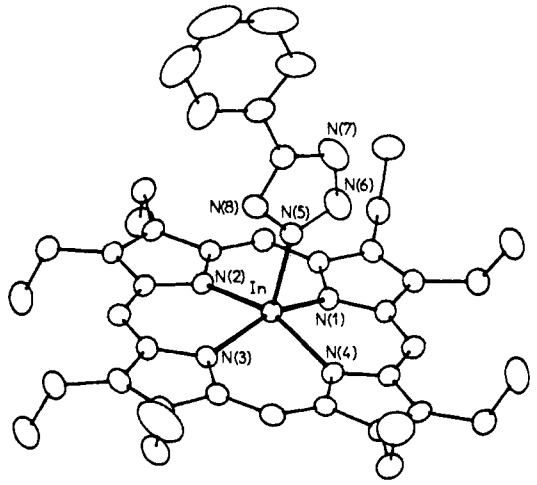

Figure 1. ORTEP view of the complex **1**. Selected bond distances (Å) and angles (°) are as follows: In-N(1), 2.126 (4); In-N(2), 2.129 (4); In-N(3), 2.132 (4); In-N(4), 2.125 (4); In-N(5), 2.183 (5); N(1)-In-N(2), 87.0 (2); N(1)-In-N(3), 155.0 (2); N(1)-In-N(4), 87.6 (2); N(1)-In-N(5), 99.0 (2); N(2)-In-N(3), 87.2 (2); N(2)-In-N(4), 154.8 (2); N(2)-In-N(5), 102.7 (2); N(3)-In-N(4), 87.3 (2); N(3)-In-N(5), 106.0 (2); N(4)-In-N(5), 102.4 (2).

predicted by ^{1}H NMR data. Finally, it is therefore likely that the compounds **2-4** bear a 4-substituted tetrazole. However, no definitive mechanism can be established.

The (azide)indium(III) porphyrins exhibit a similar reactivity toward other dipolarophiles like benzyne leading to (benzotriazolato)indium(III) porphyrins. Such reactions of azido metalloporphyrins are also observed when the central atom is a transition metal. Also the synthesis and the characterization of the corresponding iron(III) complexes are underway.

Acknowledgment. The support of the C.N.R.S. is gratefully acknowledged.

Supplementary Material Available: Tables of positional parameters, thermal parameters, interatomic distances, interatomic angles, and dihedral angles for non-hydrogen atoms (23 pages). Ordering information is given on any current masthead page.

D_{2h}-Bishomohexaprismane ("Garudane"). Design of the Face-to-Face 2 + 2 Dimer of Norbornadiene

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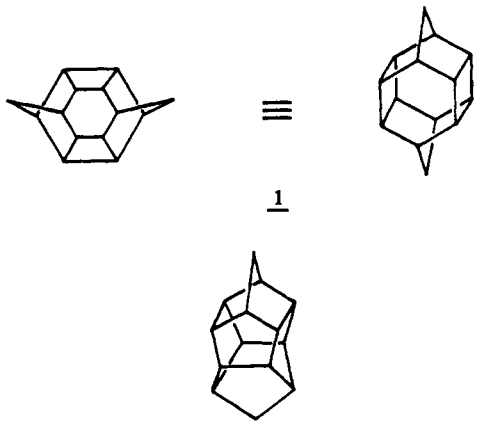
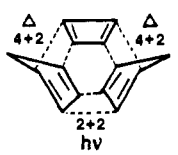
Dimerization of norbornadiene with metal complexes has been actively investigated in recent years from mechanistic and synthetic perspectives.[1] As many as five novel dimers have been characterized, but the true, face-to-face, 2 + 2 dimer **1** ("garudane"),[2] formally a 1,4-bishomohexaprismane of D_{2h} symmetry, has remained elusive. In fact, for over a quarter of a century now,[1a,b,k] the structure **1** has been repeatedly considered for one of the ubiquitous heptacyclic dimers of norbornadiene, but on incisive structural scrutiny has always yielded to the alternative formulation **2** ("isogarudane").[1f,h,j,k] Understandably, the union of two norbornadiene moieties to furnish **1** is disfavored both on entropic as well as strain energy considerations.[3] Nevertheless, **1** is architecturally a fascinating, heptacyclic, $C_{14}H_{16}$ hydrocarbon, and its synthetic design constitutes an attractive and challenging proposition. Looking further ahead, **1** and its derivatives are particularly promising precursors for hexaprismane through ring contraction protocols.[4] In this communication, we disclose our synthetic strategy leading to the *first* synthesis of 1,4-bishomohexaprismane (**1**).



