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Synthesis, optical resolution and absolute configuration of inherently chiral calixarene carboxylic acids

M.A. Kliachyna [a], O.A. Yesypenko [a], V.V. Pirozhenko [a], S.V. Shishkina [b], O.V. Shishkin [b], V.I. Boyko [a], V.I. Kalchenko [a,*]

[a] Institute of Organic Chemistry, National Academy of Sciences of Ukraine, 02660 Kyiv-94, Murmanska Str., 5, Kyiv, Ukraine
[b] STC 'Institute for Single Crystals', National Academy of Sciences of Ukraine, Lenin Ave., 60, Kharkiv 61001, Ukraine

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ABSTRACT

Both enantiomers of inherently chiral calixarene carboxylic acids with ABCD substitution patterns have been prepared by the benzoylation of 25-propoxy-27-(*R*)-*N*-(α-phenylethyl)amidomethyloxycalix[4]arene followed by resolution of the diastereomers formed, monobromination of them and removal of the benzoyl and α-phenylethylamide auxiliary groups. The absolute configuration of the calixarenes obtained has been established by X-ray analysis. Preliminary study of the chiral recognition properties of calixarene carboxylic acid was performed.

1. Introduction

Calixarenes due to their unique vase-shaped structure are widely used as effective and selective receptors of ions and molecules.[1] Chiral calixarene-based receptors able to bind and recognize optical antipodes of chiral 'guests' attract considerable attention.[2] The compounds can be used as ligands for metallocomplexing catalysts[3] or organocatalysts[4] for asymmetrical synthesis, enantioselective sensors,[2a,5] chiral stationary phases for column chromatography,[6] chiral shift reagents for NMR[7] etc. Of particular interest are 'inherently' chiral calixarenes the chirality of which derives from the asymmetric substitution of macrocyclic platform.[8] Despite a great number of 'inherently' chiral calixarenes being described, most of them have been obtained as racemates or diastereomeric mixtures.[9] Only a few of them have been resolved into individual isomers[9b–12] and characterized by X-ray structural analysis.[5b,9b,10,12a] Therefore, the development of effective methods for the synthesis of optically pure inherently chiral calixarenes and determination of their absolute configuration is of great importance.

In this work, we report on the simple and effective synthesis of optically pure inherently chiral calix[4]arenes with ABCD substitution pattern, determination of their structure in solution and crystalline state, and preliminary chiral recognition result.

2. Results and discussion

Chiral calix[4]arenes **3a** and **3b** showing an ABCD substitution of the macrocycle have been obtained from 25-propoxy-calix[4]arene **1**[13] in two stages (Scheme 1).

The reaction of calixarene **1** with 1 equiv of chiral (*R*)-*N*-(α-phenylethyl)bromoacetamide in the presence of K_2CO_3 in refluxing acetonitrile gave 25-propoxy-27-(*R*)-*N*-(α-phenylethyl)amidomethyloxycalix[4]arene **2** in 98% yield. The structure of compound **2** was proved by ^1H and ^{13}C NMR analysis. Characteristic signals of $ArCH_2Ar$ methylene protons appearing as four pairs of overlapping AB doublets with an average coupling constant $^2J_{HH}$=13.3 Hz and the difference between resonances of the axial and equatorial protons ($\Delta\delta$ is near 0.8 ppm) confirmed the *cone* conformation of calixarene **2**.[14] In the ^{13}C NMR spectrum of calixarene **2**, the carbon atoms of the methylene bridges occured as four signals between 31.38 and 31.61 ppm, which is typical for the *cone* conformation.[15] Due to the asymmetrical carbon atom on the narrow rim, some protons and carbon atoms of calixarene **2** show diastereotopicity: the $ArCH_2Ar$ protons (four pair of overlapping doublets); hydroxyl groups (two singlets at 7.51 and 7.56 ppm); OCH_2 protons of propyl group (multiplet at 3.84–3.90 ppm); and methylene protons of OCH_2-C(O)NHCH(Me)Ph residue (a pair of doublets at 4.48 and 4.57 ppm).

* Corresponding author. Tel.: +38 044 559 06 67; fax: +38 044 573 26 43.
E-mail address: vik@ioch.kiev.ua (V.I. Kalchenko).

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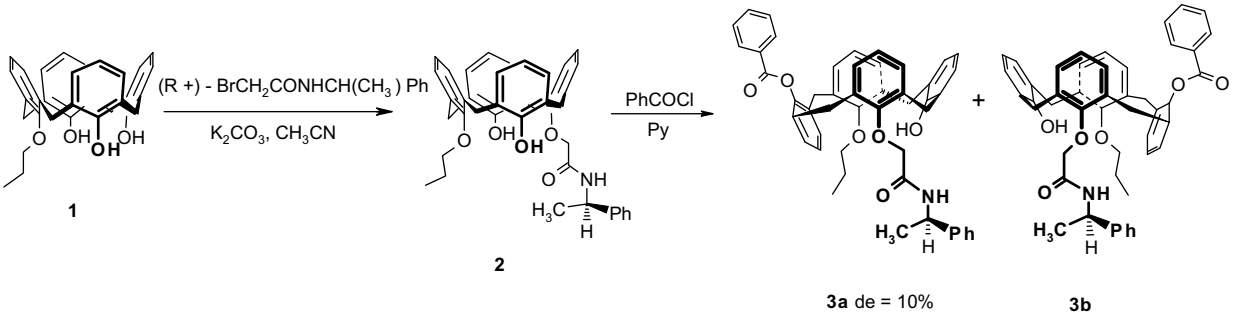


Scheme 1.

Benzoylation of one hydroxyl group of molecule **2** in pyridine solution leads to the mixture of diastereomers **3a** and **3b** in a 55:45 ratio (de **3a**=10%).[16] Diastereotopicity of **3a** and **3b** is based both on the presence of the chiral carbon atom of phenylethylamide residue and the ABCD asymmetrical substitution of the macrocyclic platform. Diastereomers **3a** and **3b** were separated by column chromatography giving 35% and 34% yields respectively. Additionally, diastereomer **3a** has been obtained by slow crystallization of a mixture of **3a** and **3b** from methanol/acetone in 33% yield. The further crystallization of the mother liquor enriched with **3b** from acetone gave diastereomer **3b** in 28% yield.

