HETEROCYCLES, Vol. 78, No. 11, 2009, pp. 2741 - 2753. © The Japan Institute of Heterocyclic Chemistry
Received, 14th March, 2009, Accepted, 14th August, 2009, Published online, 18th August, 2009
DOI: 10.3987/COM-09-11708

A NOVEL MOLECULAR CLEFT BASED ON DIOXOCIN RING, PART I: SYNTHESIS AND CONFORMATIONAL ANALYSIS

Bahareh Vafakish and Parviz Rashidi-Ranjbar*

School of Chemistry, University College of Science, University of Tehran, Tehran, Iran. E-mail: ranjbar@khayam.ut.ac.ir

Abstract – The Molecular cleft **1** using 8-methyl-16*H*-dinaphtho[2,1-*d*:1,2-*g*][1,3]dioxocin-2,14-diol as a spacer was synthesized. Density functional calculations at B3LYP/6-31G level of theory indicates that 8-methyl-16*H*-dinaphtho[2,1-*d*:1,2-*g*][1,3]dioxocin, the central part of **1**, could be populated in two stable conformations, i.e. BC and DB with difference in total energy of 0.12 kcal/mol. ^{1}H-NMR spectroscopy, based on geminal coupling constants, shows that DB form is the most populated conformation of **1** in solution.

INTRODUCTION

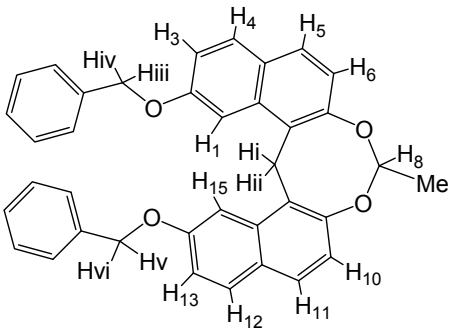
One of the most important features of supramolecular chemistry is molecular recognition, by which molecules selectively bind to form well-defined structures held together by intermolecular forces of noncovalent nature.[1] The field emerged from this area is host-guest chemistry. The past decade has witnessed an explosive growth in research involving this area,[2] and a large number of molecular receptors of varying sizes, shapes and functionalities have been synthesized and their interaction with guests have been assessed.[3]

The design of receptors is based on the fundamental molecular interactions exhibited by biological systems, particularly enzymes.[4,5] Simple synthetic receptors with molecular pockets or cavities can act as models for complicated biological systems which are important in molecular recognition of substrates by enzymes.[6,7] The study of artificial receptors should provide information about structure and stability of receptor-substrate complexes and non-covalent interactions responsible for their complex formation.

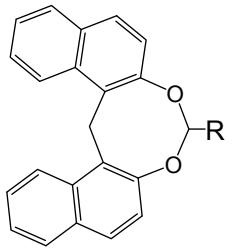
Molecular clefts,[8-27] a subgroup of hosts, are generally the combination of a semirigid cavity to which tunable arms can be appended in predictable geometries. This makes a pocket suitable for binding molecules. The concept has been known for a while, and its applicability has been proven as a viable

means of constructing a molecular receptor.[28] This class of molecules was shown to form sandwich complexes with guests through noncovalent interactions.[29-32]

We have recently synthesized the molecular cleft **1** having 1,3-dioxocin ring as the nucleus of the spacer in the cleft (Scheme 1).



1



2 (R=Me) **3** (R= H)

Scheme 1

The experimental studies on the conformations of 1,3,2-dioxasilocines,[33] 1,3,2-diazaphosphocines,[34] azocines[35] and dioxocins[36] have been carried out both in liquid and crystalline phases. The low energy conformations of boat-chair (BC), distorted boat (DB), twist (T), twist-boat (TB) and boat-boat (BB) are reported for eight-membered ring in 1,3-dioxocin.[37] The presence of planar residues could decrease the number of possible conformations which may be realized in these structures compared with saturated systems,[38] the most populated form was found to be depended on the nature of planar residue and on the type of bridging group.[39] In the structure of **1,** the eight-membered cyclic nucleus, has 1,4-diplanar residue with CH_2 group as a bridge. The dinaphtho dioxocin can act as a rigid cleft with two appended arms generating a synthetic receptor.

RESULTS AND DISSCUTION

Design, Molecular Modeling and Conformational Analysis

Continuing our studies on the dinaphtho[1,3]dioxocins,[40] 8-methyl-16*H*-dinaphtho[2,1-*d*:1,2-*g*][1,3]-dioxocin-2,14-diol was selected as a spacer to make 2,14-bis(benzyloxy)-8-methyl-16*H*-dinaphtho-[2,1-*d*:1,2-*g*][1,3]dioxocin **1** as an artificial cleft.

