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Synthesis of enantiomerically and diastereomerically pure oxazaborolo-benzoxazaborininone derivatives of resorcinarene from L-proline

Waldemar Iwanek,[a,*] Mariusz Urbaniak,[a] Barbara Gawdzik[a] and Volker Schurig[b]

[a]*Institute of Chemistry, Pedagogical University, Chęcińska 5, 25020 Kielce, Poland*
[b]*Institute of Organic Chemistry, University of Tübingen, Auf der Morgenstelle 18, 72076 Tübingen, Germany*

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Abstract—The novel oxazaborolo-benzoxazaborininone derivatives of resorcinarene were synthesised from L-proline in high diastereomeric excess (>98%). The boron compounds were used as an element linking the carboxy group, the hydroxy group as well as the lone electron pair of the nitrogen atom.
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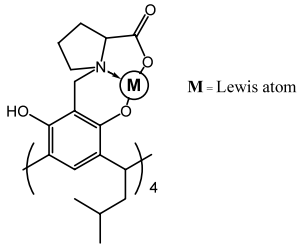
1. Introduction

Resorcinarenes are cavity-shaped macrocycles which can easily be synthesised from resorcinol and aldehydes.[1] The synthesis of chiral resorcinarenes[2] is interesting not only for the preparation of novel chiral supramolecular ligands but also for their potential use in the study of chiral discrimination as well as their application as chiral catalysts for asymmetric reactions. While the literature provides some examples of the use of resorcinarene derivatives for studies of chiral discrimination,[3] there is no evidence of their use for asymmetric reactions. The introduction of an atom which has the properties of a Lewis acid into the structure of a resorcinarene derivative should open its use as a supramolecular catalyst for a range of asymmetric reactions (Scheme 1).



Scheme 1.

Herein we describe a continuation of our studies on diastereoselective ring closure in resorcinarene derivatives.[5] It presents the synthesis of novel oxazaborolo-benzoxazaborininone derivatives of resorcinarene from L-proline.

2. Results and discussion

The first step of the synthesis is the preparation of the L-proline aminomethyl derivative **2** via a Mannich reaction (Scheme 2, step 1).

This reaction has been described previously by Schneider.[4] We have modified the procedure slightly by conducting the reaction in pure ethanol. The reaction proceeds with good yield (80%). The unpurified product is suitable for subsequent reactions after drying in vacuo. In the second step, the carboxyl group, the free hydroxy group of the phenol ring as well as the electron lone pair at the nitrogen atom of derivative **2** were linked using the boron derivative $R_1B(R_2)_2$, to give the oxazaborolo-benzoxazaborininone derivatives of resorcinarene. Depending on the derivative used, the reaction was conducted in toluene or in tetrahydrofuran. In the case of $PhB(OH)_2$, water was azeotropically removed from the reaction mixture. In the cases of $B(Et)_3$ and $B(OMe)_3$, taken in a moderate excess (5 equiv.), the reaction mixture in tetrahydrofuran was heated for several hours, until the precipitate dissolved.

* Corresponding author. E-mail: iwanek@pu.kielce.pl

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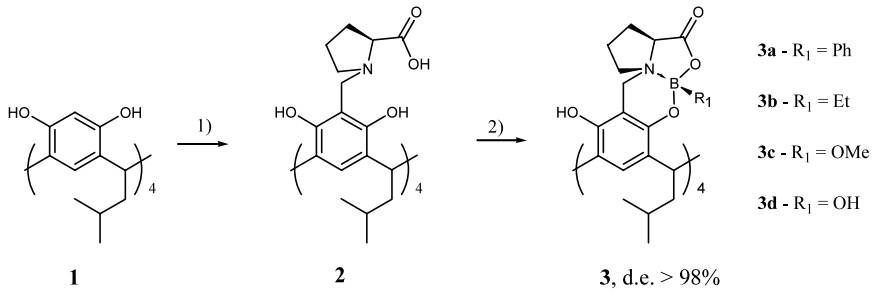


1 2 3, d.e. > 98%

Scheme 2. *Reagents and conditions*: (1) L-Proline, CH_2O, EtOH, reflux; (2) R_1-BR_2, toluene (**3a**), THF (**3b**, **3c**) CH_3CN/DMF (**3d**), reflux.

