Multiple Cycloadditive Macrocyclization: An Efficient Method for Crown Ether-Type Cyclophanes, Bis-Calix[4]arenes and Silamacrocycles

Byeang Hyean Kim,* Eun Jeong Jeong, Gil Tae Hwang, Natarajan Venkatesan

National Research Laboratory, Department of Chemistry, Center for Integrated Molecular Systems, Division of Molecular Life Science, Pohang University of Science and Technology, Pohang, 790-784, Korea
Fax +82(54)2793399; E-mail: bhkim@postech.ac.kr

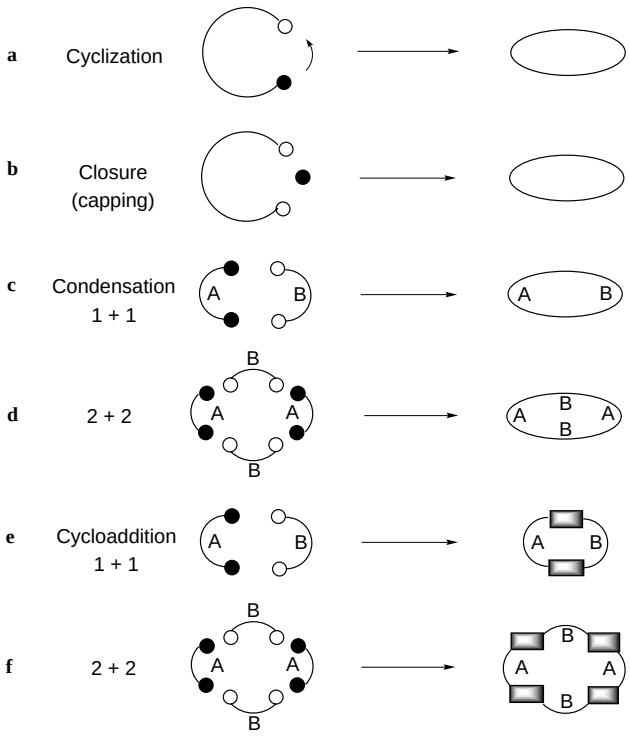
Received 28 August 2001

Abstract: Macrocycles constitute a broad spectrum of compounds, which play a significant role in host-guest supramolecular chemistry. We have rationally designed an efficient novel synthetic method to synthesize different types of artificial receptive macrocycles containing isoxazoline or isoxazole ring systems. This method involves multiple (double, triple or quadruple) cycloadditions between bifunctional dipoles and bifunctional dipolarophiles. We have presented our synthetic results to show the ease with which this one-pot synthetic method can be extended to synthesize different types of macrocycles such as cyclophanes, bis-calix[4]arenes and silamacrocycles. Hence, with appropriate combination of bifunctional dipoles and bifunctional dipolarophiles, the ring size of macrocycles could be controlled. This multiple cycloadditive macrocyclization will be a useful arsenal for the synthesis of various macrocycles.

Key words: cycloadditions, cyclophanes, macrocycles, nitrile oxides, silicon heterocycles

Introduction

Cycloaddition reaction, a pericyclic transformation, is a process in which two or more molecules containing unsaturated bonds combine to form a ring. The ability to simultaneously form and break several bonds with a wide variety of atomic substitution patterns and often with a high degree of stereocontrol has made cycloaddition reactions the subject of intense study.[1] This has traditionally been one of the best methods available to synthesize carbo- and hetero-cyclic ring systems of different shape and size. On the other hand, macrocyclic chemistry continues to attract chemists world-wide from almost all disciplines due to many of its salient features.[2] Development of efficient synthetic pathways is paramount in order to design macrocycles with the desired functionality, property, size and shape. Though there are so many synthetic methods available to make different types of macrocycles, in the recent past there have been a growing number of literatures on synthesis of macrocyclic systems using cycloaddition reactions as key step of the synthetic method. For example, one of the famous textbooks on macrocyclic chemistry written by B. Dietrich, P. Viout, and J.-M. Lehn,[3] describes several ways of obtaining macrocycles such as simple cyclization (a), cyclization in conjugation with another molecule (capping) and (b) condensation of two or four identical or different units (Scheme 1). But we have envisioned an additional novel pathway for isoxazole and isoxazoline containing macrocycles by using *double* (e) and *quadruple* (f) cycloadditions[4] (Scheme 1) as cornerstones. We call this method '*multiple cycloadditive macrocyclization*' reaction. Due to the well-defined transition state of cycloaddition reactions, the novel cycloadditive macrocyclization can afford various macrocycles in a stereoselective manner.



Scheme 1 Several methods to synthesize macrocycles

In the introduction part of this feature article, quoting relevant examples from elsewhere in the literature, it is revealed that multiple cycloadditive macrocyclization is among one of the powerful synthetic methods available to the organic chemist in macrocycle synthesis.

A variety of 1,3-dipoles such as nitrile oxides,[5] nitrile imines,[6] *O*-silylnitronates[7] and azomethine ylides[8] have been reported to be good synthetic precursors in construction of macrocyclic systems. However, most of them involve

Synthesis 2001, No. 14, 26 10 2001. Article Identifier:
1437-210X,E;2001,0,14,2191,2202,ftx,en;F06801SS.pdf.

ISSN 0039-7881

multi step sequential inter- and/or intra molecular cycloaddition with[9] or without molecular rearrangement as the crucial factor of the macrocycle formation. There are only few reports wherein one-pot synthesis of macrocycle from the dipole has been performed. For example, it has been shown that aldoximes **1** possessing long alkyl chains, on oxidation with nitrogen dioxide can lead to the formation of macrocycles **2** by 1,3-dipolar cycloaddition of the nitrile oxide with an alkene (Scheme 2).[5]

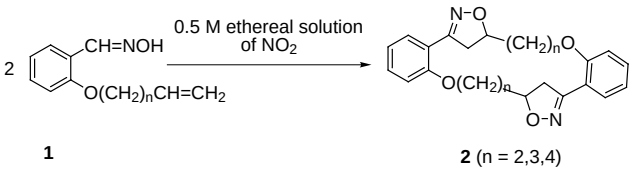
Biographical Sketches

Byeang Hyean Kim (2nd from left) was born in Busan, Korea in 1955. He got his undergraduate education at Seoul National University and obtained his M. S. degree from Korea Advanced Institute of Science and Technology (KAIST) in 1979. Then he entered Korea Research Institute of Chemical Technology as a researcher and stayed there until 1983. From 1980 to 1981, he had an opportunity to study at Tokyo Institute of Technology (TIT) as a UNESCO fellow. He worked at the laboratories of Professor Isao Kuwajima and got valuable experiences with many group members including Dr. Eiichi Nakamura (now Professor of Chemistry, Univ. of Tokyo). In the summer of 1983, he went to USA for further study and was enrolled as a graduate student at the University of Pittsburgh. He earned his Ph. D. under the guidance of Professor Dennis P. Curran in 1987 and worked as a postdoctoral associate with Professor K. C. Nicolaou at University of Pennsylvania from 1987 to 1988. After a one year stint at the KCN group, he returned to his home country to become an Assistant Professor at Pohang University of Science and Technology (POSTECH). He was promoted to Associate Professor at POSTECH in 1993 and is now Professor of Chemistry and Director of National Research Lab [MoNAS]. He was a visiting scholar at the University of Tokyo in 1995 and enjoyed his sabbatical leave in the laboratories of Professor Julius Rebek, Jr. at the Scripps Research Institute from 1996 to 1997. In 1999, he received the Jang Sehee Organic Chemistry Award given by the Korean Chemical Society (Organic Chemistry Division) and was selected as a 2000 Lectureship Awardee by The Society of Synthetic Organic Chemistry, Japan. His research interests lie in the fields of synthetic organic chemistry, bioorganic chemistry, and chemical biology. This year his laboratory was awarded to be one of National Research Laboratories (Laboratory for Modified Nucleic Acid Systems). His recent research topics include design and synthesis of receptive and responsive molecules, peptidomimetics and application toward enzyme inhibitors, synthesis of novel macrocycles, and design and synthesis of modified nucleic acid systems.

Eun Jeong Jeong (far left) was born in 1970 in Gangneung, Korea and graduated from POSTECH in 1993. She obtained her master degree in 1995 under the supervision of Professor Byeang Hyean Kim. From 1995 to 1997, she worked on TFT-LCD in the R&D division of Samsung Electronics. In 2001, she received her Ph. D. degree from Seoul National University under the direction of Professor Eun Lee. Her current research efforts include the total synthesis of natural products containing aza- or oxa-cyclic ring by the method of radical cyclization.

Gil Tae Hwang (2nd from right) was born in Daegu, Korea in 1972. He studied organic chemistry at POSTECH, where he obtained his bachelor (1996) and master degrees (1998) under the supervision of Professor Byeang Hyean Kim. He is currently completing a Ph. D. at the same University under the direction of Professor Kim. His research interests have focused on design and synthesis of novel macrocycles and the development of new fluorophores and their photophysical study.

Natarajan Venkatesan (far right) was born in Tamil Nadu, India in 1970. He completed his graduate and post-graduate degrees in chemistry at two different colleges of the University of Madras. He carried out his research work on calixarene chemistry under the supervision of Professor H. M. Chawla, Department of Chemistry, Indian Institute of Technology, Delhi from where he obtained his Ph. D. degree in August 2000. He is currently doing his post-doctoral research work with Professor Kim's research group at POSTECH.