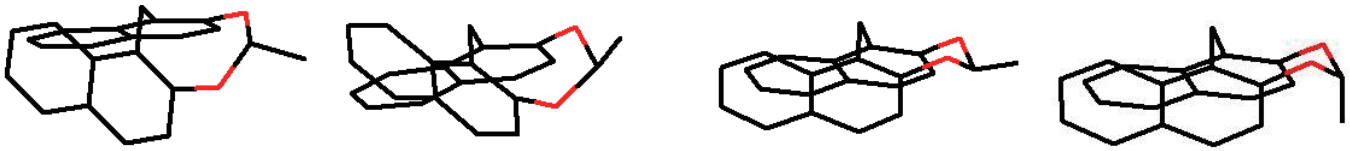
The design of **1** was done taking into account a number of structural features commonly used in the design of host molecules i.e. 1) the presence of a spacer that prevents self-association 2) a spacer that establishes a suitable distance between the pincers (plane to plane or centroid to centroid) and 3) capability of strong noncovalent interactions which stabilized the assembly of complex molecular architecture.[41]

8-Methyl-16*H*-dinaphtho[2,1-*d*:1,2-*g*][1,3]dioxocin **2** (Scheme 1) was selected as a model compound for conformational analysis of the dioxocin ring as the nucleus of the spacer in cleft **1**. The solution and/or the crystal structures of a number of dioxocins are known.[42]

6*H*,12*H*-Dinaphtho[*d,g*][1,3]dioxocin **3** (Scheme 1) could adopt a boat-chair (BC) conformation of Cs symmetry and a distorted boat (DB) conformation of C_1 symmetry.[43] In most derivatives of **3**, which were studied previously, the DB conformation has been found in the solid state.[44] In some cases the BC conformation is reported as the sole form in the solid state as well as in solution.[45] Geometry optimization at B3LYP/6-31G[46] level of theory using Gaussian 98[47] on **2** predict that DB conformation with exo methyl substitution (DB-*exo*) is the most stable form compared with BC with equatorial methyl (BC-*e*), DB form with endo methyl substitution (DB-*endo*) and BC with axial methyl (BC-*a*) (Figure 1). These conformations are true minima based on vibrational frequency calculations. The results of calculations on stable conformations performed with B3LYP/6-31G method are summarized in Table 1.

Calculated internal and torsion angles of DB-*exo*, DB-*endo*, BC-*a* and BC-*e* forms are given in Table 2. Although the axial and equatorial BC conformations have similar torsion angles, these angles are up to 30 degrees different in exo and endo DB forms.

The transition state for conversion of BC and DB forms is a half-chair(HC) conformation and the transition state between DB-*endo* and DB-*exo* is a boat-boat(BB) conformation as reported previously.[48-50] The activation energies for these interconversions were calculated with semiempirical AM1[51] method and the conformational interconversion diagram is shown in Figure 2.



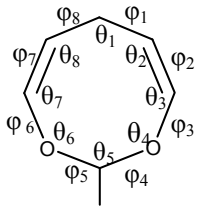
Distorted Boat with exo methyl(DB-*exo*) | Distorted Boat with endo methyl (DB-*endo*) | Boat-Chair with equatorial methyl (BC-*e*) | Boat-Chair with axial methyl (BC-*a*)

Figure 1. The stable conformations of 8-methyl-16*H*-dinaphtho[2,1-*d*:1,2-*g*][1,3]dioxocin **2** as calculated by B3LYP/6-31G level of theory.

Table 1. Calculated relative energies in kcal mol^{-1} of stable conformations of **2**.

DB with exo methyl (DB-*exo*)	0.00
BC with equatorial methyl (BC-*e*)	0.12
DB with endo methyl (DB-*endo*)	0.75
BC with axial methyl (BC-*a*)	2.66

Table 2. Calculated internal and torsion angles of BC (axial and equatorial) and DB (exo and endo) forms of **2**.



	BC- *a*	BC- *e*	DB- *endo*	DB- *exo*
φ_1	-88.35	-88.64	-89.38	-93.49
φ_2	-0.81	-0.37	5.80	2.63
φ_3	78.72	79.48	84.29	55.52
φ_4	-87.72	-90.85	-33.46	14.14
φ_5	86.31	88.50	-79.15	-103.86
φ_6	-82.17	-81.95	68.01	50.88
φ_7	12.16	12.31	-6.07	2.86
φ_8	78.34	77.79	43.23	50.14
θ_1	115.44	115.02	117.70	114.77
θ_2	118.90	118.87	118.49	119.57
θ_3	121.43	121.32	117.74	122.14
θ_4	120.61	118.85	115.52	120.71
θ_5	111.74	111.45	112.10	111.81
θ_6	123.59	122.17	124.41	120.54
θ_7	121.25	121.48	123.99	123.54
θ_8	118.80	118.92	122.04	120.58

The required energy for interconversion of DB-*exo* to BC-*e* is 16.8 kcal/mol and for DB-*endo* to BC-*a* is 17.4 kcal/mol. Calculations reveal that these barriers will raise about 4 kcal/mol if oxygens in **2** are replaced by carbons. The calculated barrier for interconversion of DB-*exo*/DB-*endo* is 10.7 kcal/mol. These results show that the eight membered ring in **2** could adopt the DB or BC conformations. The eight membered ring in **1** resemble very closely the eight membered ring in **2**, however, The DB conformation in **1** seems to be the only populated one based on coupling constant analysis of the ^{1}H-NMR spectra (see the NMR analysis section). In **1** a very rapid equilibrium between the DB-*exo* and DB-*endo* is expected with the *exo* form as the predominant form in the equilibrium.