The ^{1}H NMR analysis of diastereomers **3a** and **3b** confirmed the asymmetrical substitution pattern of the macrocyclic skeleton: Ar–CH_2–Ar methylene protons occured as four pairs of doublets; OCH_2 protons of propyl group were shown as multiplets; methylene protons of $OCH_2C(O)NHCH(Me)Ph$ residue appeared as a pair of doublets. The ^{1}H NMR spectra of the diastereomers have a range of the significant differences. For example, CH_3 and CH_2 protons of **3a** propyl group are shifted to the high field in comparison with those for calixarene **3b** ($\Delta\delta$=0.3 ppm), which can be explained by the shielding of the mentioned protons by the benzene ring of the phenylethylamide group.

Many signals in the ^{1}H NMR spectra of calixarenes **3a** and **3b** are overlap (Fig. 1), thus COSY and HETCOR techniques were used to select $ArCH_2Ar$ signals (See Supplementary data). In the ^{1}H NMR spectrum of diastereomer **3b** two pairs of $ArCH_2Ar$ doublets have the differences between the chemical shifts of equatorial and axial protons ($\Delta\delta$) 1.03 ppm (δ=3.13 and 4.16 ppm, $^2J_{HH}$=12.8 Hz) and 0.46 ppm (δ=3.45 and 3.91 ppm, $^2J_{HH}$=13.7 Hz). The $\Delta\delta$ distances (1.03 and 0.46 ppm) confirm the *syn*-orientation of the neighboring benzene rings. For the other two pairs of doublets (between 3.70 and 3.99 ppm) of $ArCH_2Ar$ protons the $\Delta\delta$ distances are less than 0.2 ppm, characteristic of *anti*-orientation of the neighboring rings. This splitting pattern confirms the *partial cone* conformation of calixarenes **3a** and **3b**.[15] Additionally, the *partial cone* conformation of calixarenes **3a** and **3b** has been proved by ^{13}C NMR spectroscopy. For example, in the ^{13}C NMR spectrum of calixarene **3b** two signals at 31.36, 31.68 ppm correspond to carbon atoms between the *syn*-oriented benzene rings and two signals at 37.90 and 37.92 ppm correspond to carbon atoms between the *anti*-oriented benzene rings[15] (See Experimental). It is interesting to note, that in the ^{1}H NMR spectra of diastereomers **3a** and **3b**, aromatic protons are shifted to high field in comparison with those of the starting compound **2**. In particular, the mentioned protons of calixarene **2** appear between 6.66–7.43 ppm, whereas aromatic protons of **3a** and **3b** occur in the 6.0–6.4 ppm range (see Experimental). For example, the two triplets of calixarene **3a** at 6.08 and 6.18 ppm represent protons in the *para* positions to both OCH_2 groups. It can be supposed, that these protons are shielded by the aromatic ring of PhCO which is attached to the *anti*-oriented benzene ring of the calixarene plarform.

To determine the structure of compounds **3a** and **3b**, and to explain the chemical shifts in their NMR spectra, X-ray diffraction studies have been carried out. X-ray analysis data approved the conclusion based on the NMR spectroscopy. Both diastereomers **3a** and **3b** adopt the *partial cone* conformation (Fig. 2).

The absolute configuration of the diastereomers **3a** and **3b** is defined in accordance with the allocation order of the substituents

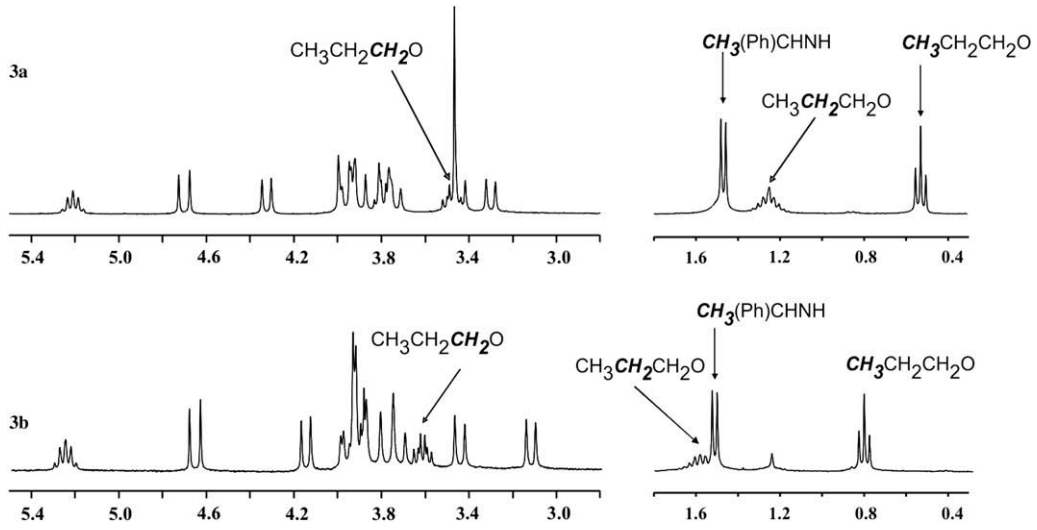


Figure 1. Representative sections of the ^{1}H NMR spectra of diastereomers **3a** and **3b** ($CDCl_3$, 20 °C).