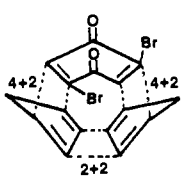
1

2

Among the various strategic options for attaining **1**, that conceptualized in **3** and involving a formal $2C_5$ (1,3-cyclopentadiene) + C_4 (cyclobutadiene) union through thermal 4 + 2 and photochemical 2 + 2 cycloaddition processes appealed to us the most. Imparting practical shape to this theme required deployment of a cyclobutadiene equivalent that could twice function as a 2 component in the 4 + 2 cycloadditions, control the stereochemistry to facilitate the intramolecular 2 + 2 photocycloaddition, and, finally make the functional group adjustment to the hydrocarbon level. Synthetic logic and literature precedences[5] led to the identification of approach **4**, the "2,5-dibromobenzoquinone between the two cyclopentadienes" as the stratagem for achieving 1,4-bishomohexaprismane (**1**).



3



4

Our synthetic pursuit commenced from the readily available but previously overlooked tricyclic quinone **5**.[6a,b] Diels-Alder reaction of **5** with cyclopentadiene furnished the desired endo, syn adduct **6** and the undesired endo, anti adduct, 65:35, in quantitative yield.[6b,7] The ene-dione moiety in **6** was regio- and stereose-

(1) (a) Lemal, D. M.; Shim, K. S. *Tetrahedron Lett.* **1961**, 368. (b) Bird, C. W.; Colinese, D. L.; Cookson, R. C.; Hudec, J.; Williams, R. O. *Tetrahedron Lett.* **1961**, 373. (c) Jolly, P. W.; Stone, F. G. A.; Mackenzie, K. *J. Chem. Soc.* **1965**, 6416. (d) Katz, T. J.; Acton, N. *Tetrahedron Lett.* **1967**, 2601. (e) Schrauzer, G. N.; Ho, R. K. Y.; Schlesinger, G. *Tetrahedron Lett.* **1970**, 543. (f) Acton, N.; Roth, R. J.; Katz, T. J.; Frank, J. K.; Maier, C. A.; Paul, I. C. *J. Am. Chem. Soc.* **1972**, *94*, 5446. (g) Ennis, M.; Manning, A. R. *J. Organomet. Chem.* **1976**, *116*, C31. (h) Neely, S. C.; van der Helm, D.; Marchand, A. P.; Hayes, B. R. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1976**, *B32*, 561. (i) Marchand, A. P.; Hayes, B. R. *Tetrahedron Lett.* **1977**, 1027. (j) Chow, T. J.; Liu, L.-K.; Chao, Y. S. *J. Chem. Soc., Chem. Commun.* **1985**, 700. (k) Hargittai, I.; Brunvoll, J.; Cyvin, S. J.; Marchand, A. P. *J. Mol. Struct.* **1986**, *140*, 219. (l) Chow, T. J.; Chao, Y.-S.; Liu, L.-K. *J. Am. Chem. Soc.* **1987**, *109*, 797.

(2) The protruding bridges ("wings") in **1** are reminiscent of "Garuda" (Sanskrit), the mythological Hindu demi-god, part-bird, part-man, see: Encyclopaedia Britannica, Micropaedia 1981; Vol. IV, p 425. According to the von Baeyer system of nomenclature: heptacyclo-(9.3.0.0^{2,5}.0^{3,13}.0^{4,8}.0^{6,10}.0^{9,12})tetradecane.

(3) The strain energy of **1** and **2** has been estimated to be 93.00 and 49.24 kcal/mol according to the MM-2 calculations performed by Professor E. Ōsawa, Hokkaido University, Japan.

(4) For an alternate approach to hexaprismane, see: Mehta, G.; Padma, S. *J. Am. Chem. Soc.* **1987**, *109*, 2212.

(5) Barborak, J. C.; Watts, L.; Petit, R. *J. Am. Chem. Soc.* **1966**, *88*, 1328.