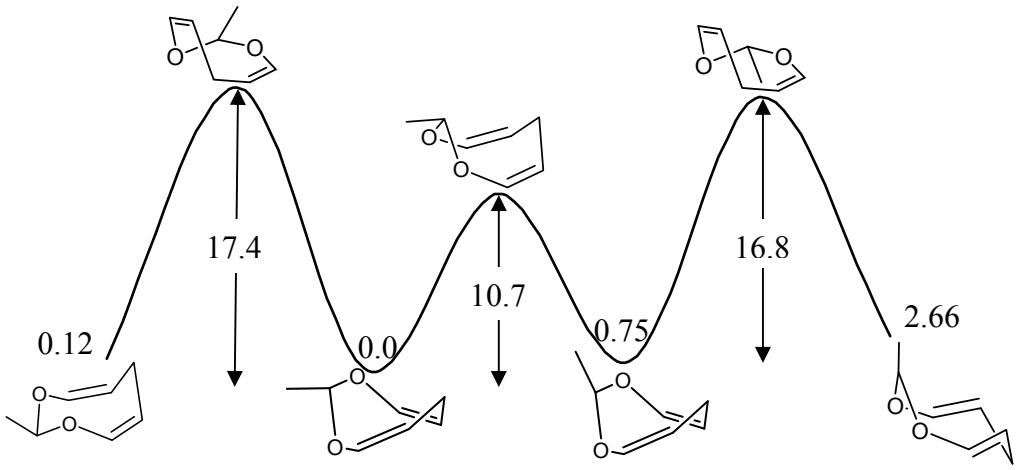
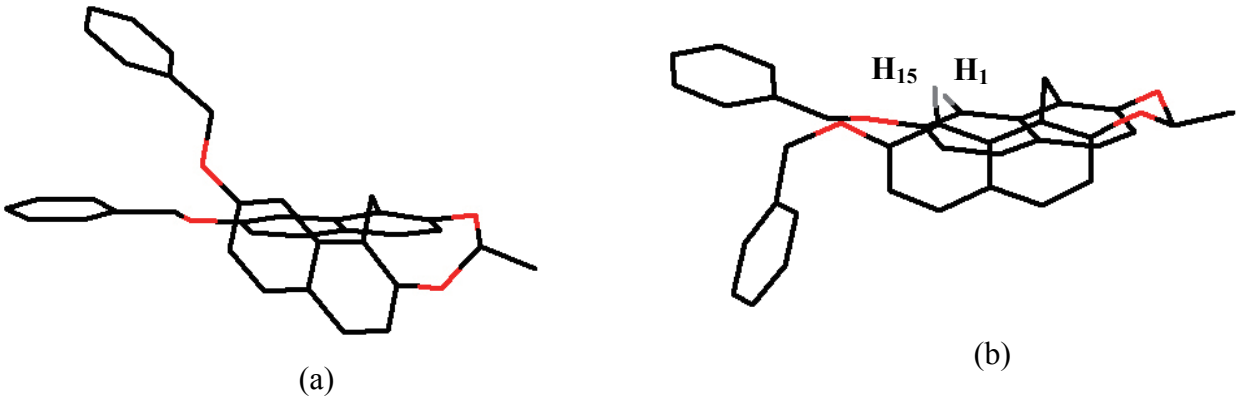


Figure 2. The results of AM1 semi-empirical calculation on conformational interconversion of 8-methyl-16*H*-dinaphtho[2,1-*d*:1,2-*g*][1,3]dioxocin (**2**). The energies are in units of kcal/mol. The naphthalene rings are omitted for simplicity.

The optimized structure of **1** at B3LYP/6-31G level of theory based on DB-*exo* in dioxocin ring is shown in Figure 3a. The optimized structure of **1** in BC-*e* form shows that there is no plane of symmetry and the naphthalene rings are partially moved up and down. This unsymmetrical structure is probably due to the disfavored interaction of the peri hydrogens 1 and 15 of the naphthalene rings (Figure 3b).

Calculations show that the resultant cleft **1** could be used to allow recognition and binding of special guest molecules. This cleft is suitable to bind guests with capability of hydrogen bond formation as well as π-π interaction. Pharmacologically important guests such as phenethylamine, amphetamine, methamphetamine and ecstacy are the proper candidate which could have host:guest interaction with **1** via hydrogen bonding and π-π interactions.



(a) (b)

Figure 3. (a)The optimized structures of **1** based on DB conformation with methyl in exo position in dioxocin ring(DB-*exo*), hydrogens are omitted for clarity. (b) The optimized structures of **1** based on BC conformation with equatorial methyl in dioxocin ring (BC-*e*); all hydrogens, except H_1 and H_{15} are omitted for clarity.

NMR Analysis

The 500 MHz ^{1}H-NMR spectra of **1** was recorded in $CDCl_3$ at 298K. This well resolved spectrum (Figure 4) clearly reflects the C_1 symmetry of molecule. The AB quartet of 2.9-4 ppm with $^2J_{HCH}$=17.05 Hz belongs to Ar-CH_2-Ar protons of dioxocin ring. This big ^2J in similar dioxocin rings or other eight-membered heterocycles contained phosphorus and silicon is attributed to DB conformation,[52] ^2J in BC form is reported to be about 13 Hz.[53] Although the calculated difference in relative energies of DB-*exo* and BC-*e* is 0.12 kcal/mol, however, the ^2J coupling constant of 17.05 Hz suggest the DB-*exo* being the predominant form, at least in solution.