The reaction with z $B(OH)_3$ was conducted at reflux in an acetonitrile/dimethylformamide mixture for several hours.

Only the crown conformers of derivatives **3a** and **3b** and **3d** are formed. To our surprise, a mixture of conformers is formed in the case of derivative **3c**. The crown and diamond conformers of **3c** were chromatographically separated using ethyl ether:acetone as the eluent. In all cases, the crown conformers of derivatives **3** are characterised by a high (>98%) diastereomeric excess. The yields are also quite high, ranging from 50 to 75%. The analysis presented below of the ^{1}H NMR spectra of derivatives aiming to elucidate the spatial structure of the derivatives **3** concerns only the crown conformers. The previous paper demonstrated the possibilities of synthesis and the crystallographic structures of the diastereomers of oxazaborolo-benzoxazaborininone derivatives prepared from resorcinarene and L-prolinol. Position of signals of methine proton, which are connected to the stereogenic center in L-proline, aminometylene protons, and protons of the boron substituents are essential to assign the structure of derivatives **3**. The coupling in the (^{1}H,^{1}H) NOESY spectra of the methine proton and the aminomethylene protons allowed us to determine the structure of derivatives **3**.

The oxazaborolidinone ring can be located inside or outside the calixarene cavity. The problem can be solved using the information on the signal of the methine proton of the L-proline moiety in the derivatives **3a** and **3d** compared to the analogous signal in the derivative **2**. Since compound **2** dissolves only in DMSO, the comparison was made in this solvent. If the oxazaborolidinone ring is directed towards the inside of the calixarene cavity, this proton should project into the calixarene cavity and its signal should shift upfield in comparison to **2**. In the oxazaborolidinone ring directed towards the outside of the cavity, the methine proton of L-proline should stay outside the cavity and its signal should shift downfield. The methine signal of **3a** is located at $\delta = 3.95$ ppm and $\delta = 3.86$ ppm for **3d**, downfield versus the corresponding signal of **2** ($\delta =$ 3.46). This observation indicates that the oxazaborolidinone ring is located outside the resorcinarene cavity (see Fig. 1).

Moreover, the methine signal, for all the derivatives **3** in chloroform, is shifted downfield in relation to the methine signal of **2** and appears at 4.16 ppm **3a**, 3.71 ppm **3b** and 3.85 ppm **3c**, respectively.

However, this evidence does not allow determination of the direction of closing the benzoxazaborinine ring, i.e. whether it proceeds clockwise or counter clockwise (viewed from inside the cavity). The coupling in NOESY spectra between the methine proton and the aminomethylene protons and between the aminomethylene protons and the L-proline proton lead to the conclusion that the oxazaborolidinone ring is closed in the clockwise direction (Fig. 2). If the oxazaborolidinone ring is closed anticlockwise, these couplings would not be observed.

The ^{1}H NMR signals of the aromatic protons of the phenol ring linked to the boron atom in the derivative **3a** as well as the signals of protons of the ethyl group linked to boron atom in the derivative **3b** can also be helpful for the structure elucidation. If the benzoxazaborinine ring closes counterclockwise, the phenol ring should stay outside the calixarene cavity. If the benzoxazaborinine ring closes clockwise, the phenol ring should be directed away from the boron atom and partly towards the calixarene cavity, and the chemical shifts of aromatic hydrogens should differ from phenylboronic acid. There are two groups of signals observed in the ^{1}H NMR spectrum of **3a** in DMSO: the first at $\delta = 7.30$ ppm for three protons ($\delta = 7.31$ ppm for $PhB(OH)_2$) and the second at $\delta = 7.41$ ppm for two protons ($\delta = 7.77$ ppm for $PhB(OH)_2$). The latter group of signals of **3a** is shifted upfield, which is probably caused by shielding of these protons by the cavity.

In turn, one can note a diversified, upper-range chemical shift of the methylene protons of the ethyl group linked to the boron atom (-B-CH_2-CH_3). These signals are very well-resolved sextets in the ^{1}H NMR spectrum, and their shifts are 0.57 and 0.68 ppm, respectively. Probably the reason is that these protons are projected into the calixarene cavity, which is a consequence of clockwise closing the benzoxazaborinine ring.