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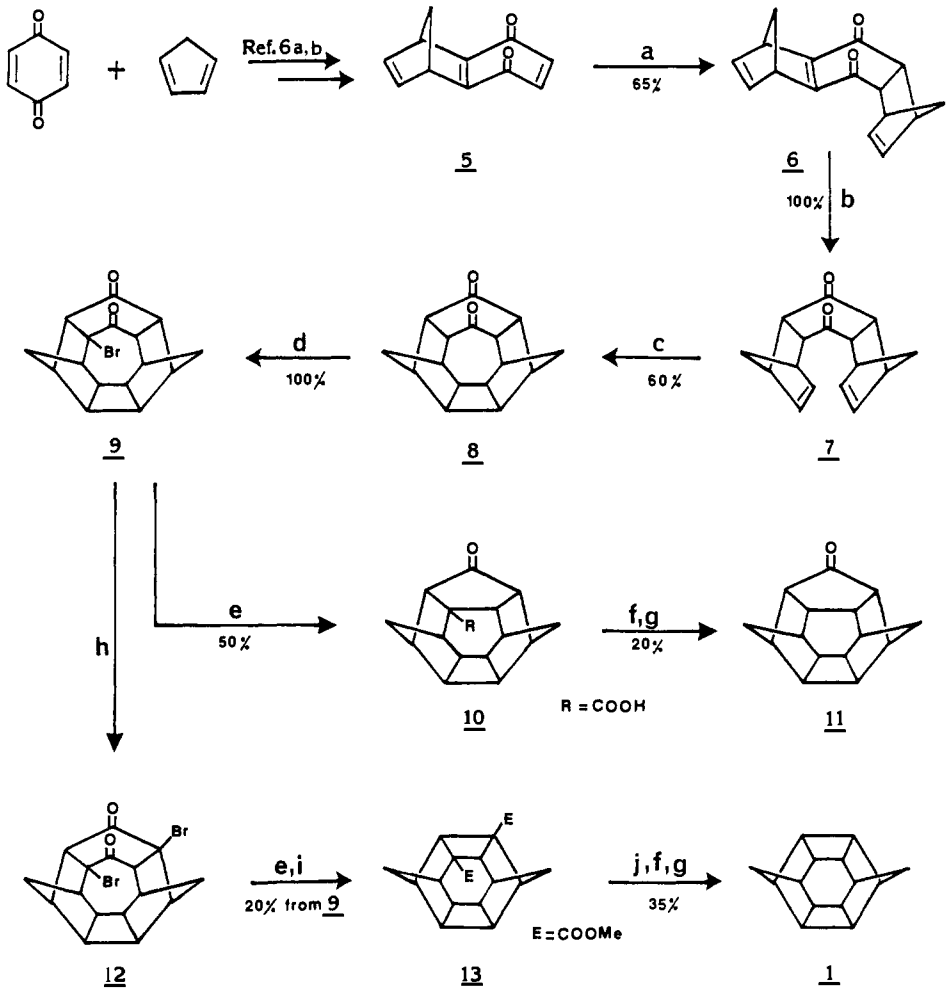
Scheme I[a]



[a] Reagents: (a) cyclopentadiene–benzene, 20 °C, 2 h; (b) 30% aqueous $TiCl_3$–acetone, room temperature, $^1/_2$ h; (c) $h\nu$, 10% acetone–benzene, vycor filter, 25 °C, 4 h; (d) NBS (1.5 equiv)–CCl_4, AIBN, reflux, 3 h, 100% based on starting material recovery; (e) NaOH–toluene, reflux, 10 h; (f) HgO–CH_2Br_2, reflux, 1 h, Br_2 reflux 2 h; (g) Li–THF–*t*-BuOH, reflux, 3 h; (h) NBS (2 equiv)–CCl_4, AIBN, reflux 8 h; (i) CH_2N_2–MeOH, 0 °C, 10 min; (j) aqueous KOH–MeOH, reflux, 2 h.

lectively reduced with the McMurry's aqueous $TiCl_3$ procedure[8] to furnish the endo, syn, endo pentacyclic dione **7**[7] in 100% yield! The next key step, the intramolecular 2 + 2 cycloaddition, was smoothly realized through acetone sensitized irradiation of **7** to furnish the heptacyclic dione **8**,[7] a 1,4-bishomo-6-seco[7]prismane derivative, Scheme I. The structure of **8** was fully consonant with its 5 line ^{13}C NMR spectrum[7] and was further confirmed through X-ray crystal structure determination.[9] The novel dione **8** is a remarkably versatile polycycle, accessible in only three steps from quinone **5**, and we emphasize in advance its potency as the precursor of [7]- and [8]prismanes and their seco- and homologues.[10]

Further elaboration of the dione **8** to the target molecule **1** required the 2 carbon ring contraction of the 1,4-cyclohexanedione ring, and we opted for the reliable Favorskii reaction.[4,11] Reaction of **8** with *N*-bromosuccinimide in the presence of AIBN led to facile bridge-head substitution, and the α-bromodione **9**[7] was realized in high yield. In a dress rehearsal for **1**, **9** was transformed into the ring contracted ketone **11**[7] in three steps involving Favorskii rearrangement to **10** followed by Hunsdiecker reaction and dehalogenation. We now ventured to fulfill the theme depicted in **4** and effect two Favorskii ring contractions. Reaction of α-bromodione **9** with excess of NBS furnished a mixture of bromides in which the dibromodione **12** predominated (>50%). The dibromide **12** was subjected to a one shot double Favorskii ring contraction, and after diazomethane esterification, the diester **13**[7] of C_2 symmetry with 9 line ^{13}C NMR spectrum was obtained in ~20% yield. Assured of the attainment of the 1,4-bishomohexaprismane framework, the last three steps (Scheme I) involving alkaline hydrolysis, Hunsdiecker reaction, and dehalogenation were

