. Dhawan, K. H. No, R. Muthukrishnan, *J. Am. Chem. Soc.* **1981**, *103*, 3782-3792; b) C. D. Gutsche in *Calixarenes – An Introduction*, Vol. 2, RSC Publishing, Cambridge, **2008**; c) W. Sliwa, C. Kozlowski, *Calixarenes and Resorcinarenes*, Wiley-VCH, Weinheim, **2009**.

[2] a) J. Harrowfield, *Chem. Commun.* **2013**, *49*, 1578-1580; b) V. Arora, H. M. Chawla, S. P. Singh, ARKIVOK **2007**, 172-200; c) W. Sliwa, M. Deska, ARKIVOK **2008**, 87-127; d) W. Sliwa, T. Girek, *J. Incl. Phenom.*

Macrocycl. Chem. **2010**, *66*, 15–41; e) R. Gramage-Doria, D. Armspach, D. Matt, *Coord. Chem. Rev.* **2013**, *257*, 776–816.

[3] a) F. Arnaud-Neu, M.-J. Schwing-Weill, J.-F. Dozol, in *Calixarenes 2001*, **2002**, pp. 642-662; b) J. F. Malone, D. J. Marrs, M. A. McKervey, P. O'Hagan, N. Thompson, A. Walker, F. Arnaud-Neu, O. Mauprivez, M.-J. Schwing-Weill, J.-F. Dozol, H. Rouquette, N. Simon, *Chem. Commun.* **1995**, 2151–2153; c) F. W. B. van Leeuwen, H. Beijleveld, C. J. H. Miermans, J. Huskens, W. Verboom, D. N. Reinhoudt, *Anal. Chem.* **2005**, *77*, 4611–4617; d) B. Mokhtari, K. Pourabdollah, N. Dallali, *Radioanal. Nucl. Chem.* **2011**, *287*, 921–934.

[4] a) X. Y. Chen, M. Ji, D. R. Fisher, C. M. Wai, *Inorg. Chem.* **1999**, *38*, 5449–5452; b) G. Henriksen, P. Hoff, R. H. Larsen, *Appl. Radiat. Isot.* **2002**, *56*, 667–671; c) P.K. Mohapatra, D.R. Raut, M. Iqbal, J. Huskens, W. Verboom, *Supramol. Chem*. **2016**, *28*, 360–366; d) J. Steinberg, D. Bauer, F. Reissig, M. Kockerling, H. J. Pietzsch, C. Mamat, *ChemOpen* **2018**, *7*, 432–438; e) D. Bauer, M. Gott, J. Steinbach, C. Mamat, *Spectrochim. Acta. A* **2018**, *199*, 50–56.

[5] a) I. A. Marques, A. R. Neves, A. M. Abrantes, A. S. Pires, E. Tavares-da-Silva, A. Figueiredo, M. F. Botelho, *Cancer Treat. Rev.* **2018**, *68*, 47-54; b) O. Bruland, T. Jonasdottir, D. Fisher, R. Larsen, *Curr. Radiopharm.* **2008**, *1*, 203–208; c) M. Gott, J. Steinbach, C. Mamat, *Open Chem.* **2016**, *14*, 118–129.

[6] a) F. Arnaud-Neu, E. M. Collins, M. Deasy, G. Ferguson, S. J. Harris, B. Kaitner, A. J. Lough, M. A. McKervey, E. Marques, *J. Am. Chem. Soc.* **1989**, *111*, 8681-8691; b) K. Iwamoto, K. Fujimoto, T. Matsuda, S. Shinkai, *Tetrahedron Lett.* **1990**, *31*, 7169-7172; c) M. A. McKervey, E. M. Seward, G. Ferguson, B. Ruhl, S. J. Harris, *Chem. Commun.* **1985**, 388-390.

[7] a) D. T. Schühle, S. Klimosch, J. Schatz, *Tetrahedron Lett.* **2008**, *49*, 5800-5803; b) V. Malytskyi, L. Troian-Gautier, A. Mattiuzzi, S. Lambotte, B. Cornelio, C. Lagrost, I. Jabin, *Eur. J. Org. Chem.* **2018**, *2018*, 6590-6595; c) X. Hu, Y. Li, H. Yang, Y. Luo, *Tetrahedron Lett.* **2006**, *47*, 7463-7465; d) J. Gagnon, M. Vézina, M. Drouin, P. D. Harvey, Can. J. Chem. 2001, 79, 1439-1446; e) S. N. Podyacheva, G. Sh. Gimazetdinova, S. N. Sudakova, D. V. Lapaev, V. V. Syakaev, R. N. Nagimov, Russ. J. Gen. Chem. 2017, 87, 1958-1968.