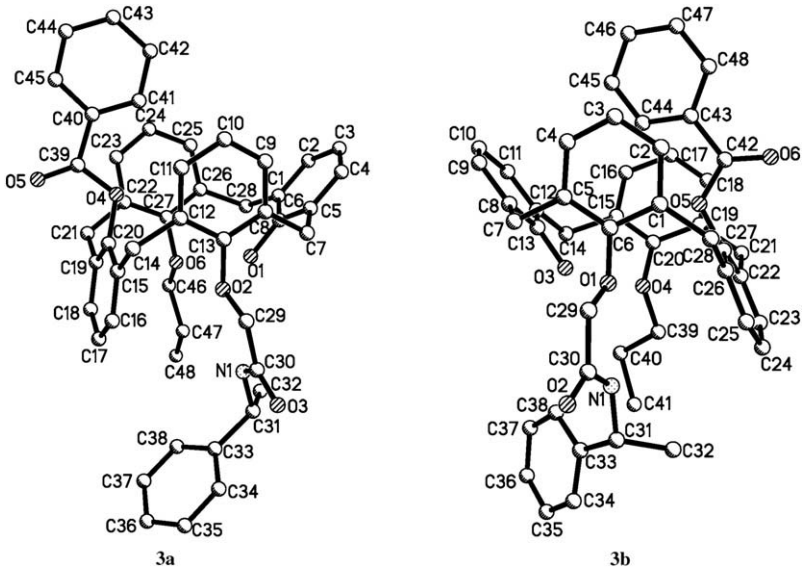


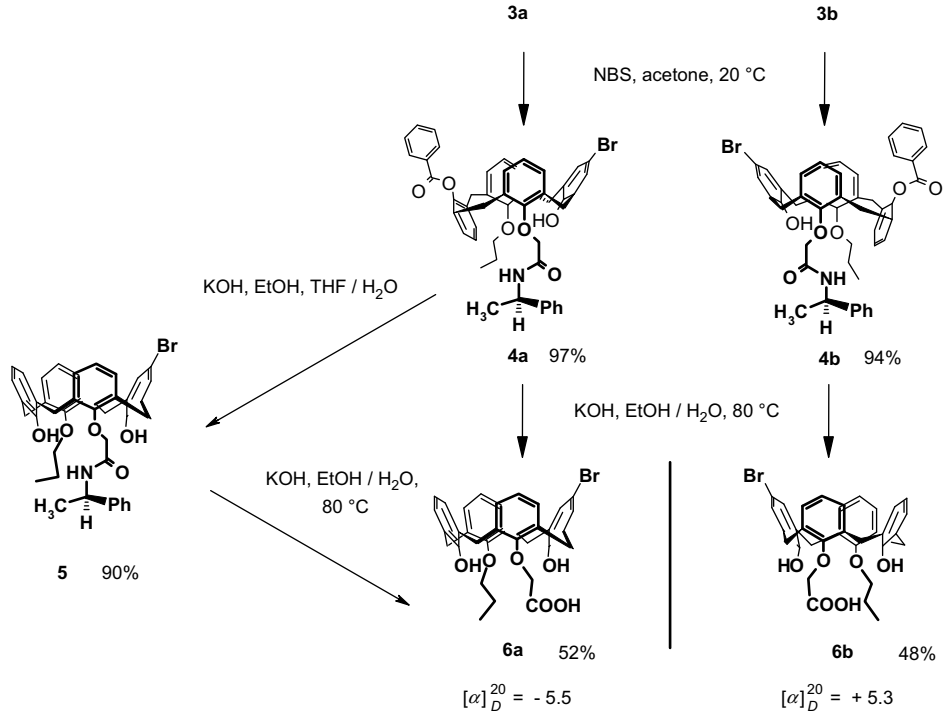
Figure 2. The molecular structure of the diastereomers **3a** and **3b** with numeration of the non-hydrogen atoms.

on the macrocyclic platform. The substituents Pr–OH–Ph(Me)CHNHC(O)CH_2–PhCO of the calixarene **3a** are situated with the clockwise sequence as compared with the counterclockwise sequence in diastereomer **3b** (view from the top).

The X-ray diffraction study demonstrates that two molecules (A and B) of compound **3a** are observed in the asymmetric part of the unit cell. These molecules differ in conformation of phenylethylamide substituent. It has antiperiplanar (*ap*)-conformation relatively the C(13)–O(2) bond in the molecule A in contrast to anticlinal (*ac*)-conformation in the molecule B (the C(13)–O(2)–C(29)–C(30) torsion angle is −162.6(2)° for A and −138.7(2)° for B). The orientation of the phenylethylamide substituent in the molecule B is additionally stabilized by the N(1)–H(1N)···OH (H···O 2.21 Å N–H···O 167°) weak intramolecular hydrogen bond in contrast to the molecule A. In both molecules the hydroxyl group forms the intramolecular hydrogen bond with the oxygen atom of the propoxy group (H···O 1.99 Å (A) 1.81 Å (B) O–H···O 156° (A) 175° (B)).

The position and the conformation of the phenylethylamide substituent in the diastereomer **3b** is similar to one in **3a**. The substituent adopts the *ap*-conformation relatively the C(6)–O(1) bond (the C(6)–O(1)–C(29)–C(30) torsion angle is −179.4(3)°). Such disposition of the phenylethylamide substituent does not allow forming intramolecular hydrogen bonds with other atoms of the molecule **3b**. The hydroxyl group forms the intramolecular hydrogen bond with the oxygen atom of the propyl substituent (H···O 1.90 Å, O–H···O 167°).

Diastereomers **3a** and **3b** were transformed in two-steps into enantiomerically pure inherently chiral calixarene carboxylic acids **6a** and **6b** with ABCD substitution patterns (Scheme 2). The regioselective bromination of **3a** or **3b** with equimolar quantities of



Scheme 2.

N-bromosuccinimide in acetone at room temperature gave monobrominated calixarenes **4a** or **4b** in the *partial cone* conformation in 97% and 94% yields respectively.

The benzoyl group of calixarene **4a** was removed by refluxing with KOH in EtOH/THF/H_2O to give amide **5** in 90% yield. The removal of the benzoyl group transforms the calixarene conformation to *cone*, which was proved by the ^1H and ^{13}C NMR analysis of amide **5**.

The phenylethylamide chiral auxiliary group of calixarene **5** was removed by refluxing in ethanol/water solution of KOH giving calixarene carboxylic acid **6a**.

The phenylethylamide and benzoyl residues of calixarenes **4a** and **4b** were also removed in a one-pot process, hence avoiding the amide **5** separation. Thus, acids **6a** and **6b** in the *cone* conformation were obtained by refluxing of **4a** or **4b** respectively with 150-fold excess of KOH in ethanol/water medium.

Enantiomeric calixarene carboxylic acids **6a** and **6b** have equal but opposite angles of polarized light rotation plane. Since bromination and hydrolysis reactions cannot change the sequence of substituents of the macrocycle the absolute configuration of acids **6a** and **6b** is analogous to diastereomers **3a** and **3b** correspondingly.