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(7) All new compounds reported here were fully characterized on the basis of their IR, ^1H NMR, and ^{13}C NMR spectral data and elemental analysis/HRMS. Compound **6**: mp 155 °C; IR (KBr) 3050, 2975, 1640, 710 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 6.78 (2 H, dd, $J_1 = J_2 = 2$ Hz), 5.79 (2 H, dd, $J_1 = J_2 = 2$ Hz), 3.98 (2 H, dd, $J_1 = J_2 = 2$ Hz), 3.46 (2 H, br s), 3.26 (2 H, m), 2.18 (2 H, m), 1.46 (2 H, m); ^{13}C NMR (25.0 MHz, $CDCl_3$) δ 195.6, 166.9, 142.7, 134.5, 72.3, 50.5, 48.7, 48.2, (2C). **7**: mp 184 °C dec; IR (KBr) 3000, 2950, 1700, 720 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 5.94 (4 H, m), 3.4 (4 H, br s), 3.24 (4 H, br s with st), 1.3 (4 H, ABq with st $J_1 = J_2 = 10$ Hz); ^{13}C NMR (25.0 MHz, $CDCl_3$) δ 209.8, 136.9, 54.0, 47.0, 43.9. **8**: mp 247–8 °C; IR (KBr) 2950, 1680 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$) δ 3.08 (4 H, br s), 2.84 (4 H, br s), 2.68 (4 H, br s), 1.55 (4 H, ABq with st $J_1 = J_2 = 10$ Hz); ^{13}C NMR (25.0 MHz, $CDCl_3$) δ 210.8 (s), 55.1 (d), 46.8 (d), 43.9 (t), 39.4 (d). **9**: mp 184–5 °C; ^{13}C NMR (25.0 MHz, $CDCl_3$) δ 207.5, 202.7, 73.8, 69.1, 56.6, 54.8, 52.6, 47.3, 47.0, 46.5, 43.6, 43.3, 39.6, 39.4, 39.2, 37.8. **11**: mp 123–5 °C; ^1H NMR (100 MHz, $CDCl_3$) δ 2.8–2.0 (12 H, m), 1.45 (4 H, ABq with st $J_1 = J_2 = 8$ Hz); ^{13}C NMR (25.0 MHz, $CDCl_3$) δ 219.9, 62.1, 45.6, 43.4, 38.9, 38.1, 35.1, 34.4. **13**: mp 93–6 °C; ^1H NMR (100 MHz, $CDCl_3$) δ 3.68 (6 H, s), 2.96 (2 H, d), 2.46 (4 H, br st), 2.26 (4 H, br), 1.4 (4 H, ABq with st $J_1 = J_2 = 10$ Hz); ^{13}C NMR (25.0 MHz, $CDCl_3$) δ 177.6, 52.1, 45.2, 42.1, 41.8, 39.5, 36.1, 32.9, 32.4.

(8) Blaszczak, L. C.; McMurry, J. E. *J. Org. Chem.* **1974**, *39*, 258.

(9) We thank Drs. T. N. Guru Row, V. G. Puranik, and S. S. Tavale, National Chemical Laboratory, Pune, for the X-ray crystal structure determination.

(10) Mehta, G.; Padma, S.; Karra, S. R., unpublished results.

(11) (a) Eaton, P. E.; Cole, T. R. *J. Am. Chem. Soc.* **1964**, *86*, 3157. (b) Eaton, P. E.; Or. Y. S.; Branca, S. J.; Shankar, B. K. R. *Tetrahedron* **1986**, *42*, 1621.

quickly and uneventfully effected in 35% yield to deliver **1**, a highly volatile waxy solid, sublimed at ~100 °C, mp 180 °C (rapid heating in sealed capillary). The HRMS of 1,4-bishomohexaprismane (**1**) exhibited molecular ion peak at 184.12558 (calcd for $C_{14}H_{16}$ 184.12528) and the ^1H NMR spectrum (100 MHz) had three resonances at δ 2.38 (br s with st), 2.0 (br s), 1.2 (dd, J = 1.3 Hz) in a ratio of 2:1:1, respectively. The ^{13}C NMR spectrum exhibited three lines at δ 43.0, 36.3, and 33.5 in accordance with its symmetry. With the acquisition of parent **1**, we are adapting the flexible strategy delineated here to obtain its functionalized derivatives that will be amenable to ring contraction to hexaprismane.

