HETEROCYCLES, Vol. 78, No. 4, 2009, pp. 891 - 897. © The Japan Institute of Heterocyclic Chemistry
Received, 17th October, 2008, Accepted, 15th December, 2008, Published online, 17th December, 2008
DOI: 10.3987/COM-08-11583

SYNTHESIS AND STRUCTURES OF NEW C_2-SYMMETRICAL CHIRAL MACROCYCLES CONTAINING THE EPHEDRINE MOIETY

Yiwen Chen,[1, 2] Mingzhang Gao,[1] Songde Tan,[1] Joseph H. Reibenspies,[1] and Ralph A. Zingaro[1*]

1. Department of Chemistry, Texas A&M University, College Station, TX 77843-3255, USA; 2. College of Bio-information, Chongqing University of Posts and Tele-communications, Chongqing, 40064, China; Zingaro@mail.chem.tamu.edu

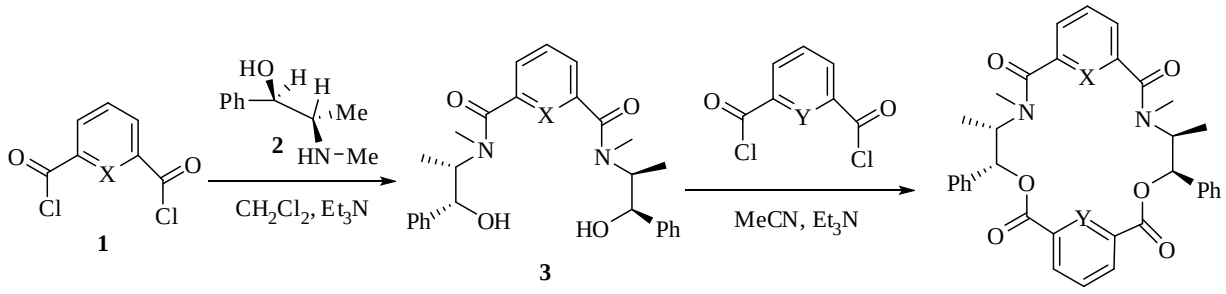
Abstract – Three kinds of novel C_2-symmetrical chiral macrocyclic compounds containing an ephedrine moiety have been designed and synthesized; two of their crystal structures have been determined.

INTRODUCTION

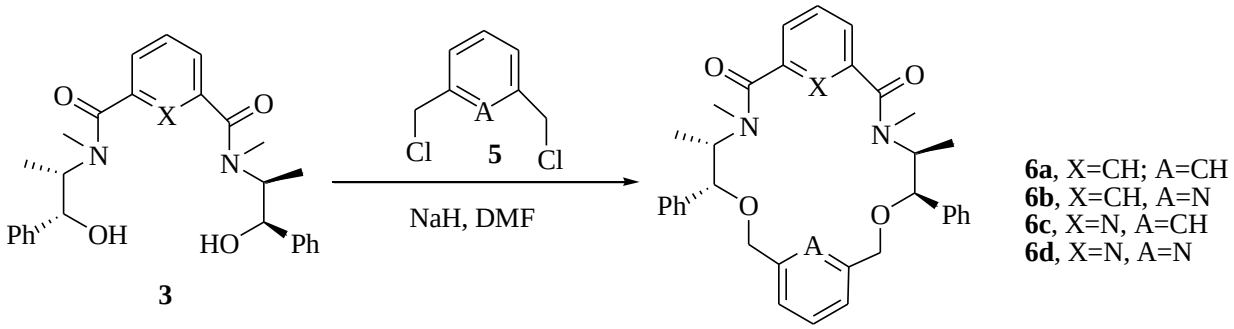
Macrocyclic lactones or macrolides such as the erythromycins and cytochalasins have been shown to display antibiotic and anticancer activities.[1-3] The incorporation of geometrical rigidity by insertion of an amide group in the ring of macrocyclic crown ether affects the binding properties and selectivity of macrocyclic compounds with metal cations [4-7] and organic molecules.[5,8,9] Kumar and co-workers have reported that diamide-ester macrocyclic compounds showed extraordinary Ag^+ binding strength with a remarkable selectivity for Ag^+ over other metal ions.[10-12] Some diamide-containing macrocyclic molecules have been utilized as new catalysts.[13] Our group has recently reported on a series of new chiral macrolides and their antifungal activity.[14] Many chiral macrocyclic compounds have been applied in chiral recognition and resolution of enantiomer and asymmetric catalytic reactions.[15-17] Development of an efficient method for their syntheses and their application has been a subject of considerable interest. In order to develop new method for the synthesis of new chiral macrocycles and investigate their application in metal complex abilities, biochemistry and asymmetric catalysis, we report the design and syntheses of three kinds of new C_2-symmetric chiral macrocycles containing the ephedrine moiety which is a good natural chiral source synthon, but has only been rarely used in chiral macrocycles.[18] The X-ray crystal structures of two of these compounds are also reported.

