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ENERGETIC MATERIALS FROM CUBANE

Interim Report
period covered 1 August 1984 through 31 July 1985

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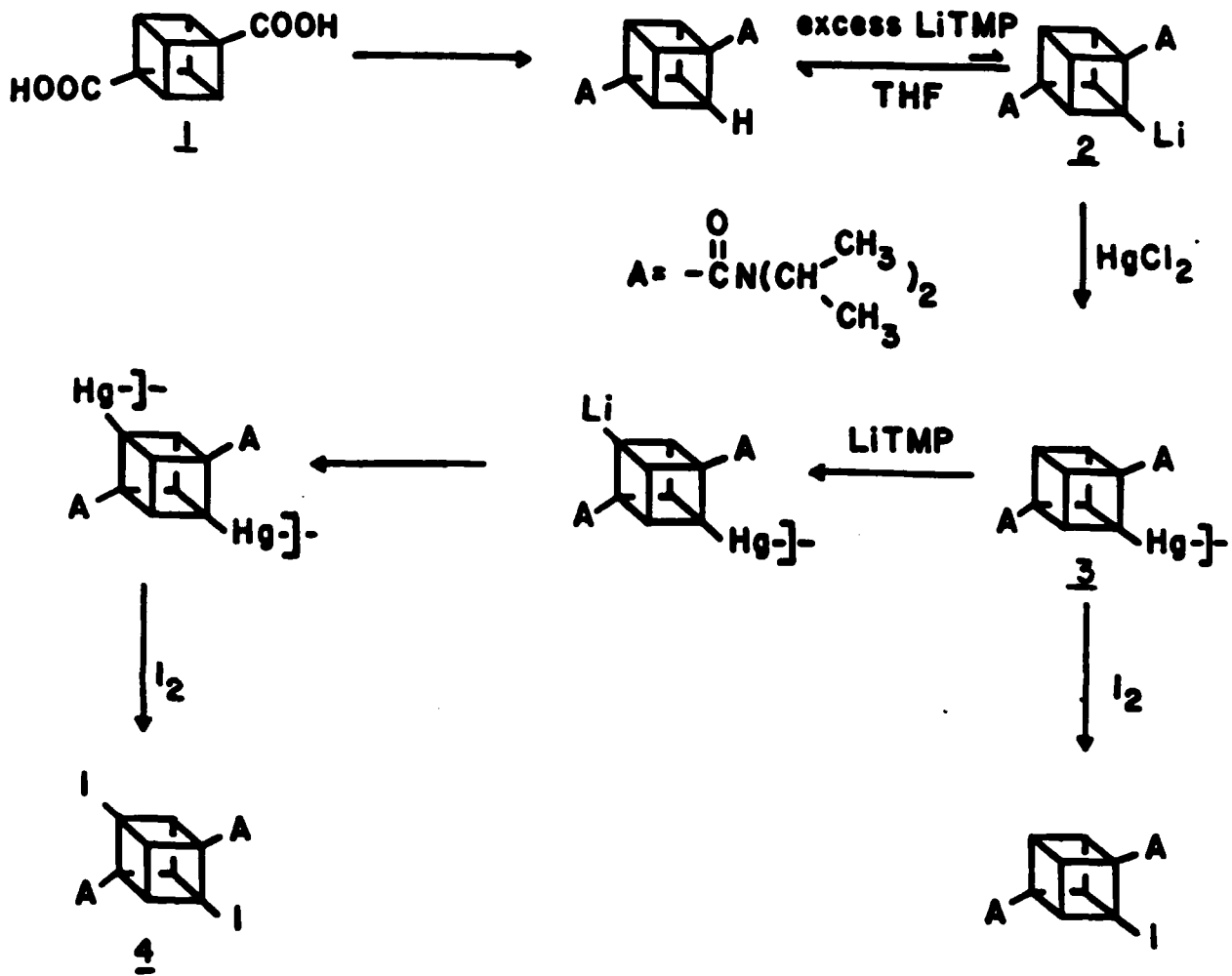
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SECTION 1

Introduction and Background

Cubanes are exceptionally strained compounds with high heats of formation. They are also very dense. The combination of these two properties along with proper substituents on the cubane nucleus should lead to highly energetic materials useful as explosives and propellant additives. Cubanes are not run-of-the-mill compounds. Although the ring system was first made twenty years ago, the chemistry of cubanes has been nowhere near fully explored. Cubane-1,4-dicarboxylic acid (1) can be fairly easily prepared from readily available starting materials; however, the methodology for the preparation of more highly substituted cubanes---those necessary for the proposed use---has not yet been developed. It is the purpose of ^{This Project} ~~ONR contract N00014-84-K-0645~~ to develop and investigate approaches to such highly substituted cubanes. This progress report describes work accomplished during the first year of the contract: August 1, 1984 through July 31, 1985.