2.1. Chiral recognition properties of the inherently chiral calixarene carboxylic acids

Chiral recognition properties of calixarene carboxylic acid **6a** towards L and D α-phenylethylamine have been investigated by the ^1H NMR technique. The signal of the methyl group of L or D α-phenylethylamine resonating at 1.38 ppm as a doublet was shifted down field to 1.63 and 1.61 ppm correspondingly upon addition of 1 equiv of calixarene acid **6a**. The broad NH_2 signal centered at 1.61 ppm was down-field shifted (4.5 and 4.35 ppm for L and D-amine correspondingly) indicating the formation of the diastereomeric ammonium salt. Moreover the signals of OCH_2, CH_2 and CH_3 protons of propyl group of calixarene acid in the salts are significantly high-field-shifted due to shielding by the benzene ring of phenylethylamine. It is interesting to note, that spectra of the D and L diastereomeric salts have a range of differences. For example, in the case of L-amine salt the diastereotopic methylene protons of OCH_2COOH group appear as two very close doublets differenced by 0.06 ppm, while for the D-amine salt the difference consists of 0.18 ppm. Moreover the OCH_2 protons of the propyl group of diastereomeric salt with L-amine are represented as triplet, while the mentioned protons of the D salt occur as two multiplets. Consequently, calixarene carboxylic acid **6a** discriminates between the D and L enantiomers of α-phenylethylamine in the NMR spectrum.

3. Conclusions

In conclusion, optically pure inherently chiral calixarene carboxylic acids with a ABCD substitution pattern have been obtained by the benzoylation of 25-propoxy-27-(*R*)-*N*-(α-phenylethyl)-amidomethyloxycalix[4]arenes followed by resolution of the diastereomers formed, monobromination of them and removal of the benzoyl and α-phenylethylamine auxiliary groups. The calixarene carboxylic acids obtained are promising reagents for the chiral recognition of optical antipodes of organic molecules. Moreover, they can be used as versatile platforms in the design of chiral advanced materials.

4. Experimental

4.1. General

Melting points were determined on a Boëtius apparatus and are uncorrected. If not mentioned, the syntheses were carried out in anhydrous solvents and in dry atmosphere. TLC was performed on silica gel 60 W Merck plates. Column chromatography was carried out using Acros Organics silica gel (0.35–0.07 mm, pore diameter 6 nm). NMR ^1H and ^{13}C spectra were recorded on a VARIAN VXR 300 instrument operating at 300 MHz and 75.4 MHz correspondingly. The chemical shifts are referenced to TMS as internal standard. The optical rotation angles were measured on Perkin Elmer polarimeter 341.

4.2. Synthesis of calixarene 2

A suspension of 25-propoxy-calix[4]arene **1** (2.80 g, 6 mmol), (*R*)-*N*-(α-phenylethyl)bromoacetamide (1.50 g, 6.2 mmol) and K_2CO_3 (0.49 g, 3.6 mmol) in acetonitrile (280 mL) was stirred at reflux for 9 h. After cooling, the solvent was removed under reduced pressure. The remaining solid was triturated with HCl (10% solution, 5 mL). Then water was added (70 mL) and product was extracted with $CHCl_3$ (3×25 mL). The organic layer was separated, washed with water (40 mL) and then dried over Na_2SO_4. The solvent was evaporated in vacuo to give compound **2**. Yield 3.68 g (98%). Mp=120–121 °C. ^1H NMR ($CDCl_3$), δ: 0.97 (t, 3H, $^3J_{HH}$=7.4 Hz, $CH_3CH_2CH_2O$), 1.67 (d, 3H, $^3J_{HH}$=7.1 Hz, CH_3(Ph)CHNH), 1.74–1.86 (m, 2H, $^3J_{HH}$=7.4 Hz, $CH_3CH_2CH_2O$), 3.34 (d, 1H, $^2J_{HH}$=13.3 Hz, $ArCH_{2eq}$), 3.40 (d, 2H, $^2J_{HH}$=13.1 Hz, $ArCH_{2eq}$), 3.44 (d, 1H, $^2J_{HH}$=13.3 Hz, $ArCH_{2eq}$), 3.84–3.90 (m, 2H, $^3J_{HH}$=7.4 Hz, $CH_3CH_2CH_2O$), 4.16 (d, 1H, $^2J_{HH}$=13.3 Hz, $ArCH_{2ax}$), 4.22 (d, 1H, $^2J_{HH}$=13.3 Hz, $ArCH_{2ax}$), 4.24 (d, 2H, $^2J_{HH}$=13.1 Hz, $ArCH_{2ax}$), 4.48 (d, 1H, $^2J_{HH}$=15.1 Hz, NHC(O)CH_2), 4.57 (d, 1H, $^2J_{HH}$=15.1 Hz, NHC(O)CH_2), 5.33 (m, 1H, CH_3(Ph)CHNH), 6.66–6.74 (m, 4H, ArH), 6.82–6.87 (m, 4H, ArH), 6.98–7.11 (m, 5H, ArH), 7.18–7.21 (m, 2H, ArH), 7.43 (d, 2H, $^3J_{HH}$=7.1 Hz, ArH), 7.51 (s, 1H, OH), 7.56 (s, 1H, OH), 8.81 (d, 1H, $^3J_{HH}$=7.9 Hz, NH). ^{13}C NMR ($CDCl_3$), δ: 10.38, 22.25, 23.09, 31.38 (2C), 31.52, 31.61, 48.74, 74.52, 78.84, 119.65 (2C), 125.35, 125.87, 126.18 (2C), 127.01, 127.73, 127.81, 127.98, 128.05, 128.41 (2C), 128.65, 128.70, 128.75, 128.78, 128.94, 129.06, 129.24, 129.33, 132.55, 132.76, 132.79, 143.26, 151.72, 152.66, 152.70, 167.64. Anal. Found: C, 78.14%; H, 6.65%; N, 2.26%. Calcd for $C_{41}H_{41}NO_5$: C, 78.44%; H, 6.58%; N, 2.23%.

4.3. Acylation of calix[4]arene 2 with benzoyl chloride[13,17]

Calix[4]arene **2** (1.30 g, 2.07 mmol) and PhCOCl (4.95 g, 35.19 mmol) were stirred in dry pyridine (20 mL) at room temperature for 48 h. Pyridine was removed in vacuo and 10% solution of HCl (30 mL) was added. Product was extracted with $CHCl_3$ (3×15 mL), then washed with 5% solution of HCl (50 mL), water (2×40 mL), and dried over Na_2SO_4. The solvent was removed in vacuo. The remaining crude product was washed with hot hexane (80 mL) to remove benzoic acid, which is a side product of the reaction.