[8] a) E. M. Collins, M. A. McKervy, E. Madigan, M. B. Moran, M. Owens, G. Ferguson, S. J. Harris, J. Chem. Soc. Perkin Trans 1, 1991, 3137–3142; b) R. Hosseinzadeh, M. Nemati, R. Zadmard, M. Mohadjerani, *Beilstein J. Org. Chem.* **2016**, *12*, 1749-1757; c) L. S. Arora, H. M. Chawla, M. Shahid, N. Pant, *Org. Prep. Proc. Int.* **2017**, *49*, 228-235

[9] C. D. Gutsche in *Calixarenes – An Introduction*, Vol. 2, RSC Publishing, Cambridge, **2008**, pp.116-146.

[10] a) A. Casnati, M. Fochi, P. Minari, A. Pochini, M. Reggiani, R. Ungaro, D. N. Reinhoudt, *Gazz. Chim. Ital.* **1996**, *126*, 99–106; b) Y. Yang, G. Arora, F. A. Fernandez, J. D. Crawford, K. Surowiec, E. K. Lee, R. A. Bartsch, *Tetrahedron* **2011**, *67*, 1389–1397; c) B. Genorio, *Acta Chim. Slov.* **2016**, 63, 496–508.

[11] I. Smukste, B. E. House, D. B. Smithrud, *J. Org. Chem.* **2003**, *68*, 2559-2571.

[12] H. Hioki, R. Nakaoka, A. Maruyama, M. Kodama, *J. Chem. Soc., Perkin Trans. 1* **2001**, 3265-3268.

[13] B. Drevermann, A. Lingham, H. Hügel, P. Marriott, *Tetrahedron Lett.* **2005**, *46*, 39-41.

[14] a) P. O. Brown, K. A. Udachin, G. D. Enright, J. A. Ripmeester, *Chem. Eur. J.* **2006**, *12*, 8240-8252; b) J. A. Ripmeester, G. D. Enright, C. I. Ratcliffe, K. A. Udachin, I. L. Moudrakovski, *Chem. Commun.* **2006**, 4986-4996; c) S. H. Dale, M. R. J. Elsegood, C. Redshaw, *CrystEngComm* **2003**, *5,* 368-373.

[15] a) G. Mehta, *Synthesis* **1972**, 262-262; b) F. Alvarez, A. N. Watt, *J. Org. Chem.* **1968**, *33*, 2143-2144; c) J. McNulty, S. Cheekoori, J. J. Nair, V. Larichev, A. Capretta, A. J. Robertson, *Tetrahedron Lett.* **2005**, *46*, 3641-3644.

[16] A. N. Matralis, D. Xanthopoulos, G. Huot, S. Lopes-Paciencia, C. Cole, H. de Vries, G. Ferbeyre, Y. S. Tsantrizos, *Bioorg. Med. Chem.* **2018**, *26*, 5547-5554.

[17] a) G. M. Sheldrick, *Acta Crystallogr.* **2008**, *64*, 112–122; b) G. M. Scheldrick, *Acta Crystallogr.* **2015**, *71*, 3–8; c) G. M: Sheldrick, Shelx, Programs for the Refinement of Crystal Structures, University of Göttingen, Göttingen, **2014**.

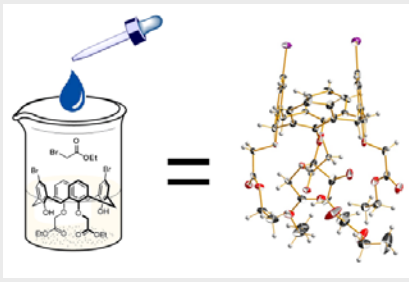
[18] The crystallographic data for this paper can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Entry for the Table of Contents

Layout 1:

FULL PAPER

Water makes a difference. The presence of water in the solvent system enables a selective *O*-alkylation reaction of brominated calix[4]arenes with ethyl bromoacetate. When no water is present, the expected alkylation occurs instead.



*David Bauer, Sergej Stipurin, Martin Köckerling, Jörg Steinbach, and Constantin Mamat**

Page No. – Page No.

Title

Additional Author information for the electronic version of the article.

Author: David Bauer ORCID identifier 0000-0002-3051-7997
Author: Sergej Stipurin ORCID identifier
Author: Martin Köckerling ORCID identifier 0000-0001-7666-6990
Author: Jörg Steinbach ORCID identifier 0000-0002-1708-6440
Author: Constantin Mamat ORCID identifier 0000-0003-1906-3186