Before starting on the present contract, we had discovered that it was possible to use amide groups on the cubane nucleus to activate adjacent positions for lithiation. Further, we had shown that such ortho-lithiated cubanes (e.g. 2) could be intercepted with mercury salts to produce cubyl mercurials (e.g. 3). The carbon-mercury bond in such compounds was shown to be reactive toward iodine; the final result being the production of cubyl iodides. Thus, as shown in the overall scheme illustrated overleaf, we succeeded in preparing and characterizing 2,7-diiodo-1,4-bis(N,N-diisopropylcarboxamido)cubane (4), the first tetrasubstituted cubane.



From this starting point, we have shown during the year of the contract just finished:

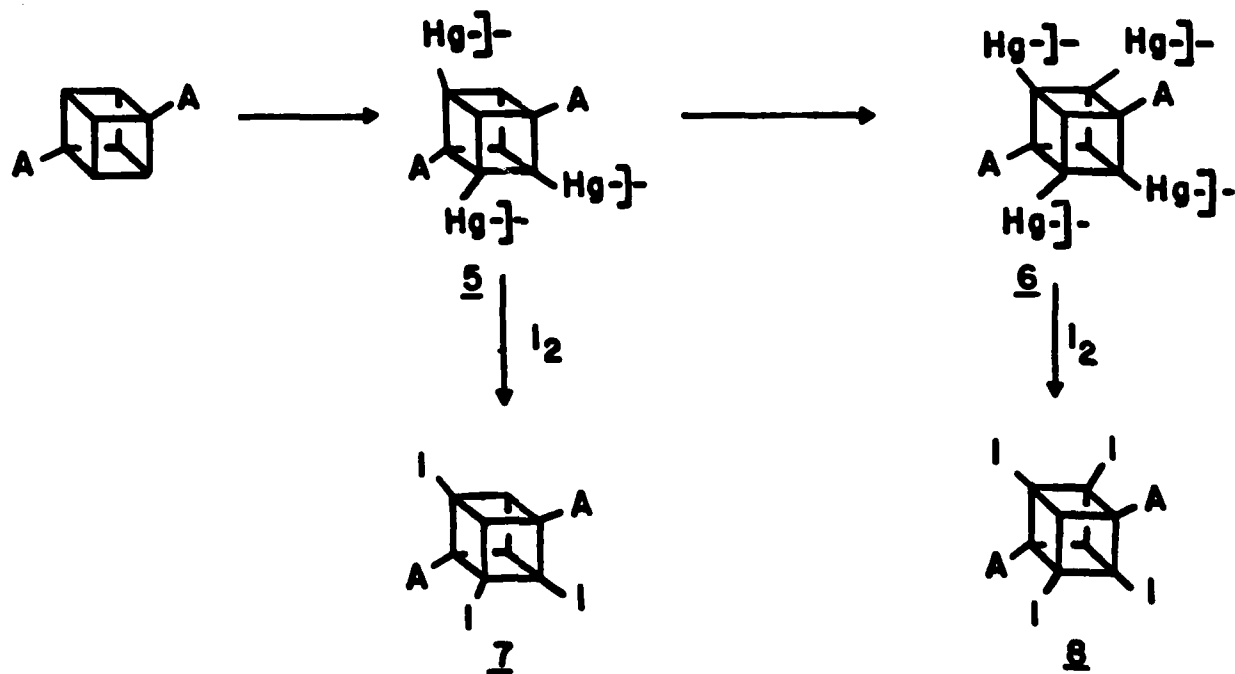
1. How to make triiodo- and tetraiodo-cubane diamides; the first known penta- and hexa-substituted cubanes, respectively;
2. How to make and use the zinc, cadmium, magnesium and boron derivatives of cubyl amides;
3. How to introduce new carbon-carbon bonds onto the cubane framework and thus produce the first cubanes with three and four carbon substituents;
4. How to use cubyl iodides for the introduction of other hetero atoms onto the cubane nucleus;
5. How to convert the cubyl amide group to groups more amenable to further manipulation.