RESULTS AND DISCUSSION

As is shown in Scheme 1, benzene-1,3- or pyridine-2,6- dicarbonyl dichlorides undergoing the reaction with (1*R*,2*S*)-(-)-ephedrine to give compounds **3**: **3a**, N^1,N^3-bis(1*R*,2*S*)-1-hydroxy-1-phenylpropan -2-yl)-N^1,N^3-dimethylisophthalamide (or **3b**, N^2,N^6-bis(1*R*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-N^2,N^6-dimethylpyridine-2,6-dicarboxamide) in 96% yields. In the subsequent step, benzene-1,3-dicarbonyl dichloride, or pyridine-2,6- dicarbonyl dichloride, undergo condensation with compounds **3** in Et_3N plus DMAP dual-base catalyst system to form the macrolides **4a, 4b, 4c, 4d** in about 20-40% yield.[19]



Scheme 1



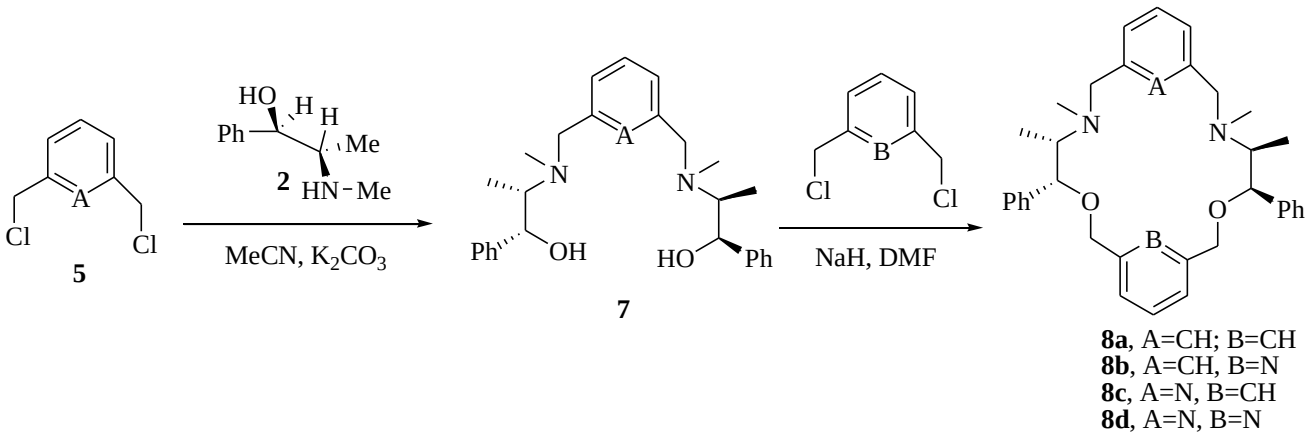
Scheme 2

In scheme 2, compounds **3** undergo condensation with 2,6-bis(chloromethyl)pyridine, or 2,6-bis(chloromethyl)benzene to give compounds **6a**, **6b**, **6c**, **6d** in about 20-30% yield using sodium hydride as the base in a highly diluted DMF solution.[19]

As is shown in Scheme 3, 2,6-bis(chloromethyl)pyridine or 2,6-bis(chloromethyl) benzene undergo reaction with ephedrine to form compounds **7** (1*R*,1'*R*,2*S*,2'*S*)-2,2'- (1,3-phenylenebis(methylene))bis (methylazanediyl)bis(1-phenylpropan-1-ol) or (1*R*,1'*R*, 2*S*,2'*S*)-2,2'- (pyridine-2,6-diylbis(methylene)) bis(methylazanediyl) bis(1-phenylpropan-1-ol) in acetonitrile using K_2CO_3 (or Et_3N) as the base at room temperature in about 95% yield, and compounds **7** condense with 2,6-bis(chloromethyl)benzene or 2,6-bis(chloromethyl)pyridine in DMF by using sodium hydride as base, stirring at room temperature for 24 h to give compounds **8a**, **8b**, **8c**, **8d** in 15-30% yield.[19]