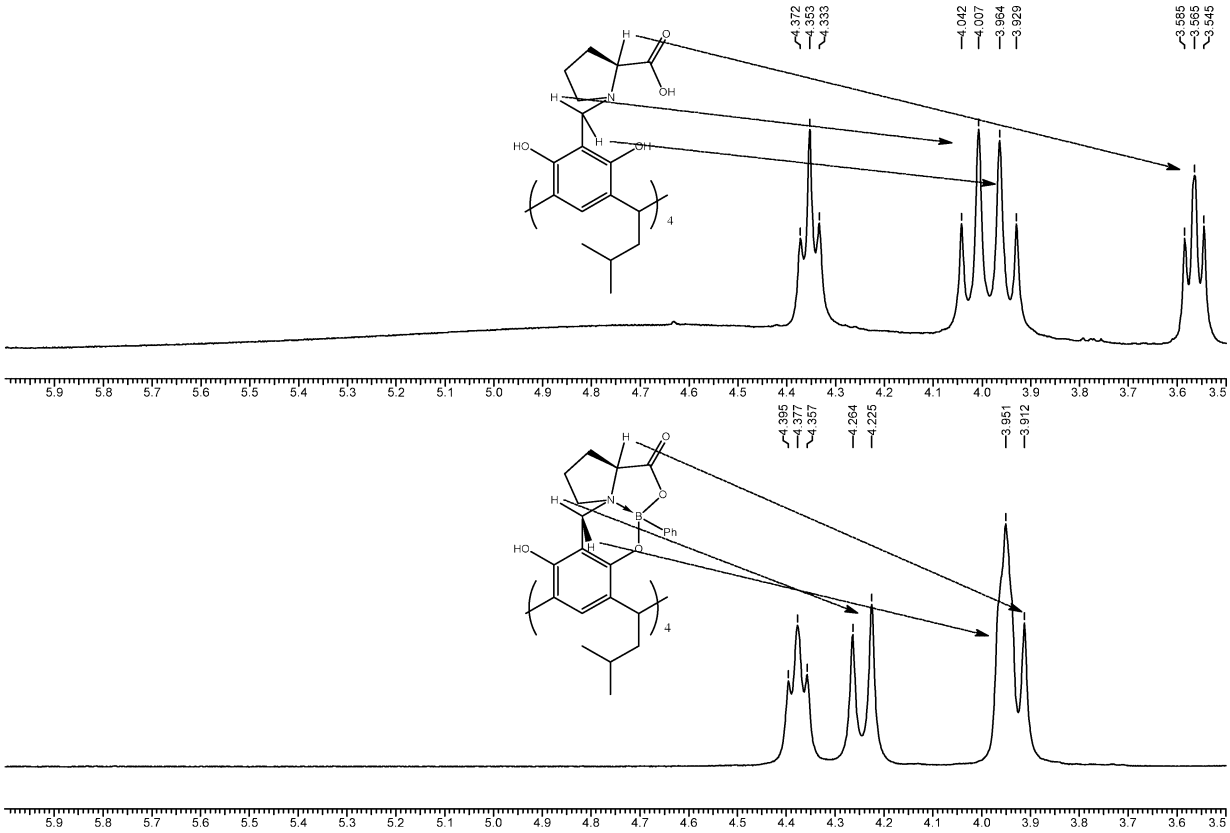


Figure 1. A comparison of the selected fragment of ^{1}H NMR spectra in DMSO-d_6 of the derivatives **2** (top) and **3a** (bottom).

All the above-presented observations led us to propose the structure of the oxazaborolo-benzoxazaborininone derivative of resorcinarene **3** as a structure, whose benzoxazaborinine ring is closed clockwise and the oxazaborolidinone ring projects outwards the calixarene cavity. The L-proline ring is oriented in such a way that the stereogenic carbon atom is outside the cavity. The structures of **3a**, optimised by molecular mechanics (MM+)[6] are shown in Figure 3.