4.3.1. Optical resolution

Method 1. The residue was subjected to the column chromatography using ethyl acetate/hexane=1:3 (v/v) as eluent. $R_{f\mathbf{3a}}$=0.16, $R_{f\mathbf{3b}}$=0.13. Yield of **3a** 0.51 g (35%), **3b** 0.49 g (34%). Method 2. The residue was purified from the resin by silica gel. The mixture of diastereomers (1.24 g, **3a**/**3b**=55:45) was crystallized from the mixture of methanol (4 mL) and acetone (3.5 mL) to give **3a** in 33% yield. The mother liquor was evaporated and the residue (0.64 g) was crystallized from acetone (1.5 mL) to give calixarene **3b** in 28% yield.

*4.3.2. Diastereomer **3a***

Mp=172–173 °C. ^1H NMR ($CDCl_3$), δ: 0.54 (t, 3H, $^3J_{HH}$=7.6 Hz, $CH_3CH_2CH_2O$), 1.17–1.36 (m, 2H, $^3J_{HH}$=7.6 Hz, $CH_3CH_2CH_2O$), 1.47 (d, 3H, $^3J_{HH}$=6.8 Hz, CH_3(Ph)CHNH), 3.30 (d, 1H, $^2J_{HH}$=12.6 Hz, $ArCH_2$),

3.42–3.53 (d+m, 3H, ArCH_2+$CH_3CH_2CH_2O$), 3.72–4.00 (m, 6H, ArCH_2+$CH_3CH_2CH_2O$+NHC(O)CH_2), 4.33 (d, 1H, $^2J_{HH}$=12.6 Hz, ArCH_2), 4.70 (d, 1H, $^2J_{HH}$=15.0 Hz, NHC(O)CH_2), 5.16–5.26 (m, 1H, CH_3(Ph)C*H*NH), 6.08 (t, 1H, $^3J_{HH}$=7.5 Hz, ArH), 6.18 (t, 1H, $^3J_{HH}$=7.5 Hz, ArH), 6.41–6.50 (m, 4H, ArH), 6.63 (t, 2H, $^3J_{HH}$=7.7 Hz, ArH), 6.75–6.81 (m, 2H, ArH), 6.86 (t, 1H, $^3J_{HH}$=7.5 Hz, ArH), 7.13–7.38 (m, 11H, ArH), 7.77 (s, 1H, OH), 8.22 (d, 1H, $^3J_{HH}$=7.9 Hz, NH). ^{13}C NMR ($CDCl_3$), δ: 9.65, 22.20, 22.43, 31.14, 31.49, 37.74 (2C), 48.08, 71.38, 75.62, 119.78, 123.95, 124.80, 125.30, 126.00, 126.86, 126.91, 127.11, 127.90, 128.24, 128.53, 128.63, 128.77, 128.91, 129.07, 129.12, 129.57, 129.71, 129.80, 129.91, 132.21, 132.30, 132.38, 132.54, 132.87, 133.21, 143.10, 148.01, 152.10, 152.31, 154.46, 163.26, 168.85. Anal. Found: C, 78.67%; H, 6.25%; N, 1.96%. Calcd for $C_{48}H_{45}NO_6$: C, 78.77%; H, 6.20%; N, 1.91%.

4.3.3. Diastereomer ***3b***

Mp=218–219 °C. ^{1}H NMR ($CDCl_3$), δ: 0.82 (t, 3H, $^3J_{HH}$=7.4 Hz, C$H_3CH_2CH_2O$), 1.52 (d, 3H, $^3J_{HH}$=7.2 Hz, CH_3(Ph)CHNH), 1.56–1.66 (m, 2H, $^3J_{HH}$=7.4 Hz, $CH_3CH_2CH_2O$), 3.13 (d, 1H, $^2J_{HH}$=12.8 Hz, ArCH_2), 3.45 (d, 1H, $^2J_{HH}$=13.7 Hz, ArCH_2), 3.58–3.66 (m, 1H, $^3J_{HH}$=7.2 Hz, $CH_3CH_2CH_2O$), 3.70–3.99 (m, 7H, ArCH_2+$CH_3CH_2CH_2O$+NHC(O)CH_2), 4.16 (d, 1H, $^2J_{HH}$=12.8 Hz, ArCH_2), 4.66 (d, 1H, $^2J_{HH}$=15.1 Hz, NHC(O)CH_2), 5.21–5.30 (m, 1H, CH_3(Ph)C*H*NH), 6.07 (t, 1H, $^3J_{HH}$=7.5 Hz, ArH), 6.21 (t, 1H, $^3J_{HH}$=7.5 Hz, ArH), 6.40 (d, 1H, $^3J_{HH}$=7.5 Hz, ArH), 6.46 (d, 1H, $^3J_{HH}$=7.5 Hz, ArH), 6.52–6.54 (m, 2H, ArH), 6.63–6.71 (m, 3H, ArH), 6.80–6.88 (m, 2H, ArH), 7.08–7.23 (m, 7H, ArH), 7.27–7.35 (m, 4H, ArH), 7.64 (s, 1H, OH), 8.12 (d, 1H, $^3J_{HH}$=8.3 Hz, NH). ^{13}C NMR ($CDCl_3$), δ: 10.11, 22.24, 22.83, 31.36, 31.68, 37.90, 37.92, 48.12, 71.58, 75.74, 77.20, 119.62, 123.82, 124.74, 125.18, 125.92, 126.69, 126.81, 127.06, 128.59, 128.69, 128.73, 129.11, 129.19, 129.59, 129.71, 129.73, 129.99, 132.18, 132.20, 132.31, 132.41, 132.57, 132.86, 133.23, 142.96, 148.07, 152.22, 152.28, 154.31, 163.09, 168.28. Anal. Found: C, 78.56%; H, 6.27%; N, 1.99%. Calcd for $C_{48}H_{45}NO_6$: C, 78.77%; H, 6.20%; N, 1.91%.

4.4. Bromination of calixarenes 3a and 3b with *N*-bromosuccinimide (NBS)

4.4.1. General procedure

To a solution of calixarene (1.30 g, 1.78 mmol) in acetone (50 mL, freshly distilled) the solution of NBS (0.33 g, 1.87 mmol) in 50 mL of acetone was added dropwise. The reaction mixture was stirred for 18 h at 20 °C. After removal of acetone under reduced pressure the residue was treated with 5 mL of MeOH and 20 mL of H_2O. The colourless precipitate was filtered off, washed with water and dried in the air.

