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Formation of calix[4]arenes with acyloxycarboxylate functions

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

[a] Institut für Radiopharmazeutische Krebsforschung, Helmholtz-Zentrum Dresden-Rossendorf, Bautzner Landstraße 400, 01328 Dresden, Germany
[b] Fakultät Chemie und Lebensmittelchemie der TU Dresden, 01062 Dresden, Germany
[c] Institut für Chemie, Anorganische Festkörperchemie der Universität Rostock, Albert-Einstein-Straße 3a, 18059 Rostock, Germany

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ABSTRACT

Calix[4]arenes are an exciting class of multifunctional compounds. Their ability to bind small molecules and ions actively makes them useful tools for many applications. While looking for a suitable chelating agent, a particular modification of the calix[4]arene led to an unexpected side reaction. In this work, we will describe the selective formation of the observed acyloxyacetate derivatives. The according yields can be regulated by controlling the water content of the solvent system. All new compounds were obtained in yields higher than 45% and fully characterized by NMR, MS, EA, and X-ray crystallography. By performing and analyzing several reactions with different calix[4]arenes and monomeric derivatives, an explanation for the reaction mechanism was postulated. Further, we report on the modification of reaction conditions which were investigated to verify our findings' veracity. In total, three acyloxyacetate derivatives were synthesized and characterized to support our conclusions.

1. Introduction

Compounds based on calix[4]arenes arise from the field of supramolecular chemistry and consist of four phenolic units linked by methylene bridges [1–3]. This arrangement creates a cavity that forms inclusion complexes with small neutral molecules or ions [4–8]. One major field of application is their use as extraction agents/chelators for nuclear waste treatment [9–12], since they interact particularly strongly with heavy group 2 metals [13–17]. Modifying their backbone modulates the cavity properties, allowing for an appropriate alignment for the required task. Remarkably, the regioselective alkylation of the phenolic hydroxy 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 [1–3]. Multimodality is a requirement for the use of these class of molecules, e.g., as 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 [18–20], 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.

2. Results and discussion

We aimed to synthesize a variety of multimodal calix[4]arenes that offer oxygen donors with proton-ionizable groups to bind ions of heavy alkaline earth metals strongly, and further contain functional groups (e.g., bromine) at the upper rim for additional modifications.

A common method to add more donor atoms to the calix backbone is to alkylate the phenolic hydroxy groups, e.g., with ethyl bromoacetate, followed by saponification of the ester to obtain carboxylate donors. Therefore, **1a** and **1b** were reacted with a high excess of ethyl bromoacetate (40 equiv.) under basic conditions, which led to the exhaustedly alkylated products **2a** and **2b** in high yields [21–23].

The compounds **2a** and **2b**, and – after saponification – their corresponding acids, provide hard donor atoms. The next contemplated step to produce a calix[4]arene-based radiopharmaceutical relevant precursor, is to functionalize the upper calix-rim of these compounds by mono- or dibromination. This would

* Corresponding author. Institut für Radiopharmazeutische Krebsforschung, Helmholtz-Zentrum Dresden-Rossendorf, Bautzner Landstraße 400, 01328, Dresden, Germany.
E-mail address: c.mamat@hzdr.de (C. Mamat).

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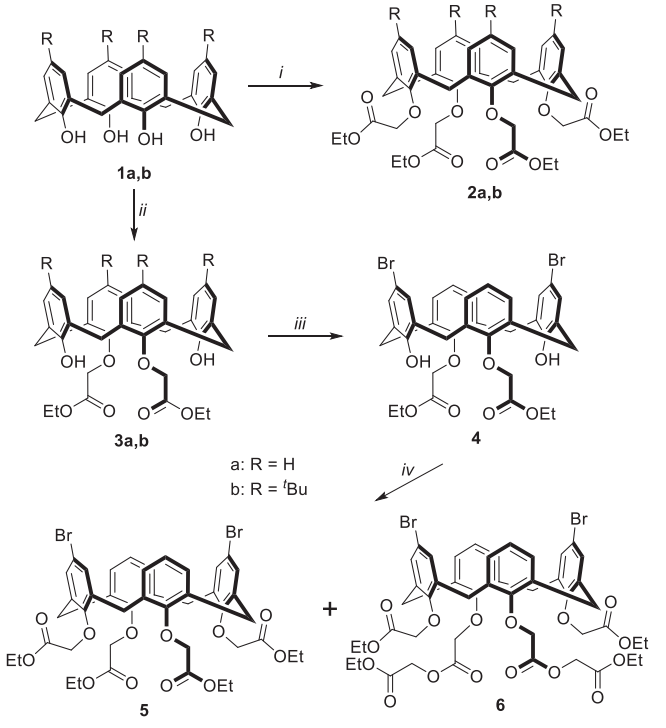
allow to couple the chelator with a suitable targeting molecule (e.g., by Suzuki reaction). However, it was found to be disadvantageous to brominate the calix[4]arene at this stage. Notably, a straightforward, regioselective mono- or dibromination of **2a** or **2b** is not described in the literature, since the reactivity for all four phenolic units is equal [1–3].