The benzylic methylene groups of the pendant arms give rise to two separate AB quartet systems at 4.6-4.8 and 5.1-5.2 ppm respectively, which are assigned based on NMR calculations performed by Gauge-Including Atomic Orbital (GIAO)[54] method on cleft **1** with DB-*exo* form of dioxocin ring. To compare the calculated data with the experimental ones, the calculated absolute shieldings have been subtracted from the calculated absolute shielding of TMS protons.

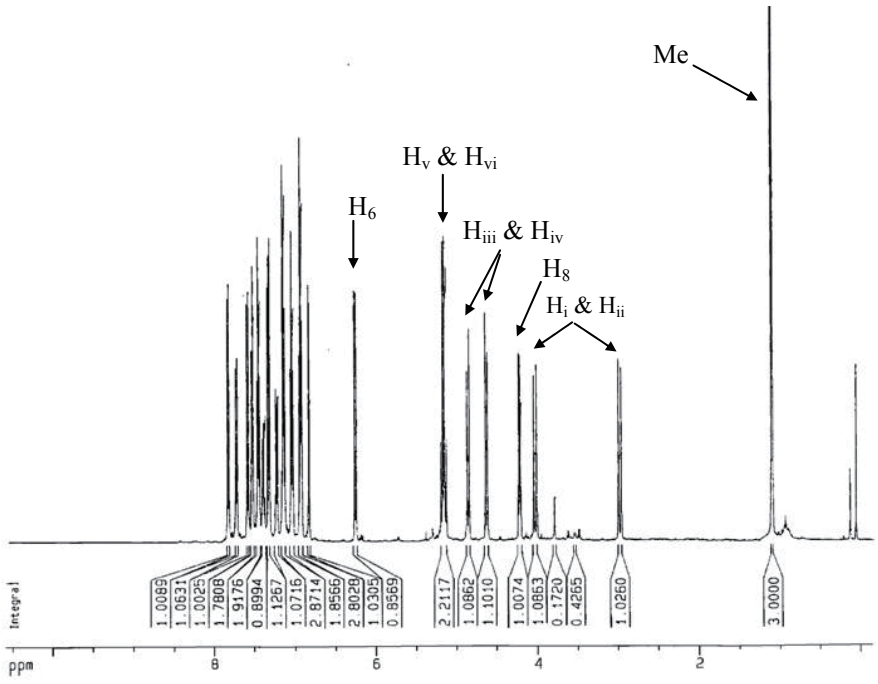


Figure 4. ^{1}H-NMR spectrum of **1**(for the numbering see Scheme 1).

The difference in chemical shifts of H_6 (6.25 ppm) and H_{10} (6.92 ppm) (Table 3) is intresting as H_6 is shielded considerably. GIAO calculations show a difference of 0.2 ppm and predict the difference in the right order.

Table 3. Comparison between the experimental and calculated chemical shifts (ppm) of **1** (for the numbering see Scheme 1).

Nuclei	Experimental	Calculated	Difference
CH_3	1.00	1.59	0.59
H_1	6.83	6.7	-0.13
H_3	6.94	6.94	0
H_4	7.14	7.32	0.18
H_5	7.57	7.4	-0.17
H_6	6.25	6.54	0.29
H_8	4.21	6.26	2.05
H_{10}	6.92	7.07	0.15
H_{11}	7.82	7.54	-0.28
H_{12}	7.19	7.42	0.23
H_{13}	7.22	7.1	-0.12
H_{15}	7.13	7.45	0.32
H_i	2.98	4.4	1.42
H_{ii}	4.02	4.5	0.48
H_{iii}	4.62	4.53	-0.09
H_{iv}	4.85	5.01	0.16
H_v	5.13	5.17	0.04
H_{vi}	5.18	5.2	0.02

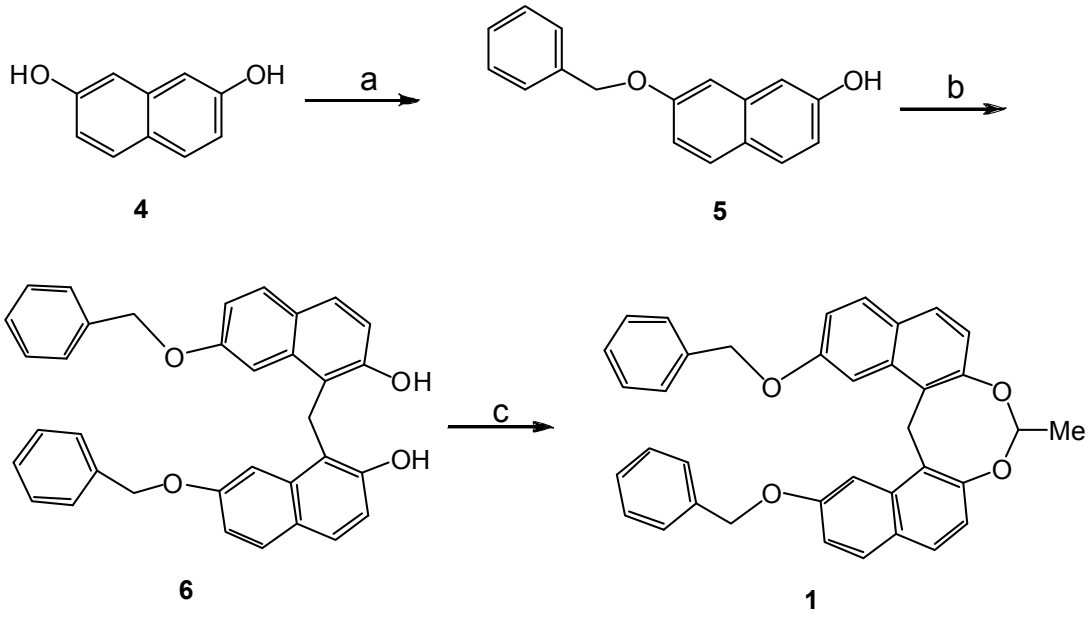
Pulay *et al*[55] in a discussion of the GIAO method noted that since the chemical shift range of hydrogen is the smallest of all atoms, it will be very sensitive to variation in the geometry, methodology and basis set. Also, since the hydrogens are located on the periphery of the molecule, their chemical shift will be more sensitive to intermolecular interactions i.e. solvent effects, which have so far not been included in the NMR calculations.