Monobrominated calixarene **4a** obtained from **3a**. Yield 1.38 g (97%). Mp=231–232 °C. ^{1}H NMR ($CDCl_3$), δ: 0.54 (t, 3H, $^3J_{HH}$=7.5 Hz, C$H_3CH_2CH_2O$), 1.14–1.33 (m, 2H, $CH_3CH_2CH_2O$), 1.46 (d, 3H, $^3J_{HH}$=7.0 Hz, CH_3(Ph)CHNH), 3.26 (d, 1H, $^2J_{HH}$=12.8 Hz, ArCH_2), 3.38 (d, 1H, $^2J_{HH}$=13.8 Hz, ArCH_2), 3.42–3.51 (m, 1H, $CH_3CH_2CH_2O$), 3.71–3.98 (m, 7H, ArCH_2+$CH_3CH_2CH_2O$+OCH_2CONH), 4.29 (d, 1H, $^2J_{HH}$=12.8 Hz, ArCH_2), 4.69 (d, 1H, $^2J_{HH}$=15.2 Hz, OCH_2CONH), 5.16–5.26 (m, 1H, CH_3(Ph)C*H*NH), 6.14 (t, 1H, $^3J_{HH}$=7.5 Hz, ArH), 6.24 (t, 1H, $^3J_{HH}$=7.5 Hz, ArH), 6.43–6.54 (m, 4H, ArH), 6.70–6.82 (m, 4H, ArH), 7.11–7.16 (m, 1H, ArH), 7.24–7.39 (m, 10H, ArH), 7.91 (s, 1H, OH), 8.09 (d, 1H, $^3J_{HH}$=7.9 Hz, NH). ^{13}C NMR ($CDCl_3$), δ: 9.69, 22.10, 22.44, 30.96, 31.35, 37.78 (2C), 48.13, 71.55, 75.75, 111.23, 124.17, 125.06, 125.35, 126.10, 126.98, 127.22, 128.04, 128.30, 128.74, 129.03, 129.08, 129.30, 129.78, 129.97, 130.17, 130.50, 131.15, 131.81, 131.86, 132.09, 132.43, 132.62, 132.69, 133.30, 143.15, 148.16, 151.67, 152.15, 154.59, 163.24, 168.62. Anal. Found: C, 70.86%; H, 5.14%; N, 1.93%; Br, 9.66%. Calcd for $C_{48}H_{44}BrNO_6$: C, 71.11%; H, 5.47%; N, 1.73%; Br, 9.86%.

Monobrominated calixarene **4b** obtained from **3b**. Yield 1.35 g (94%). Mp=221–222 °C. ^{1}H NMR ($CDCl_3$), δ: 0.82 (t, 3H, $^3J_{HH}$=7.4 Hz, C$H_3CH_2CH_2O$), 1.51–1.64 (d+m, 3H+2H, $^3J_{HH}$=7.1 Hz, CH_3(Ph)CHNH+$CH_3CH_2CH_2O$), 3.06 (d, 1H, $^2J_{HH}$=12.6 Hz, ArCH_2), 3.39 (d, 1H, $^2J_{HH}$=13.8 Hz, ArCH_2), 3.56–3.64 (m, 1H, $CH_3CH_2CH_2O$), 3.71–3.99 (m, 7H, ArCH_2+$CH_3CH_2CH_2O$+OCH_2CONH), 4.10 (d, 1H, $^2J_{HH}$=12.8 Hz, ArCH_2), 4.66 (d, 1H, $^2J_{HH}$=14.9 Hz, OCH_2CONH), 5.22–5.31 (m, 1H, CH_3(Ph)C*H*NH), 6.13 (t, 1H, $^3J_{HH}$=7.3 Hz, ArH), 6.27 (t, 1H, $^3J_{HH}$=7.3 Hz, ArH), 6.43 (d, 1H, $^3J_{HH}$=7.2 Hz, ArH), 6.49 (d, 1H, $^3J_{HH}$=7.3 Hz, ArH), 6.56–6.58 (m, 2H, ArH), 6.69–6.78 (m, 3H, ArH), 6.82 (d, 1H, $^3J_{HH}$=7.3 Hz), 7.11–7.13 (m, 3H, ArH), 7.18–7.22 (m, 1H, ArH), 7.28–7.36 (m, 7H, ArH), 7.77 (s, 1H, OH), 7.98 (d, 1H, $^3J_{HH}$=8.7 Hz, NH). ^{13}C NMR ($CDCl_3$), δ: 9.93, 21.95, 22.71, 30.94, 31.31, 37.73, 37.75, 47.97, 71.51, 75.70, 78.98, 111.16, 120.85, 124.12, 125.10, 126.02, 127.27, 128.02, 128.38, 128.41, 128.70, 128.76, 128.80, 128.89, 128.96, 129.07, 129.17, 129.28, 129.41, 129.77, 130.04, 130.19, 130.42, 131.09, 131.87, 132.09, 132.45, 132.58, 132.69, 133.29, 134.19, 142.92, 148.16, 149.17, 151.66, 152.21, 154.47, 163.35, 168.43. Anal. Found: C, 70.86%; H, 5.14%; N, 1.93%; Br, 9.77%. Calcd for $C_{48}H_{44}BrNO_6$: C, 71.11%; H, 5.47%; N, 1.73%; Br, 9.86%.

