# Syntheses of Chiral Calix[4]arene Derivatives Bearing Amino Acid Residue†

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**The syntheses of chiral calix[4]arene derivatives bearing amino acid residue at the lower rim or upper rim by three different methods were reported.**

**Keywords** calix[4]arene, amino acid, chiral

## Introduction

Calixarenes are very useful building blocks in molecular recognition.[1-3] They have been attracted considerable interests as the receptors for cations, anions and organic molecules.[4] In recent years, more attention has been focused on the application of calixarenes in biological systems. Some groups have reported on the synthesis and properties of functionalized calixarenes with biological molecular moieties, such as amino acids,[5-16] peptides[17-19] and sugars.[20,21] These calixarene derivatives have shown interesting *in vitro* biological activities. Thus the introduction of amino acid residue at the upper or lower rim of calixarene is significant not only for preparation of chiral water-soluble receptors, but also for mimic of the biological function.

There are several papers describing the methodology of derivation of calixarene with amino acid, and most of the linkages were amide bonds. At the upper rim, carboxy or amino groups were firstly introduced in the *para* position of phenol units, then condensated with relative *N*- or *C*-protected amino acid to synthesize the functionalized receptors.[6-11] At the lower rim, in general, calixarenes were alkylated with haloacetic acid ester, hydrolysis, and then condensated with the amino acid ester in the presence of DCC, or converted to relative acetyl chloride to react.[12-16] Otherwise, the linkage by disulfide bond between calixarene and cysteine has also reported by Shinkai *et al*.[5]

## Results and discussion

Herein we afford further the following three methods for syntheses of calix[4]arene derivatives bearing amino acid residues.

In the first method, calix[4]arene diamino derivative **3**, which was prepared through alkylation of calix[4]arene **1** with bromoacetonitrile followed by reduction according to the reported procedure,[22,23] was reacted with *N*-*t*-Boc-*L*-amino acids **4** in the presence of DCC to give the chiral calix[4]arene derivatives **5** bearing the amino acid residues at the lower rim in high yields as shown in Scheme 1.

The structures of products **5** were confirmed by spectroscopic data and elemental analyses. The $^1$H NMR spectra of all these chiral calix[4]arenes show a typical AB pattern ($J = ca.$ 13 Hz, $\Delta\delta = 0.8$—$1.0$) of the methylene protons between the phenyl rings indicating that **5** exists in a cone conformation in $CDCl_3$. The split of the signals of ArH shows that the chirality still exists in products **5**.

In the second method, the chiral calix[4]arene derivatives **7** bearing the amino acid residues also at the lower rim were obtained directly by reaction of calix[4]-arene **6** with **4** in the presence of DCC in low to moderate yields as shown in Scheme 2.

The structures of product **7** were also confirmed by spectroscopic data and elemental analyses. When **4b**—**4e**, **4g** and **4h** were reacted with **6**, the **7c**—**7e**, **7g** and **7h** obtained are di-substituted esters at the *distal* position. Due to the chiral center of amino acid residues near to the calixarene moiety, the split of the signals of the most protons are more evident in the $^1$H NMR spectra. Especially two sets of AB pattern of the methylene protons appeared,

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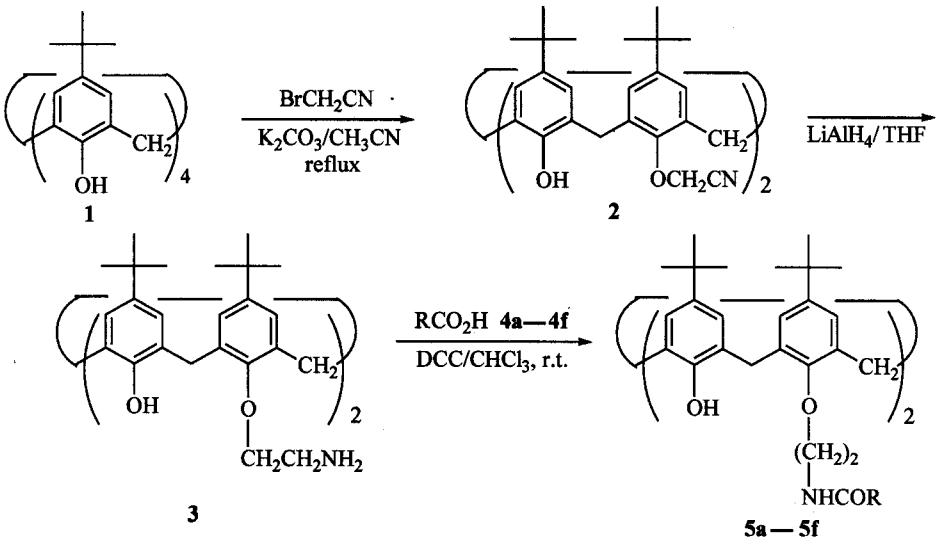
which also indicate that these products exist in cone conformation in $CDCl_3$. However, when **4f** was reacted with **6**, only mono-substituted ester **7f** was obtained, which may be due to the steric as well as electronic effect. Owing to the chirality and unsymmetry existing in **7f** at the same time, the $^1H$ NMR spectrum of **7f** is more complicated.