Scheme 2 Inter- and intramolecular cycloadditive macrocyclization reactions of aldoximes **1**

J. Nishimura et al.,[10] have developed a new synthetic method involving the inter- and intramolecular [2+2] photo-cycloaddition of vinylarenes to synthesize a series of cyclophanes such as naphthalenophanes, phenanthrenophanes, thiophenophanes and carbazolophanes tethered with cyclopropyl or cyclobutyl rings. This was further extended to synthesize selective ionophoric calixarenes and crown ethers.[11]

The synthetic utility of [4+2] Diels–Alder cycloaddition reactions in macrocyclic chemistry have increasingly been realized from the recent reports on direct synthesis of achiral or chiral[12] cyclophanes and in the syntheseses of modified naturally occurring macrocyclic systems.[13] However, there are only a few reports relevant to the topic of this feature article, namely one-pot direct macrocycle formation by multiple [4+2] Diels–Alder reactions. For example, a few representatives of this class of compounds (Figure 1) known as [n] Beltenes **3**, [n] collarenes **4** and [n] cyclacenes **5** have been prepared using repetitive [4+2] Diels–Alder annulations as the key step. Stoddart and coworkers, in a series of their contributions have shown that the stereoselective construction of cyclacenes and polyacenes derivatives is possible by '*structure-directed synthesis*' involving repetitive Diels–Alder reactions by the correct choice of *polyfunctional dienes* and *polyfunctionlal dienophiles*.[14] For instance, the treble diastereoselectivities exhibited by Diels–Alder reactions between diene **6** and dienophiles of the type **7** have been utilized to construct compounds with different molecular architectures such as belts, cups and cages.[14a] Similarly, A.-D. Schluter et al., have observed that the repetitive Diels–Alder cyclizations of bifunctional dienes and bifunctional dienophiles are good ways for the synthesis of macrocycles such as [6]-beltene **8** under specified reaction conditions.[15] A convergent synthesis of [8]-cyclacene **9** via a key step involving stereospecific double Diels–Alder macroannulations of a rigid planar bisdienophile by a flexible non-planar bisdiene has been reported from R. M. Corey's laboratories.[16] It has been observed that the flexibility of the bisdienes is crucial for the success of this reaction. On the other hand, Stoddart's research group have employed rigid non-planar bisdienes and rigid non-planar bisdienophiles in the synthesis of rigid macrocyclic cyclophanes.[14]

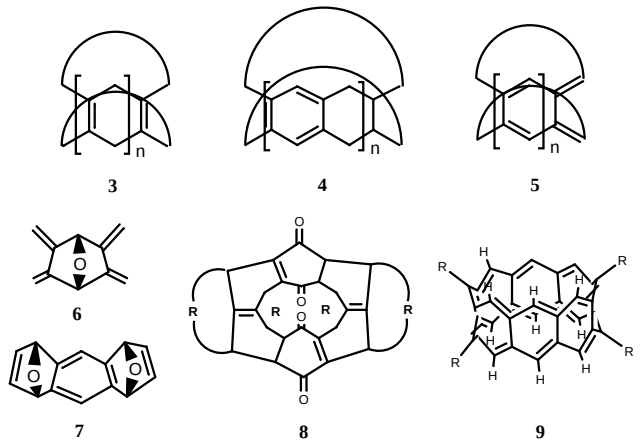


Figure 1 Diene, dienophile and [4 + 2] cycloadducts

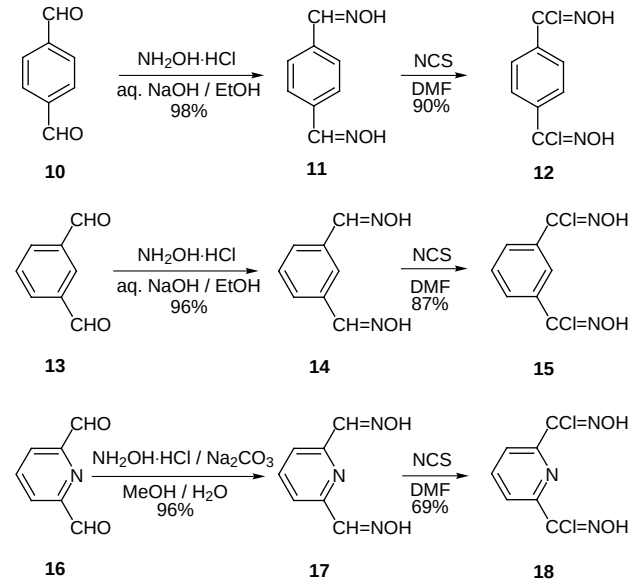
Results and Discussion

We have prepared various macrocycles including crown ether-type cyclophanes, bis-calix[4]arenes and silamacrocycles by using double, triple, and quadruple cycloadditive macrocyclizations as key steps. In this part, we summarize the synthesis of bifunctional dipoles, dipolarophiles and macrocycles synthesized by the multiple cycloadditive macrocyclizations. Silamacrocycles have been synthesized based on our simple rationale that replacing either the dipole or dipolarophile with a metal containing derivative would lead to metalo-macrocycles with additional binding sites.

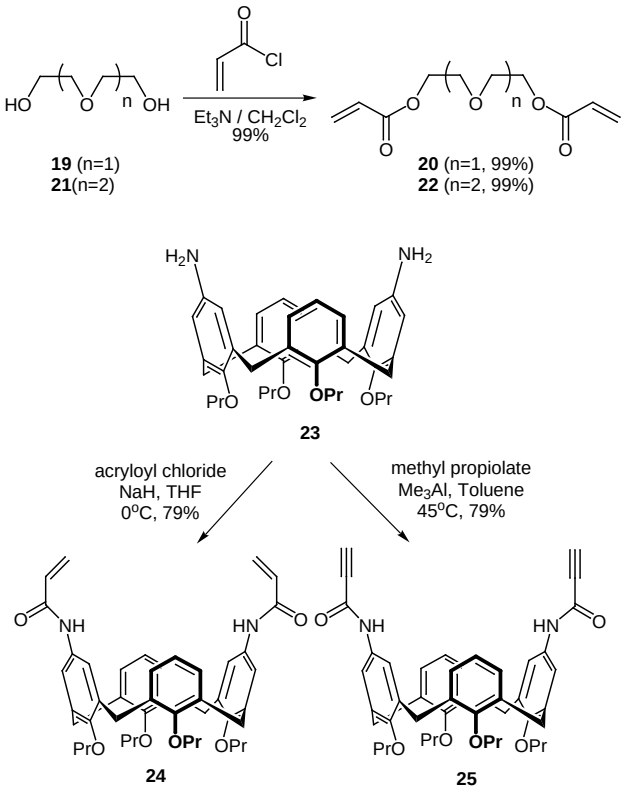
Synthesis of Bifunctional Dipoles and Bifunctional Dipolarophiles

As illustrated in the introduction, arriving at a given macrocycle by cycloadditive macrocyclization route relies mainly on the proper choice of bifunctional dipole (bis-nitrile oxides) and bifunctional dipolarophile. The bifunctional hydroxamic acid chlorides **12**, **15** and **18** were prepared from their corresponding dialdehydes (**10, 13** and **16**) in a two-step procedure as given in Scheme 3.[17] The bifunctional dipoles were generated in situ by the dehydrochlorination of the corresponding hydroxamic acid chlorides under the reaction conditions for macrocycle synthesis.

All the divinyl dipolarophiles (diethylene glycol divinyl ether, triethylene glycol divinyl ether and 1,3-divinyltetramethyldisiloxane) and tetraethylene glycol diacrylate were obtained from commercial sources. Other diacrylate dipolarophiles i.e., diethylene glycol diacrylate (**20**) and triethylene glycol diacrylate (**22**) were prepared in almost quantitative yields, by treating the corresponding glycols (**19** and **21**) with acryloyl chloride (Scheme 4). Similarly, the calix[4]arene based bifunctional dipolarophiles[18] **24** and **25** were obtained from diaminocalix[4]arene **23**[19] by N-acryloylation and N-propiolation, respectively (Scheme 4).



Scheme 3 Preparation of bifunctional hydroxamic acid chlorides **12**, **15** and **18**



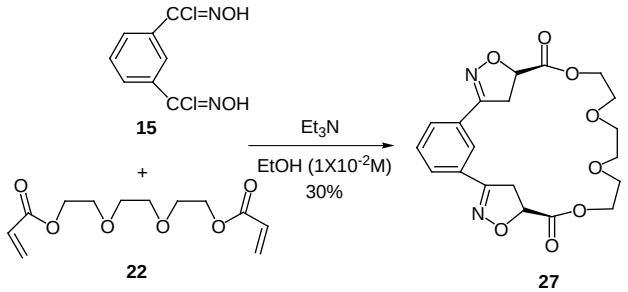
Scheme 4 Preparation of bifunctional dipolarophiles **20**, **22**, **24** and **25**

Synthesis of Macrocycles by Nitrile Oxide Cycloadditive Macrocyclization

Crown-ether type macrocycles,[4] silamacrocycles[20] and bis-calix[4]arenes[21] were synthesized by appropriate combination of bifunctional dipoles and bifunctional dipolarophiles. The ring size of the resulting macrocycles could be controlled through 1+1 double cycloadditive macrocyclization, 2+1 triple cycloadditive macrocyclization, or 2+2 quadruple cycloadditive macrocyclization. In an m+n multiple cycloaddition, m and n denote respectively, the number of bisdipole(s) and bisdipolarophile(s) involved in the cycloadditive macrocyclization reaction.

1+1 Double Cycloadditive Macrocyclization[4]

In reactions of ethylene glycol diacrylates with *meta*-related bifunctional dipoles (isophthaldinitrile oxide[22] and 2,6-pyridinedinitrile oxide), the 1+1 double cycloadducts were obtained as major products. A typical synthesis of 21-membered macrocycle **27** is shown in Scheme 5, whereas in the case of tetraethylene glycol diacrylate, the 1+1 cycloadduct was obtained as the major product (Figure 2). This interesting observation could be explained due to the difference in chain length. In tetraethylene glycol diacrylate, the chain length was long enough to react even with terephthaldinitrile oxide (a *para*-related bifunctional dipole) in a 1+1 fashion, which does not seem to be feasible in the case of di- or triethylene glycol diacrylate. The structures of macrocycles **27** and **30** were confirmed by their X-ray crystallographic data (Figure 3) and the configurations of the other 1+1 cycloadducts were tentatively assigned by analogy.