4.5. Removal of benzoyl group of calixarene 4a

To the ethanol/water (3.5 mL of EtOH and 2 mL of H_2O) solution of KOH (0.48 g, 8.53 mmol) the solution of calixarene **3a** (0.230 g, 2.84 mmol) in THF (5 mL) was added. The reaction mixture was refluxed for 5 h. After the removal of solvent under reduced pressure, 10 mL of 3% solution of HCl and 1 mL of EtOH were added. The precipitated product was filtered off, washed with water and dried in the air. Yield of **5**, 0.19 g (95%). Mp=139–140 °C. ^{1}H NMR ($CDCl_3$), δ: 0.98 (t, 3H, $^3J_{HH}$=7.4 Hz, C$H_3CH_2CH_2$), 1.67 (d, 3H, $^3J_{HH}$=7.0 Hz, CH_3(Ph)CHNH), 1.74–1.88 (m, 2H, $^3J_{HH}$=7.5, 7.2 Hz, $CH_3CH_2CH_2O$), 3.30–3.44 (4d overlapping, 4H, $^2J_{HH}$=13.8, 13.2, 13.6, 13.2 Hz, ArCH_{2eq}), 3.79–3.93 (m, 2H, $CH_3CH_2CH_2O$), 4.13 (d, 1H, $^2J_{HH}$=13.6 Hz, ArCH_{2ax}), 4.16 (d, 1H, $^2J_{HH}$=13.2 Hz, ArCH_{2ax}), 4.17 (d, 1H, $^2J_{HH}$=13.8 Hz, ArCH_{2ax}), 4.2 (d, 1H, $^2J_{HH}$=13.2 Hz, ArCH_{2ax}), 4.42 (d, 1H, $^2J_{HH}$=15.1 Hz, OCH_2CONH), 4.56 (d, 1H, $^2J_{HH}$=15.1 Hz, OCH_2CONH), 5.27–5.37 (m, 1H, CH_3(Ph)C*H*NH), 6.54–6.62 (m, 2H, ArH), 6.72–6.81 (m, 5H, ArH), 7.06–7.11 (m, 2H, ArH), 7.19–7.23 (m, 5H, ArH), 7.39–7.41 (m, 2H, ArH), 7.43 (s, 1H, OH), 7.64 (s, 1H, OH), 8.72 (d, 1H, $^3J_{HH}$=7.9 Hz, NH). ^{13}C NMR ($CDCl_3$), δ: 10.40, 17.14, 22.19, 23.10, 31.11, 31.31, 31.39, 31.58, 48.73, 74.55, 78.91, 111.07, 119.78, 125.47, 125.99, 126.17, 127.08, 127.71, 127.76, 128.41, 128.71, 128.89, 129.09, 129.18, 129.34, 129.61, 129.75, 130.14, 131.02, 131.04, 131.59, 131.95, 132.62, 132.73, 143.10, 151.70, 151.99, 152.54, 167.49. Anal. Found: C, 69.91%; H, 5.63%; N, 1.87%; Br, 11.02%. Calcd for $C_{41}H_{40}BrNO_5$: C, 69.69%; H, 5.71%; N, 1.98%; Br, 11.31%.

4.6. Removal of phenylethylamide auxiliary group of calixarene 5

To the ethanol/water (4 mL of EtOH, 6 mL of H_2O) solution of KOH (6.42 g, 114.62 mmol) calixarene **5** (0.54 g, 7.64 mmol) was added. The reaction mixture was refluxed for 120 h. The 10% solution of HCl (30 mL) was added at stirring, then mixture was refluxed for 1.5 h. The precipitate was filtered off, washed with large amounts of hot water and dried in the air. The product was extracted from the solid with 30 mL of hot $CHCl_3$. The crude product was purified by column chromatography using ethyl acetate/hexane 1:1 as eluent. Yield of **6a** 0.22 g (48%). Mp=298–300 °C. $[\alpha]_D^{20}$ −5.5 (*c* 0.5083 g/100 mL, $CHCl_3$). ^{1}H NMR ($CDCl_3$), δ: 1.25 (t, 3H, $^3J_{HH}$=7.2 Hz, C$H_3CH_2CH_2$), 2.06–2.17 (m, 2H, $^3J_{HH}$=7.2 Hz, $CH_3CH_2CH_2O$), 3.39–3.49 (d+d, 2H+1H, $^2J_{HH}$=13.6, 13.4 Hz, ArCH_{2eq}), 3.50 (d, 1H, $^2J_{HH}$=13.4 Hz, ArCH_{2eq}), 4.01–4.10 (t+d, 2H+2H, $^3J_{HH}$=6.7 Hz, $^2J_{HH}$=13.6 Hz, $CH_3CH_2CH_2O$+ArCH_{2ax}), 4.15–4.21 (d+d, 1H+1H, $^2J_{HH}$=13.4 Hz, ArCH_{2ax}), 4.61 (d, 1H,

$^{2}J_{HH}$=15.7 Hz, OCH_2CONH), 4.71 (d, 1H, $^{2}J_{HH}$=15.7 Hz, OCH_2CONH), 6.72 (t, 1H, $^{3}J_{HH}$=7.5 Hz, ArH), 6.81–6.86 (m, 2H, ArH) 6.93–7.00 (m, 4H, ArH), 7.09 (d, 2H, $^{3}J_{HH}$=7.2 Hz, ArH), 7.19 (s, 2H, ArH), 8.14 (s, 2H, OH). ^{13}C NMR (DMSO-d_6), δ: 10.67, 22.93, 29.99, 30.10, 30.53, 30.56, 72.29, 78.10, 109.71, 118.91, 125.16, 125.29, 127.51, 127.63, 128.43, 128.82, 128.87, 129.01, 129.15, 130.18, 130.48, 130.50, 132.72, 133.06, 133.54, 133.83, 151.78, 152.01, 152.09, 152.48, 169.99. Anal. Found: C, 65.61%; H, 5.23%; Br, 13.09%. Calcd for $C_{33}H_{31}BrO_6$: C, 65.68%; H, 5.18%; Br, 13.24%.

4.7. One pot removal of phenylethylamide and benzoyl groups of calixarenes 4a and 4b

To the ethanol/water solution (19 mL of EtOH, 25 mL of H_2O) of KOH (14.28 g, 255.00 mmol) calixarene **4a** or **4b** (1.38 g, 1.70 mmol) was added. The reaction mixture was refluxed for 130 h. After cooling to the room temperature 10% HCl (100 mL) was added when stirring. The mixture was refluxed for 2 h. The precipitated solid containing calixarene carboxylic acid and a large amount of KCl was filtered off, washed with 150 mL of hot water and dried in the air. The solid obtained was refluxed with $CHCl_3$ (4×30 mL), the mixture was filtered off. The filtrate was evaporated under reduced pressure. The remaining crude product was subjected to the column chromatography on silica gel (hexane/ethyl acetate 1:1). Product was dried in vacuo for 20 h.

Acid **6a**. Yield 52%. All physical constants and spectral data are analogous to compound **6a**, obtained from calixarene **5** according to the method described before.

Acid **6b**. Yield 48%. $[\alpha]_D^{20}$ +5.3 (*c* 0.5081 g/100 mL, $CHCl_3$). Mp and all spectral data are analogous to compound **6a**.

4.8. The investigation of chiral recognition properties of acid 6a

Chiral D- and L-α-phenylethylamines were dissolved in dry $CDCl_3$ (stored under Ag) to give solutions with concentration *c*=0.1657 mmol/1 g. The samples **a**, **b**, **c**, and **d** (see Fig. 3) for the ^{1}H NMR spectra measurement were prepared by the next procedure.