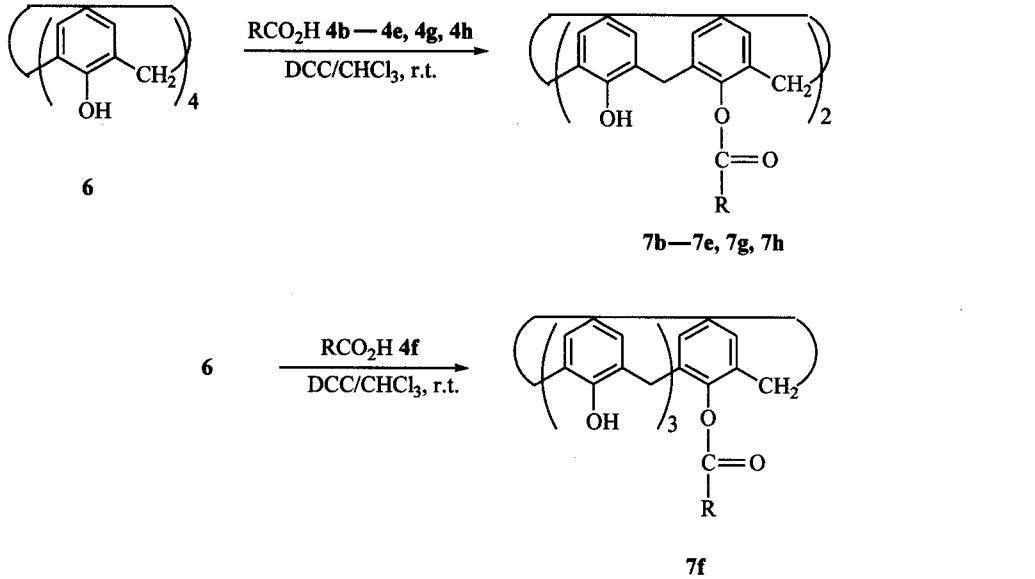
**Scheme 1**




| 4 | a | b | c | d | e |
|---|---|---|---|---|---|
| R | $CH_2$—<br>NHBoc | $CH_3$—CH—<br>NHBoc | $(CH_3)_2CHCH_2$—CH—<br>NHBoc | $C_6H_5CH_2$—CH—<br>NHBoc | $CH_3SCH_2CH_2$—CH—<br>NHBoc |

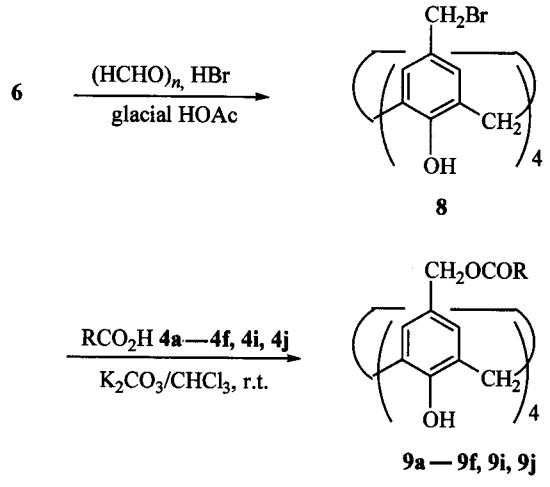
| 4 | f | g | h | i | j |
|---|---|---|---|---|---|
| R | N<br>Boc | $(CH_3)_2CH$—CH—<br>NHBoc | $C_6H_5CH_2OCOCH_2CH_2$—CH—<br>NHBoc | $C_6H_5CH_2OCH_2$—CH—<br>NHBoc | $C_6H_5CH_2OCOCH_2$—CH—<br>NHBoc |

**Scheme 2**



In the third method, tetra(bromomethyl)calix[4]-arene (**8**)[24] reacted with **4** in the presence of potassium carbonate to give the tetra-substituted calix[4]arene derivatives **9** bearing the amino acid residues at the upper rim in good yields as shown in Scheme 3.

**Scheme 3**




The structures of products **9** were also confirmed by spectroscopic data and elemental analyses. The typical AB pattern of the methylene protons in the $^1$H NMR spectra show that products **9** exist in cone conformation in $CDCl_3$. The split of some signals of proton is due to the chiral center of amino acid residues.

## Experimental

Mps of compounds are uncorrected. IR spectra were recorded with a Perkin-Elmer 782 spectrometer as KBr discs. $^1$H NMR spectra were recorded in $CDCl_3$ solution with TMS as internal standard on a Varian Unity 200 spectrometer. Mass spectra were performed on Finnigan MAT 90 spectrometer. The specific rotations were measured on an Optical Acitivity Ltd. AA-10R polarometer. Elemental analyses were carried out at the Analytical Laboratory of the Institute.

*General procedure for synthesis of* **5**

A mixture of **3** (200 mg, 0.27 mmol), *N*-*t*-Boc-amino acid **4** (0.54 mmol) and DCC (112 mg, 0.54 mmol) in 5 mL of chloroform was stirred at room temperature for 3 h. The white precipitate (DCU) was filtered, and the filtrate was evaporated under reduced pressure. Then the residue was subjected to preparative TLC [silica gel ($60GF_{254}$, 10—40), chloroform] to remove the small amount of DCU and the products **5** were obtained.