Nevertheless, a regioselective alternating dibromination is possible by taking additional steps [24–29]. Regioselectively alkylated calix[4]arenes **3a** and **3b** were obtained in yields of approx. 90%, when using a stoichiometric amount (1–1.5 equiv. per OH group) of ethyl bromoacetate instead of 40 equiv [21,30–32]. The regioselective alkylation of **1a** and **1b** (Scheme 1) is provided by intramolecular hydrogen bonds and the resulting gradation of the hydroxy-pK_a values [33]. Due to the +I inductive effect of alkyl groups, the alkylated phenolic units in **3a** and **3b** will not undergo the bromination reaction with elemental bromine, as reported in the literature [34–36]. Accordingly, bromination led to a rapid and quantitative formation of compound **4** [37]. After the selective modification of the upper rim, the two remaining hydroxy 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, the reaction conditions were chosen according to the preparation of comparable derivatives [38].

2.1. Side reactions

During the synthesis route mentioned above, an unexpected side reaction attracted our interest. After the reaction of compound **4** with an excess of ethyl bromoacetate according to conditions *iv* in Scheme 1 (Table 1, entry 12), two compounds were isolated. The desired product **5** gave a yield of only 5%. The main product (40% yield) could initially not be identified. 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 identify the molecular structure of compound **6** unambiguously (Fig. 1) (see Table 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
Reaction conditions for the conversion of the starting material **4** to the calix-compounds **5** and **6**.

Entry	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%

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

Compound	2b	6
Formula	$C_{60}H_{80}O_{12}$ x 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
w*R2* (all data)[b]	0.139	0.139
Larg. diff. peak/hole (e·Å^3)	0.77/-0.69	1.94/-1.06

Interestingly, a selective saponification and alkylation of the ester moieties attached to the unbrominated phenolic units have occurred in the reaction from compound **4** to product **6**. In general, the formation of the acyloxyacetate moiety itself is reported [39–42]. However, there are only a few reports in the literature on examples for the selectivity [43], which was observed for compound **6**.

Hereafter, 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 isolated as the main product; no formation of calix **6** was obtained. However, when traces of water were present in DMF, product **6** was formed. All reaction conditions and yields are summarized in Table 1.

Worthy of mention is the absence of products **5** or **6** when using KO^{t}Bu as a base (Table 1, entries 2, 6, and 10). Compound **5** was obtained in yields of 45% and 55%, respectively, when using anhydrous DMF with K_2CO_3 or NaH as base (Table 1, entries 1 and 3). Compound **6** was obtained in the highest yield of 40% using NaOH as base (Table 1, entry 12). Since an appropriate protocol to synthesize the acyloxyacetic acid ethyl ester was found, it had to be