Sample **a**: solution of D-α-phenylethylamine (0.01657 mmol) in $CDCl_3$ (1.000 g).

Sample **b**: acid **6a** (0.010 g, 0.01657 mmol) was dissolved in $CDCl_3$ (1.000 g).

Sample **c**: to acid **6a** (0.010 g, 0.01657 mmol) L-α-phenylethylamine (0.01657 mmol) in $CDCl_3$ (1.000 g) was added.

Sample **d**: to acid **6a** (0.010 g, 0.01657 mmol) D-α-phenylethylamine (0.01657 mmol) in $CDCl_3$ (1.000 g) was added.

The ^{1}H NMR spectra of the samples were recorded at 20 °C.

4.9. The X-ray diffraction study

The colorless crystals of **3a** ($C_{48}H_{45}NO_6\cdot 0.5H_2O$) are orthorhombic. At −173 K *a*=11.4038(3), *b*=13.5053(4), *c*=51.799(1) Å, *V*=7977.6 Å^3, M_r=1481.72, *Z*=4, space group $P2_12_12_1$, d_{calcd}=1.234 g/cm^3, μ(Mo Kα)=0.081 mm^{-1}, *F*(000)=3144. Intensities of 19,623 reflections (12,434 independent, R_{int}=0.038) were measured on the

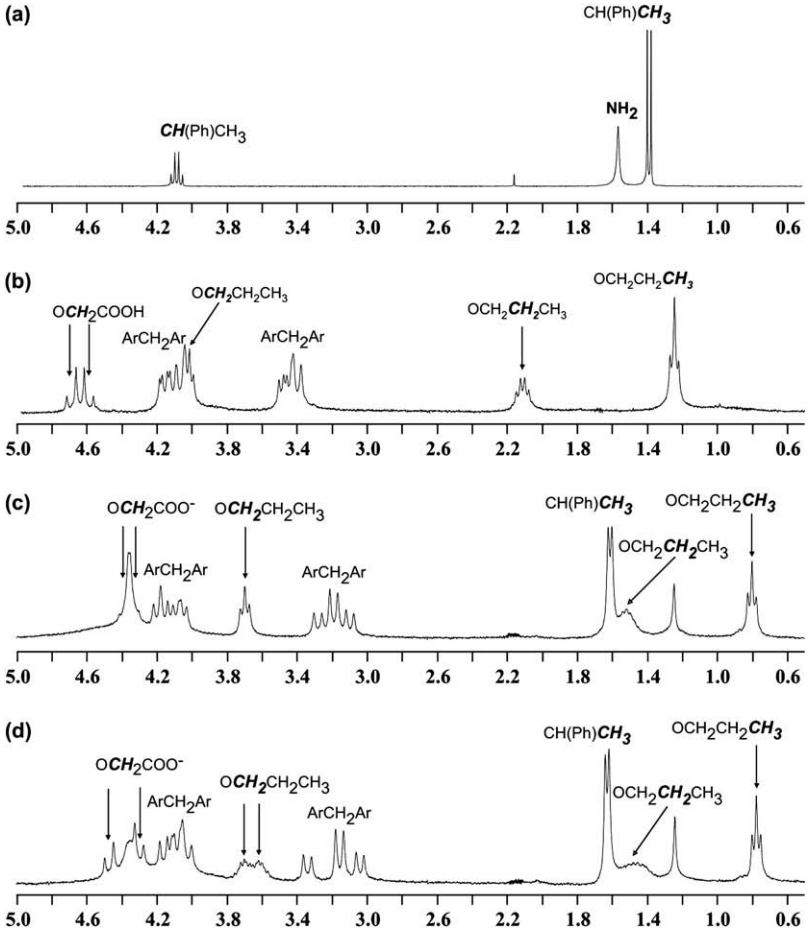


Figure 3. The ^{1}H NMR spectra of α-phenylethylamine (a), calixarene carboxylic acid **6a** (b), salt of L-α-phenylethylamine with acid **6a** (c) and salt of D-α-phenylethylamine with acid **6a** (d) at 20 °C in $CDCl_3$ (sections from 0.6 to 5.0 ppm are shown).

'Xcalibur-3' diffractometer (graphite monochromated Mo Kα radiation, CCD detector, ω-scaning, $2\Theta_{max}=50^\circ$).

The colourless crystals of **3b** ($C_{48}H_{45}NO_6$) are orthorhombic. At −173 K a=18.4708(6), b=17.4476(8), c=11.9839(3) Å, V=3862.1(2) Å^3, M_r=731.85, Z=4, space group $P2_12_12_1$, d_{calcd}=1.259 g/cm^3, μ(Mo Kα)=0.082 mm^{-1}, F(000)=1552. Intensities of 16,530 reflections (8290 independent, R_{int}=0.060) were measured on the 'Xcalibur-3' diffractometer (graphite monochromated Mo Kα radiation, CCD detector, ω-scaning, $2\Theta_{max}=55^\circ$).

The structures were solved by direct method using SHELXTL package.[18] The restrictions on the Csp^3–O and Csp^3–Csp^3 bond lengths (1.43 Å and 1.54 Å, respectively) in the disordered fragment were applied in the refinement of the structure **3b**. Positions of the hydrogen atoms were calculated geometrically and refined by 'riding' model with $U_{iso}=nU_{eq}$ of the carrier atom (n=1.5 for methyl group and n=1.2 for other hydrogen atoms). The hydrogen atoms of the structure **3a** participating in the formation of the hydrogen bonds were refined in isotropic approximation. Absolute configuration was established relatively of the known absolute configuration of the phenylethylamide fragment.

Full-matrix least-squares refinement of the structures against F^2 in anisotropic approximation for non-hydrogen atoms using 12,155 (**3a**), 8192 (**3b**) reflections was converged to: wR_2=0.099 (R_1=0.050 for 8906 reflections with $F>4\sigma(F)$, S=1.012) for structure **3a** and wR_2=0.178 (R_1=0.072 for 5402 reflections with $F>4\sigma(F)$, S=1.046) for structure **3b**. The final atomic coordinates, and crystallographic data for molecules **3a** and **3b** have been deposited to the Cambridge Crystallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk) and are available on request quoting the deposition numbers CCDC 721896 for **3a** and CCDC 721895 for **3b**.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.06.039.

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