The above-described cyclisation reaction causes formation of new stereogenic centres at the nitrogen and boron atoms. In the case of the products obtained from $PhB(OH)_2$ and $B(Et)_3$, the nitrogen and boron atoms adopt an (*S*)-configuration, while in the case of $B(OMe)_3$ and $B(OH)_3$ the nitrogen and boron atoms adopt (*S*)- and (*R*)-configurations, respectively. This is shown in Scheme 3.

In summary, the novel bora-oxazino-oxazolidinone derivatives of resorcinarene were synthesised from L-proline in high diastereomeric excess. The boron compounds were used as an element binding the carboxy group, the hydroxy group as well as the lone electron pair of the nitrogen atom. In the case of **3a** and **3b**, only the crown conformers are formed, while in the case of **3c**, both the crown and diamond conformers are obtained. The spatial structure of these products was proposed on the basis of comparison of ^{1}H NMR spectra of the synthesised crown conformers with the spectra of the bora-oxazino-oxazolidine derivatives of resorcinarene as well as on the basis of the analysis of the L-proline methine proton shift.

The studies on synthesis of oxazaborolo-benzoxazaborininone derivatives of resorcinarene using other amino acids are in progress.

3. Experimental

^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC 400 (400 MHz). FAB-mass spectra were obtained with a Finnigan MAT90 mass spectrometer using *m*-nitrobenzoyl alcohol (NBA) as a matrix. Mps were determined with a Buchi B-540 melting point apparatus and are uncorrected. Reagents and solvents were obtained from Fluka and Merck and were used without purification. Chromatographic separations were performed on silica gel 60 (SiO_2, Merck, particle size 0.040–0.063 mm, 230–240 mesh).

3.1. Procedure for compound 2

To a solution of the resorcinarene **1** (5 g, 7.01 mmol) in 100 ml of ethanol, formaldehyde (37%, 2.13 ml, 2.8 mmol) and L-proline (3.23 g, 2.8 mmol) was added and refluxed. After 3 h the precipitate was filtered off and dried under vacuum. The product thus obtained was normally already spectroscopic pure, with 80% yield. **2** (crown): mp >300°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.92 (d, $J=6.56$ Hz, 24H), 1.38 (m, 4H), 1.65 (m,