5, 11, 17, 23-*Tetra*-*tert*-*butyl*-25, 27-*bis*[(*N*-*t*-*Boc*-*glycyl*)*aminoethoxy*]-26,28-*dihydroxycalix*[4]*arene* (**5a**) Yield 90%; m.p. 116—118 ℃; $^1$H NMR ($CDCl_3$) $\delta$: 8.53 (s, 2H, OH), 8.32 (s, 2H, NH), 7.05 (s, 4H, ArH), 6.98 (s, 4H, ArH), 5.43—5.49 (m, 2H, NHBoc), 4.22 (d, $J$ = 12.8 Hz, 4H, ArC**H**$_2$Ar), 4.12 (t, $J$ = 6.0 Hz, 4H, $OCH_2$), 3.94 (s, 4H, $CH_2$), 3.84—3.94 (m, 4H, $NCH_2$), 3.40 (d, $J$ = 12.8 Hz, 4H, ArC**H**$_2$Ar), 1.40 (s, 18H, $C(CH_3)_3$), 1.25 (s, 18H, $C(CH_3)_3$), 1.10 (s, 18H, $C(CH_3)_3$); IR (KBr) $\nu$: 3360, 3320 (OH, NH), 1710, 1670 (C=O), 1480 $cm^{-1}$; MS (EI) $m/z$ (%): 1049 ($[M+1]^+$, 3), 949 (22), 849 (22), 748 (9), 145 (59), 101 (100). Anal. calcd for $C_{62}H_{88}N_4O_{10}$: C 70.96, H 8.45, N 5.34; found C 70.54, H 8.33, N 5.46.

5, 11, 17, 23-*Tetra*-*tert*-*butyl*-25, 27-*bis*[(*N*-*t*-*Boc*-*L*-*alanyl*)*aminoethoxy*]-26,28-*dihydroxycalix*[4]*arene* (**5b**) Yield 82%; m.p. 113—115 ℃; $[\alpha]_D^{25}$ −4.4; $^1$H NMR ($CDCl_3$) $\delta$: 8.79 (s, 2H, OH), 8.62 (s, 2H, NH), 6.79—7.06 (m, 8H, ArH), 5.34 (d, $J$ = 8.2 Hz, 2H, NHBoc), 4.30—4.38 (m, 2H, CH), 4.26 (d, $J$ = 13.1 Hz, 4H, ArC**H**$_2$Ar), 3.95—4.05 (m, 4H, $OCH_2$), 3.70—3.80 (m, 4H, $NCH_2$), 3.37 (d, $J$ = 13.1 Hz, 4H, ArC**H**$_2$Ar), 1.42 (s, 18H, $C(CH_3)_3$), 1.35 (d, $J$ = 6.2 Hz, 6H, $CH_3$), 1.25 (s, 18H, $C(CH_3)_3$), 1.12 (s, 18H, $C(CH_3)_3$); IR (KBr) $\nu$: 3360, 3320 (OH, NH), 1710, 1660 (C=O), 1480 $cm^{-1}$; MS (EI) $m/z$ (%): 1077 ($[M+1]^+$, 2), 977 (18), 877 (22), 762 (10), 159 (100). Anal. calcd for $C_{64}H_{92}N_4O_{10}$: C 71.34, H 8.61, N 5.20; found C 71.22, H 8.60, N 5.14.

5, 11, 17, 23-*Tetra*-*tert*-*butyl*-25, 27-*bis*[(*N*-*t*-*Boc*-*L*-*leucyl*)*aminoethoxy*]-26,28-*dihydroxycalix*[4]*arene* (**5c**) Yield 86%; m.p. 118—120 ℃; $[\alpha]_D^{25}$ −20.8; $^1$H NMR ($CDCl_3$) $\delta$: 9.10 (s, 2H, OH), 9.00 (s, 2H, NH), 6.95—7.10 (m, 8H, ArH), 5.08 (d, $J$ = 9.0 Hz, 2H, NHBoc), 4.36—4.44 (m, 2H, CH), 4.35 (d, $J$ = 12.8 Hz, 4H, ArC**H**$_2$Ar), 4.11 (t, $J$ = 9.2 Hz, 4H, $OCH_2$), 3.89 (t, $J$ = 9.0 Hz, 4H, $NCH_2$), 3.64—3.74 (m, 2H, CH), 3.47 (t, $J$ = 12.0 Hz, 4H, $CH_2$), 3.35 (d, $J$ = 12.8 Hz, 4H, ArC**H**$_2$Ar), 1.45 (s, 18H, $C(CH_3)_3$), 1.24 (s, 18H, $C(CH_3)_3$), 1.16 (s, 18H, $C(CH_3)_3$), 0.72 (d, $J$ = 6.0 Hz, 6H, $CH_3$), 0.50 (d, $J$ = 6.0 Hz, 6H, $CH_3$); IR (KBr) $\nu$: 3400, 3320 (OH, NH), 1700, 1660 (C=O), 1480 $cm^{-1}$; MS (EI) $m/z$ (%): 1161 ($[M+1]^+$, 3), 1061 (27), 961 (19), 804 (12), 201 (100). Anal. calcd for $C_{70}H_{104}N_4O_{10}$: C 72.38, H 9.03, N 4.82; found C 72.37, H 8.74, N 4.87.