Scheme 5

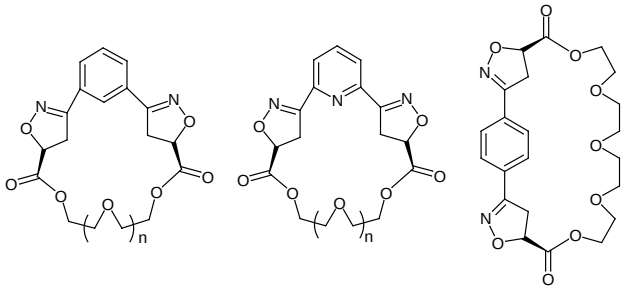


Figure 2 1+1 Double cycloadducts

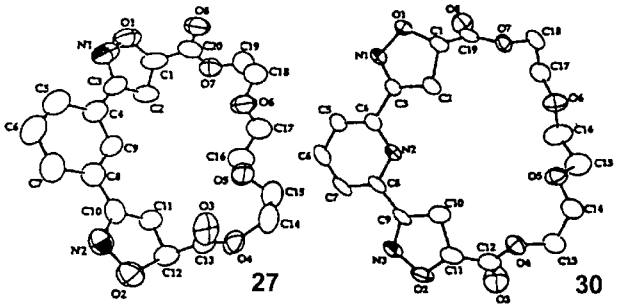


Figure 3 X-ray crystal structures of macrocycles **27** and **30**

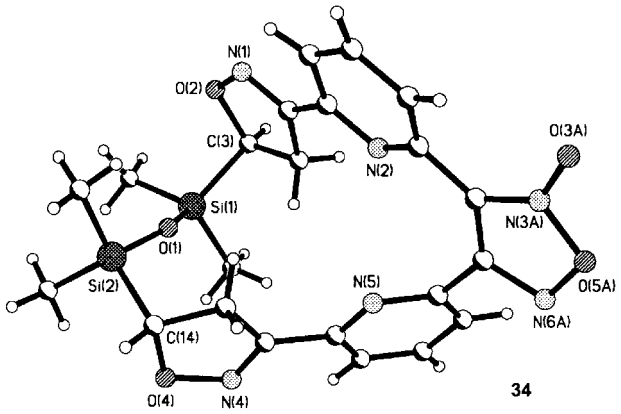
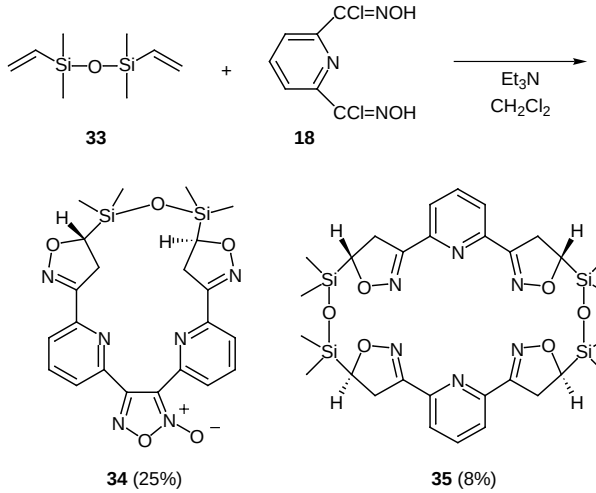


Figure 4 X-ray crystal structure of macrocycle **34**

2+1 Triple Cycloadditive Macrocyclization[20]

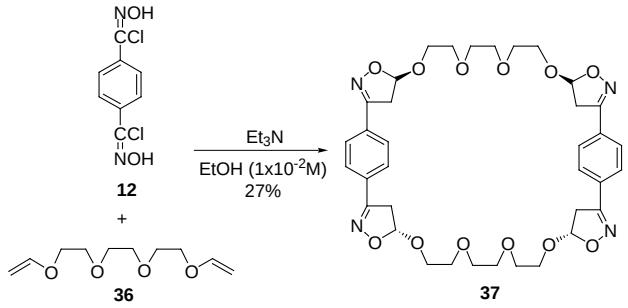
Silamacrocycle **34** was synthesized as the major product (25% overall yield) by unusual 2+1 triple cycloadditions between **18** and **33** (Scheme 6), while the regular 2+2 quadruple cycloadduct **35** could be isolated in 8% overall yield. Mioskowski and coworkers reported the synthesis of medium- and large-size ring systems by intramolecular nitrile oxide dimerization, which results in the formation of furoxan moiety.[23] During the dimerization process, one of the nitrile oxides acts as a dipole whereas the other acts as a dipolarophile. Formation of compound **34** could be explained by a similar mechanism i.e. via 2+1 double cycloadditions followed by intramolecular nitrile oxide dimerization. Generation of this rather unusual product **34** may also be attributable to the stability of 2,6-pyridinedinitrile oxides and the proximity between two nitrile oxide moieties. The crystal structure of **34** clearly indicates that compound **34** is a 2+1 triple cycloadduct (Figure 4).



Scheme 6 Formation of 2 + 1 triple cycloadditive macrocyclization product **34**

2+2 Quadruple Cycloadditive Macrocyclization[4,20,21]

In all reactions of divinyl ether (diethylene glycol and triethylene glycol) dipolarophiles with bifunctional dipoles, macrocycles formed via 2+2 quadruple cycloadditions were obtained as major products. Synthesis of the 40-membered macrocycle **37** is a representative (Scheme 7) of this type. The isolated yield of the final quadruple cycloadduct **37** was 27%, which corresponds to 72% per cycloaddition. Similar to divinyl ether (diethylene glycol and triethylene glycol) dipolarophiles, reactions of terephthaldinitrile oxide with diethylene glycol diacrylate **20** as well as triethylene glycol diacrylate **22** afforded 2+2 quadruple cycloadducts **43** and **44** as major products. The structures and isolated yields of all the major macrocyclic products have been summarized in Figure 5.



Scheme 7

The relative stereochemistry of all 2+2 quadruple cycloadducts was tentatively assigned based on the X-ray crystal structure of **37** (Figure 6). Terephthaldinitrile oxide and the calix[4]arene dipolarophile **24** provided the bis-calix[4]arene **45** in 27% isolated yield by 2+2 quadruple cycloadditions. Similarly, the bis-calix[4]arene **46** was prepared from the corresponding dipolarophile by 2+2 quadruple cycloadditive macrocyclization (Scheme 8). The X-ray crystal analysis of **45** clearly shows the chemical structures including the relative stereochemistry of the four stereogenic centers (Figure 7).

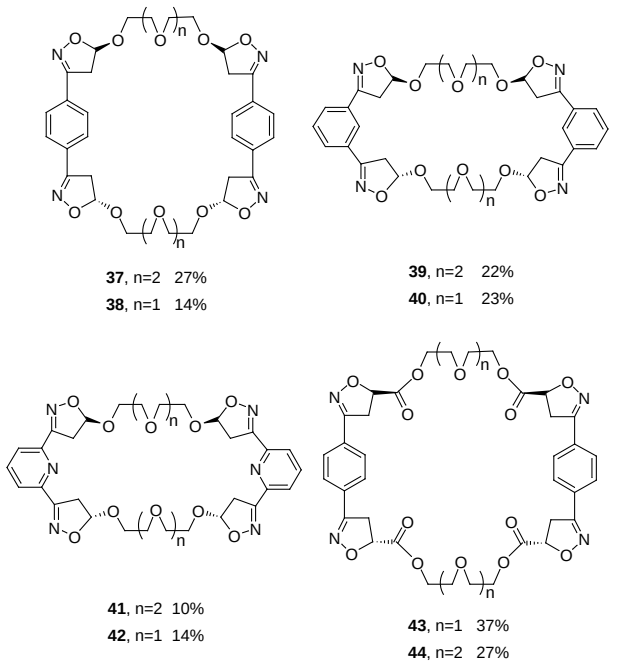


Figure 5 2 + 2 Quadruple cycloadducts **37**–**44**

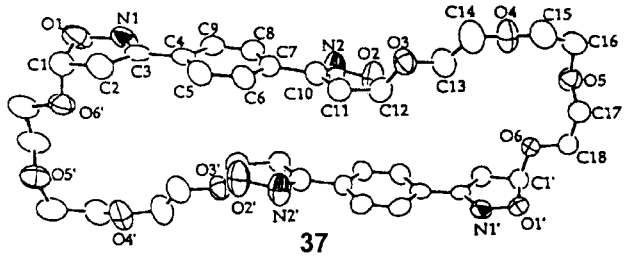
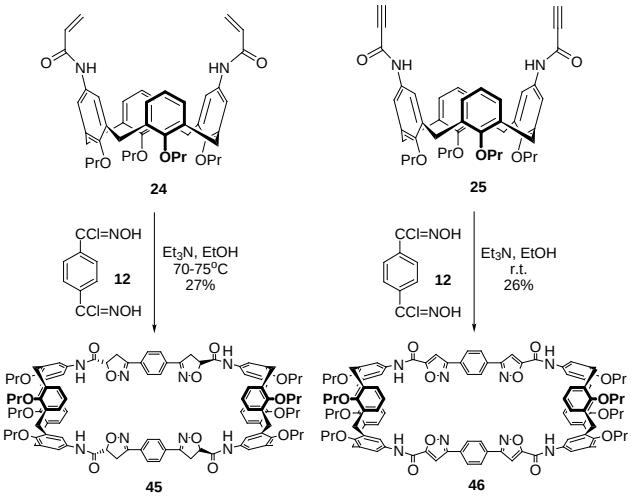


Figure 6 X-ray crystal structure of macrocycle **37**



Scheme 8 Synthesis of bis-calix[4]arenes **45** and **46**

Silamacrocycles[24] were synthesized in a two-step sequence by using cycloadditive macrocyclization methodology. Double cycloadditions between in situ generated isophthaldinitrle oxide and 1,3-divinyltetramethyldisiloxane provided 1+2 cycloadduct **47** as the major intermediate, which on subjection to cycloaddition with isophthaldinitrile oxide afforded the final 2+2 cycloadduct **48** as the major product in 25% yield. In a similar fashion, silamacrocycle **50** was prepared by treating terephthaldinitrile oxide and 1,3-divinyltetramethyldisiloxane **33** (Scheme 9). Thus, 1,3-divinyltetramethyldisiloxane **33** served well as a bifunctional dipolarophile suitable for 1+2 double cycloaddition reactions. The relative stereochemistry of all silamacrocycles was tentatively assigned by the X-ray crystal structure of the 2+2 cycloadduct **48** (Figure 8).

