Double Cycloadditive Macrocyclization: An Efficient Method for Cyclophane

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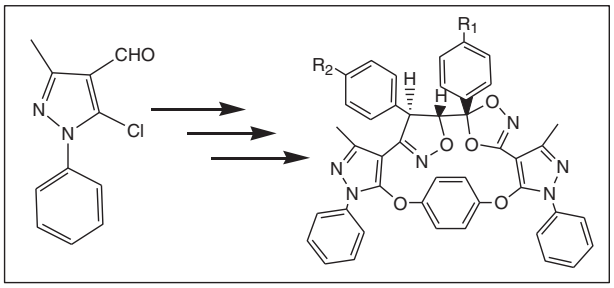

A series of macrocycles containing isoxazoline and [1,4,2]dioxazole were synthesized for the first time. The structures of the newly synthesized macrocycles were characterized and confirmed by IR, ^{1}H NMR, mass spectra, and elemental analysis. The solid-state structure of macrocycle (**6d**) was further studied by single-crystal X-ray diffraction analysis.

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INTRODUCTION

The synthesis of [2.2]paracyclophanes by Cram and Steinberg was a revolutionary breakthrough in the field of cyclophane chemistry [1]. The sophistication of the design and synthesis of novel and functional cyclophane host molecules has always been one driving force to promote the major advances in supramolecular chemistry. In the synthesis of cyclophanes, the ring-closing step is often crucial and various reagents and reaction conditions have been developed for this purpose [2–4]. Development of efficient synthetic pathways is paramount to design macrocycles with the desired functionality, property, size, and shape [5–7]. We have envisioned a new pathway for macrocycles containing isoxazole, isoxazoline, and [1,4,2]dioxazole by using double different cycloadditive macrocyclization as a key step [8]. Compared with other cyclophane methods [9–12], this approach has several advantages: (1) few steps and good overall yields; (2) excellent stereoselectivity due to the well-defined transition state of [3 + 2] dipolar cycloaddition; and (3) accessibility to structural diversity by changing dipole and dipolarophile components.

Moreover, isoxazolines are versatile intermediates for the synthesis of bifunctional and naturally occurring compounds [13–17] and also display important biological activities such as antibacterial [18], antitubercular [19], phosphodiesterase inhibitory [20], anti-inflammatory [21], and immunostimulatory [22], whereas compounds incorporating the pyrazole substructure have stimulated much interest in medicinal and biological chemistries. Meanwhile, functionalized macrocycles are frequently seen in pharmaceutics and natural products [23,24], in addition to being important as pharmaceuticals.

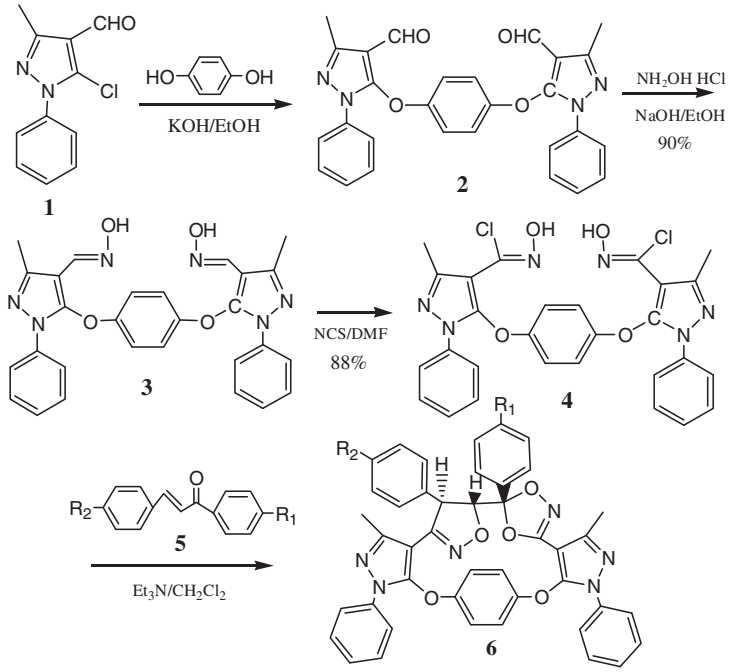
The biological importance of isoxazolines, isoxazole, and [1,4,2]dioxazole and our ongoing research program on the construction of novel heterocycles led us to recently investigate the 1,3-dipolar cycloaddition of α,β-unsaturated ketones. In our studies, we have reported an efficient synthetic method for macrocycles via cycloaddition of nitrile oxides to α,β-unsaturated ketones as a key step. To our knowledge, there is no precedent for the generation of macrocycles by using double different cycloadditions as comerstones.