5, 11, 17, 23-*Tetra*-*tert*-*butyl*-25, 27-*bis*[(*N*-*t*-*Boc*-*L*-*phenylalanyl*)*aminoethoxy*]-26,28-*dihydroxycalix*[4]*arene* (**5d**) Yield 84%; m.p. 100—101 ℃; $[\alpha]_D^{25}$ −13.9; $^1$H NMR ($CDCl_3$) $\delta$: 8.92 (s, 2H, OH), 8.80 (s, 2H, NH), 6.70—7.10 (m, 18H, ArH), 5.12 (d, $J$ = 8.0 Hz, 2H, NHBoc), 4.48 (q, $J$ = 7.5 Hz, 2H, CH), 4.25 (d, $J$ = 13.0 Hz, 4H, ArC**H**$_2$Ar), 3.95 (t, $J$ = 10.0 Hz, 4H, $OCH_2$), 3.67 (t, $J$ = 10.0 Hz, 4H, $NCH_2$), 3.42 (d, $J$ = 13.0 Hz, 4H, ArC**H**$_2$Ar), 3.00 (d, $J$ = 8.0 Hz, 4H, $CH_2$), 1.25 (s, 18H, $C(CH_3)_3$),

1.20 (s, 18H, $C(CH_3)_3$), 1.09 (s, 18H, $C(CH_3)_3$); IR (KBr) $\nu$: 3360, 3320 (OH, NH), 1705, 1660 (C=O), 1480 $cm^{-1}$; MS (EI) *m/z* (%): 1229 ($[M+1]^+$, 2), 1129 (21), 1029 (15), 838 (8), 235 (62), 191 (63), 120 (100). Anal. calcd for $C_{76}H_{100}N_4O_{10}$: C 74.27, H 8.20, N 4.56; found C 74.14, H 8.23, N 4.34.

5,11,17,23-*Tetra-tert-butyl*-25,27-*bis*[(*N-t-Boc-L-methionyl*)*aminoethoxy*]-26,28-*dihydroxycalix*[4]*arene* (**5e**) Yield 89%; m.p. 98—100 ℃; $[\alpha]_D^{25}$ -22.7; $^1H$ NMR ($CDCl_3$) $\delta$: 9.07 (s, 2H, OH), 9.01 (s, 2H, NH), 7.10 (s, 4H, ArH), 7.04 (s, 4H, ArH), 5.27 (d, $J$=8.9 Hz, 2H, NHBoc), 4.35 (d, $J$=13.1 Hz, 4H, $ArCH_2Ar$), 4.08 (t, $J$=9.2 Hz, 4H, $OCH_2$), 3.98—4.04 (m, 2H, CH), 3.92 (t, $J$=9.2 Hz, 4H, $NCH_2$), 3.55 (t, $J$=13.2 Hz, 4H, $SCH_2$), 3.38 (d, $J$=13.1 Hz, 4H, $ArCH_2Ar$), 2.15—2.40 (m, 4H, $CH_2$), 1.83 (s, 6H, $SCH_3$), 1.42 (s, 18H, $C(CH_3)_3$), 1.22 (s, 18H, $C(CH_3)_3$), 1.17 (s, 18H, $C(CH_3)_3$); IR (KBr) $\nu$: 3380, 3330 (OH, NH), 1700, 1655 (C=O), 1480 $cm^{-1}$; MS (EI) *m/z* (%): 1197 ($[M+1]^+$, 1.5), 1097 (20), 997 (15), 822 (10), 219 (62), 175 (100). Anal. calcd for $C_{68}H_{100}N_4O_{10}S_2$: C 68.19, H 8.42, N 4.68; found C 68.08, H 8.10, N 4.53.

5,11,17,23-*Tetra-tert-butyl*-25,27-*bis*[(*N-t-Boc-L-prolyl*)*aminoethoxy*]-26,28-*dihydroxycalix*[4]*arene* (**5f**) Yield 78%; m.p. 114—115 ℃; $[\alpha]_D^{25}$ -12.7; $^1H$ NMR ($CDCl_3$) $\delta$: 8.42 (s, 2H, OH), 7.87 (s, 2H, NH), 7.05 (s, 4H, ArH), 6.90 (s, 4H, ArH), 4.25 (d, $J$=13.2 Hz, 4H, $ArCH_2Ar$), 4.10—4.18 (m, 2H, CH), 3.90—3.98 (m, 4H, $OCH_2$), 3.46—3.54 (m, 4H, $NCH_2$), 3.36 (d, $J$=13.2 Hz, 4H, $ArCH_2Ar$), 1.90—2.20 (m, 8H, $CH_2$), 1.70—1.90 (m, 4H, $CH_2$), 1.45 (s, 18H, $C(CH_3)_3$), 1.27 (s, 18H, $C(CH_3)_3$), 1.03 (s, 18H, $C(CH_3)_3$); IR (KBr) $\nu$: 3380, 3300 (OH, NH), 1690, 1660 (C=O), 1475 $cm^{-1}$; MS (EI) *m/z* (%): 1129 ($[M+1]^+$, 1), 1029 (19), 929 (10), 788 (7), 185 (21), 70 (100). Anal. calcd for $C_{68}H_{96}N_4O_{10}$: C 72.31, H 8.57, N 4.96; found C 72.26, H 8.44, N 4.95.

*General procedure for synthesis of* **7**

A mixture of calix[4]arene **6** (250 mg, 0.59 mmol), **4** (1.18 mmol) and DCC (244 mg, 1.18 mmol) in 15 mL of chloroform was stirred at room temperature for 8 h. Then it was worked up as above procedure. The products were purified by recrystallization from dichloromethane/methanol.