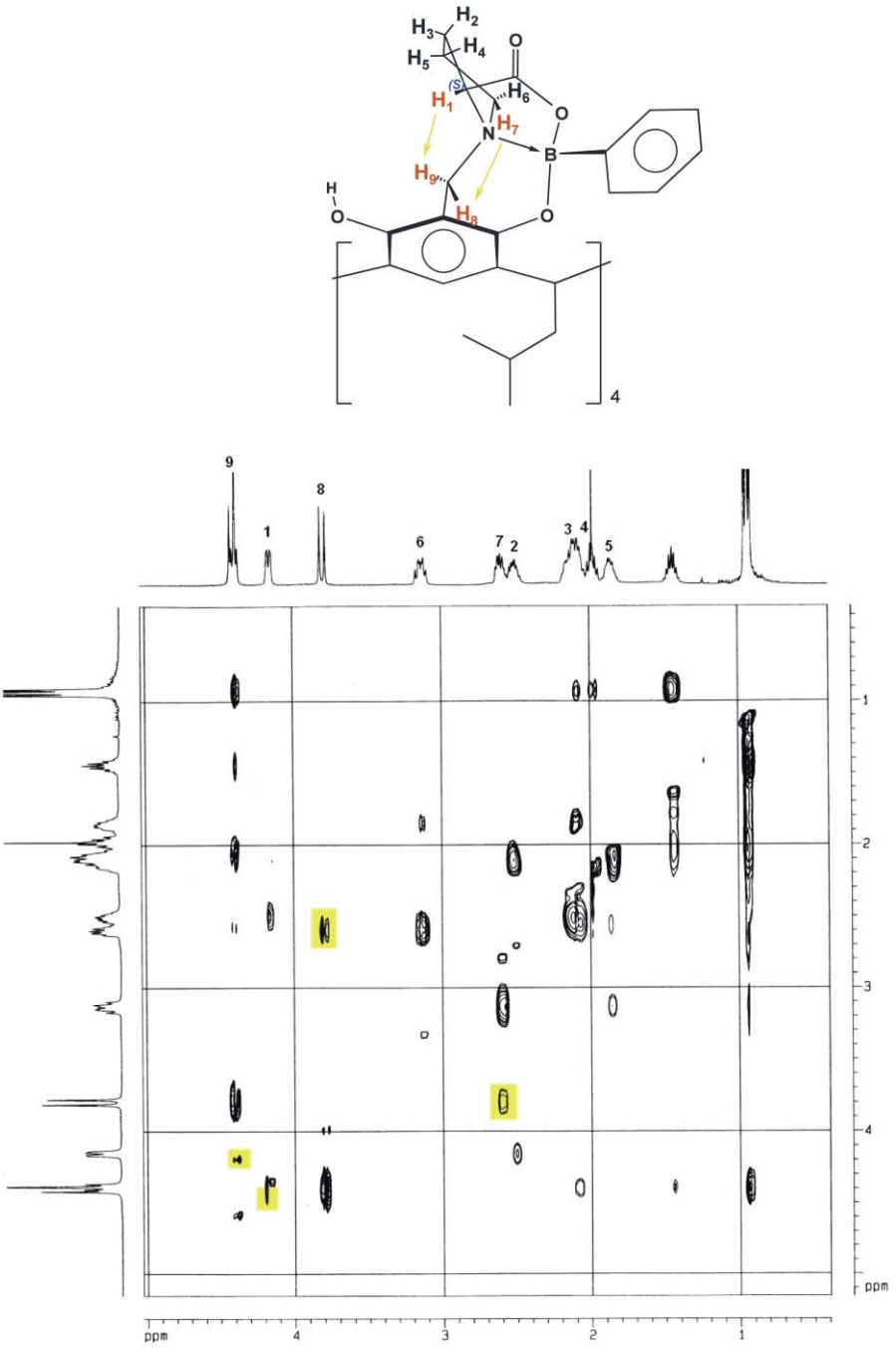


Figure 2. At the top of the figure is the fragment of structure of derivatives **3a** with labelled positions of the protons. Below is the fragment of (^{1}H,^{1}H) NOESY spectra (400 MHz) of derivatives **3a** with marked the coupling protons.

4H), 1.81 (m, 8H), 2.1 (m, 12H), 2.61 (dd, $J=8.59$ Hz, 4H), 3.03 (m, 4H), 3.56 (m, 4H), 3.98 (dd, $J=13.89$ Hz, 8H), 4.35 (t, $J=7.84$ Hz), 4.61 (br.s, 8H), 7.42 (s, 4H). ^{13}C NMR (DMSO, 100 MHz): 18.58, 22.76, 26.02, 28.10, 28.18, 31.47, 41.41, 41.44, 53.35, 53.39, 56.05, 66.78, 107.72, 124.37, 124.42, 150.94, 151.04, 172.02. MS-FAB (NBA) m/z: 1220.6347 (calcd 1220.6508).

3.2. Procedure for compound 3a (crown)

To a suspension of compound **2** (1.0 g, 0.82 mmol) in toluene was added phenyl boronic acid (0.4 g, 3.28 mmol) and heated for 4 h at 140°C with azeotropic socket. The solvent was removed under reduced pressure and the acetonitrile was added. The resulting solution was precipitated and subsequent recrystallization from acetone/acetonitrile afforded 0.96 g (75%) of white crystals, mp >300°C. $[\alpha]_D^{25}=-16.9$ (c 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.94 (dd, $J=6.82$ Hz, 24H), 1.45 (m, 4H), 1.87 (m, 4H), 1.99 (m, 4H), 2.11 (m, 12H), 2.52 (m, 4H), 2.61 (m, 4H), 3.14 (m, 4H), 3.81 (d, $J=13.89$ Hz, 4H), 4.16 (dd, $J=2.78$ Hz, 4H), 4.40 (m, 4H), 4.42 (d, $J=13.89$ Hz, 4H), 7.11 (s, 4H), 7.34 (m, 12H), 7.46 (s, 4H), 7.58 (m, 12H). ^{13}C NMR (acetone-d_6, 100 MHz) δ: 22.91, 23.35, 23.49, 26.77,