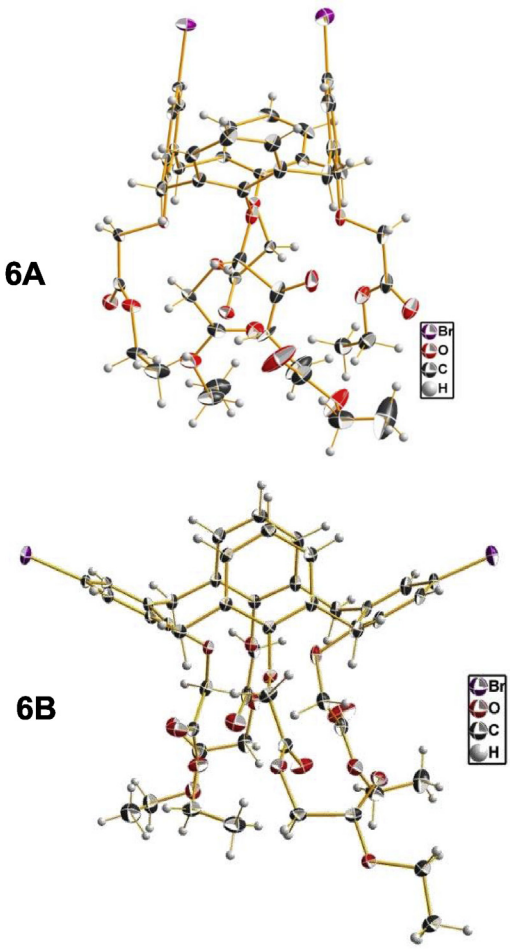
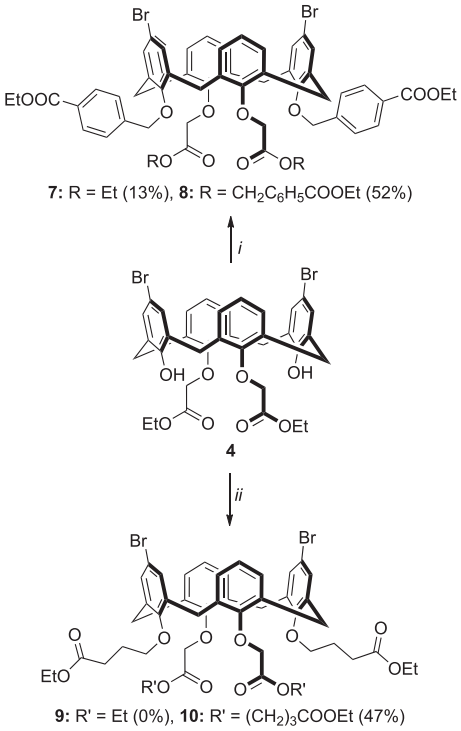


Fig. 1. Molecular structure of the two symmetry-independent conformers **6A** and **6B** in crystals of **6**.



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.

further investigated whether other alkylating agents react with compound **4** to produce analogs of product **6**.

2.2. Investigations of the side reaction with different substrates

Traces of water combined with basic conditions seem to be required to form the acyloxyacetate moiety. It is evident that an intramolecular transesterification combined with saponification are part of the reaction mechanism. However, it has to be clarified why this reaction selectively takes place on both non-brominated 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. All reactions were worked-up identically, and all compounds were isolated and analyzed.

When using ethyl 4-(bromomethyl)benzoate, product **7**, as well as acyloxyacetate derivative **8**, were isolated in yields of 13% and 52%, respectively. In contrast, when using ethyl 4-bromobutyrate, compound **9** was not observed. Instead, the acyloxyacetate derivative **10** was isolated in a yield of 47%. These findings prove that the formation of the acyloxy ester reproducibly takes place exclusively on the unbrominated phenolic units. Additionally, compounds **2a,b** and, **5** were treated under the conditions of entry 12 in Table 1, but no chain-elongated product was observed.

These results lead to the assumption that this reaction is somehow promoted by the molecular structure of compound **4**, and is influenced to a lesser degree by the alkylation agent.

2.3. Evaluation of the crystal structures

The 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.

The structure of acyloxyacetate compound **6** (Fig. 1) 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 Fig. 1. 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 [44–46] where the two different isomers are the result from the interaction with solvent molecules. For compound **6**, true polymorphism was observed. This fact is 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 moved and started to broaden, revealing the existence of the two conformers **6A** and

6B. The same behavior might be anticipated for the other calix[4]arenes.

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 the change in the molecular structure, this might also apply for compound **6** in solution. Conformer **6A** might possess a particular arrangement, which could be one of the reasons why the ester moieties of the non-brominated phenyl rings readily undergo alkylation. To confirm the necessity of this arrangement for the observed reaction, additional experiments were performed.