25,27-*Bis*(*N-t-Boc-L-alanyloxy*)-26,28-*dihydroxycalix*[4]*arene* (**7b**) Yield 70%; m.p. 212—213 ℃; $[\alpha]_D^{25}$ -40.0; $^1H$ NMR ($CDCl_3$) $\delta$: 8.45 (s, 1H, OH), 8.42 (s, 1H, OH), 6.70—7.13 (m, 12H, ArH), 5.85 (s, 2H, NHBoc), 4.53 (quin, 2H, CH), 4.10 (d, $J$=13.5 Hz, 2H, $ArCH_2Ar$), 3.92 (d, $J$=13.5 Hz, 2H, $ArCH_2Ar$), 3.40 (d, $J$=13.5 Hz, 4H, $ArCH_2Ar$), 1.75 (d, $J$=7.2 Hz, 6H, $CH_3$), 1.42 (s, 9H, $C(CH_3)_3$), 1.35 (s, 9H, $C(CH_3)_3$); IR (KBr) $\nu$: 3480, 3440 (OH, NH), 1720, 1682 (C=O), 1440 $cm^{-1}$; MS (FAB) *m/z* (%): 766 ($[M]^+$, 100). Anal. calcd for $C_{44}H_{50}N_2O_{10}$: C 68.91, H 6.57, N 3.65; found C 68.59, H 6.63, N 3.59.

25,27-*Bis*(*N-t-Boc-L-leucyloxy*)-26,28-*dihydroxycalix*[4]*arene* (**7c**) Yield 69%; m.p. 207—208 ℃; $[\alpha]_D^{25}$ -23.4; $^1H$ NMR ($CDCl_3$) $\delta$: 8.48 (s, 1H, OH), 8.44 (s, 1H, OH), 6.68—7.15 (m, 12H, ArH), 5.82 (s, 2H, NHBoc), 4.38—4.50 (m, 2H, CH), 4.08 (d, $J$=13.7 Hz, 2H, $ArCH_2Ar$), 3.87 (d, $J$=13.7 Hz, 2H, $ArCH_2Ar$), 3.38 (d, $J$=13.7 Hz, 4H, $ArCH_2Ar$), 2.04—2.12 (m, 4H, $CH_2$), 1.72—1.80 (m, 2H, CH), 1.33 (s, 18H, $C(CH_3)_3$), 1.05 (d, $J$=5.6 Hz, 6H, $CH_3$), 1.00 (d, $J$=5.6 Hz, 6H, $CH_3$); IR (KBr) $\nu$: 3480, 3330 (OH, NH), 1720, 1680 (C=O), 1440 $cm^{-1}$; MS (EI) *m/z* (%): 851 ($[M+1]^+$, 100), 752 (22), 538 (13). Anal. calcd for $C_{50}H_{62}N_2O_{10}$: C 70.56, H 7.34, N 3.29; found C 70.45, H 7.09, N 3.33.

25,27-*Bis*(*N-t-Boc-L-phenylalanyloxy*)-26,28-*dihydroxycalix*[4]*arene* (**7d**) Yield 34%; m.p. 206—208 ℃; $[\alpha]_D^{25}$ -19.2; $^1H$ NMR ($CDCl_3$) $\delta$: 8.56 (s, 1H, OH), 8.52 (s, 1H, OH), 6.73—7.48 (m, 22H, ArH), 5.73 (s, 2H, NHBoc), 4.64—4.74 (m, 2H, CH), 4.05 (d, $J$=13.5 Hz, 2H, $ArCH_2Ar$), 3.88 (d, $J$=13.5 Hz, 2H, $ArCH_2Ar$), 3.38 (d, $J$=15.0 Hz, 4H, $CH_2$), 3.28 (d, $J$=13.5 Hz, 2H, $ArCH_2Ar$), 1.27 (s, 18H, $C(CH_3)_3$); IR (KBr) $\nu$: 3475, 3340 (OH, NH), 1725, 1680 (C=O), 1430 $cm^{-1}$; MS (EI) *m/z* (%): 920 ($[M+1]^+$, 12), 820 (100), 720 (17), 425 (15). Anal. calcd for $C_{56}H_{58}N_2O_{10}$: C 73.18, H 6.36, N 3.05; found C 72.85, H 6.37, N 3.14.

25,27-*Bis*(*N-t-Boc-L-methionyloxy*)-26,28-*dihydroxycalix*[4]*arene* (**7e**) Yield 45%; m.p. 192—193 ℃; $[\alpha]_D^{25}$ -31.1; $^1H$ NMR ($CDCl_3$) $\delta$: 8.53 (s, 1H, OH), 8.49 (s, 1H, OH), 6.72—7.14 (m, 12H, ArH), 5.76 (s, 2H, NHBoc), 4.58—4.70 (m, 2H, CH), 4.03 (d, $J$=13.6 Hz, 2H, $ArCH_2Ar$), 3.86 (d, $J$=13.6 Hz, 2H, $ArCH_2Ar$), 3.40 (d, $J$=13.5 Hz, 4H, $ArCH_2Ar$), 2.76—2.90 (m, 4H, $SCH_2$), 2.25—2.38 (m, 4H, $CH_2$), 2.17 (s, 6H, $SCH_3$), 1.30 (s, 18H, $C(CH_3)_3$); IR (KBr) $\nu$: 3485, 3320 (OH, NH), 1725, 1675 (C=O), 1440 $cm^{-1}$; MS (EI) *m/z* (%): 888 ($[M+1]^+$, 100), 787 (34), 556 (12), 425 (15). Anal. calcd for $C_{48}H_{58}N_2O_{10}S_2$: C 64.99, H 6.59, N 3.16; found C 64.87, H 6.48, N 3.16.