It is normally difficult to obtain the desired macrocycles in high yields during the last step of the

intermolecular condensing cyclization for the following reasons: 1) the intermolecular cyclization procedure, 2) the inclusion of two geometrically rigid aromatic moieties and two amide bond units, 3) an unfavorable decrease in the entropy of reaction and 4) the facile formation of chain and polymeric by-products. For the purpose of minimizing these problems, the effect of solvent on ease of cyclization was investigated. Acetonitrile was found to be the most satisfactory solvent for compounds **4** and DMF was found to be better for compounds **6** and **8**. Subsequently, various bases were studied in synthesis of compounds **4**. The inorganic bases, potassium carbonate and sodium hydroxide were found to have little effect on cyclization. Triethylamine and pyridine can be used as bases, but the speed of cyclization and the yield of product are relatively low. Alternatively, the combination of a base and a catalyst was investigated for the purpose of promoting the cyclization. It was found that in the presence of pyridine or triethylamine and 4-(dimethylamino)pyridine as catalysts, higher yields were achieved in the synthesis of macrocycle **4**. By employing the new dual-base catalyst combination, the reaction rate was also found to increase significantly. All of the desired products have the crown ether-like structure. In the progress of condensation, if some kind of transition intermediates could form by using K^+, Ca^{2+} or other metal ions as templates, it was possible to obtain the desired compound in higher yield. In the synthesis of compounds **6** and **8**, it was found that the rates and the yields of cyclization were increased remarkably by the use of sodium hydride as a catalyst in anhydrous DMF. But to decrease the formation of polymers or other side products, a highly diluted DMF solution was found to be necessary for the synthesis of compounds **6** and **8**.



Scheme 3

In order to obtain a deep and better understanding of the sterochemical properties of the new chiral macocycles, crystallographic investigations were conducted. Colorless single crystals of **6c**, **8d** were obtained by slowly evaporation from a mixture of methanol and chloroform (1:1 in volume), and their X-ray crystal structures were successfully determined as illustrated in Figures 1 and 2.[20] In **6c** the two amide oxygens lie on opposite sides of the pyridine plane. The two amide groups N2-C6-O3 and N3-C19-O4 are twisted by 42.03(2)^o and 63.22(2)^o with respect to the pyridine ring. The two ester O,

py-N and two amide nitrogens are directed inwards toward the cavity. In **8d** the molecule possess a chair-like structure with two pyridine moieties occupying opposite positions. The dihedral angle between two pyridine moieties is 5.11(2)^{o}. The two phenyl groups are located on either sides of the molecule.

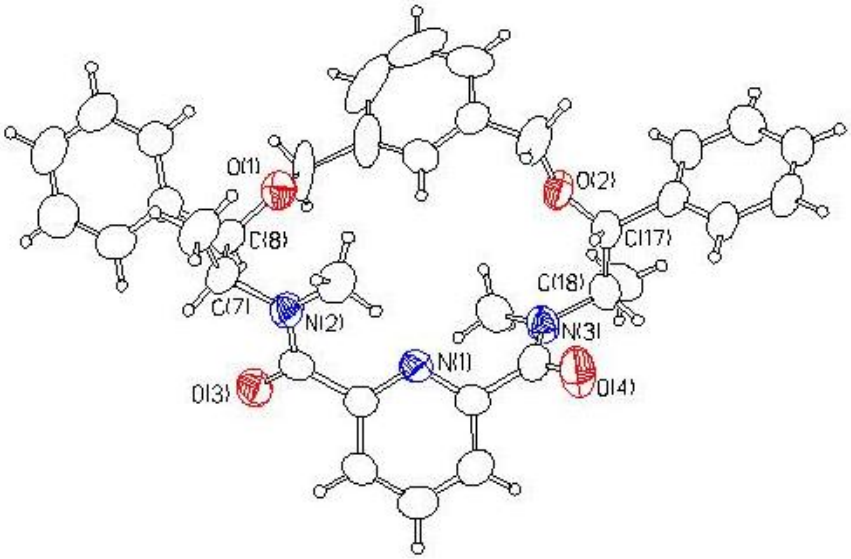


Figure 1. Molecular structure of **6c** (50% probability ellipsoids, arbitary atom numbering).