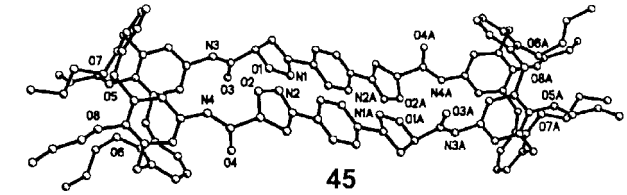
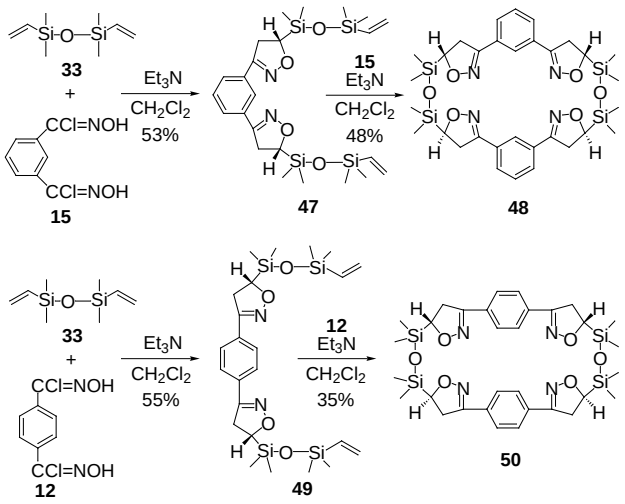


Figure 7 X-ray crystal structure of bis-calix[4]arene **45**



Scheme 9 Synthesis of silamacrocycles **48** and **50**

Conclusion

Here it has been demonstrated that multiple (double, triple or quadruple) cycloadditive macrocyclization is a novel and important synthetic method to design and synthesize diverse artificial receptive macrocyclic systems. We call this method '*multiple cycloadditive macrocyclization*' wherein an appropriate combination of bifunctional dipole and bifunctional dipolarophile can lead to a macrocycle of desired ring size and functionality. Different macrocycles such as crown ether-type cyclophanes, sil-

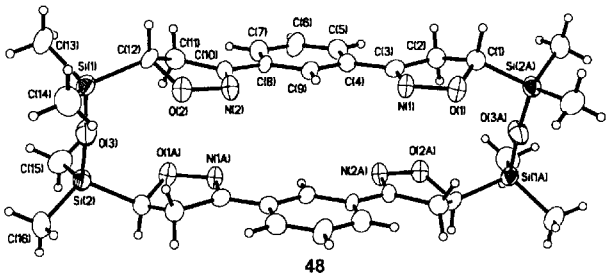


Figure 8 X-ray crystal structure of macrocycle **48**

amacrocycles and bis-calix[4]arenes have been synthesized in good yields. Thus, the multiple cycloadditive macrocyclization is a useful arsenal for the synthesis of various macrocycles. An added advantage of this method is the simultaneous formation of two to four isoxazoline heterocycles, which can be readily converted to β-hydroxy ketone moieties by reductive cleavage.[25] This feature makes it feasible to accesses an interesting class of macrocycles with poly-oxy functionalities. Further studies in this direction are being carried out in our laboratories.

Mps were determined on an Electrothermal IA 9000 series melting point apparatus and are uncorrected. IR spectra were recorded using a Bomem FT-IR spectrometer (PS55+ and DA8). ^{1}H and ^{13}C NMR spectra were taken on a Bruker NMR spectrometer (Aspect 300 MHz). Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. EI and FAB mass spectra were measured on a KRATOS mass spectrometer (MS 25 RFA) and JEOL four sector tandem mass spectrometer (JMS-HX/HX110A). Elemental analyses were done either in Gallbraith Laboratories, Knoxville, USA or in Center for Biofunctional Molecules (CBM), POSTECH, Korea.

All the chemicals used were obtained from Aldrich or Lancaster and used without further purification. All solvents were carefully dried and distilled prior to use. All reactions were carried out with dry glassware under Ar atmosphere. Analytical TLC was carried out on Merck 60 F254 silica gel plate and column chromatography was performed on Merck 60 silica gel (230–400 mesh).

Preparation of Dialdoximes 11, 14, and 17; General Procedure
To a solution of the dialdehyde **10**, **13** or **16** (37.3 mmol) and $NH_2OH{\cdot}HCl$ (87.1 mmol) in EtOH–H_2O, 1:1 (35 mL) was added an aq solution of NaOH (199.2 mmol) dropwise. After stirring the suspension for an hour at 0 °C, the solvent was removed under reduced pressure and the mixture was extracted with EtOAc. The collective organic phase was washed with H_2O and dried over anhydrous $MgSO_4$. The crude product obtained after evaporating the solvent was purified by column chromatography (SiO_2, hexane−EtOAc, 2:1 for **17**; hexane−EtOAc, 3:1 for **11** and **14**) to give dialdoximes **11**, **14** or **17** as a white solid.

Terephthalaldehyde Dioxime (11)
Mp 220 °C dec.

IR (KBr): 3150, 3050, 2983, 2887, 2764, 1456, 1296, 970, 856, 818 cm^{-1}.

^{1}H NMR (300 MHz, acetone-d_6): δ = 11.10 (s, 2 H, OH), 8.13 (s, 2 H, ArCH), 7.64 (s, 4 H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 149.6, 135.4, 127.9.

EIMS *m/z*: [M$^+$] 164.

Isophthalaldehyde Dioxime (14)
Mp 185–186 °C.

IR (KBr): 3360, 3163, 2989, 1486, 1309, 958, 720, 679 cm^{-1}.

^{1}H NMR (300 MHz, acetone-d_6): δ = 10.40 (s, 2 H, OH), 8.17 (s, 1 H, ArCH), 7.88 (s, 1 H, ArH), 7.63 (d, 1 H, *J* = 7.5 Hz, ArH), 7.62 (d, 1 H, *J* = 7.7 Hz, ArH), 7.42 (t, 1 H, J = 7.7 Hz, ArH).

^{13}C NMR (75 MHz, acetone-d_6): δ = 149.0, 134.7, 129.6, 128.2, 122.5.

EIMS *m/z*: [M$^+$] 164.

Pyridine-2,6-dicarbaldehyde Dioxime (17)
Aqueous Na_2CO_3 was used instead of aqueous NaOH solution.

Mp 202 °C dec.

IR (KBr): 3247, 3111, 3007, 2897, 2802, 1589, 1472, 1330, 1162, 996, 939, 810, 691 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$–DMSO-d_6): δ = 11.29 (s, 2 H, OH), 8.14 (s, 2 H, ArCH), 7.79–7.68 (m, 3 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$–DMSO-d_6): δ = 151.7, 148.5, 136.1, 199.4.

EIMS *m/z*: [M$^+$] 165.

Preparation of Bis(hydroxamic acid chlorides) 12, 15 and 18; General procedure
To a DMF solution (0.33 mL per mmol) of aldoxime (36.6 mmol) was added *N*-chlorosuccinimide (76.1 mmol). The resulting mixture was stirred for 20 min. It was then poured into H_2O and extracted with EtOAc. The organic phase was washed several times with H_2O and dried over anhydrous $MgSO_4$. Purification by column chromatography (SiO_2, hexane−EtOAc, 2:1 for **18**; hexane−EtOAc, 4:1 for **15**; hexane−EtOAc, 5:1 for **12**) gave bis(hydroxamic acid chloride) **12**, **15** or **18** as a white solid.

***N*,*N*-Dihydroxybenzene-1,4-dicarboximidoyl Dichloride (12)**
Mp 188–190 °C.

IR (KBr): 3281, 3041, 2900, 1640, 1507, 1404, 1246, 1190, 997, 935, 843 cm^{-1}.

^{1}H NMR (300 MHz, CD_3OD): δ = 7.88 (s, 4 H, ArH).

^{13}C NMR (75 MHz, CD_3OD): δ = 151.9, 138.7, 123.7.

EIMS *m/z*: [M$^+$] 233.

***N*,*N*-Dihydroxybenzene-1,3-dicarboximidoyl Dichloride (15)**
Mp 162–163 °C.

IR (KBr): 3281, 3041, 2900, 1640, 1441, 1405, 1246, 997, 935, 842, 683 cm^{-1}.

^{1}H NMR (300 MHz, acetone-d_6): δ = 11.44 (s, 2 H, OH), 8.34 (s, 1 H, ArH), 7.96 (d, 1 H, *J* = 7.8 Hz, ArH), 7.95 (d, 1 H, *J* = 7.9 Hz, ArH), 7.55 (t, 1 H, *J* = 7.9 Hz, ArH).

^{13}C NMR (75 MHz, acetone-d_6): δ = 136.7, 129.9, 129.4, 125.7.

EIMS *m/z*: [M$^+$] 233.

***N,N*-Dihydroxypyridine-2,6-dicarboximidoyl Dichloride (18)**
Mp 147–148 °C.

IR (KBr): 3209, 3035, 2879, 1647, 1567, 1458, 1391, 1292, 1046, 1008, 939, 813, 733 cm^{-1}.

^1H NMR (300 MHz, CD_3OD): δ = 6.47–6.35 (m, 3 H, ArH).

^{13}C NMR (75 MHz, CD_3OD): δ = 151.9, 138.7, 123.7.

EIMS *m/z*: $[M^+]$ 233.

Diethylene Glycol Diacrylate (20)
To a vigorously stirred solution of diethylene glycol **19** (52.7 mmol) in CH_2Cl_2 (100 mL) was added Et_3N (158.0 mmol), followed by acryloyl chloride (121.2 mmol). After stirring the mixture at r.t. for 1 h, it was poured into H_2O (70 mL) and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$ and evaporated in vacuo. The resulting product on purification by column chromatography (SiO_2, hexane–EtOAc, 5:1) yielded **20** (99%) as a colorless oil.

IR ($CHCl_3$): 3023, 2956, 2889, 1723, 1638, 1619, 1409, 1285, 1193, 1136, 1070, 978, 810 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.26 (dd, 2 H, *J* = 17.5, 1.6 Hz, $CH=CH_2$), 5.99 (dd, 2 H, *J* = 17.5, 10.4 Hz, $CH=CH_2$), 5.68 (dd, 1H, *J* = 10.4, 1.6 Hz, $CH=CH_2$), 4.17–4.14 (m, 4 H, OCH_2), 3.61–3.58 (m, 4 H, OCH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.6, 130.6, 128.0, 68.7, 63.2.