25-(*N-t-Boc-L-prolyloxy*)-26,27,28-*trihydroxycalix*[4]*arene* (**7f**) Yield 35%; m.p. 129—130 ℃; $[\alpha]_D^{25}$ -5.5; $^1H$ NMR ($CDCl_3$) $\delta$: 9.72 (s, 1H, OH), 9.37 (s, 1H, OH), 8.52 (s, 1H, OH), 6.60—7.15 (m, 12H, ArH), 4.80—4.87 (m, 1H, CH), 4.47, 4.38, 4.30, 4.21 (4sets, d, $J$=14.2 Hz, 4H, $ArCH_2Ar$), 3.58—3.70 (m, 2H, $CH_2$), 3.50, 3.44, 3.42, 3.37 (4sets, d, $J$=14.2 Hz, 4H, $ArCH_2Ar$), 2.60—

2.77 (m, 1H, $CH_2$), 2.44—2.60 (m, 1H, $CH_2$), 2.23—2.37 (m, 1H, $CH_2$), 2.05—2.18 (m, 1H, $CH_2$), 1.48 (s, 9H, $C(CH_3)_3$); IR (KBr) $\nu$: 3260 (OH), 1725, 1625 (C=O), 1440 $cm^{-1}$; MS (EI) *m/z* (%): 622 ($[M+1]^+$, 100), 522 (25), 425 (13). Anal. calcd for $C_{38}H_{39}NO_7$: C 73.41, H 6.32, N 2.25; found C 72.99, H 6.30, N 2.32.

25,27-*Bis* (*N-t-Boc-L-valyloxy*)-26,28-*dihydroxycalix*[4]*arene* (**7g**) Yield 59%; m.p. 209—210 ℃; $[\alpha]_D^{25}$ -24.3; $^1H$ NMR ($CDCl_3$) $\delta$: 8.40 (s, 1H, OH), 8.36 (s, 1H, OH), 6.72—7.12 (m, 12H, ArH), 5.70 (s, 2H, NHBoc), 4.32—4.40 (m, 2H, CH), 4.00 (d, $J$ = 14.4 Hz, 2H, ArC**H**$_2$Ar), 3.96 (d, $J$ = 14.4 Hz, 2H, ArC**H**$_2$Ar), 3.38 (d, $J$ = 14.4 Hz, 4H, ArC**H**$_2$-Ar), 2.40—2.52 (m, 2H, CH), 1.38 (d, $J$ = 7.7 Hz, 6H, $CH_3$), 1.30 (s, 18H, $C(CH_3)_3$), 1.18 (d, $J$ = 7.7 Hz, 6H, $CH_3$); IR (KBr) $\nu$: 3480, 3320 (OH, NH), 1725, 1675 (C=O), 1440 $cm^{-1}$; MS (FAB) *m/z* (%): 822 ($[M]^+$, 100). Anal. calcd for $C_{48}H_{58}N_2O_{10}$: C 70.05, H 7.10, N 3.40; found C 70.08, H 7.00, N 3.84.

25,27-*Bis*(*N-t-Boc-γ-benzyl-L-glutamyloxy*)-26,28-*dihydroxycalix*[4]*arene* (**7h**) Yield 30%; m.p. 95—96 ℃; $[\alpha]_D^{25}$ -4.8; $^1H$ NMR ($CDCl_3$) $\delta$: 8.50 (s, 1H, OH), 8.46 (s, 1H, OH), 6.76—7.32 (m, 22H, ArH), 5.62 (s, 2H, NHBoc), 5.10—5.28 (m, 4H, $OCH_2$), 4.52—4.65 (m, 2H, CH), 3.85 (d, $J$ = 13.6 Hz, 2H, ArC**H**$_2$Ar), 3.78 (d, $J$ = 13.6 Hz, 2H, ArC**H**$_2$Ar), 3.48 (d, $J$ = 13.6 Hz, 4H, ArC**H**$_2$Ar), 2.67—2.82 (m, 4H, $COCH_2$), 2.30—2.47 (m, 2H, $CH_2$), 2.57—2.30 (m, 2H, $CH_2$), 1.40 (s, 18H, $C(CH_3)_3$); IR (KBr) $\nu$: 3450, 3320 (OH, NH), 1710, 1680 (C=O), 1435 $cm^{-1}$; MS (EI) *m/z* (%): 1064 ($[M+1]^+$, 98), 964 (100), 743 (9), 424 (18). Anal. calcd for $C_{62}H_{66}N_2O_{14}$: C 70.04, H 6.26, N 2.64; found C 69.95, H 6.37, N 2.68.

*General procedure for synthesis of* **9**

A mixture of **8** (366 mg, 0.5 mmol), **4** (2 mmol) and potassium carbonate (138 mg, 1 mmol) in 10 mL of chloroform was stirred at room temperature for 12 h. The solution was washed with saturated sodium bicarbonate solution (2 × 10 mL) and water (3 × 10 mL) successively and dried with anhydrous sodium sulfate. After removing of solvent, **9** were obtained as white crystals.