The experimental and theoretical results, with their differences are presented in Table 3. The calculated and experimental ^{1}H-chemical shifts are correlated with r^2=0.9094. Similar calculations on cleft **1** with DB-*endo*, BC-*e* and BC-*a* forms of dioxocin ring show correlations with r^2=0.8672, 0.8574 and 0.7858 respectively, which are all less than the DB-*exo* correlation coefficient.

Synthesis

This cleft was synthesized by the use of molecular "Lego" set consisting of naphthalene diol, benzyl chloride, formaldehyde and vinyl acetate.

The key precursor in the synthesis of host **1** was the [1,3]dioxocin ring, which is prepared according to the route depicted in the Scheme 2. In brief, 2,7-naphthalenediol **4** was allowed to react with 1.2 equivalent benzyl chloride in DMF using potassium carbonate as base following a literature procedure[56] to produce **5**. The subsequent coupling of **5** with formaldehyde in the presence of sodium acetate in refluxing MeOH afforded compound **6** in an overall yield of 63%. Compound **6** upon reaction with vinyl acetate and bis(acetonitrile)dichloro palladium as catalyst in dry THF at 60 °C for 12 h underwent cyclization to yield molecular cleft **1** in 25% yield.



a: benzyl chloride, DMF, K_2CO_3, 60 °C, 16 h; **b**: formaldehyde, sodium acetate, MeOH, 65 °C, 2 h

c: vinyl acetate, $PdCl_2(MeCN)_2$, dry THF, 60 °C, 12 h

Scheme 2

CONCLUSION

In summary, molecular cleft **1** based on dioxocin ring was synthesized in three steps and its conformation is characterized by NMR spectroscopy. The conformation of dioxocin ring was assigned DB based on the geminal $^2J_{HH}$ coupling constant. Conformational analysis of model compound **2** reveals that the most populated forms is DB-*exo*, with BC-*e*, DB-*endo* and BC-*a* being 0.12, 0.754 and 2.66 kcal/mol higher in energy, respectively. This compound is of interest in view of its potential to act as a host.

COMPUTATIONAL METHODS

The geometry optimization was performed at the B3LYP/6-31G level of theory using the Gaussian 98.[47] The proton chemical shifts were calculated at the B3LYP/6-31G* level of theory by GIAO. AM1 Semiemprical calculations were carried out by Polak-Ribiere algorithm in the Hyperchem program.[57]

EXPERIMENTAL

Materials and Spectroscopy**.** All chemicals and solvents were obtained from Merck and were used as received without further purification. Analytical and preparative TLC was performed on precoated silica gel plates purchased from Merck. All reactions were carried out in oven-dried glassware. Column chromatography was run on silica gel(60 mesh). ^{1}H-NMR and ^{13}C-NMR spectra were recoded on a DRX Avance Bruker-500 MHz spectrometer. IR spectra were recorded on Bruker model Equinox 55 spectrophotometer.

7-(Benzyloxy)-2-naphthol 5. In a 25 mL round bottom flask was dissolved 2,7-naphthalenediol **2** (0.5g, 3.12 mmol) and K_2CO_3 (0.57 g, 4.1 mmol) in DMF (10 mL) and the mixture purged with N_2. Benzyl chloride (0.6 mL, 5.1 mmol) was added under N_2 atmosphere and the reaction was stirred at 60 °C for 24 h. The solution was cooled and filtered. The white precipitate was washed with acetone and dried under vacuum, MeOH (20 mL) was added and boiled and filtered to separate the dibenzylated derivative which is insoluble in MeOH. The filtrate was concentrated under vacume. The crude product was purified by column chromatography (silicagel 60 mesh, 40g, 40×2cm) using 95:5 hexane:EtOAc as eluent. Yield was 45%. ^{1}H-NMR ($CDCl_3$): 5.1 (s, 2H), 7.01-7.03 (d, J = 8.74Hz, 1H), 7.08-7.12 (m, 3H), 7.38-7.53 (m, 5H), 7.68-7.70 (m, 2H), 8.08 (s, 1H); ^{13}C-NMR ($CDCl_3$): 70.46, 106.52, 109.27, 115.73, 117.09, 124.96, 128.00, 128.45, 129.05, 129.78, 130.03, 136.34, 137.34, 154.38, 157.92; IR (KBr; cm^{-1}): 3165 (m), 1738 (w), 1626 (m), 1552 (m), 1448 (m), 1377 (m), 1354 (m), 1282 (w), 1201 (s), 1158 (m), 1118 (m), 999 (m), 953 (w), 864 (m), 800 (w), 750 (m), 700 (m).