EIMS *m/z*: $[M^+ + H]$ 215.

Triethylene Glycol Diacrylate (22)
To a vigorously stirred solution of triethylene glycol **21** (7.5 mmol) in CH_2Cl_2 (20 mL) was added Et_3N (22.5 mmol), followed by acryloyl chloride (17.3 mmol). After stirring the reaction mixture for 1 h at r.t., it was poured into H_2O (15 mL) and extracted with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$ and evaporated in vacuo. The resulting product on column chromatographic (SiO_2, hexane–EtOAc, 5:1) purification yielded **22** (99%) as a colorless oil.

IR ($CHCl_3$): 3021, 2954, 2889, 2401, 1722, 1637, 1409, 1298, 1196, 1127, 810, 725 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.20 (dd, 2 H, *J* = 17.0, 1.2 Hz, $CH=CH_2$), 5.94 (dd, 2 H, *J* = 17.0, 10.2 Hz, $CH=CH_2$), 5.63 (dd, 2 H, *J* = 10.2, 1.2 Hz, $CH=CH_2$), 4.11–4.08 (m, 4 H, OCH_2), 3.55–3.51 (m, 4 H, OCH_2), 3.45 (s, 4 H, OCH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.4, 130.3, 127.9, 70.1, 68.6, 63.1.

EIMS *m/z*: $[M^+ + H]$ 259.

5,17-Bis(acrylamido)-25,26,27,28-tetrapropoxycalix[4]arene (24)
5,17-Diaminocalix[4]arene **23** (1.98mmol) was dissolved in THF (20mL) at 0 °C containing NaH (5.00 mmol, 60% dispersion in mineral oil) and it was further treated with acryloyl chloride (4.93 mmol). After stirring the mixture for 10 min, it was poured into excess H_2O to destroy unreacted sodium hydride. The reaction mixture was extracted with CH_2Cl_2. Column chromatographic (SiO_2, CH_2Cl_2–EtOAc, 9:1) purification of the crude product yielded **24** (79%) as a white powder.

Mp 195 °C dec.

IR ($CHCl_3$): 3062, 2962, 2934, 2875, 2740, 1914, 1665 (C=O), 1603 (C=C), 1544, 1465, 1419, 1385, 1332, 1303, 1287, 1217, 1162, 1131, 1106, 1081, 1067, 1038, 1006, 966 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.58 (s, 2 H, NH). 6.94 (d, 4 H, *J* = 7.3 Hz, ArH), 6.80 (t, 2 H, *J* = 7.4 Hz, ArH), 6.39 (s, 4 H, ArH), 6.24 (dd, 2 H, *J* = 14.3, 1.3 Hz, $CH=CH_2$), 6.00 (dd, 2 H, *J* = 16.8, 10.3 Hz, $CH=CH_2$), 5.54 (dd, 2 H, *J* = 11.2, 1.3 Hz, $CH=CH_2$), 4.42 (d, 4 H, *J* = 13.3 Hz, $ArCH_2Ar$), 3.95 (t, 4 H, *J* = 7.9 Hz, OCH_2), 3.66 (t, 4 H, *J* = 6.8 Hz, OCH_2), 3.10 (d, 4 H, *J* = 13.4 Hz, $ArCH_2Ar$), 2.00–1.79 (m, 8 H, CH_2CH_3), 1.05 (t, 6 H, *J* = 14.8 Hz, CH_3), 0.90 (t, 6 H, *J* = 14.9 Hz, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.9, 157.8, 153.5, 136.5, 134.7, 132.1, 131.7, 129.2, 127.1, 122.5, 121.1, 77.3, 77.0, 31.4, 23.8, 23.4, 11.1, 10.4.

MS (FAB) *m/z*: $[M^+ + H]$ 731.0, $[M^+]$ 730.0.

5,17-Bis(ethynylamido)-25,26,27,28-tetrapropoxycalix[4]arene (25)
To a solution of 5,17-diaminocalix[4]arene **23** (3.03 mmol) in toluene (15 mL) at 0 °C was added Me_3Al (15.2 mmol, 2.0 M in toluene) dropwise. After complete addition the mixture was allowed to warm to 25 °C and stirred for 1 h. To this aluminum complex was added methyl propiolate (15.7 mmol), the reaction mixture was heated to 45 °C and stirred for an hour. After completion of the reaction, the solution was cooled to r.t., a 20% aq solution of Rochelle's salt was added and the product was extracted with CH_2Cl_2. The collective organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo to give the crude product. This on purification by column chromatography (SiO_2, hexane–EtOAc, 4:1) gave **25** (79%).

Mp 177–179 °C.

IR ($CHCl_3$): 3219, 3261 (NH), 3062, 2962, 2933, 2876, 2108 (C≡C), 1660 (C=O), 1646, 1604, 1542, 1464, 1418, 1384, 1287, 1217, 1160, 1131, 1160, 1131, 1079, 1067, 1038, 1006, 966 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.64 (s, 2 H, NH), 6.97 (d, 4 H, *J* = 7.3 Hz, ArH), 6.83 (t, 2 H, *J* = 7.3 Hz, ArH), 6.36 (s, 4 H, ArH), 4.42 (d, 4 H, *J* = 13.2 Hz, $ArCH_2Ar$), 3.96 (t, 4 H, *J* = 7.8 Hz, OCH_2), 3.66 (t, 4 H, *J* = 6.8 Hz, OCH_2), 3.21 (d, 4 H, *J* = 13.3 Hz, $ArCH_2Ar$), 2.42(s, 2 H, CCH), 1.98–1.83 (m, 8 H, CH_2CH_3), 1.05 (t, 6 H, *J* = 7.3 Hz, CH_3), 0.90 (t, 6 H, *J* = 7.3 Hz, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.7, 153.8, 150.3, 136.4, 134.9, 130.8, 129.3, 122.9, 121.3, 78.2, 77.0, 74.9, 31.4, 23.8, 23.4, 11.1, 10.3.

MS (FAB) *m/z*: $[M^+ + H]$ 727.4, $[M^+]$ 726.4.

Anal. Calcd for $C_{46}H_{50}N_2O_6$: C, 76.01; H, 6.81; N, 3.68. Found: C, 75.75; H, 6.93; N, 3.85.

Macrocycles by Cycloadditive Macrocyclization; General procedure
To a mixture of bis(hydroxamic acid chloride) (2.15 mmol) and bifunctional dipolarophile (2.15 mmol) in EtOH (250 mL) was added drop wise a solution of Et_3N (4.95 mmol) in EtOH (10 mL) using a syringe pump over a period of 10 h. The reaction mixture was stirred for an additional period of 10 h at r.t. Evaporation of solvent followed by column chromatography afforded cycloadducts **26**–**32**, **34**–**35**, and **37**–**44** as white crystalline solids in moderate to good yields.

Macrocycle (26)
(SiO_2, CH_2Cl_2−MeOH, 25:1).

Mp 221 °C dec.

IR (KBr): 2964, 2884, 1761, 1734, 1454, 1374, 1335, 1204, 1127, 1052, 954, 927 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$–DMSO-d_6, 1:1): δ = 8.09–8.03 (m, 2 H, ArH), 7.50–7.43 (m, 2 H, ArH), 5.28–5.23 (m, 1 H, $OCHCH_2$), 4.91–4.87 (m, 1 H, $OCHCH_2$), 4.85–4.54 (m, 3 H), 4.30–4.16 (m, 3 H), 3.87–3.38 (m, 6 H).

MS (FAB) *m/z*: $[M^+ + H]$ 375.

Macrocycle (27)
(SiO_2, CH_2Cl_2–EtOAC–MeOH, 40:10:1).

Mp 197.7–198.2 °C.

IR ($CHCl_3$): 3023, 2915, 1751, 1579, 1458, 1388, 1343, 1257, 1197, 1135, 1040, 919 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.03–8.00 (m, 2 H, ArH), 7.53–7.47 (m, 1 H, ArH), 7.41–7.40 (m, 1 H, ArH), 5.27–5.22 (m, 2 H, $OCHCH_2$), 4.45–4.39 (m, 2 H, $OCHCH_2$), 4.29–4.22 (m, 2 H, $OCHCH_2$), 3.76–3.57 (m, 8 H, OCH_2), 3.52–3.39 (m, 4 H, OCH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 156.0, 130.4, 129.9, 129.3, 126.7, 78.6, 71.4, 69.9, 65.4, 40.4.

MS (FAB) *m/z*: $[M^+ + H]$ 419.

Anal. Calcd for $C_{20}H_{22}N_2O_8$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.36; H, 5.49; N, 6.62.

Crystal data for **27**: $C_{20}H_{22}N_2O_8$, M = 418.41, space group: orthorhombic, *Pbca*, a = 9.586(1) Å, b = 19.362(2) Å, c = 21.499(2) Å, V = 3980.9(8) $Å^3$, Z = 8, d_{calc} = 1.39 g cm^{-3}, T = 23 °C, Siemens SMART diffractometer with CCD detector, M_o K_α (λ = 0.71073 Å), μ = 1.02cm^{-1}, of 3164 measured data, 3164 were independent (R_{int} = 0.0699), R1 [I>2σ (I)] = 0.051, *w*R2 (all data) = 0.048 and GOF = 0.46.

Macrocycle (28)
(SiO_2, CH_2Cl_2–EtOAC–MeOH, 40:10:1).

Mp 158.4–158.8 °C.

IR ($CHCl_3$): 3020, 2891, 1745, 1443, 1331, 1286, 1216, 1129, 1040, 901, 773, 668 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.93 (s, 1 H, ArH), 7.81–7.78 (m, 2 H, ArH), 7.51–7.46 (m, 1 H, ArH), 5.27–5.22 (m, 2 H, $OCHCH_2$), 4.38–4.35 (m, 4 H, $OCHCH_2$), 3.78–3.33 (m, 16 H, OCH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6, 155.9, 130.0, 129.9, 129.3, 125.7, 78.7, 71.1, 69.3, 65.1, 40.0.