Section 2

RESULTS AND DISCUSSION

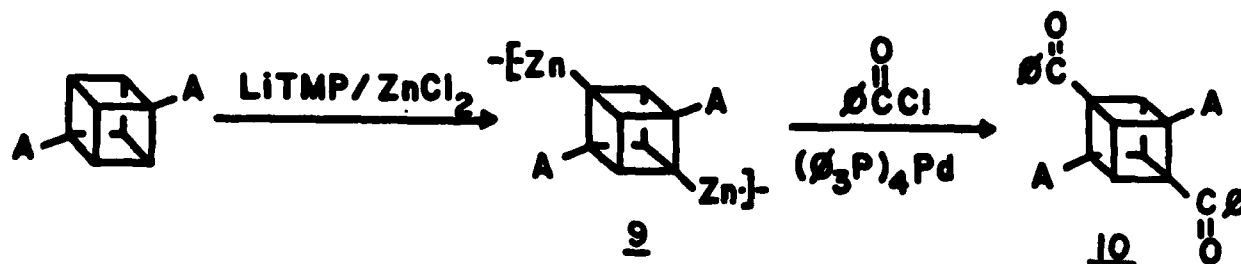
The ortho-lithiation of amide activated cubanes with lithium tetramethyl piperidide as the base is an equilibrium process in which, even in the presence of a large excess of base, there is only a few percent of the lithiated cubane.¹ Although an amide group on cubane is capable of activating each of the three positions ortho to it, once one lithiation occurs electrostatics dictates against further reaction. No dilithiation of a cubane has ever been observed, even in the extreme case where there are two amides diagonally across from one another on the cubane nucleus, activating, hypothetically, all of the cubyl hydrogens. In order to use ortho-lithiation effectively, the equilibrium must be drawn to the right by forming less ionic cubyl metal bonds. Thus, transmetalation with mercury salts,

the original discovery, leads to the complete formation of the cubyl mercury. In addition, and of striking importance, such transmetalation reduces the electrostatic effects and permits further metalation on the cube. Thus, as we have come to understand it, the formation of dimercury derivatives of cubane diamide occurs by the sequence: ortho-lithiation, transmetalation (mercuration), a second ortho-lithiation, then a second transmetalation (mercuration). Given this interpretation, it should be possible to take the reaction further by escalating the reaction conditions. Indeed, we have now shown that by increasing the concentration of the reagents and by extending the reaction time it is possible to produce the trimercurated (5) and tetramercurated (6) compounds, characterized by iodine cleavage to the respective triiodo (7) and tetraiodo (8) cubanes. This is the first time that such highly substituted cubanes have been made by direct and