RESULTS AND DISCUSSION

As illustrated in the Introduction section, arriving at a given macrocycle by cycloadditive macrocyclization route relies mainly on bifunctional dipole (bis-nitrile oxides) and bifunctional dipolarophile. The bifunctional hydroxamic acid chlorides (**4**) were prepared from their corresponding aldehydes (**1**) in a two-step procedure as given in Scheme 1.

The 1,3-dipolar cycloaddition of nitrile oxide and α,β-unsaturated ketones led to the formation of cyclophane (**6**) arising from the nitrile oxide addition to C═C and C═O bonds. All of the cycloadducts (**6a–o**) were separated through flash column chromatography by using petroleum ether–ethyl acetate as eluent. The structures of the cycloadducts were characterized by ^{1}H NMR spectroscopic data. The structures of all compounds were also confirmed by mass spectral analysis. The mass spectra show molecular

Scheme 1



a. R_1 = H, R_2 = H; 26% **b**. R_1 = H, R_2= Cl; 25% **c**. R_1 = H, R_2 = OCH_3; 33%
d. R_1 = H, R_2 = CH_3; 32% **e**. R_1 = H, R_2 = NO_2; 28% **f**. R_1 = Cl, R_2 = H; 24%
g. R_1 = Cl, R_2 = Cl; 30% **h**. R_1 = Cl, R_2 = OCH_3;35% **i**. R_1 = Cl, R_2 = CH_3; 21%
j. R_1 =Cl, R_2 = NO_2; 24% **k**. R_1 = OCH_3, R_2 = H; 29% **l**. R_1 = OCH_3, R_2 = Cl; 21%
m.R_1 = R_2 = OCH_3; 35% **n**. R_1 = OCH_3, R_2 = CH_3; 23% **o.** R_1 = OCH_3, R_2 = NO_2; 28%

ion peaks (M+) at corresponding masses of respective moleculars. The structure of macrocycles **6d** was also further confirmed by a single crystal X-ray crystallography analysis. (Fig. 1) [25].

With a view to finding the order of occurrence of the cycloaddition of nitrile oxide to the C=C and C=O bonds leading to the formation of the cyclophane, the reaction was intercepted at early stages before completion of the reaction at 30 min and 1 h, and the reaction mixture afforded isoxazoline and failed to afford dioxazole (Scheme 2), thus suggesting that macrocycles (**6d**) might result from further cycloaddition to the intermediate (**7**). To confirm this, the reaction of the intermediate with a nitrile oxide was performed in a separate experiment under the same reaction conditions as those of the overall reaction. This reaction furnished macrocycle (**6d**), suggesting its formation from the intermediate (**7**).

In conclusion, we have described an efficient and convenient method for the synthesis of cyclophane. Macrocycles (**6a–o**) were synthesized for the first time by the reaction of 1,3-dipolar cycloaddition of α,β-unsaturated ketones as a key step in the presence of triethylamine (Scheme 1). Compounds (**6a–o)** reported are new and have been characterized by spectral and analytical data (Table 1).

EXPERIMENTAL

All purchased solvents and chemicals were of analytical grade and were used without further purification. Melting points were measured on a mettler FP-5 capillary melting point apparatus and were uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400 elemental analyzer. The solid-state IR spectra were recorded from potassium bromide pellet on a Bruker Tensor 27 spectrophotometer. The ^{1}H NMR spectra were recorded on a Varian Inova-400 spectrophotometer by using $CDCl_3$as the deuterated solvent and TMS as the internal standard at room temperature. EI–MS spectra were obtained with an Agilent 5975 apparatus. The results were found to be in good agreement with the calculated values. All reagents were of commercial availability. The compounds **1** [26], **2** [27], and **5** [28] were prepared according to the previously reported procedures.