MS (FAB) *m/z*: $[M^+ + H]$ 463.

Macrocycle (29)
(SiO_2, CH_2Cl_2–EtOAc, 11:1).

Mp 234 °C dec.

IR ($CHCl_3$): 3021, 2891, 1745, 1443, 1331, 1286, 1216, 1129, 1040, 901, 773, 668 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.99–7.97 (m, 2 H, ArH), 7.87–7.82 (m, 1 H, ArH), 5.27–5.23 (m, 2 H, $OCHCH_2$), 4.54–4.47 (m, 2 H, $OCHCH_2$), 4.36–4.30 (m, 2 H, $OCHCH_2$), 4.18–4.11 (m, 2 H, OCH_2), 3.73–3.54 (m, 6 H, OCH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1, 159.2, 148.3, 138.3, 122.9, 78.6, 70.3, 65.7, 39.3.

MS (FAB) *m/z*: $[M^+ + H]$ 376.

Anal. Calcd for $C_{17}H_{17}N_3O_7$: C, 54.40; H, 4.57; N, 11.20. Found: C, 53.99; H, 4.56; N, 10.91.

Macrocycle (30)
(SiO_2, CH_2Cl_2–EtOAC, 8:1).

Mp 200.2–201.0 °C.

IR ($CHCl_3$): 3023, 2915, 1751, 1579, 1458, 1343, 1257, 1197, 1135, 1040, 919, 815 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.08–8.05 (m, 2 H, ArH), 7.84–7.79 (m, 1 H, ArH), 5.28–5.22 (m, 2 H, $OCHCH_2$), 4.54–4.48 (m, 2 H, $OCHCH_2$), 4.25–4.18 (m, 2 H, $OCHCH_2$), 3.90–3.48 (m, 12 H, OCH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2, 158.0, 148.5, 137.7, 123.0, 78.4, 71.4, 69.8, 65.4, 40.1.

MS (FAB) *m/z*: $[M^+ + H]$, 420.

Anal. Calcd for $C_{19}H_{21}N_3O_8$: C, 54.41; H, 5.05; N, 10.02. Found: C, 54.21; H, 5.10; N, 9.83.

Crystal data for **30**: $C_{19}H_{21}N_3O_8$, M = 419.39, space group: orthorhombic, *Pbca*, a = 8.6721(11) Å, b = 11.469(2) Å, c = 40.554(5) Å, V = 4033.5(11) $Å^3$, Z = 8, d_{calc} = 1.38 g cm^{-3}, T = 23 °C, Siemens SMART diffractometer with CCD detector, M_o K_α (λ = 0.71073 Å), μ = 1.02cm^{-1}, of 3638 measured data, 3638 were independent (R_{int} = 0.0699), R1 [I>2σ(I)] = 0.067, *w*R2 (all data) = 0.063 and GOF = 0.87.

Macrocycle (31)
(SiO_2, CH_2Cl_2–EtOAC, 2:1).

Mp 160.2–162.3 °C .

IR ($CHCl_3$): 3021, 1753, 1643, 1541, 1473, 1215, 1136, 923, 776, 750 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.08–8.05 (m, 2 H, ArH), 7.82–7.77 (m, 1 H, ArH), 5.30–5.19 (m, 2 H, $OCHCH_2$), 4.50–4.43 (m, 2 H, $OCHCH_2$), 4.34–4.27 (m, 2 H, $OCHCH_2$), 3.89–3.43 (m, 16 H, OCH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 157.7, 148.7, 137.6, 123.1, 78.8, 71.2, 71.1, 69.3, 64.8, 39.9.

MS (FAB) *m/z*: $[M^+ + H]$ 464 .

Anal. Calcd for $C_{21}H_{25}N_3O_9$: C, 54.43; H, 5.44; N, 9.07. Found: C, 54.37; H, 5.52; N, 8.73.

Macrocycle (32)
(SiO_2, CH_2Cl_2–EtOAC–MeOH, 40:10:1).

Mp 227 °C dec.

IR (KBr): 2890, 1741, 1449, 1352, 1276, 1197, 1138, 1093, 1032, 889, 859 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$–DMSO-d_6, 1:1): δ = 7.76 (s, 4 H, ArH), 5.28–5.24 (m, 2 H, $OCHCH_2$), 4.45–4.38 (m, 2 H, $OCHCH_2$), 4.26–4.20 (m, 2 H, $OCHCH_2$), 3.82–3.33 (m, 8 H, OCH_2), 3.31–3.28 (m, 4 H, OCH_2), 3.04–2.98 (m, 2 H, OCH_2), 2.97–2.80 (m, 8 H, OCH_2).

^{13}C NMR (75 MHz, $CDCl_3$–DMSO-d_6, 1:1): δ = 169.0, 155.0, 130.0, 126.7, 78.0, 69.1, 69.2, 68.0, 63.0, 38.9.

MS (FAB) *m/z*: 463 $[M^+ + H]$.

Anal. Calcd for $C_{22}H_{26}N_2O_9$: C, 57.14; H, 5.67; N, 6.06. Found: C, 57.01; H, 5.89; N, 6.01.

Macrocycle (34)
(SiO_2, CH_2Cl_2–EtOAC, 3:1).

IR ($CHCl_3$): 2959, 2919, 2850, 1579, 1467, 1382, 1340, 1257, 1061, 924, 797 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.20–8.10 and 7.95–7.89 (2m, 6 H, ArH), 4.29–4.15 (m, 2 H, CH), 3.29–3.03 and 2.87–2.69 (2m, 4 H, CH_2), 0.30, 0.28, 0.10 and 0.07 (4s, 12 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.4, 157.3, 150.2, 150.2, 147.2, 143.9, 137.6, 137.5, 123.9, 123.8, 123.0, 122.7, 77.1, 76.9, 35.8, 35.7, –1.4, –1.6.

MS (FAB) *m/z*: $[M^+ + H]$ 509.1.

Anal. Calcd for $C_{22}H_{24}N_6O_5Si_2$: C, 51.95; H, 4.76; N, 16.52. Found: C, 51.60; H, 4.72; N, 16.25.

Crystal data for **34**: $C_{22}H_{24}N_6O_5Si_2$, M = 508.65, crystal system: triclinic, space group: PT, a = 8.6725(2) Å, α = 75.9570(10)°, b = 8.6733(2) Å, β = 86.1690(10)°, c = 17.7650(2) Å, γ

= 71.1580(10)°, V = 1226.77(4) Å^3, Z = 1, d_{calc} = 0.689 g cm^{-3}, T = 193(2) K, Siemens SMART diffractometer with CCD detector, Mo K_α (λ = 0.71073 Å), μ = 0.95cm^{-1}, of 5079 measured data, 3725 were independent (R_{int} = 0.0130), R1 [I>2σ(I)] = 0.0388, *w*R2 (all data) = 0.0997 and GOF = 1.104.

Macrocycle (35)
(SiO_2, CH_2Cl_2–EtOAC, 3:1).

IR ($CHCl_3$): 2959, 2919, 2850, 1579, 1467, 1382, 1340, 1257, 1061, 924, 797 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 (d, 2 H, *J* = 7.9 Hz, ArH), 7,76–7.67 (m, 4 H, ArH), 4.12–3.98 (m, 4 H, CH), 3.63–3.20 (m, 8 H, CH_2), 0.33–0.26 (m, 24 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.0, 149.1, 136.7, 122.1, 74.8, 36.5, –0.8, –1.8, –2.1, –2.5.

MS (FAB) *m/z*: [M$^+$+H] 695.2.

Macrocycle (37)
(SiO_2, CH_2Cl_2–EtOAC–MeOH, 40:10:1).

Mp 148.3–149.2 °C.

IR ($CHCl_3$): 3021, 2401, 1521, 1425, 1216, 929, 758, 670 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57 (s, 8 H, ArH), 5.82–5.80 (m, 4 H, $OCHCH_2$), 3.96–3.89 (m, 4 H, $OCHCH_2$), 3.85–3.73 (m, 4 H, $OCHCH_2$), 3.71–3.61 (m, 16 H, OCH_2), 3.41–3.16 (m, 8 H, OCH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.2, 131.4, 127.8, 104.5, 71.5, 71.3, 68.4, 42.0.

MS (FAB) *m/z*: [M$^+$+H] 726.

Anal. Calcd for $C_{36}H_{44}N_4O_{12}$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.52; H, 6.42; N, 7.61.

Crystal data for **37**: $C_{36}H_{44}N_4O_{12}$, M = 724.77, space group: $P2_{1/c}$ (No. 14), a = 19.591(5) Å, b = 9.937(1) Å, c = 9.107(3) Å, V = 1765.1(8) Å^3, Z = 2, d_{calc} = 1.369 g cm^{-3}, T = 25 °C, Siemens SMART diffractometer with CCD detector, M_o K_α (λ = 0.70926 Å), μ = 0.97cm^{-1}, of 3383 measured data, 3189 were independent (R_{int} = 0.0699), R1 [F_o^2>3σ(F_o^2)] = 0.063, *w*R2 (all data) = 0.060.

Macrocycle (38)
(SiO_2, CH_2Cl_2–EtOAC, 2:1).

Mp 198 °C dec.

IR ($CHCl_3$): 2917, 1726, 1418, 1355, 1290, 1188, 1102, 929, 889, 841 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84–7.52 (m, 8 H, ArH), 5.80–5.95 (m, 4 H, $OCHCH_2$), 3.83–3.10 (m, 24 H, OCH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.4, 129.9, 126.2, 102.5, 69.8, 65.9, 28.8.

MS (FAB) *m/z*: [M$^+$+H] 637.

Macrocycle (39)
(SiO_2, CH_2Cl_2–EtOAC–MeOH, 40:10:1).

Mp 190.1–190.7 °C.