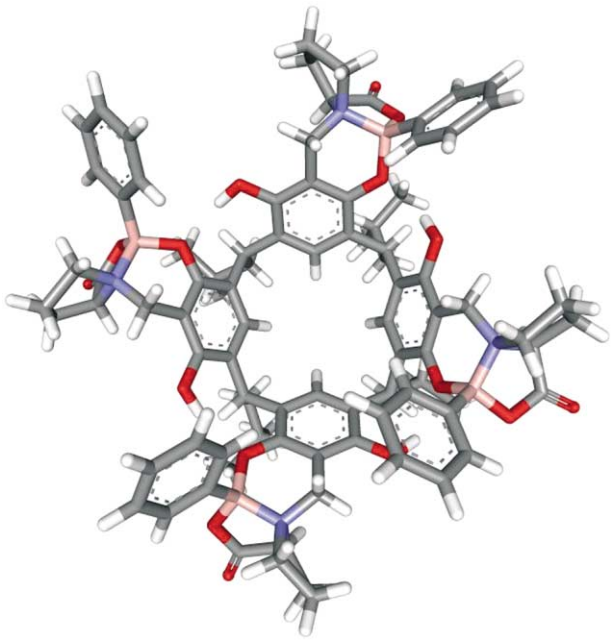
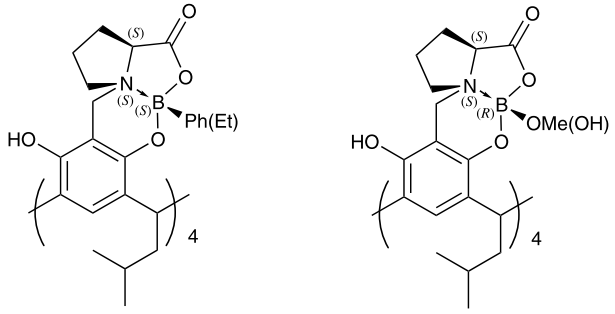


Figure 3. The calculated structures of the bora-oxazino-oxazolidinone derivatives of resorcinarene **3a**.



3a, 3b **3c, 3d**

Scheme 3.

27.15, 32.00, 43.02, 50.19, 60.49, 68.02, 105.76, 125.14, 125.59, 125.76, 128.41, 129.09, 133.06, 150.16, 150.61, 174.58. FAB-MS (NBA) m/z: 1564.7346 (calcd 1564.7819).

3.3. Procedure for compounds 3b (crown) and 3c (crown and diamond)

To a suspension of compound **2** (1.0 g, 0.82 mmol) in THF was added BEt_3 (1 M solution in THF, 4.1 ml) or B(OMe) (0.46 ml, 4.1 mmol) and refluxed for 4 h. The solvent was removed under reduced pressure and the acetonitrile was added. The resulting solution was precipitated and subsequent recrystallization from acetonitrile afforded 0.67 g (60%) of white crystals for **3b** (mp >300°C) and 0.56 g (50%, mixture of conformers) for **3c**. This mixture was subjected to column chromatography (SiO_2, ethyl ester:hexan), obtained **3c** (crown, 30%) and **3c** (diamond, 20%). **3b**: $[\alpha]_D^{25} = -11.5$ (c 1.01, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.57 (sextet, $J = 7.83$ Hz, 4), 0.68 (sextet, $J = 7.83$ Hz, 4H), 0.98 (d, $J = 6.56$ Hz, 24H), 1.02 (t, $J = 7.83$, 12H), 1.45 (m, 4H), 1.90–2.40 (m, 28H), 3.09 (m, 4H), 3.40 (m, 4H), 3.72 (m, 4H), 3.82 (d, $J = 15.16$ Hz, 4H), 4.36 (d, $J = 15.16$ Hz, 4H), 4.45 (t, $J = 7.83$ Hz, 4H), 7.11 (s, 4H), 7.93 (s, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 8.22, 22.68, 22.92, 25.13, 25.99, 29.68, 30.72, 42.64, 50.28, 58.08, 67.22, 103.68, 123.42, 124.087, 124.87, 148.61, 149.64, 174.12. FAB-MS (NBA) m/z: 1372.9 (calcd 1372.8103).