Preparation of dialdoxime (3). An aqueous solution of NaOH (8 mol) was added dropwise to a solution of the dialdehyde **2** (4 mol) and NH_2OH-HCl (8 mol) in EtOH–H_2O (60 mL). After stirring the suspension overnight at 0°C, the solid was collected by filtration and washed with water. The solid was crystallized from ethanol to give dialdoximes **3** as a pale-yellow solid. This compound was obtained as white crystals in 90% yield; mp: 212–213°C; IR (KBr)υ: 3429 (OH), 3051 (Ar-H), 2924, 1474 (CH3), 1580 (C=N), 1086 (C–O–C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.59 (s, 2H, CH=N), 7.62–6.98 (m, 14H, Ar-H), 2.50 (s, 6 H, $-CH_3$); MS (EI) *m/z*: 508 (M^+).

Table 1

Physical and analytical data of compounds **6**.

Compound no.	Molecular formula	Yield (%)	mp (°C)	Analysis (%) found/calcd		
				C	H	N
6a	$C_{43}H_{32}N_6O_5$	26	167–168	72.46	4.53	11.79
				72.42	4.60	11.82
6b	$C_{43}H_{31}ClN_6O_5$	25	152–153	69.12	4.18	11.25
				69.20	4.17	11.22
6c	$C_{44}H_{34}N_6O_6$	33	194–195	71.15	4.61	11.31
				71.55	4.71	11.38
6d	$C_{44}H_{34}N_6O_5$	32	182–183	72.71	4.72	11.56
				72.84	4.71	11.47
6e	$C_{43}H_{31}N_7O_7$	28	124–125	68.16	4.12	12.94
				68.25	4.12	12.89
6f	$C_{43}H_{31}ClN_6O_5$	24	212–213	69.12	4.18	11.25
				69.16	4.21	11.26
6g	$C_{43}H_{30}Cl_2N_6O_5$	30	192–193	66.07	3.87	10.75
				66.18	3.79	10.84
6h	$C_{44}H_{33}ClN_6O_6$	35	166–167	67.99	4.28	10.81
				68.06	4.31	10.84
6i	$C_{44}H_{33}ClN_6O_5$	21	133–134	69.42	4.37	11.04
				69.50	4.22	11.17
6j	$C_{43}H_{30}ClN_7O_7$	24	149–151	65.19	3.82	12.38
				65.22	3.74	12.41
6k	$C_{44}H_{34}N_6O_6$	29	224–225	71.15	4.61	11.31
				71.19	4.70	11.27
6l	$C_{44}H_{33}Cl_2N_6O_6$	21	177–178	67.99	4.28	10.81
				68.08	4.29	10.73
6m	$C_{45}H_{36}N_6O_7$	35	169–170	69.94	4.70	10.87
				70.02	4.59	10.85
6n	$C_{45}H_{36}N_6O_6$	23	145–148	71.42	4.79	11.10
				71.43	4.68	11.15
6o	$C_{44}H_{33}N_7O_8$	28	162–165	67.08	4.22	12.45
				67.11	4.31	12.41

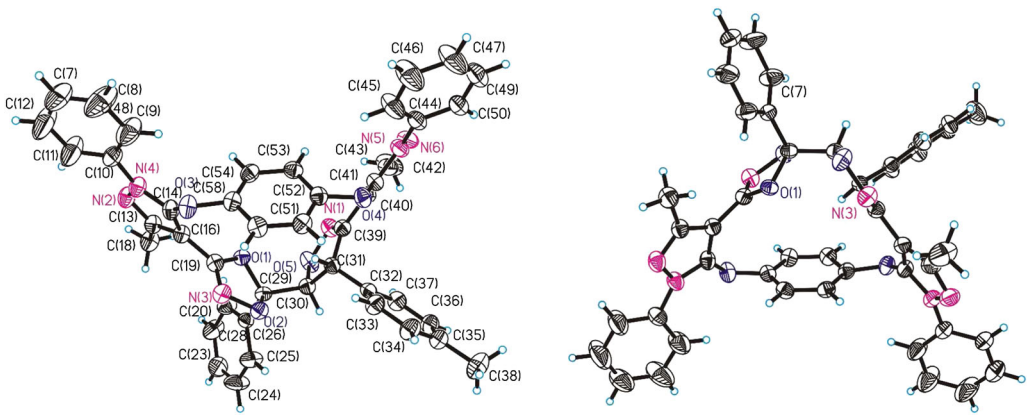
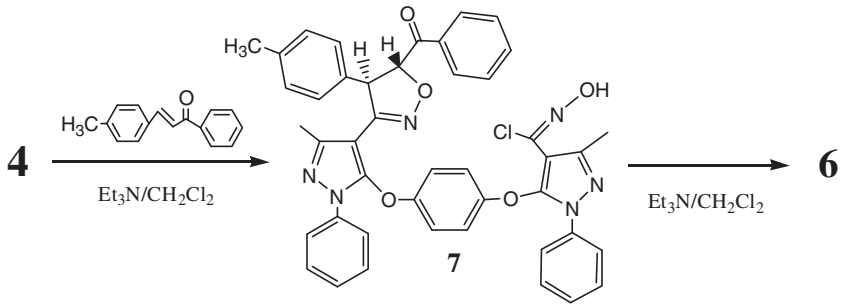