Almost rectangular relations exist between the phenyl rings in crystals of **2b**. Two of them are inclined by 2.6° (practically parallel) and the other two by 92.5°. One of the ^{t}Bu groups of **2b** shown in Fig. 2 is disordered. This has been modeled by a split refinement. Bond lengths and angles are within expected ranges.

2.4. Alkylation of a simplified, "monomeric" system

To find a reasonable explanation for the formation of the acyloxyacetate derivatives, the influence of the calixarene skeleton was investigated. Therefore, the two compounds 2,6-dimethylphenol **11a** and 4-bromo-2,6-dimethylphenol **11b**, which can be seen as monomeric calixarenes units, were reacted with ethyl bromoacetate (Scheme 3) under the above elaborated conditions (entry 12 in Table 1). Resultantly, the reaction of compounds **11a/b** with ethyl bromoacetate was performed to give the expected alkylated products **12a/b** 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, a mechanism was formulated to explain the observed results of these various reactions.

2.5. Proposed mechanism

The formation of the acyloxyacetic derivative **6,** as well as of compound **8** and **10** was rather unexpected, since the reaction

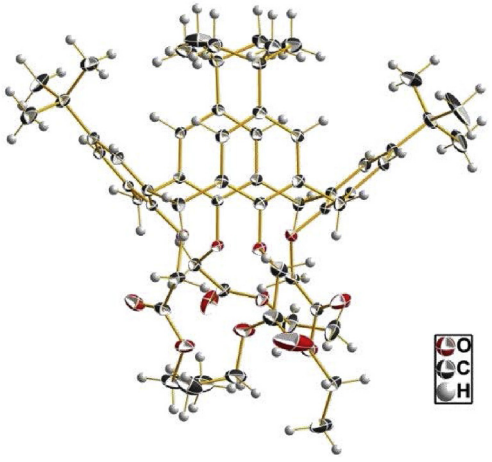
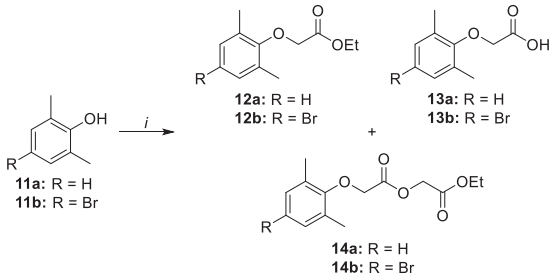


Fig. 2. Molecular structure of **2b**, without showing the co-crystallized solvent molecules (only one of the two disordered ^{t}Bu groups is shown).

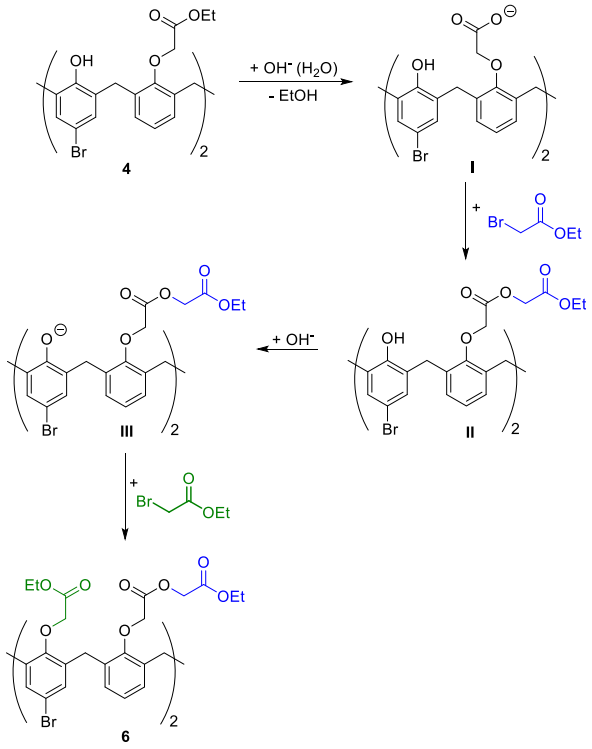


Scheme 3. Alkylation of the monomeric compounds **11a,b**. Reaction conditions: *i*) $BrCH_2COOEt$, NaOH, DMF (+0.1% water), 90 °C.

selectively took place on only those two opposing ester moieties attached to the non-brominated phenol units.