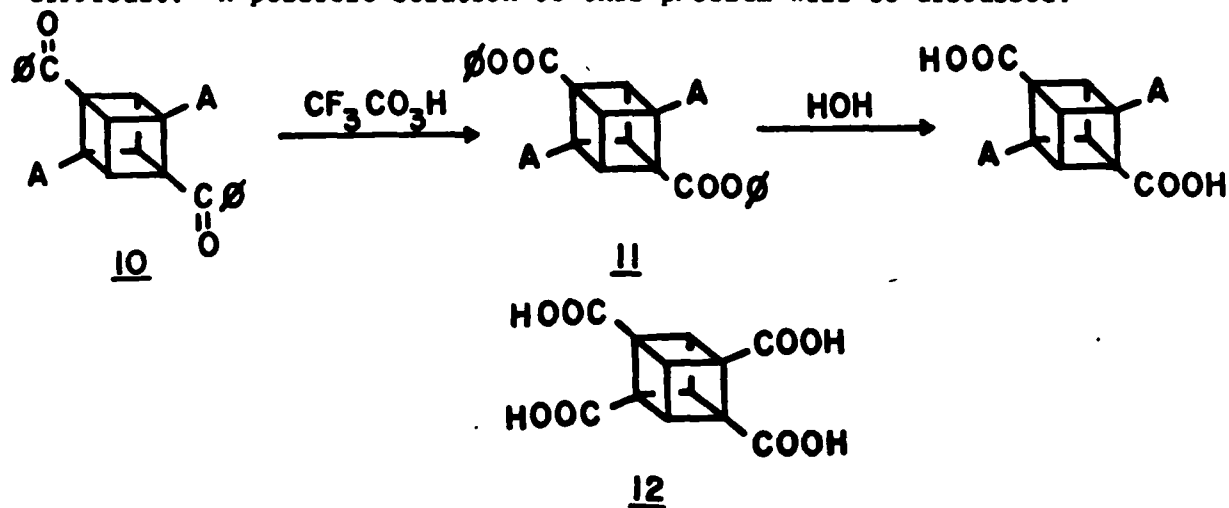


controlled reactions right on the cubane nucleus. In all probability, further increases in reaction time and reactant concentration would permit the formation of yet more highly substituted cubanes. At this point in the investigation doing so would serve little purpose and further work along this line is reserved to the time that we know how to manipulate organometallic and/or iodine substituents on the cubane nucleus and transform them into the desired nitrogen containing substituents.

To such ends, we have moved forward on several fronts. The first of these is the preparation of organometallic cubane derivatives more reactive than cubyl mercuries. We have been able to prepare, and characterize by way of their reactions, the zinc, cadmium and magnesium derivatives of cubyl amides. To make these, we used appropriate transmetalation reagents, substituting, for example, zinc chloride for mercury chloride in the original recipe. The zinc compound is the most interesting of those prepared to date. Organozincs are much more reactive than organomercuries. Thus, we have been able to take the dizinc compound 9 prepared from cubane-1,4-dicarboxamide by treatment with lithium tetramethyl piperidine and zinc chloride, and react it successfully with benzoyl chloride activated by tetra(triphenylphosphine)palladium(0).² This is a very complex synthetic transformation, requiring careful control of time and conditions, but it has permitted us to convert in one pot the simple cubane-1,4-diamide to the tetrasubstituted cubane 10, the first example of a cubane bearing four carbon substituents.



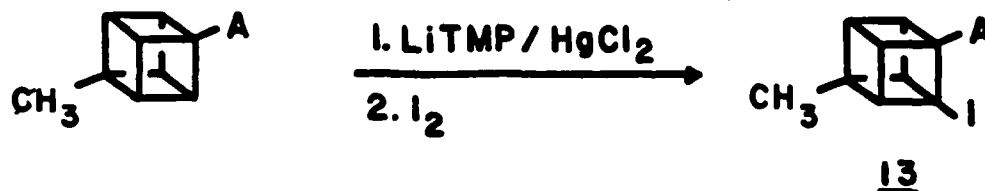
Baeyer-Villiger oxidation of compound 10 with trifluoroperoxyacetic acid produces the corresponding phenylester 11. We are looking now at the hydrolytic conversion of this material to the corresponding tetracarboxylic acid 12. In theory, this requires only hydrolysis of the amide and ester groups. Hydrolysis of the latter is trivial, but unfortunately hydrolysis of the amide group is very difficult. A possible solution to this problem will be discussed.



Earlier we demonstrated that it is easy to convert cubane dicarboxylic acid to the corresponding dinitrocubane.³ We expect that once we have cubane tetracarboxylic acid in hand we will be able by essentially identical procedures to prepare tetranitrocubane, a key intermediate goal in the whole research program directed to the preparation of dense polynitro polycyclic compounds.

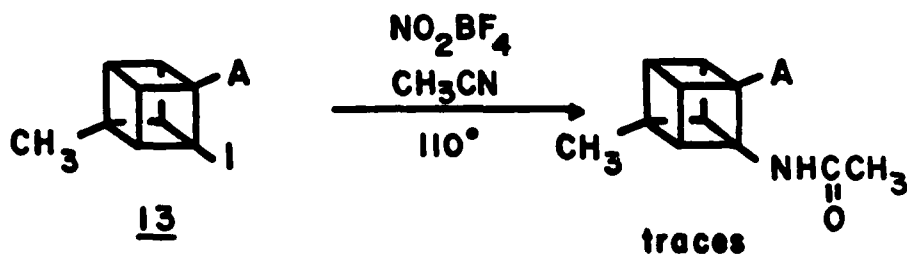
As mentioned earlier, the cleavage of cubyl mercuries with elemental iodine gives excellent and easy access to iodocubanes, indeed to polyiodocubanes. The question arises: it is possible to convert such iodocubanes into nitro-substituted cubanes? To probe this question we have started to examine the fundamental chemistry of iodine attached to the cubane nucleus.⁴ To simplify the early work, we have prepared and used the moniodo derivative 13 of the amide of the known 4-methylcubane carboxylic acid.⁵ The NMR of this compound is easily understood; the methyl group acts as a convenient marker and helps to simplify

determination of the distribution and number of products from reactions of this compound.