Figure 1. X-ray crystal structure of macrocycle **6d**.

Preparation of bis(hydroxamic acid chlorides) (4). *N*-chlorosuccinimide (15 mmol) was added to a DMF solution (12.5 mL) of aldoxime **3** (10 mmol). The resulting mixture was stirred for 50 min. It was then poured into H_2O (80 mL) and extracted with EtOAc. The organic phase was washed several times with H_2O. The solid was collected by filtration and crystallized from ethanol to give bis(hydroxamic acid chloride) **4** as a white solid. This compound was obtained as white crystals in 88% yield; mp:180–181°C; IR (KBr) υ: 3438 (OH), 3051 Ar-H), 2974, 1477 (CH3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.60–6.91 (m, 14H, Ar-H), 2.45 (s, 6H, -CH_3); MS (EI) *m/z*: 580 (M^+).

General procedure for the preparation of macrocycles by cycloadditive macrocyclization (6a–o). A solution of Et3N (5 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a mixture

Scheme 2



of bis(hydroxamic acid chloride) (**4**) (2 mmol) and the chalcones (**5**) (2.5 mmol) in CH_2Cl_2 (50 mL). Then, the solution was stirred at room temperature for further 12 h. The solid mass separated out was filtered off, and the solvent was evaporated in vacuo and the residue was subjected to flash column chromatography on silica gel (petroleumether–ethyl acetate 10:1) to afforded macrocycle **6** as white crystalline solids.

Macrocycle (6a). This compound was obtained as white crystals in 26% yield; mp 167–168°C; IR (KBr) υ: 3051 (Ar-H), 1567 (C=N), 2924, 1490 (CH3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.71–7.00 (m, 24H, Ar-H), 4.71 (d, H, H_5, J_{ab} = 8.4 Hz), 3.77 (d, H, H_4, J_{ab} = 8.4 Hz), 2.05 (s, 6H, $-CH_3$); MS (EI) *m/z*: 712 (M^+). *Anal*. Calcd for $C_{43}H_{32}N_6O_5$: C, 72.46; H, 4.53; N, 11.79. Found: C, 72.42; H, 4.60; N, 11.82.

Macrocycle (6b). This compound was obtained as white crystals in 25% yield; mp 152–153°C; IR (KBr) υ: 3052 (Ar-H), 1562 (C=N), 2922, 1487 (CH3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.71–7.01 (m, 23H, Ar-H), 4.67 (d, H, H_5, J_{ab} = 8.4 Hz), 3.74 (d, H, H_4, J_{ab} = 8.4 Hz), 2.05 (s, 6H, $-CH_3$); MS (EI) *m/z*: 747 (M^+). *Anal*. Calcd for $C_{43}H_{31}ClN_6O_5$: C, 69.12; H, 4.18; N, 11.25. Found: C, 69.20; H, 4.17; N, 11.22.

Macrocycle (6c). This compound was obtained as white crystals in 33% yield; mp 194–195°C; IR (KBr) υ: 3045 (Ar-H), 1581 (C=N), 2924, 1491 (CH3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.55–7.01 (m, 23H, Ar-H), 4.69 (d, H, H_5, J_{ab} = 8.4 Hz), 3.77 (d, H, H_4, J_{ab} = 8.4 Hz), 3.83 (s, 3H, $-OCH_3$), 2.05 (s, 6H, $-CH_3$); MS (EI) *m/z*: 742(M^+). *Anal*. Calcd for $C_{44}H_{34}N_6O_6$: C, 71.15; H, 4.61; N, 11.31. Found: C, 71.55; H, 4.71; N, 11.38.