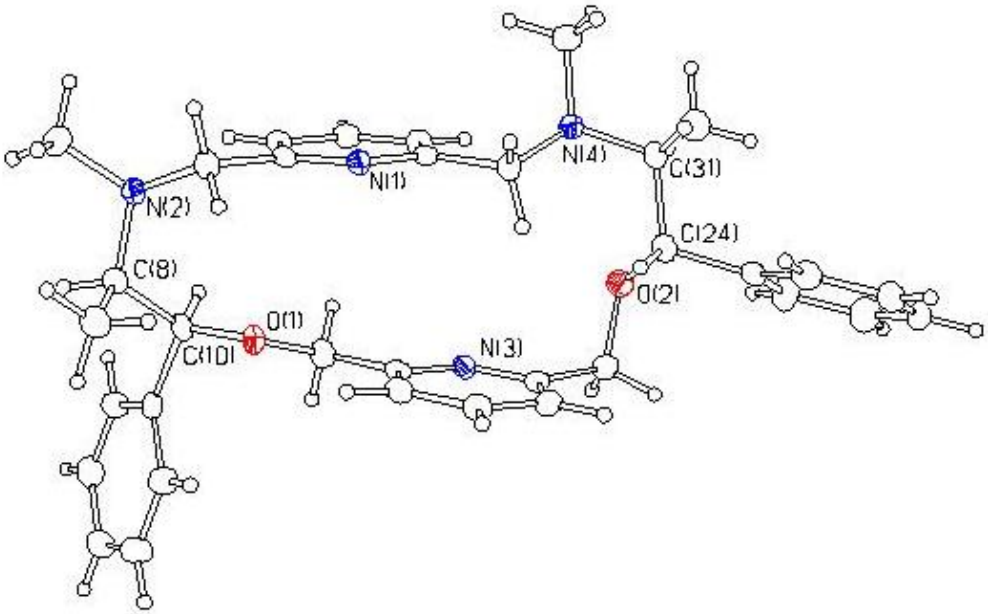


Figure 2. Molecular structure of **8d** (50% probability ellipsoids, arbitary atom numbering).

In summary, the syntheses of three kinds of new C_2-symmetric chiral macrocyclic compounds containing ephedrine moiety is described. The X-ray crystal structures of two of them have been obtained. The application of these new compounds will be studied in the future.

ACKNOWLEDGEMENTS

The authors acknowledge the assistance of the Robert A. Welch Foundation (A-084).