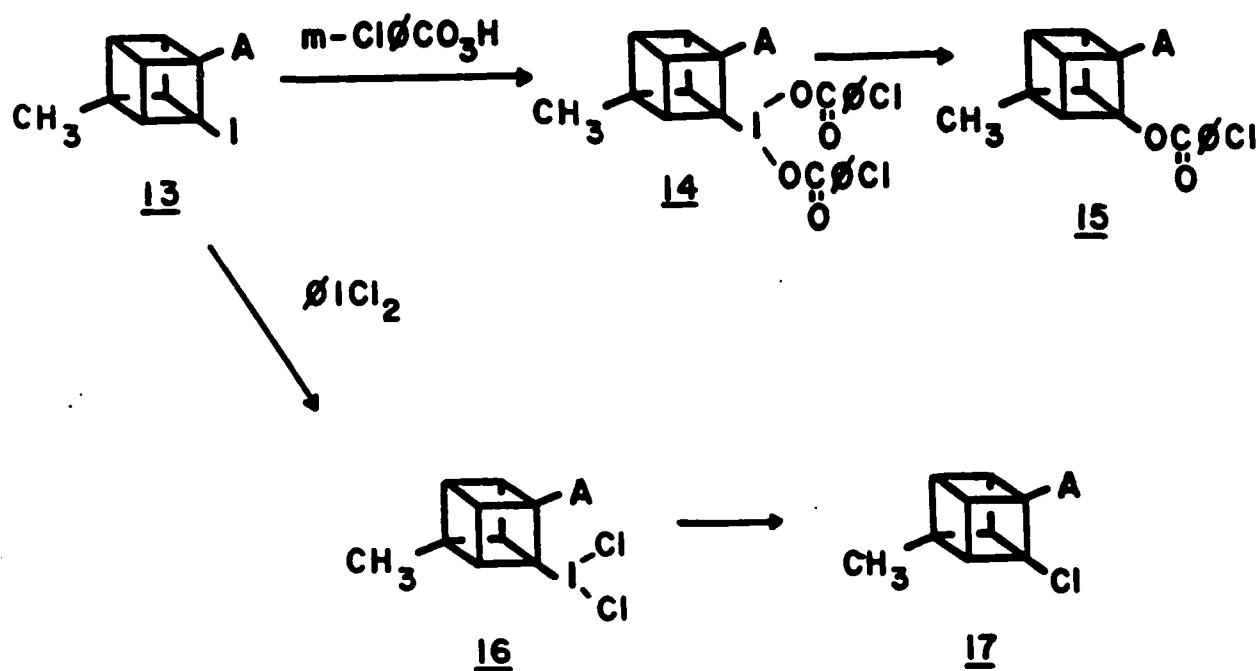


In simple aliphatic iodides it is possible to displace the halogen with an amine in standard S_N1 or S_N2 reactions. These reactions are not applicable to cubane. The corresponding ionization to the cubyl cation or backside displacement on the carbon bearing the iodine are not feasible reactions in systems of such geometry. Quite a different tack to the replacement of the iodine must be taken. We have examined instead both the photo-Ritter reaction⁶ and the nitronium tetrafluoroborate induced Ritter reaction.⁷ At least to date, the photo-Ritter reaction has not been successful; the amide makes the cubyl ring susceptible to photolytic degradation. It may prove in subsequent work that when the amide group is modified (*vide infra*) we will be able to use this approach more successfully. Use of the Bach-Ritter reaction,⁷ that is treatment of the iodide with nitronium (or nitrosyl) tetrafluoroborate in slightly wet acetonitrile, gave some indication of success. The NMR spectra of the crudes clearly show the introduction of a new amide substituent onto cubane attached, as desired, via nitrogen. However, the total reaction mixture is of such complexity, a result of the instability of acetonitrile at the elevated temperatures needed for reaction, that there is no

possibility to turn this procedure into something productive. We looked instead elsewhere and have discovered some particularly exciting chemistry.