Macrocycle (6d). This compound was obtained as white crystals in 32% yield; mp 182–183°C; IR (KBr) υ: 3038 (Ar-H), 1579 (C=N), 2922, 1487 (CH3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.69–6.97 (m, 23H, Ar-H), 4.66 (d, H, H_5, J_{ab} = 8.4 Hz), 3.77 (d, H, H_4, J_{ab} = 8.4 Hz), 2.45 (s, 3H, $-CH_3$), 2.06 (s, 6H, $-CH_3$); MS (EI) *m/z*: 726 (M^+). *Anal*. Calcd for $C_{44}H_{34}N_6O_5$: C, 72.71; H, 4.72; N, 11.56. Found: C, 72.84; H, 4.71; N, 11.47.

Macrocycle (6e). This compound was obtained as white crystals in 28% yield; mp 124–125°C; IR (KBr) υ: 3034 (Ar-H), 1582 (C=N), 2925, 1490 (CH3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.80–6.94 (m, 23H, Ar-H), 4.57 (d, H, H_5, J_{ab} = 8.4 Hz), 3.83 (d, H, H_4, J_{ab} = 8.4 Hz), 2.04 (s, 6H, $-CH_3$); MS (EI) *m/z*: 757 (M^+). *Anal*. Calcd for $C_{43}H_{31}N_7O_7$: C, 68.16; H, 4.12; N, 12.94. Found: C, 68.25; H, 4.12; N, 12.89.

Macrocycle (6f). This compound was obtained as white crystals in 24% yield; mp 212–213°C; IR (KBr) υ: 3038 (Ar-H), 1577 (C=N), 2924, 1492 (CH3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.71–6.99 (m, 23H, Ar-H), 4.66 (d, H, H_5, J_{ab} = 8.3 Hz), 3.72 (d, H, H_4, J_{ab} = 8.3 Hz), 2.05 (s, 6H, $-CH_3$); MS (EI) *m/z*: 747 (M^+). *Anal*. Calcd for $C_{43}H_{31}ClN_6O_5$: C, 69.12; H, 4.18; N, 11.25. Found: C, 69.16; H, 4.21; N, 11.26.

Macrocycle (6g). This compound was obtained as white crystals in 30% yield; mp 192–193°C; IR (KBr) υ: 3036 (Ar-H), 1579 (C=N), 2925, 1491 (CH3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.79–7.01 (m, 22H, Ar-H), 4.67 (d, H, H_5, J_{ab} = 8.4 Hz), 3.77 (d, H, H_4, J_{ab} = 8.4 Hz), 2.07 (s, 6H, $-CH_3$); MS (EI) *m/z*: 781 (M^+). *Anal*. Calcd for $C_{43}H_{30}Cl_2N_6O_5$: C, 66.07; H, 3.87; N, 10.75. Found: C, 66.18; H, 3.79; N, 10.84.

Macrocycle (6h). This compound was obtained as white crystals in 35% yield; mp 166–167°C; IR (KBr) υ: 3038 (Ar-H), 1577 (C=N), 2920, 1494 (CH3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.84–6.99 (m, 22H, Ar-H), 4.65 (d, H, H_5, J_{ab} = 8.4 Hz), 3.83 (d, H, H_4, J_{ab} = 8.4 Hz), 3.80 (s, 3H, $-OCH_3$), 2.05 (s, 6H, $-CH_3$); MS (EI) *m/z*: 777(M^+). *Anal*. Calcd for $C_{44}H_{33}ClN_6O_6$: C, 67.99; H, 4.28; N, 10.81. Found: C, 68.06; H, 4.31; N, 10.84.

Macrocycle (6i). This compound was obtained as white crystals in 21% yield; mp 133–134°C; IR (KBr) υ: 3034 (Ar-H), 1578 (C=N), 2919, 1492 (CH3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.69–7.02 (m, 22H, Ar-H), 4.70 (d, H, H_5, J_{ab} = 8.6 Hz), 3.77 (d, H, H_4, J_{ab} = 8.6 Hz), 2.45 (s, H, $-CH_3$), 2.05 (s, 6H, $-CH_3$); MS (EI) *m/z*: 761 (M^+). *Anal*. Calcd for $C_{44}H_{33}ClN_6O_5$: C, 69.42; H, 4.37; N, 11.04. Found: C, 69.50; H, 4.22; N, 11.17.