REFERENCES AND NOTES

1. C. J. Roxburgh, *Tetrahedron*, 1995, **51**, 9767.
2. V. K. Frensch and F. Vögtle, *Tetrahedron Lett.*, 1977, **18**, 2573.
3. P. Wipf, S. Venkatraman, C. P. Miller, and S. J. Geib, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1516.
4. S. Irie, M. Yamamoto, K. Kishikawa, S. Kohmoto, and K. Yamada, *Synthesis*, 1995, 1179.
5. T. Fujita and J.-M. Lehn, *Tetrahedron Lett.*, 1988, **29**, 1709.
6. S. L. Wu, S. J. Frahklin, K. N. Raymond, and W. D. Horrocks, *Inorg. Chem.*, 1996, **35**, 162.
7. M. Z. Gao, J. H. Reibenspies, B. Wang, Z. L. Xu, and R. A. Zingaro, *J. Heterocyclic Chem.*, 2004, **41**, 899.
8. C. A. Hunter, *Chem. Soc. Rev.*, 1994, **23**, 101.
9. M. C. Mitchell, A. Cawley, and T. P. Kee, *Tetrahedron Lett.*, 1995, **36**, 287.
10. S. Kumar, R. Singh, and H. Singh, *Bioorg. Med. Chem. Lett.*, 1993, **3**, 363.
11. S. Kumar, N. Kaur, and H. Singh, *Tetrahedron*, 1996, **52**, 13483.
12. S. Kumar, N. Kaur, and H. Singh, *Tetrahedron Lett.*, 1996, **37**, 2071.
13. H. Sharghi, A. R. Massah, H. Eshghi, and K. Niknam, *J. Org. Chem.*, 1998, **63**, 1455.
14. M. Z. Gao, J. Gao, Z. L. Xu, and R. A. Zingaro, *Tetrahedron Lett.*, 2002, **43**, 5001.
15. X. X. Zhang, J. S. Bradshaw, and R. M. Izatt, *Chem. Rev.*, 1997, **97**, 3313.
16. M. Z. Gao, Y. Q. Yang, and Z. L. Xu, *Chin. J. Org. Chem.*, 2001, **21**, 477.
17. Z. B. Li, J. Lin, M. Sabat, M. Hyacinth, and L. Pu, *J. Org. Chem.*, 2007, **72**, 4905.
18. F. Wudl and F. Gaeta, *J. Chem. Soc., Chem. Commum.*, 1972, 107.
19. The general synthetic procedure for intermediates **3**: To a cold (0 ^{o}C) solution of (1*R*,2*S*)-(-)-ephedrine **2** (3.63 g, 22 mmol) and triethylamine (4.0 ml) in 80 mL of CH_2Cl_2 was added a solution of benzene-1,3- or pyridine-2,6- dicarbonyl dichloride **1** (10 mmol) in 10 mL of CH_2Cl_2 over a period of 1 h. The reaction mixture was stirred at 0 ^{o}C for 3 h and then at rt for additional 5 h. The precipitated from the solution was filtered, washed with 20 mL of CH_2Cl_2 and combined organic layer was washed with 20 mL of H_2O, dried over Na_2SO_4, concentrated. The crude product was purified by column chromatography with silica gel as adsorbent and acetone-hexanes (2:1) as the eluent to give pure compound **3** as a white solid. **3a**, 96 % yield; mp 119-121 ^{o}C; $[\alpha]_D^{25}$ -3.74° (C 0.3, MeOH); ^{1}H-NMR (300 MHz, acetone-d_6) δ: 1.16 (6H, d, J = 2.0 Hz, CH_3), 2.99 (2H, d, J = 9.0 Hz, OH), 3.76 (6H, s, NCH_3), 4.58-4.98 (4H, m, NCH and OCH), 6.68-7.48 (14H, m, Ar-H); MS(FAB): 461 (M^++1, 60%), 443, 353, 296, 251, 154 (100%). **3b**, 93 % yield; mp 157-159 ^{o}C; $[\alpha]_D^{25}$ -12.2° (C 0.3, acetone); ^{1}H-NMR (300 MHz, acetone-d_6) δ: 1.32 (6H, d, J = 2.4 Hz, CH_3), 2.88 (6H, s, NCH_3), 3.20 (2H, d, J = 9.6 Hz, OH), 4.04-5.04 (4H, m, NCH and OCH), 6.98-7.88 (13H, m, Ar-H); MS (FAB): 462 (M^++1, 50 %), 445, 353 (100%). General procedure for the preparation of the compounds **4**. To a hot (50 – 70 ^{o}C) solution of compound **3** (1.0 mmol) in 40 mL of MeCN was