IR ($CHCl_3$): 3015, 2915, 1719, 1457, 1418, 1343, 1301, 1231, 1189, 1103, 932, 892 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.74 (m, 2 H, ArH), 7.74–7.60 (m, 4 H, ArH), 7.34–7.30 (m, 2 H, ArH), 5.79–5.75 (m, 4 H, $OCHCH_2$), 3.91–3.85 (m, 4 H, $OCHCH_2$), 3.82–3.75 (m, 4 H, $OCHCH_2$), 3.67–3.63 (m, 16 H, OCH_2), 3.38–3.12 (m, 8 H, OCH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.2, 130.4, 129.7, 129.0, 125.8, 104.3, 71.2, 71.1, 68.1, 42.0.

MS (FAB) *m/z*: [M$^+$+H] 726.

Anal. Calcd for $C_{36}H_{44}N_4O_{12}$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.24; H, 6.22; N, 7.57.

Macrocycle (40)
(SiO_2, CH_2Cl_2–EtOAC–MeOH, 40:10:1).

Mp 203.4–204.1 °C.

IR ($CHCl_3$): 2964, 2884, 1761, 1734, 1453, 1374, 1335, 1204, 1127, 1052, 927, 811 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78–7.54 (m, 6 H, ArH), 7.40–7.27 (m, 2 H, ArH), 5.88–5.73 (m, 4 H, $OCHCH_2$), 3.95–3.60 (m, 16 H, $OCHCH_2$, OCH_2), 3.38–3.16 (m, 8 H, $OCHCH_2$, OCH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.0, 130.2, 129.7, 128.9, 125.8, 103.9, 70.9, 67.8, 41.9.

MS (FAB) *m/z*: [M$^+$+H] 637.

Anal. Calcd for $C_{32}H_{36}N_4O_{10}$: C, 60.39; H, 5.60; N, 8.66. Found: C, 60.29; H, 5.67; N, 8.80.

Macrocycle (41)
(SiO_2, CH_2Cl_2–EtOAC, 1:1).

Mp 106.2–106.9 °C.

IR ($CHCl_3$): 3020, 2907, 2401, 1541, 1473, 1419, 1346, 1232, 1202, 928, 898, 800 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.02–7.98 (m, 4 H, ArH), 7.78–7.73 (m, 2 H, ArH), 5.86–5.83 (m, 4 H, $OCHCH_2$), 3.94–3.44 (m, 32 H, $OCHCH_2$, OCH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4, 149.3, 137.5, 122.9, 104.7, 71.3, 68.3, 41.8.

MS (FAB) *m/z*: [M$^+$+H] 727.

Anal. Calcd for $C_{34}H_{42}N_6O_{12}$: C, 56.19; H, 5.82; N, 11.56. Found: C, 55.95; H, 5.84; N, 11.13.

Macrocycle (42)
(SiO_2, CH_2Cl_2–EtOAC, 2:1).

Mp 126.0–126.5 °C.

IR ($CHCl_3$): 3020, 2936, 1577, 1472, 1391, 1348, 1241, 1180, 1095, 906, 822 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03–8.00 (m, 4 H, ArH), 7.76–7.70 (m, 2 H, ArH), 5.79–5.76 (m, 4 H, $OCHCH_2$), 3.99–3.44 (m, 24 H, $OCHCH_2$, OCH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.4, 149.4, 137.5, 122.9, 104.6, 71.4, 68.0, 41.6.

MS (FAB) *m/z*: [M$^+$+H] 639.

Anal. Calcd for $C_{30}H_{34}N_6O_{10}$: C, 56.42; H, 5.37; N, 13.16. Found: C, 56.76; H, 5.55; N, 13.10.

Macrocycle (43)
(SiO_2, CH_2Cl_2–MeOH, 25:1).

Mp 220 °C dec.

IR (KBr): 2923, 1744, 1438, 1349, 1254, 1207, 1133, 1048, 879 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63 (s, 8 H, ArH), 5.21–5.18 (m, 4 H, $OCHCH_2$), 4.32–4.29 (m, 8 H, $OCHCH_2$), 3.72–3.61 (m, 16 H, OCH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171, 157, 131, 128, 78, 69, 66, 38.

MS (FAB) *m/z*: [M$^+$+H] 749.

Macrocycle (44)
(SiO_2, CH_2Cl_2–EtOAC–MeOH, 40:10:1).

Mp 178.6–179.3 °C.

IR (KBr): 2907, 1747, 1439, 1350, 1207, 1132, 1042, 877 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.60 (s, 8 H, ArH), 5.20–5.14 (m, 4 H, $OCHCH_2$), 4.31–4.28 (m, 8 H, $OCHCH_2$), 3.77–3.57 (m, 24 H, OCH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8, 155.4, 130.2, 127.1, 78.2, 70.5, 68.6, 64.7, 38.5.

MS (FAB) *m/z*: [M^++H] 837.

Anal. Calcd for $C_{40}H_{44}N_4O_{16}$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.51; H, 5.52; N, 6.57.

Bis-calix[4]arene (45)
Terephthaldicarboximoyl chloride **12** (3.43 mmol) and bis(acrylamido)calix[4]arene **24** (3.43 mmol) were dissolved in EtOH (330 mL) at 70–75 °C. To the reaction mixture was added slowly a solution of Et_3N (7.89 mmol) in EtOH (16 mL) using syringe pump over a period of 3 h. The reaction mixture was stirred further for 2 h at the same temperature, cooled to r.t., solvent was evaporated in vacuo to give the crude product. This on purification by column chromatography (SiO_2, CH_2Cl_2–EtOAc, 4:1) followed by recrystallization from $CHCl_3$–MeOH yielded **45** (27%) as a white crystalline solid.

Mp 238 °C dec.

IR ($CHCl_3$): 3396, 3317 (NH), 2962, 2875, 1687 (C=O), 1602 (C=N), 1534, 1465, 1420, 1386, 1353, 1289, 1216, 1133, 1080, 1038, 1007, 996 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.00 (br d, 4 H; NH), 7.61–7.54 (m, 8 H, ArH), 6.71 (m, 14 H, ArH), 6.52 (d, 2 H, *J* = 7.1 Hz, ArH), 6.44 (s, 4 H, ArH), 5.07–5.01 (m, 4 H, $OCHCH_2$), 4.43 (d, 8 H, *J* = 13.3 Hz, $ArCH_2Ar$), 3.88 (t, 8 H, *J* = 7.3 Hz, OCH_2), 3.62–3.20 (m, 8 H, $OCHCH_2$), 3.18–3.09 (m, 8 H, $ArCH_2Ar$), 1.98–1.84 (m, 16 H, CH_2CH_3), 1.02–0.86 (m, 24 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.1, 156.9, 136.0, 135.0, 131.0, 130.7, 130.5, 128.8, 127.6, 122.9, 119.8, 79.5, 77.6, 39.3, 31.4, 23.6, 10.8, 10.7.

MS (FAB) m/z: [M^++H] 1781.8, [M^+] 1780.7.

Anal. Calcd for $C_{108}H_{116}N_8O_{16}\cdot 4H_2O$: C, 69.96; H, 6.74; N, 6.04. Found: C, 70.13; H, 6.77; N, 6.02.

Crystal data for **45**: $C_{108}H_{116}N_8O_{16}\cdot C_2H_6SO$, M = 1860.22, crystal system: triclinic, space group: P1, a = 9.9175(9) Å, α = 87.248(2)°, b = 10.6381(10) Å, β = 81.458(2)°, c = 30.730(3) Å, γ = 71.205(2)°, V = 3035.2(5) $Å^3$, Z = 1, d_{calc} = 1.018 g cm^{-3}, T = 188(2) K, Siemens SMART diffractometer with CCD detector, M_o K_α (λ = 0.71073 Å), μ = 0.85cm^{-1}, of 12412 measured data, 8866 were independent (R_{int} = 0.0699), R1 [I>2σ(I)] = 0.2481, *w*R2 (all data) = 0.5358 and GOF = 2.644.

Bis-calix[4]arene (46)
Terephthaldicarboximoyl chloride **12** (1.27mmol) and bis(ethynylamido)calix[4]arene **25** (1.27mmol) were dissolved in EtOH (120 mL). To this reaction mixture was added slowly a solution of Et_3N (2.87 mmol) in EtOH (5.7 mL) using syringe pump over a period of 3 h at r.t. The reaction mixture was further stirred for 2 h, solvent was evaporated in vacuo to give the crude product. This on purification by column chromatography (SiO_2, CH_2Cl_2–EtOAc, 15:1) and then recrystallization from $CHCl_3$–EtOH yielded **46** (26%) as a white solid.

Mp 249 °C dec.

IR ($CHCl_3$): 3419 (NH), 2923, 2852, 1684 (C=O), 1608 (C=N), 1546, 1465, 1424, 1384, 1217, 1122, 1005, 966 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.82 (s, 4 H, NH), 7.37 (s, 8 H, ArH), 7.13 (d, 8 H, *J* = 7.4 Hz, ArH), 6.83 (s, 4 H, CH), 6.38 (s, 8 H, ArH), 4.41 (d, 8 H, *J* = 13.4 Hz, $ArCH_2Ar$), 3.99 (t, 8 H, *J* = 8.1 Hz, OCH_2), 3.59 (t, 8 H, *J* = 6.6 Hz, OCH_2), 3.10 (d, 8 H, *J* = 13.4 Hz, $ArCH_2Ar$), 1.97–1.77 (m, 16 H, CH_2CH_3), 1.04 (t, 12 H, *J* = 7.3 Hz, CH_3), 0.82 (t, 12 H, *J* = 7.4 Hz, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.7, 162.1, 158.0, 152.9, 152.3, 136.8, 134.3, 130.9, 129.2, 127.0, 122.5, 119.0, 104.7, 77.2, 31.1, 23.5, 22.9, 10.8, 9.8.

MS (FAB) *m/z*: [M^++H] 1773.8, [M^+] 1772.7.

Anal. Calcd for $C_{108}H_{108}N_8O_{16}\cdot 2H_2O$: C, 71.66; H, 6.24; N, 6.19. Found: C, 71.60; H, 6.48; N, 6.30.