7-(Benzyloxy)-1-{[7-(benzyloxy)-2-hydroxy-1-naphthyl]methyl}-2-naphthol 6. Compound **3** (0.1 g, 0.4 mmol) was dissolved in MeOH (2 mL), formaldehyde as aqueous solution 35% (38 µL, 0.4 mmol) and sodium acetate trihydrate (0.052 g, 0.4 mmol) were added. The mixture was refluxed for 2 h, cooled and filtered. MeOH was removed under reduced pressure and the residue was purified by column chromatography (silica gel 60 mesh, 20 g, 20×1.5cm) using 95:5 hexane:EtOAc as eluent with yield of 70%. ^{1}H-NMR ($CDCl_3$): 4.75 (s, 2H), 4.78 (s, 4H), 6.40 (s, 2H), 6.95 (d, J = 8.69 Hz, 2H), 7.07 (d, J = 8.85 Hz, J = 2.28 Hz, 2H), 7.30-7.39 (m, 10H), 7.59 (d, J = 8.70 Hz, 2H), 7.67 (d, J = 2.15 Hz, 2H), 7.71 (d, J = 8.88 Hz, 2H); ^{13}C-NMR ($CDCl_3$): 70.41, 104.51, 115.95, 116.15, 117.02, 125.609, 127.97, 128.30,

128.56, 128.86, 129.00, 130.91, 135.33, 137.28, 152.38, 158.26; IR (KBr; cm^{-1}): 3352 (m), 3119 (m), 3078 (w), 1923 (w), 1732 (w), 1611 (w), 1590 (s), 1490 (s), 1332 (s), 1290 (s), 1200 (s), 1169 (m), 1110 (s), 955 (m), 865 (m), 843 (m), 795 (s), 751 (s); Anal. Calcd for $C_{35}H_{28}O_4$. (512): C, 82.02; H, 5.69. Found: C, 80.37; H, 5.35.

2,14-Bis(benzyloxy)-8-methyl-16*H*-dinaphtho[2,1-*d*:1,2-*g*][1,3]dioxocin 1. To a stirred solution of vinyl acetate (0.5 mL, 5.2 mmol) and $PdCl_2(MeCN)_2$ (0.03 g, 0.1 mmol) in dry THF (2 mL) was added compound **6** (0.096 g, 0.2 mmol). This was stirred in an oil bath at 60 °C for 12 h. Volatiles were removed under reduced pressure and the crude product was purified by column chromatography (silica gel 60 mesh, 40 g, 40×1.5 cm) using 95:5 hexane:EtOAc as eluent. Yield was 45%. ^{1}H-NMR: 1.09(d, *J* = 6.25 Hz, 3H), 2.98 (d, *J* = 17.05 Hz, 1H), 4.02 (d, *J* = 17.05 Hz, 1H), 4.21 (q. *J* = 6.26 Hz, 1H), 4.63 (d, *J* = 12.34 Hz, 1H), 4.85 (d, *J* = 12.34 Hz, 1H), 5.13 (d, *J* = 11.34 Hz, 1H), 5.18(d., *J* = 11.34 Hz, 1H), 6.25 (d, *J* = 9.73 Hz, 1H), 6.82 (d, *J* = 2.45 Hz, 1H), 6.91-6.94 (m, 3H), 7.04 (t, *J* = 7.51Hz, 1H), 7.13-7.13 (m, 3H), 7.21-7.23 (d, *J* = 8.72 Hz, *J* = 2.41 Hz, 1H), 7.31-7.33 (m, 2H), 7.38-7.39 (m, 1H), 7.43-7.46 (t, *J* = 7.65 Hz, 2H), 7.51-7.52 (d, *J* = 7.13 Hz, 2H), 7.57 (d, *J* = 9.75 Hz, 1H), 7.71 (d, *J* = 8.79 Hz, 1H), 7.82 (d, *J* = 8.89 Hz, 1H); ^{13}C-NMR: 15.85, 33.76, 53.78, 69.79, 70.34, 114.29, 114.97, 115.22, 116.21, 116.65, 123.07, 125.09, 127.64, 128.03, 128.12, 128.42, 128.66, 128.96, 130.66, 131.59, 134.37, 136.30, 137.18, 144.44, 147.07, 153.13, 158.05, 160.55; IR (KBr; cm^{-1}): 3413 (w), 3030 (w), 2932 (w), 1894 (w), 1681 (m), 1620 (m), 1595 (m), 1511 (m), 1456 (m), 1434 (m), 1391 (m), 1370 (m), 1267 (m), 1208 (s), 1061 (s), 1019 (s), 832 (s), 741 (s), 727 (s); Anal. Calcd for $C_{37}H_{30}O_4$. (538): C, 82.53; H, 5.58. Found: C, 81.03; H, 5.49.