added 4-(dimethylamino)pyridine (DMAP, 25 mg, 0.20 mmol), followed by a solution of compound **1** (2.0 mmol) in 20 mL of MeCN over a period of about 40 min. Then triethylamine (2.0 mL) was added slowly to the reaction mixture over a period of 1 - 2 h and the reaction mixture was stirred for another 10 h. A white precipitate, triethylamine hydrochloride formed, and was removed by filtration. The filtrate was evaporated under reduced pressure to afford a residue, which was purified by column chromatography (silica gel, acetone-hexanes) to provide white solid product **4**. Selected spectral data for compound **4a**: mp: 242-244 ^{o}C. $[\alpha]_D^{25}$ -335˚ (C 0.1, acetone). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.06 (6H, d, *J* = 7.0 Hz, CH_3), 3.05 (6H, s, NCH_3), 4.52-4.63 (2H, m, NCH), 6.11 (2H, d, *J* = 10.5 Hz, OCH), 7.26-8.90 (18H, m, Ar-H). ^{13}C-NMR (75 MHz, $CDCl_3$): 169.3, 167.5, 136.2, 135.0, 132.3, 129.7, 128.8, 128.5, 128.3, 128.1, 126.0, 124.2, 81.5, 61.8, 33.6, 9.9. MS (FAB): 591 (M^++1, 16%), 310, 222 (100%). HRMS (ESI) calcd for $C_{36}H_{35}N_2O_6$, 591.2495 $(M+H)^+$; found 591.2499. General synthetic procedure of compounds **6** or **8**. The intermediate **3** or **7** (1.0 mmol) was dissolved in 60 mL of anhydrous DMF; sodium hydride (72 mg, 3.0 mmol) was added into the solution at 0 ^{o}C with stirring over 30 min. Then the compound **5** (1.0 mol) in 20 mL of DMF was then added slowly into the solution, the stirring was kept for 24 h at rt. The mixture solution was poured into 200 mL of H_2O, extracted with $CHCl_3$ (3 × 40 mL). The combined organic layer was washed with water, dried over the Na_2SO_4, filtered and concentrated. The residue was purified on the silica gel column, eluented with the solution of $CHCl_3$ and MeOH (100:2). The pure product **6** or **8** was obtained as a white solid. Selected spectral data for compound **6c**: mp 207-208 ^{o}C. $[\alpha]_D^{22}$ + 358˚ (C 0.1, MeOH). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.10 (6H, d, *J* = 6.6 Hz, CH_3), 3.29 (6H, s, NCH_3), 4.32-4.35 (2H, m, NCH), 4.62 (2H, d, *J* = 10.2 Hz, OCH), 4.80-5.10 (4H, m, OCH_2), 7.10-7.60 (14H, m, Ar-H), 7.70-8.20 (3H, m, Ar-H); ^{13}C-NMR (75 MHz, $CDCl_3$): 168.51, 153.78, 139.47, 138.97, 138.43, 129.99, 128.72, 128.43, 127.98, 127.69, 126.79, 125.06, 84.93, 73.39, 55.60, 33.95, 9.91; MS (ESI): 570 (M^++Li, 100%). HRMS (ESI) calcd for $C_{35}H_{38}N_3O_4$, 564.2862 $(M+H)^+$; found 564.2867. Selected spectral data for compound **8d**: mp 141-142 ^{o}C. $[\alpha]_D^{22}$ + 77˚ (C 0.1, MeOH). ^{1}HNMR (300 MHz, $CDCl_3$) δ: 1.14 (6H, d, *J* = 6.6 Hz, CH_3), 2.32 (6H, s, NCH_3), 2.86-2.90 (2H, m, NCH), 3.50-4.00 (4H, m, NCH_2), 4.36 (2H, d, *J* = 6.6 Hz, OCH), 4.68-4.72 (4H, m, OCH_2), 7.00-7.42 (14H, m, Ar-H), 7.42-7.80 (2H, m, Ar-H); ^{13}C-NMR (75 MHz, $CDCl_3$): 160.58, 158.28, 141.78, 136.74, 136.52, 128.38, 127.19, 126.93, 121.24, 120.65, 82.13, 72.09, 65.28, 58.74, 42.10, 8.44. MS (ESI): 537 (M^++1, 100%). HRMS (ESI) calcd for $C_{34}H_{41}N_4O_2$, 537.3229 $(M+H)^+$; found 537.3219.

20. Crystallographic measurements were carried out on a Siemens P4 diffractometer with graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å) and 12 kW rotating generator. The data were collected at 110 K. The structures were solved and refined using the programs SHELXS-97 (Sheldrick, 1997) and SHELXL (Sheldrick, 1997). The program X-Seed (Barbour, 1999) was used

as an interface to the SHELX programs. X-ray analysis for **6c**. $C_{35}H_{37}N_3O_4$, MW = 563.69, Monoclinic, *P2(1)*, Z = 2, a = 9.828(9) Å, b = 10.310(10) Å, c = 15.902(15) Å, α = 90°, β = 96.400(15)°, γ = 90°, *V* = 1601(3) $Å^3$, Dcalcd = 1.171 g/cm^{-3}, Mo Ka (λ = 0.71073 Å), F(000) = 602, T = 293K, full-matrix least squares base on F^2, R_1 = 0.0764, wR_2 = 0.1545, 379 parameters, GOF = 1.041. X-ray analysis for **8d**. $C_{34}H_{40}N_4O_2$, MW = 536.70, Triclinic, *P1*, Z = 1, a = 6.2713 (4) Å, b = 8.1494(4) Å, c = 15.4947(8) Å, α = 80.944(4)°, β = 84.321(4)°, γ = 69.951(4)°, *V* = 733.77(7) $Å^3$, Dcalcd = 1.215 g/cm^{-3}, Mo Ka (λ = 1.54178 Å), F(000) = 288, T = 110K, full-matrix least squares base on F^2, R_1 = 0.0284, wR_2 = 0.0727, 366 parameters, GOF = 1.079. Crystallographic data for the structures **6c** and **8d** in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 711112 and 711113. Copies of the data can be obtained, free for charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0)-1223-336033 or email: deposit@ccdc.cam.ac.uk).