Macrocycle (6j). This compound was obtained as white crystals in 24% yield; mp 149–151°C; IR (KBr) υ: 3043 (Ar-H), 1578 (C=N), 2926, 1490 (CH3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.12–7.07 (m, 22H, Ar-H), 4.65 (d, H, H_5, J_{ab} = 8.4 Hz), 3.83 (d, H, H_4, J_{ab} = 8.4 Hz), 2.04 (s, 6H, $-CH_3$); MS (EI) *m/z*: 791 (M^+). *Anal*. Calcd for $C_{43}H_{30}ClN_7O_7$: C, 65.19; H, 3.82; N, 12.38. Found: C, 65.22; H, 3.74; N, 12.41.

Macrocycle (6k). This compound was obtained as white crystals in 29% yield; mp 224–223°C; IR (KBr) υ: 3037 (Ar-H), 1577 (C=N), 2925, 1494 (CH3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.71–6.96 (m, 23H, Ar-H), 4.72 (d, H, H_5, J_{ab} = 8.4 Hz), 3.78 (d, H, H_4, J_{ab} = 8.4 Hz), 3.80 (s, 3H, $-OCH_3$), 2.05 (s, 6H, $-CH_3$); MS (EI) *m/z*: 743 (M^+). *Anal*. Calcd for $C_{44}H_{34}N_6O_6$: C, 71.15; H, 4.61; N, 11.31. Found: C, 71.19; H, 4.70; N, 11.27.

Macrocycle (6l). This compound was obtained as white crystals in 21% yield; mp 177–178°C; IR (KBr) υ: 3036 (Ar-H), 1578 (C=N), 2924, 1490 (CH3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.02–7.00 (m, 22H, Ar-H), 4.49 (d, H, H_5, J_{ab} = 8.4 Hz), 3.79 (d, H, H_4, J_{ab} = 8.4 Hz), 3.81 (s, 3H, $-OCH_3$), 2.04 (s, 6H, $-CH_3$); MS (EI) *m/z*: 777 (M^+). *Anal*. Calcd for $C_{44}H_{33}Cl_2N_6O_6$: C, 67.99; H, 4.28; N, 10.81. Found: C, 68.08; H, 4.29; N, 10.73.

Macrocycle (6m). This compound was obtained as white crystals in 35% yield; mp 169–170°C; IR (KBr) υ: 3042 (Ar-H), 1579 (C═N), 2922, 1491 (CH3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.05–6.97(m, 22H, Ar-H), 4.50 (d, H, H_5, J_{ab} = 8.4 Hz), 3.80 (d, H, H_4, J_{ab} = 8.4 Hz), 3.80 (s, 3H, $-OCH_3$), 3.81 (s, 3H, $-OCH_3$), 2.04 (s, 6H, $-CH_3$); MS (EI) *m/z*: 772 (M^+). *Anal.* Calcd for $C_{45}H_{36}N_6O_7$: C, 69.94; H, 4.70; N, 10.87. Found: C, 70.02; H, 4.59; N, 10.85.

Macrocycle (6n). This compound was obtained as white crystals in 23% yield; mp 145–148°C; IR (KBr) υ: 3034 (Ar-H), 1578 (C═N), 2920, 1493 (CH3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.97–7.05(m, 22H, Ar-H), 4.60 (d, H, H_5, J_{ab} = 8.0 Hz), 3.78 (d, H, H_4, J_{ab} = 8.0 Hz), 3.81 (s, 3H, $-OCH_3$), 2.32 (s, 3H, $-CH_3$), 2.05 (s, 6H, $-CH_3$); MS (EI) *m/z*: 756 (M^+). *Anal.* Calcd for $C_{45}H_{36}N_6O_6$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.43; H, 4.68; N, 11.15.

Macrocycle (6o). This compound was obtained as white crystals in 28% yield; mp 162–165°C; IR (KBr) υ: 3037 (Ar-H), 1580 (C═N), 2924, 1490 (CH3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.10–6.96 (m, 22H, Ar-H), 4.71 (d, H, H_5, J_{ab} = 8.4 Hz), 3.81 (d, H, H_4, J_{ab} = 8.4 Hz), 3.80 (s, 3H, $-OCH_3$), 2.08 (s, 6H, $-CH_3$); MS (EI) *m/z*: 787 (M^+). *Anal.* Calcd for $C_{44}H_{33}N_7O_8$: C, 67.11; H, 4.31; N, 12.41. Found: C, 67.08; H, 4.22; N, 12.45.