3c (crown): mp >300°C; $[\alpha]_D^{25} = +10.8$ (c 1.02, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.94 (t, $J = 6.57$ Hz, 24H), 1.41 (m, 4H), 1.85 (m, 4H), 1.95–2.14 (m, 20H), 2.23 (m, 8H), 3.01 (m, 4H), 3.53 (s, 12H), 3.77 (m, 4H), 3.82 (d, $J = 13.89$ Hz, 4H), 3.85 (m, 4H), 4.36 (d, $J = 13.89$ Hz, 4H), 4.42 (t, $J = 7.84$ Hz, 4H), 7.02 (s, 4H), 7.54 (s, 4H). ^{13}C NMR (acetone-d_6, 100 MHz) δ: 22.734, 22.79, 23.30, 25.84, 27.03, 42.49, 50.74, 50.91, 57.93, 68.29, 105.61, 123.24, 123.55, 124.74, 148.68, 149.63, 171.80. FAB-MS (NBA) m/z: 1384.5732 (calcd 1384.7581).

3c (diamond): mp >300°C; $[\alpha]_D^{25} = +11.6$ (c 1.01, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.97 (m, 24H), 1.41 (m, 4H), 1.74–2.17 (m, 24H), 2.25 (m, 4H), 3.02 (m, 4H), 3.54 (s, 9H), 3.60–3.84 (m, 7H), 3.87 (m, 3H), 4.08 (t, $J = 8.35$ Hz, 4H), 4.33 (m, 4H), 4.41 (m, 4H), 6.95 (d, 2H), 7.09 (d, 4H), 7.41 (br s, 2H), 7.66 (br s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 22.49, 22.52, 22.59, 22.97, 23.04, 23.11, 23.13, 23.16, 23.23, 23.65, 23.70, 25.88, 25.89, 25.93, 26.48, 26.65, 27.64, 27.99, 30.87, 30.90, 30.98, 42.47, 42.58, 42.62, 50.42, 50.63, 50.67, 50.78, 50.88, 51.28, 57.84, 57.91, 58.05, 58.45, 68.02, 68.27, 68.32, 105.36, 106.01, 106.32, 122.73, 122.76, 123.90, 123.94, 124.47, 124.56, 124.63, 124.70, 124.90, 148.36, 148.40, 149.03, 149.12, 149.44, 149.94, 171.49, 171.63, 172.07, 172.09. FAB-MS (NBA) m/z: 1384.5732 (calcd 1384.7581).

3.4. Procedure for compound 3d

To a suspension of compound **2** (1.0 g, 0.82 mmol) in acetonitrile was added $B(OH)_3$ (0.2 g, 3.28 mmol) and to warm solution DMF was added for the solution of compound **2**. This solution was heated for 3 h at 90°C. The solvents was removed under reduced pressure and the acetonitrile was added. The resulting yellow powder was dissolved in acetone and to this solution Et_2O was added. The resulting solution was precipitated, affording 0.6 g (55%) of a white microcrystalline powder, mp >300°C.

3d (crown): $[\alpha]_D^{25} = +41.0$ (c 05, MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.92 (dd, $J = 6.57$ Hz, 24H), 1.38 (m, 4H), 1.85 (m, 4H), 1.95–2.14 (m, 20H), 2.19 (m, 8H), 3.08 (m, 4H), 3.30–3.60 (m, 12H), 3.85 (d, $J = 7.83$ Hz, 4H), 3.94 (d, $J = 14.91$ Hz), 4.08 (d, $J = 13.89$ Hz, 4H), 4.36 (t, $J = 7.58$ Hz, 4H), 5.24 (s, 4H), 7.46 (s, 4H), 8.04 (s, 4H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 22.68, 22.08, 22.95, 23.30, 25.98, 26.23, 30.83, 41.43, 50.91, 57.93, 68.26, 105.58, 124.20, 124.34, 124.94, 148.24, 149.94, 172.01. FAB-MS (NBA) m/z: 1324.6493 (calcd 1324.6647).

Acknowledgements

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