5,11,17,23-*Tetrakis*[(*N-t-Boc-glycyloxy*)*methyl*]-25,26,27,28-*tetrahydroxycalix*[4]*arene* (**9a**) Yield 85%; m.p. 170 ℃ (dec.); $^1H$ NMR ($CDCl_3$) $\delta$: 10.20 (s, 4H, OH), 7.05 (s, 8H, ArH), 5.15—5.23 (m, 4H, NHBoc), 4.98 (s, 8H, $OCH_2$), 4.25 (d, $J$ = 14.2 Hz, 4H, ArC**H**$_2$Ar), 3.90 (s, 8H, $CH_2$), 3.55 (d, $J$ = 14.2 Hz, 4H, ArC**H**$_2$Ar), 1.42 (s, 36H, $C(CH_3)_3$); IR (KBr) $\nu$: 3350, 3160 (OH, NH), 1735, 1700 (C=O), 1505, 1470 $cm^{-1}$. Anal. calcd for $C_{60}H_{76}N_4O_{20}$: C 61.41, H 6.53, N 4.78; found C 61.71, H 5.98, N 4.64.

5,11,17,23-*Tetrakis*[(*N-t-Boc-L-alanyloxy*)*methyl*]-25,26,27,28-*tetrahydroxycalix*[4]*arene* (**9b**) Yield 84%; m.p. 123—124 ℃; $[\alpha]_D^{25}$ -17.5; $^1H$ NMR ($CDCl_3$) $\delta$: 10.20 (s, 4H, OH), 7.05 (s, 8H, ArH), 5.05—5.18 (m, 4H, NHBoc), 4.98 (s, 8H, $OCH_2$), 4.25—4.36 (m, 4H, CH), 4.25 (d, $J$ = 14.4 Hz, 4H, ArC**H**$_2$Ar), 3.55 (d, $J$ = 14.4 Hz, 4H, ArC**H**$_2$Ar), 1.40 (s, 36H, $C(CH_3)_3$), 1.38 (d, $J$ = 7.0 Hz, 12H, $CH_3$); IR (KBr) $\nu$: 3350, 3160 (OH, NH), 1725, 1700 (C=O), 1500, 1450 $cm^{-1}$. Anal. calcd for $C_{64}H_{84}N_4O_{20}$: C 62.52, H 6.89, N 4.56; found C 62.86, H 6.75, N 4.21.

5,11,17,23-*Tetrakis*[(*N-t-Boc-L-leucyloxy*)*methyl*]-25,26,27,28-*tetrahydroxycalix*[4]*arene* (**9c**) Yield 81%; m.p. 92—94 ℃; $[\alpha]_D^{25}$ -15.2; $^1H$ NMR ($CDCl_3$) $\delta$: 10.20 (s, 4H, OH), 7.07 (s, 8H, ArH), 5.00—5.12 (m, 4H, NHBoc), 4.97 (s, 8H, $OCH_2$), 4.28—4.38 (m, 4H, CH), 4.25 (d, $J$ = 14.0 Hz, 4H, ArC**H**$_2$Ar), 3.55 (d, $J$ = 14.0 Hz, 4H, ArC**H**$_2$Ar), 1.40—1.72 (m, 12H, $CH_2$, CH), 1.43 (s, 18H, $C(CH_3)_3$), 1.38 (s, 18H, $C(CH_3)_3$), 0.96 (d, $J$ = 7.0 Hz, 12H, $CH_3$), 0.90 (d, $J$ = 7.0 Hz, 12H, $CH_3$); IR (KBr) $\nu$: 3340, 3170 (OH, NH), 1725, 1700 (C=O), 1495, 1470, 1460 $cm^{-1}$. Anal. calcd for $C_{76}H_{108}N_4O_{20}$: C 65.31, H 7.79, N 4.01; found C 65.31, H 7.55, N 3.96.

5,11,17,23-*Tetrakis*[(*N-t-Boc-L-phenylalanyloxy*)-*methyl*]-25,26,27,28-*tetrahydroxycalix*[4]*arene* (**9d**) Yield 72%; m.p. 100—101 ℃; $[\alpha]_D^{25}$ +3.45; $^1H$ NMR ($CDCl_3$) $\delta$: 10.15 (s, 4H, OH), 6.97—7.15 (m, 28H, ArH), 4.95—5.07 (m, 4H, NHBoc), 4.90 (s, 8H, $OCH_2$), 4.54—4.62 (m, 4H, CH), 4.25 (d, $J$ = 14.4 Hz, 4H, ArC**H**$_2$Ar), 3.53 (d, $J$ = 14.4 Hz, 4H, ArC**H**$_2$Ar), 2.98—3.06 (m, 8H, $CH_2$), 1.40 (s, 36H, $C(CH_3)_3$); IR (KBr) $\nu$: 3350, 3160 (OH, NH), 1730, 1700 (C=O), 1490, 1450 $cm^{-1}$. Anal. calcd for $C_{88}H_{100}N_4O_{20}$: C 68.91, H 6.57, N 3.65; found C 68.53, H 6.59, N 3.55.