Acknowledgment. We thank UGC for a Special Assistance Programme in Organic Chemistry and for COSIST support in Organic Synthesis. S.P. thanks CSIR for a Junior Research Fellowship. We thank K. Srinivas Rao for his assistance in obtaining NMR (^1H and ^{13}C) spectra of several compounds reported here.

Supplementary Material Available: ^1H NMR spectrum (100 MHz) of 1,4-bishomohexaprismane (1 page). Ordering information is given on any current masthead page.

^{15}N NMR Studies of the Complex of Carbonic Anhydrase with the Novel Carbonyl Hydration Substrate Pyruvamide. Evidence for the Coordination of the Deprotonated Amide Group to the Active Site Zinc

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Carbonic anhydrase, an extremely efficient catalyst of the reversible hydration of carbon dioxide,[1-5] also catalyzes the reversible hydration of carbonyl groups of aldehydes and some ketones[3] and the hydrolysis of aromatic and α-keto esters.[3,4] It is almost universally assumed that a zinc-bound OH is a nucleophile or general base in the mechanism of catalysis of all these substrates.[2-7] Due to weak binding and limited solubility, it has hitherto not been possible to study tightly formed 1:1 enzyme complexes with hydration substrates, so that the role of the metal as a Lewis acid catalyst has not been adequately explored. We now report the identification of pyruvamide as a novel carbonyl hydration substrate of carbonic anhydrase and ^{15}N NMR studies of its tight enzyme complex in which the coordination of a *deprotonated* primary amide to the active site zinc of a metalloenzyme is uniquely demonstrated.

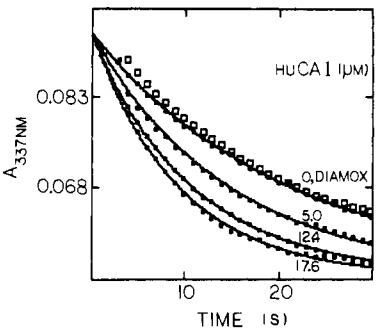

Figure 1. Catalysis of hydration of the keto group of pyruvamide by human carbonic anhydrase I at pH 6.0 in 0.05 M MES buffer. The reaction was followed spectrophotometrically at the keto absorption band (337 nm) and was carried out at ambient (24 °C) temperature. Substrate, as a 10-μL aliquot of a stock solution in p-dioxane, was added to 1.0 mL of buffer containing the micromolar concentrations of enzyme shown in the figure. The open squares represent an experiment in which the buffer contained 12.4 μM enzyme and 0.1 mM diamox inhibitor.

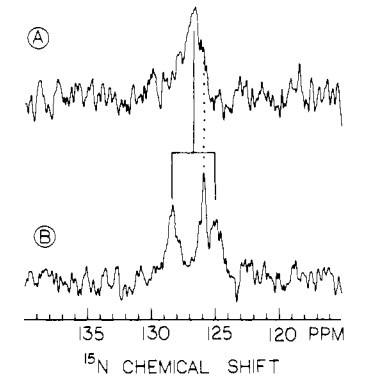

Figure 2. ^{15}N NMR (20.28 MHz) spectra of human carbonic anhydrase I (6.26 mM) containing 1 equiv of 99%-enriched [^{15}N]pyruvamide in 5.0 mM bis-Tris buffer at pH 7.0 in 18% D_2O. Acquisition conditions were as follows: (A) 0.5 W proton broadband decoupling; 130 K scans; decoupler gated off for 3 s following each pulse; (B) no proton decoupling, no delay, 715 K scans. In both cases temperature was 30-32 °C, and acquisition time was 0.48 s, with 8 K data and 16 K transforms, and 3-Hz line broadening.

Figure 1 shows that human carbonic anhydrase I (formerly HCAB) specifically catalyzes the hydration of pyruvamide to the *gem*-diol. The rate increase is linear with enzyme concentration, and catalysis is prevented by the prior addition of the specific inhibitor diamox (acetazolamide). Similar results were obtained with the bovine and human isozymes II. Pocker and co-workers have previously reported that the enzyme catalyzes the hydration of the related pyruvic acid and its alkyl esters,[8] but the affinity of these substrates for the enzyme is very weak. In contrast, we have independently determined[15] that the dissociation constant for binding of pyruvamide approaches 10^{-4} M, making its 1:1 enzyme complexes more favorable for study than any known substrate.

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