Silamacrocycles; General procedure
To a mixture of bis(hydroxamic acid chloride) (1.38 mmol) and 1,3-divinyltetramethyldisiloxane **33** (2.76 mmol) in CH_2Cl_2 (28 mL) was added Et_3N (3.04 mmol). The reaction mixture was stirred for 5 h at r.t. After completion of the reaction, the solvent was evaporated under reduced pressure. The resulting solid was subjected to column chromatography on SiO_2 to afford 1+2 cycloadduct (**47** or **49**). The macrocycle **48** or **50** was prepared by treating the corresponding [1+2] cycloadduct (**47** or **49**) with 1.1 equivalents of bis(hydroxamic acid chloride) (**15** or **12**) in CH_2Cl_2 under the same reaction condition and purification methods described for 1+2 cycloadducts.

Macrocycle (48)
(SiO_2, CH_2Cl_2–EtOAC, 3:1).

Mp 267–270 °C.

IR ($CHCl_3$): 2957, 1560, 1438, 1339, 1328, 1303, 1252, 1149, 1104, 903, 896, 883, 873, 841, 814, 789 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.77 (s, 2 H, ArH), 7.60 (d, 4 H, *J* = 7.8 Hz, ArH), 7.34 (t, 2 H, *J* = 7.8 Hz, ArH), 3.98 (dd, 4 H, *J* = 15.7, 11.3 Hz, CH), 3.42–3.22 (m, 8 H CH_2), 0.33 and 0.28 (2s, 24 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.9, 130.8, 127.2, 127.0, 126.9, 74.3, 37.0, –1.6, –1.6, –1.9, –2.0.

MS (FAB) *m/z*: [M^++H] 693.3.

Anal. Calcd for $C_{32}H_{44}N_4O_6Si_4$: C, 55.46; H, 6.40; N, 8.08. Found: C, 55.60; H, 6.15; N, 7.60.

Crystal data for **48**: $C_{32}H_{44}N_4O_6Si_4$, M = 693.07, crystal system: triclinic, space group: PT, a = 6.8037(8) Å, α = 82.616(2)°, b = 9.3283(11) Å, β = 77.729(2)°, c = 15.4738(18) Å, γ = 78.150(2)°, V = 953.48(19) $Å^3$, Z = 1, d_{calc} = 1.230 g cm^{-3}, T = 298(2) K, Siemens SMART diffractometer with CCD detector, Mo K_α (λ = 0.71073Å), μ = 2.04cm^{-1}, of 3728 measured data, 2750 were independent (R_{int} = 0.0196), R1 [I>2σ(I)] = 0.0574, *w*R2 (all data) = 0.1297 and GOF = 1.161.

Macrocycle (50)
(SiO_2, CH_2Cl_2–EtOAC, 3:1).

Mp 261–263 °C.

IR ($CHCl_3$): 2923, 2853, 1597, 1329, 1252, 1104, 874, 842, 789 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.59–7.32 (m, 8 H, ArH), 4.08–3.97 (m, 4 H, CH), 3.39–3.04 (m, 8 H, CH_2), 0.40–0.29 (m, 24 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.6, 130.4, 126.7, 125.9, 74.4, 36.9, –0.7, –1.0.

MS (FAB) *m/z*: [M^++H] 693.3.

Anal. Calcd for $C_{32}H_{44}N_4O_6Si_4$: C, 55.46; H, 6.40; N, 8.08. Found: C, 55.18; H, 6.22; N, 7.59.

Acknowledgement

This work has been supported by Korea Science and Engineering Foundation (KOSEF) through CBM and CIMS. We are grateful to BK21 program for the student scholarship.

References

(1) (a) In *Advances in Cycloaddition*, Vol 4; Curran, D. P., Ed.; Jai press: London, **1997**. (b) Kim, B. H. *Synth. Commun.* **1987**, *17*, 1199. (c) Kim, B. H. *Progress in Chemistry and Chemical Industry* **1991**, *31*, 242. (d) Kim, B. H.; Lee, J. Y.; Kim, K.; Whang, D. *Tetrahedron: Asymmetry* **1991**, *2*, 27. (e) Kim, B. H.; Lee, J. Y. *Tetrahedron: Asymmetry* **1991**, *2*, 1359. (f) Keum, G.; Chung, Y. J.; Kim, B. H. *Bull. Korean Chem. Soc.* **1992**, *13*, 343. (g) Kim, B. H.; Lee, J. Y. *Tetrahedron Lett.* **1992**, *33*, 2557. (h) Kim, B. H.; Chung, Y. J.; Keum, G.; Kim, J.; Kim, K. *Tetrahedron Lett.* **1992**, *33*, 6811. (i) Kim, B. H.; Curran, D. P. *Tetrahedron* **1993**, *49*, 293. (j) Kim, K. S.; Kim, B. H.; Park, W. M.; Cho, S. J.; Mhin, B. J. *J. Am. Chem. Soc.* **1993**, *115*, 7472. (k) Lee, J. Y.; Kim, B. H. *Tetrahedron Lett.* **1995**, *36*, 3361. (l) Lee, J. Y.; Kim, B. H. *Tetrahedron* **1996**, *52*, 571. (m) Kim, S. J.; Lee, J. Y.; Kim, B. H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1313.

(2) (a) In *Macrocyclic Synthesis: A practical Approach*; Parker, D., Ed.; Oxford University Press: Oxford, **1996**. (b) Inone, Y.; Gokel, G. W. In *Cation Binding by Macrocycles: Complexation of Cationic Species by Crown Ethers*; Marcel Dekker: New York, **1990**.

(3) Dietrich, B.; Viout, P.; Lehn, J.-M. In *Macrocyclic Chemistry*; VCH: Weinheim, **1993**.

(4) Kim, B. H.; Jeong, E. J.; Jung, W. H. *J. Am. Chem. Soc.* **1995**, *11*, 6390.

(5) (a) Garanti, L.; Sala, A.; Zecchi, G. *J. Org. Chem.* **1975**, *40*, 2403. (b) Heinz, I.; Knoll, K.; Muller, R.; Eberbach, W. *Chem. Ber.* **1989**, *122*, 2147; and references cited therein.

(6) Broggni, G.; Garanti, L.; Molteni, G.; Zecchi, G. *Tetrahedron* **1998**, *54*, 2843; and the references recited therein.

(7) Asaoka, M.; Mukuta, T.; Takei, H. *Tetrahedron Lett.* **1981**, *22*, 735.

(8) Engelbach, M.; Imming, P.; Seitz, G.; Tegethoff, R. *Heterocycles* **1995**, *40*, 69.

(9) Mass, G.; Gettwert, V.; Krebs, F.; Schmidtberg, G. *Chem.—Eur. J.* **2000**, *6*, 1646.

(10) Nishimura, J.; Nakamura, Y.; Hayashida, Y.; Kudo, T. *Acc. Chem. Res.* **2000**, *33*, 679.

(11) (a) Nishimura, J.; Nakamura, Y.; Hayashida, Y.; Kudo, T. *Synlett* **1994**, 884. (b) Okada, Y.; Nishimura, J. *J. Inclusion Phenom.* **1994**, *19*, 41.

(12) Sato, M.; Uehara, F.; Sato, K.; Yamaguchi, M.; Kabuto, C. *J. Am. Chem. Soc.* **1999**, *121*, 8270.

(13) (a) Callot, H. L.; Johnson, A. W.; Sweeney, A. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1424. (b) Mettath, S.; Dougherty, T. J.; Pandey, R. K. *Tetrahedron Lett.* **1999**, *40*, 6171. (c) Sheng, G.; Shibata, M.; Dougherty, T. J.; Pandey, R. K. *J. Org. Chem.* **2000**, *65*, 543.

(14) (a) Girrester, U.; Giuffrida, D.; Kohnke, F. H.; Mathias, J. P.; Philip, D.; Stoddart, J. F. *Pure Appl. Chem.* **1993**, *65*, 119. (b) Kohnke, F. H.; Slawin, A. M. Z.; Stoddart, J. F.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1987**, *29*, 892. (c) Stoddart, J. F. *J. Inclusion Phenom.* **1989**, *7*, 227.

(15) Godt, A.; Enkelmann, V.; Schluter, A.-D. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1680.

(16) Cory, R. M.; McPhill, C. L.; Dikmans, A. J.; Vital, J. J. *Tetrahedron Lett.* **1996**, *37*, 1983.

(17) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565.

(18) (a) Gutsche, C. D. *Top. Curr. Chem.* **1984**, *123*, 1. (b) Gutsche, C. D. In *Calixarenes: Monographs in Supramolecular Chemistry*, Vol. 1; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, **1989**. (c) Gutsche, C. D. In *Calixarenes Revisited: Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, **1998**.

(19) Rudkevich, D. M.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **1994**, *59*, 3683.

(20) Lee, C. W.; Hwang, G. T.; Kim, B. H. *Tetrahedron Lett.* **2000**, *41*, 4177.

(21) Hwang, G. T.; Kim, B. H. *Tetrahedron Lett.* **2000**, *41*, 10055.

(22) Iwakura, Y.; Akiyama, M.; Nagakubo, K. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 767.

(23) Maugein, N.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **1999**, *64*, 8428.

(24) (a) König, B.; Rödel, M.; Bubenitschek, P.; Jones, P. G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 661. (b) Kauffmann, T.; Kniese, H.-H. *Tetrahedron Lett.* **1973**, *41*, 4043. (c) Birkofer, L.; Stuhl, O. *J. Organomet. Chem.* **1979**, *177*, C16. (d) Kaes, C.; Hosseini, M. W.; Ruppert, R.; De Cian, A.; Fischer, J. *Tetrahedron Lett.* **1994**, *35*, 7233. (e) Kaes, C.; Hosseini, M. W.; De Cian, A.; Fischer, J. . *Chem. Commun.* **1997**, 2229. (f) Jung, M. E.; Xia, H. *Tetrahedron Lett.* **1988**, *29*, 297.

(25) (a) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826. (b) Kim, B. H.; Chung, Y. J.; Ryu, E. J. *Tetrahedron Lett.* **1993**, *34*, 8465. (c) Kim, B. H.; Ryu, E. J.; Chung, Y. J. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2799. (d) Kim, D. H.; Choi, K. Y.; Chung, Y. J.; Kim, B. H. *J. Appl. Pharm.* **1994**, *2*, 155. (e) Chung, Y. J.; Ryu, E. J.; Keum, G.; Kim, B. H. *Bioorg. Med. Chem.* **1996**, *4*, 209.