5,11,17,23-*Tetrakis*[(*N-t-Boc-L-methionyloxy*)*methyl*]-25,26,27,28-*tetrahydroxycalix*[4]*arene* (**9e**) Yield 70%; m.p. 90—92 ℃; $[\alpha]_D^{25}$ -8.85; $^1H$ NMR ($CDCl_3$) $\delta$: 10.15 (s, 4H, OH), 7.08 (s, 8H, ArH), 5.23—5.34 (m, 4H, NHBoc), 5.00 (s, 8H, $OCH_2$), 4.36—4.44 (m, 4H, CH), 4.25 (d, $J$ = 14.3 Hz, 4H, ArC**H**$_2$Ar), 3.55 (d, $J$ = 14.3 Hz, 4H, ArC**H**$_2$Ar), 2.40—2.50 (m, 8H, $SCH_2$), 1.84—1.96 (m, 8H, $CH_2$) 1.90 (s, 12H, $SCH_3$), 1.40 (s, 18H, $C(CH_3)_3$), 1.39 (s, 18H, $C(CH_3)_3$); IR (KBr) $\nu$: 3340, 3165 (OH, NH), 1730, 1700 (C=O), 1500, 1475, 1450 $cm^{-1}$. Anal. calcd for $C_{72}H_{100}N_4O_{20}S_4$: C 58.83, H 6.86, N 3.81; found C 58.35, H 6.93, N 3.35.

5,11,17,23-*Tetrakis*[(*N-t-Boc-L-prolyloxy*)*methyl*]-25,26,27,28-*tetrahydroxycalix*[4]*arene* (**9f**) Yield 88%; m.p. 129—131 ℃; $[\alpha]_D^{25}$ -43.35; $^1H$ NMR ($CDCl_3$) $\delta$: 10.22 (s, 4H, OH), 7.08 (s, 8H,

ArH), 4.95 (s, 8H, $OCH_2$), 4.25 (d, $J$ = 14.1 Hz, 4H, $ArCH_2Ar$), 3.55 (d, $J$ = 14.1 Hz, 4H, $ArCH_2$-Ar), 3.38—3.50 (m, 4H, CH), 2.13—2.25 (m, 8H, $CH_2$), 1.84—1.96 (m, 16H, $CH_2$), 1.45 (s, 18H, $C(CH_3)_3$), 1.15 (s, 18H, $C(CH_3)_3$); IR (KBr) $\nu$: 3340, 3160 (OH, NH), 1735, 1685 (C = O), 1475, 1455 $cm^{-1}$. Anal. calcd for $C_{72}H_{92}N_4O_{20}$: C 64.85, H 6.95, N 4.20; found C 64.54, H 6.70, N 3.80.

5, 11, 17, 23-*Tetrakis* [(*N-t-Boc-O-benzyl-L-seryloxy*)*methyl*]-25, 26, 27, 28-*tetrahydroxycalix* [4] *arene* (**9i**) Yield 73%; m.p. 105—108 ℃; $[\alpha]_D^{25}$ −2.5; $^1$H NMR ($CDCl_3$) $\delta$: 10.15 (s, 4H, OH), 7.16—7.30 (m, 20H, ArH), 7.00 (s, 8H, ArH), 5.40—5.50 (m, 4H, NHBoc), 4.96 (s, 8H, $OCH_2$), 4.45—4.55 (m, 4H, CH), 4.46 (s, 8H, $PhCH_2O$), 4.20 (d, $J$ = 14.4 Hz, 4H, $ArCH_2Ar$), 3.65—3.90 (m, 8H, $CH_2$), 3.42 (d, $J$ = 14.4 Hz, 4H, $ArCH_2Ar$), 1.40 (s, 36H, $C(CH_3)_3$); IR (KBr) $\nu$: 3330, 3170 (OH, NH), 1730, 1700 (C = O), 1480, 1450 $cm^{-1}$. Anal. calcd for $C_{92}H_{108}N_4O_{24}$: C 66.81, H 6.58, N 3.39; found C 67.35, H 6.72, N 3.00.

5, 11, 17, 23-*Tetrakis* [(*N-t-Boc-O-benzyl-L-asparatyloxy*)*methyl*]-25, 26, 27, 28-*tetrahydroxycalix* [4] *arene* (**9j**) Yield 71%; m.p. 83—85 ℃; $[\alpha]_D^{25}$ + 3.35; $^1$H NMR ($CDCl_3$) $\delta$: 10.13 (s, 4H, OH), 7.33 (s, 20H, ArH), 7.00 (s, 8H, ArH), 5.53—5.58 (m, 4H, NHBoc), 5.10 (s, 8H, $PhCH_2O$), 4.92 (s, 8H, $OCH_2$), 4.52—4.62 (m, 4H, CH), 4.18 (d, $J$ = 14.0 Hz, 4H, $ArCH_2Ar$), 3.47 (d, $J$ = 14.0 Hz, 4H, $ArCH_2Ar$), 2.82—3.05 (m, 8H, $COCH_2$), 1.33 (s, 36H, $C(CH_3)_3$); IR (KBr) $\nu$: 3350, 3160 (OH, NH), 1725, 1700 (C = O), 1490, 1450 $cm^{-1}$. Anal. calcd for $C_{96}H_{108}N_4O_{28}$: C 65.29, H 6.16, N 3.17; found C 65.07, H 6.20, N 2.79.

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