To investigate the influence of the bromine atoms attached at the para-position of two opposing phenols (cf. compounds **6**, **8** and **10**), the alkylation with ethyl bromoacetate was tested on the non-brominated compounds **2a** and **2b**, as well as on the fourfold alkylated calix[4]arene **5**. Although identical conditions were used for the synthesis of compound **6** (entry 12 in Table 1), no formation of the corresponding acyloxyacetic derivatives was observed with these molecules. It should also be noted that no saponified products were found. Even the monomeric species **11a,b** did not deliver the acyloxyacetic derivatives **14a,b**, but delivered saponified products **13a,b** partly. This leads to the assumption that compound **4** is mandatory as the starting material.

According to these results, we suggest a possible mechanism, which is illustrated in Scheme 4. The first step could be the saponification of the present ethyl ester of **4**. The formed acetate **I** undergoes a nucleophilic reaction with ethyl bromoacetate, which is used in excess to form the observed acyloxyacetic moiety, followed by the deprotonation of the remaining free phenolic OH



Scheme 4. Suggested mechanism for the formation of compound **6**.

groups of **II**. Due to the bromine atom in *para*-position, these groups are slightly more acidic. In the final step, the two phenolate units of **III** react with ethyl bromoacetate to form compound **6**. Calix[4]arene derivatives with free carboxylate groups or with an intramolecular formed lactone moiety were not observed.

3. Conclusion

During our investigation, we found that reacting the calix[4]arene derivative **4** with ethyl bromoacetate an unexpected regioselective side reaction occured, leading to the acyloxyacetic acid ester derivative **6**. Various reaction conditions were tested to control the yield ratio between the expected and novel products. Finally, reproducible protocols were established for the synthesis of the desired compounds **6**, **8**, and **10**.

When using the "monomeric phenolic units" 2,6-dimethylphenol (**11**) and 4-bromo-2,6-dimethylphenol (**11b**) instead of calix[4]arene **4**, the *O*-alkylation was not viable. The same applies to the fourfold alkylated compounds **2a,b**, and **5**. This mechanism requires a specific chemical environment provided by the restricted calix[4]arene skeleton formed by brominated and non-brominated phenolic units of calix **4** in contrast to the monomeric molecules.

4. Experimental section

4.1. 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** [21], **3a** and **3b** [32] were prepared according to the literature. Spectra of compounds **12a** and **13a** are in accordance with those, previously published [47]. ^{1}H and ^{13}C NMR spectra were recorded on Agilent DD2 NMR spectrometers (400 or 600 MHz) 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 methods and refined against F^2 by full-matrix least-squares using the program suites from G. M. Sheldrick [48–50]. 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 **6**. The crystallographic data for this paper can be obtained free of charge from The Cambridge Crystallographic Data Centre. 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), methanol, chloroform, and ethyl acetate (Fisher Scientific, HPLC grade).

4.2. Syntheses

4.2.1. 5,17-Dibromo-25,27-bis((ethoxycarbonyl)methoxy)-26,28-dihydroxycalix[4]arene (*4*)

25,27-Bis((ethoxycarbonyl)methoxy)-26,28-dihydroxycalix[4]arene (**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, ^{3}J = 7.2 Hz, 6H, CH_3), 3.33 (d, ^{2}J = 13.2 Hz, 4H, CH_2), 4.33 (q, ^{3}J = 7.2 Hz, 4H, OCH_2), 4.43 (d, ^{2}J = 13.2 Hz, 4H, CH_2), 4.70 (s, 4H, $CH_2C{=}O$), 6.81 (t, ^{3}J = 7.5 Hz, 2H, ArH), 6.93 (d, ^{3}J = 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.

4.2.2. 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 × 20 mL) and water (2 × 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, ^{3}J = 7.2 Hz, 12H, CH_3), 3.20 (d, ^{2}J = 13.7 Hz, 4H, CH_2), 4.20 (q, ^{3}J = 7.2 Hz, 8H, OCH_2), 4.67 (s, 4H, $CH_2C{=}O$), 4.72 (s, 4H, $CH_2C{=}O$), 4.84 (d, ^{2}J = 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.