ACKNOWLEDGMENTS

This work is supported by grants from the research council of University of Tehran. We express our appreciation to Prof. Uday Maitra (Department of Organic Chemistry, Indian Institute of Science, Bangalore, India) for his helpful discussion. We are also grateful to Prof. S. W. Ng for making us available his software (G98w) and hardware (computational time) facilities.

REFRENCES

1. J.-M. Lehn, 'Supramolecular Chemistry, Concepts and Perspectives', VCH: Weinheim, 1995.
2. J. L. Atwood, J. E. D. Davies, D. D. MacNicol, and F. Vögtle, 'Comprehensive Supramolecular Chemistry; Eds.', Pergamon: Oxford, U.K., 1996.
3. M. C. T. Fyfe and J. F. Stoddart, *Acc. Chem. Res.*, 1997, **10**, 393.
4. L. J. D' Souza and U. Maitra, *J. Org. Chem.*, 1996, **61**, 9494.

5. a) E. Fischer, *Ber. Dtsch. Chem. Ges.*, 1894, **27**, 2985; b) D. Yang, M. K. Rosen, and S. L. Schreiber, *J. Am. Chem. Soc.,* 1993, **115**, 819; c) M. K. Rosen, D. Yang, P. K. Martin, and S. L. Schreiber, *J. Am. Chem. Soc.,* 1993, **115**, 821.
6. C. W. Chen and H. W. Whitlock, Jr., *J. Am. Chem. Soc.,* 1978, **100**, 4921.
7. S. K. Burley and G. A. Petsko, *Adv. Protein Chem.,* 1988, **39**, 125; S. K. Burley and G. A. Petsko, *Science*, 1985, **229**, 23.
8. M. Harmata and T. J. Murray, *J. Org. Chem.*, 1989, **54**, 3761.
9. M. Harmata and C. L. Barnes, *Tetrahedron Lett.*, 1990, **31**, 1825.
10. M. Harmata and C. L. Barnes, *J. Am. Chem. Soc.*, 1990, **112**, 5655.
11. M. Harmata, C. L. Barnes, S. R. Karra, and S. Elahmad, *J. Am. Chem. Soc.*, 1994, **116**, 8392.
12. M. Harmata and S. Tyagarajan, Mol. Recognit. Inclusion Proc. Int. Symp. 9th, 1998, 353.
13. M. Harmata, M. Kahraman, S. Tyagarajan, C. L. Barnes, and C. J. Welch, Mol. Recognit. Inclusion Proc. Int. Symp. 9th, 1998, 109.
14. J. Fleischhauer, M. Harmata, M. Kahraman, A. Koslowski, and C. J. Welch, *Tetrahedron Lett.*, 1997, **38**, 8655.
15. a) U. Maitra and L. J. D'Souza, *J. Chem. Soc., Chem. Commun.*, 1994, **24**, 2793; b) N. Vijayalakshmi and U. Maitra, *Org. Lett.*, 2005, **7**, 2727.
16. U. Maitra, L. J. D'Souza, and P. V. Kumar, *Supramol. Chem.*, 1998, **10**, 97.
17. T. Tjivikua, A. Muehldorf, G. Deslongchamps, M. Famulok, and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1991, **113**, 201.
18. J. F. Blake and W. L. Jorgensen, *J. Am. Chem. Soc.*, 1990, **112**, 7269.
19. S. C. Zimmerman, C. M. VanZyl, and G. S. Hamilton, *J. Am. Chem. Soc.*, 1989, **111**, 1373.
20. T. Korenaga, T. Kosaki, Y. Kawauchi, T. Ema, and T. Sakai, *J. Fluorine Chem.*, 2006, **127**, 604.
21. S. C. Zimmerman, W. Wu, and Z. Zeng, *J. Am. Chem. Soc.*, 1991, **113**, 196.
22. S. C. Zimmerman, *Top. Curr. Chem.*, 1993, **165**, 71.
23. S. C. Zimmerman, *Bioorg. Chem. Front.*, 1991, **2**, 33.
24. S. C. Zimmerman, M. Mrksich, and M. Baloga, *J. Am. Chem. Soc.*, 1989, **111**, 8528.
25. S. C. Zimmerman and W. Wu, *J. Am. Chem. Soc.*, 1989, **111**, 8054.
26. S. C. Zimmerman and C. M. VanZyl, *J. Am. Chem. Soc.*, 1987, **109**, 7894.
27. V. K. Potluri and U. Maitra, *J. Org. Chem.*, 2000, **65**, 7764.
28. F. G. Klarner and B. Kahlert, *Acc. Chem. Res.*, 2003, **36**, 919.
29. M. Perry, P. J. Stansfeld, J. Leaney, C. Wood, M. Groot, D. Leishman, M. J. Sutcliffe, and J. S. Mitcheson, *Mol. Pharmacol.* 2006, **69**, 509.