REFERENCES AND NOTES

[1] Cram, D. J.; Steinberg, H. J Am Chem Soc 1951, 73, 5691.

[2] Andrea, D.; Henry, K.; Alan, F.; Kieran, N. Tetrahedron Lett 2007, 48, 1017.

[3] Byeang, H. K.; Eun, J. J.; Gil, T. H.; Natarajan, V. Synthesis 2001, 14, 2191.

[4] Perumal, R.; Merikapudi, G. S. Tetrahedron 2006, 62, 12041.

[5] Wipf, P.; Furegati, M. Org Lett 2006, 8, 1901.

[6] Yu, J.; Wang, T.; Liu, X.; Deschamps, J.; Anderson, J. F.; Liao, X.; Cook, J. M. J Org Chem 2003, 68, 7565.

[7] Nussbaum, F. V. Angew Chem Int Ed 2003, 42, 3068.

[8] Raju, S. K.; Stephen, M. R.; Subbu, P.; Perumal, Y. Tetrahedron 2010, 21, 1315.

[9] Macrocyclic Synthesis: A Practical Approach; Parker, D., Ed.; Oxford University Press: Oxford, 1996.

[10] Inone, Y.; Gokel, G. W. In Cation Binding by Macrocycles: Complexation of Cationic Species by Crown Ethers; Marcel Dekker: New York, 1990.

[11] Dietrich, B.; Viout, P.; Lehn, J.-M. In Macrocyclic Chemistry; VCH: Weinheim, 1993.

[12] Gil, T. H.; Byeang, H. K. Tetrahedron Lett 2000, 41, 10055.

[13] Bran, A.; Cicchi, S.; Cordero, F. M.; Goti, A. Chem Rev 2003, 103, 1213.

[14] Bacher, E.; Demnitz, F. W.; Joachi, H. T. Tetrahedron 1997, 53, 14317.

[15] Galley, G.; Jones, P. G.; Patzel, M. Tetrahedron 1996, 7, 2073.

[16] Martin, S. F.; Colapret, J. A.; Dappen, M. S.; Dupre, B.; Murphy, C. J. J Org Chem 1989, 54, 2209.

[17] Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Simoni, D. Synthesis 1987, 67, 857.

[18] Kang, Y. K.; Shin, K. J.; Yoo, K. H.; Seo, K. J.; Hong, C.Y.; Lee, C.; Park, S. Y.; Kim, D. J.; Park, S. W. Bioorg Med Chem Lett 2000, 10, 95.

[19] Ghali, A. H.; Abdelali, K. B.; Brahim, B.; Mohamed, D.; Maria, B.; Taibi, H. Arkivoc 2008, 12, 42.

[20] Venkata, P.; Sarala, B.; Nidhi, G.; Salman, M.; Nagarajan, R.; Raghu, M.; Kumar, K. M.; Kumar, B. L.; Vasantrao, K. V.; Abhijit, R.; Sunanda, D. PCT. Int. Appl. WO 2006, 2006085212.

[21] Chowdhury, P.; Das, A. M.; Goswami, P. Steroids 2005, 70, 494.

[22] Ryng, S.; Machon, Z.; Wieczorek, Z.; Zimecki, M.; Mokrosz, M. Eur J Med Chem 1998, 33, 831.

[23] Howarth, J.; Hanlon, K. Bioorg Med Chem Lett 2003, 13, 2017.

[24] Howarth, J.; Hanlon, K. Tetrahedron Lett 2001, 42, 751.

[25] Crystallographic data for the structures in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication. Their CCDC numbers are 6d (CCDC 832509), Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44-1223 -336033, e-mail: data_request@ccdc.cam.ac.uk.

[26] Becher, J.; Olesen, P.; Knudsen, N.;Toftlund, H. Sulfur Lett 1986, 4, 175.

[27] Liu, K. C.; Shelton, B. R. J Org Chem 1980, 45, 3916.

[28] Xie, Z. F.; Mo, X. X.; Liu, F. M. J. Heterocycl Chem 2008, 45, 1485.