4.2.3. 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 × 20 mL) and water (2 × 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 **6** 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, ^{2}J = 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, ^{2}J = 13.7 Hz, 4H, CH_2), 4.95 (s, 4H, $CH_2C{=}O$), 6.66 (s, 4H, ArH), 6.86 (t, ^{3}J = 7.5 Hz, 2H, ArH), 7.50 ppm (d, ^{3}J = 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.

4.2.4. 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 × 20 mL) and water (2 × 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.

4.2.5. 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 4-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 × 20 mL) and water (2 × 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.

4.2.6. 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 bromoacetate(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 × 40 mL) and water (2 × 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].

4.2.7. 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 bromoacetate(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 × 40 mL) and water (2 × 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** (154 mg, 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.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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References

[1] C.D. Gutsche, B. Dhawan, K.H. No, R. Muthukrishnan, J. Am. Chem. Soc. 103 (1981) 3782–3792.
[2] C.D. Gutsche, in: Calixarenes – an Introduction, vol. 2, RSC Publishing, Cambridge, 2008.
[3] W. Sliwa, C. Kozlowski, Calixarenes and Resorcinarenes, Wiley-VCH, Weinheim, 2009.
[4] J. Harrowfield, Chem. Commun. 49 (2013) 1578–1580.
[5] V. Arora, H.M. Chawla, S.P. Singh, ARKIVOK (2007) 172–200.
[6] W. Sliwa, M. Deska, ARKIVOK (2008) 87–127.
[7] W. Sliwa, T. Girek, J. Inclusion Phenom. Macrocycl. Chem. 66 (2010) 15–41.
[8] R. Gramage-Doria, D. Armspach, D. Matt, Coord. Chem. Rev. 257 (2013) 776–816.
[9] F. Arnaud-Neu, M.-J. Schwing-Weill, J.-F. Dozol, Calixarenes 2002 (2001) 642–662.
[10] 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.
[11] F.W.B. van Leeuwen, H. Beijleveld, C.J.H. Miermans, J. Huskens, W. Verboom, D.N. Reinhoudt, Anal. Chem. 77 (2005) 4611–4617.
[12] B. Mokhtari, K. Pourabdollah, N. Dallali, Radioanal. Nucl. Chem. 287 (2011) 921–934.
[13] X.Y. Chen, M. Ji, D.R. Fisher, C.M. Wai, Inorg. Chem. 38 (1999) 5449–5452.
[14] G. Henriksen, P. Hoff, R.H. Larsen, Appl. Radiat. Isot. 56 (2002) 667–671.
[15] P.K. Mohapatra, D.R. Raut, M. Iqbal, J. Huskens, W. Verboom, Supramol. Chem. 28 (2016) 360–366.
[16] J. Steinberg, D. Bauer, F. Reissig, M. Köckerling, H.-J. Pietzsch, C. Mamat, ChemistryOpen 7 (2018) 432–438.
[17] D. Bauer, M. Gott, J. Steinbach, C. Mamat, Spectrochim. Acta 199 (2018) 50–56.
[18] I.A. Marques, A.R. Neves, A.M. Abrantes, A.S. Pires, E. Tavares-da-Silva, A. Figueiredo, M.F. Botelho, Canc. Treat Rev. 68 (2018) 47–54.
[19] O. Bruland, T. Jonasdottir, D. Fisher, R. Larsen, Curr. Rad. 1 (2008) 203–208.
[20] M. Gott, J. Steinbach, C. Mamat, Open Chem 14 (2016) 118–129.