30. a) M. M. Conn, G. Deslongchamps, J. de Mendoza, and J. Rebek, Jr., *J. Am. Chem. Soc.*, 1993, **115**, 3548; b) G. A. Jeffrey and W. Saenger, 'Hydrogen Bonding in Biological Structures', Springer, Berlin, 1994.
31. T. H. Webb and C. S. Wilcox, *Chem. Soc. Rev.*, 1993, **22**, 282.
32. a) S. S. Yoon and W. C. Still, *J. Am. Chem. Soc.*, 1993, **115**, 823; b) L. F. Newcomb, T. S. Haque, and S. H. Gellmann, *J. Am. Chem. Soc.*, 1995, **117**, 6509.
33. L. P. Burke, A. D. DeBellis, H. Fuhrer, H. Meier, S. D. Pastor, G. Rihs, G. Rist, R. K. Rodebaugh, and S. P. Shum, *J. Am. Chem. Soc.*, 1997, **119**, 8313.
34. T. S. Cameron, *J. Chem. Soc., Perkin Trans. 2*, 1972, **5**, 591.
35. A. D. Hardy and F. R. Ahmed, *Acta Cryst. Sect. B*, 1974, **30**, 1674.
36. I. V. Anonimova, K. A. Ilyasov, T. E. Yabukov, E. G. Yarkova, N. R. Safiullina, V. V. Klochkov, and B. A. Arbuzov, *Zh. Obshch. Khim.*, 1991, **6**, 173.
37. R. P. Arshinova, A. Kh. Plyamovatyi, R. A. Kadyrov, S. G. Gnevashev, and B. A. Arbuzov, *Phosphorus, Sulfur Silicon Relat. Elem.,* 1989, **41**, 449.
38. R. N. Renaud, J. W. Bowenkamp, R. Fraser, and J. L. Roustan, *Can. J. Chem.*, 1977, **55**, 3456.
39. P. Hug, S. Kolly, H. Meir, R. Pitteloud, D. Poppinger, G. Rihs, and G. Rist, *Helv. Chim. Acta*, 1990, **73**, 618.
40. P. Rashidi-Ranjbar, A. Khoramabadi-Zad, and M. Roohi, *Phosphorus, Sulfur Silicon Relat. Elem.,* 2000, **159**, 229.
41. B. J. Whitlock and H. W. Whitlock, Jr., *J. Am. Chem. Soc.*, 1994, **116**, 2301 and references cited therein.
42. I. V. Anonimova, E. G. Yarkova, R. A. Shaikhutdinov, V. V. Klochkov, and B. A. Arbozov, *Zh. Obshch. Khim*., 1993, **63**, 2405.
43. R. S. Khadiullin, R. P. Arshinova, I. V. Anonimova, A. K. Plyamovatyi, and R. R. Shagidullin, *J. Mol. Struct.*, 1991, **245**, 165.
44. O. N. Kataeva, I. A. Litvinov, V. A. Naumov, and I. V. Anonimova, *Bull. Acad. Sci. USSR Div. Chem. Sci.*, 1989, 1159.
45. O. N. Kataeva, I. A. Litvinov, V. A. Naumov, and I. V. Anonimova, *J. Mol. Struct.*, 1995, **344**, 95.
46. C. Lee, W. Yang, and R. G. Parr, *Phys. Rev. B*, 1998, **37**, 785; B. Miehlich, A. Savin, H. Stoll, and H. Preuss, *Chem. Phys. Lett*. 1989, **157**, 200; A. D. Becke, *Phys. Pev. A*, 1988, **38**, 3098.
47. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B.

Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A.Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 1998.

48. J. Wohnert, J. Brenn, M. Stoldt, O. Aleksiuk, F. Grynszpan, I. Thondorf, and S. E. Biali, *J. Org. Chem.*, 1998, **63**, 3866.
49. F. A. L. Anet and I. Yavari, *J. Am. Chem. Soc.*, 1977, **99**, 6986.
50. F. E. Elhadi, W. D. Ollis, and J. F. Stoddart, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 224.
51. M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, 1977, **99**, 4499; L. P. Davis, *J. Comp. Chem*. 1981, **2**, 433; M. J. S. Dewar, M. L. McKee, and H. S. Rzepa, *J. Am. Chem. Soc.*, 1978, **100**, 3607; M. J. S. Dewar, E. G. Zoebisch, and E. F. Healy, *J. Am. Chem. Soc.*, 1985, **107**, 3902.
52. R. S. Glass, 'Conformational Analysis of Medium-Sized Heterocycles', VCH: New York, 1988.
53. S. D. Pastor and J. D. Spivak, *J. Org. Chem.*, 1984, **49**, 1297.
54. K. Wolinski, J. F. Hilton, and P. Pauly, *J. Am. Chem. Soc.*, 1990, **112**, 8251; J. L. Dodds, R. McWeeny, and A. J. Sadlej, *Mol. Phys*., 1980, **41**, 1419; R. Ditchfield, *Mol. Phys*. 1974, **27**, 789; R. McWeeny, *Phys. Rev*., 1962, **126**, 1028; F. London, *J. Phys. Radium, Paris*, 1937, **8**, 397.
55. P. Pulay, and J. F. Hinton, 'Encyclopedia of Nuclear Magnetic Resonance', ed. by D. M. Grant and R. K. Haris, Wiley: New York, 1995, pp. 4334-4345.
56. A. K. Bandyopadhyaya, N. M. Sangeetha, and U. Maitra, *J. Org. Chem.*, 2000, **65**, 8239.
57. Hyperchem, Release 7.0; Hypercube, Inc, 2002.