[21] 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. 111 (1989) 8681–8691.
[22] K. Iwamoto, K. Fujimoto, T. Matsuda, S. Shinkai, Tetrahedron Lett. 31 (1990) 7169–7172.
[23] M.A. McKervey, E.M. Seward, G. Ferguson, B. Ruhl, S. Harris, J. *Chem. Commun.* (1985) 388–390.
[24] R. Lavendomme, S. Zahim, G. De Leener, A. Inthasot, A. Mat tiuzzi, M. Luhmer, O. Reinaud, I. Jabin, Asian J. Org. Chem. 4 (2015) 710–722.
[25] D.T. Schühle, S. Klimosch, J. Schatz, Tetrahedron Lett. 49 (2008) 5800–5803.
[26] V. Malytskyi, L. Troian-Gautier, A. Mattiuzzi, S. Lambotte, B. Cornelio, C. Lagrost, I. Jabin, Eur. J. Org Chem. (2018) 6590–6595.
[27] X. Hu, Y. Li, H. Yang, Y. Luo, Tetrahedron Lett. 47 (2006) 7463–7465.
[28] J. Gagnon, M. Vézina, M. Drouin, P.D. Harvey, Can. J. Chem. 79 (2001) 1439–1446.
[29] S.N. Podyacheva, G.S. Gimazetdinova, S.N. Sudakova, D.V. Lapaev, V.V. Syakaev, R.N. Nagimov, Russ. J. Gen. Chem. 87 (2017) 1958–1968.
[30] E.M. Collins, M.A. McKervy, E. Madigan, M.B. Moran, M. Owens, G. Ferguson, S. Harris, J. *J. Chem. Soc. Perkin Trans* 1 (1991) 3137–3142.
[31] R. Hosseinzadeh, M. Nemati, R. Zadmard, M. Mohadjerani, Beilstein J. Org. Chem. 12 (2016) 1749–1757.
[32] L.S. Arora, H.M. Chawla, M. Shahid, N. Pant, Org. Prep. Proced. Int. 49 (2017) 228–235.
[33] C.D. Gutsche, in: Calixarenes – an Introduction, vol. 2, RSC Publishing, Cambridge, 2008, pp. 66–70.
[34] A. Casnati, M. Fochi, P. Minari, A. Pochini, M. Reggiani, R. Ungaro, D.N. Reinhoudt, Gazz. Chim. Ital. 126 (1996) 99–106.
[35] Y. Yang, G. Arora, F.A. Fernandez, D.J. Crawford, K. Surowiec, E.K. Lee, R.A. Bartsch, Tetrahedron 67 (2011) 1389–1397.
[36] B. Genorio, Acta Chim. Slov. 63 (2016) 496–508.
[37] I. Smukste, B.E. House, D.B. Smithrud, J. Org. Chem. 68 (2003) 2559–2571.
[38] H. Hioki, R. Nakaoka, A. Maruyama, M. Kodama, J. Chem. Soc., Perkin Trans. 1 (2001) 3265–3268.
[39] B. Drevermann, A. Lingham, H. Hügel, P. Marriott, Tetrahedron Lett. 46 (2005) 39–41.
[40] G. Mehta, Synthesis (1972), 262–262.
[41] F. Alvarez, A.N. Watt, J. Org. Chem. 33 (1968) 2143–2144.
[42] J. McNulty, S. Cheekoori, J.J. Nair, V. Larichev, A. Capretta, A.J. Robertson, Tetrahedron Lett. 46 (2005) 3641–3644.
[43] I.I. Stoikov, A.A. Yantemirova, R.V. Nosov, I. Kh Rizvanov, A.R. Julmetov, V.V. Klochkov, I.S. Antipin, A.I. Konovalov, I. Zharov, Org. Biomol. Chem. 9 (2011) 3225–3235.
[44] P.O. Brown, K.A. Udachin, G.D. Enright, J.A. Ripmeester, Chem. Eur J. 12 (2006) 8240–8252.
[45] J.A. Ripmeester, G.D. Enright, C.I. Ratcliffe, K.A. Udachin, I.L. Moudrakovski, Chem. Commun. (2006) 4986–4996.
[46] S.H. Dale, M.R.J. Elsegood, C. Redshaw, CrystEngComm 5 (2003) 368–373.
[47] A.N. Matralis, D. Xanthopoulos, G. Huot, S. Lopes-Paciencia, C. Cole, H. de Vries, G. Ferbeyre, Y.S. Tsantrizos, Bioorg. Med. Chem. 26 (2018) 5547–5554.
[48] G.M. Sheldrick, Acta Crystallogr. 64 (2008) 112–122.
[49] G.M. Scheldrick, Acta Crystallogr. 71 (2015) 3–8.
[50] G.M. Sheldrick, Shelx, Programs for the Refinement of Crystal Structures, University of Göttingen, Göttingen, 2014.