We have found that oxidation of 13 with *m*-chloroperoxybenzoic acid leads to oxidation of the iodide to give what we take to be the corresponding iododibenzoate 14. This compound on warming to 40°C undergoes a useful, if little understood, conversion to the cubyl benzoate 15. Along these same lines we have observed that reaction of 13 with iodobenzene dichloride gives the iododichloride 16 and that this "oxidized" iodide smoothly rearranges on warming to the corresponding chlorocubane 17. These reactions are extraordinary. There exists only a few precedents in the literature for such conversions,⁴ and the fact that these apply at all to the cubane case is truly remarkable. We believe now that developing methods to oxidize at iodine so as to make iodine-nitrogen bonds will provide a way, via rearrangements similar to those just presented, to replace iodines on the cubyl ring system with nitrogen. In the year ahead this will be one of our major goals.



The diisopropyl amide group which we used to activate the cubane nucleus for ortho-lithiation is carried "by default" into all further cubane derivatives. As useful as the amide group is in the initial step, it is a terrible nuisance thereafter. Such highly substituted amides are very difficult to hydrolyze, particularly as strong acid methodology is ruled out when dealing with the cubane nucleus. It is essential that we develop other methodology to remove this group once it has served its purpose. We have now taken the first step toward achieving this seemingly simple need. In a model case, we have shown that an easy addition/oxidation sequence can be substituted for hydrolysis. Thus, treatment of the cubane-1,4-bisamide with excess vinyl Grignard in refluxing THF gives a mixture of adducts which on oxidation are all converted to the desired diacid. Although this is a roundabout method to achieve our goal, in actuality it can be

done in good yield, and will probably develop to be competitive with any simple method for amide hydrolysis.

SECTION 3

Experimental Procedures

Preparation of diiodo (4), triiodo (7), and tetraiodo (8) cubane-1,4-bisamides

A solution of lithium tetramethylpiperide was prepared by adding slowly at -45°C under argon a solution of *n*-BuLi in hexane (18.0 ml, 27.0 mmol) to a stirred solution of tetramethylpiperidine (4.62 ml, 27.4 mmol) in 20 ml of dry THF (freshly distilled from benzophenone ketyl). The cooling bath was removed, and the reaction mixture was allowed to come to 0°C (15 min) and held there for 10 min longer. Anhydrous mercuric chloride (1.12 g, 4.11 mmol) and finely ground 1,4-bis(*N,N*-diisopropylaminocarbonyl)cubane (0.491 g, 1.37 mmol) were added together (one portion) maintaining the inert atmosphere. The reaction mixture was stirred at 0°C for 4 hours, then iodine (11.16 g, 41.1 mmol) was added in several portions, keeping the mixture cooled (the initial reaction is very exothermic). After stirring overnight at room temperature, the reaction was quenched with water at 0°C and diluted with 50 ml of chloroform. The organic layer was washed with 5% HCl solution (3 x 30 ml), with an aqueous solution of sodium sulfite (3 x 30 ml), and then with brine (2 x 30 ml), and dried over sodium sulfate. The solvent was removed under reduced pressure leaving a brown residue. From the NMR of this crude reaction the ratio of di:tri:tetra iodide was estimated as 57:37:6. This residue was chromatographed on a Chromatotron (4 mm silica gel rotor dried overnight at 80°C) using gradient dichloromethaneethyl acetate as eluent. The

separation afforded the following products without any evidence of starting material:.

2,7-Diodo-1,4-bis(N,N-diisopropylaminocarbonyl)cubane 4 (355 mg): mp 242-244°C (dec); IR (CHCl₃) ν 1630 cm⁻¹ (CO); (500 MHz, CDCl₃) δ 1.33 (12H, d, J = 6 Hz); 1.47 (12H, d, J = 6 Hz); 3.42 (2H, heptet, J = 6 Hz); 3.51 (2H, heptet, J = 6 Hz); 4.56 ppm (4H, s).

2,3,7-Triiodo-1,4-bis(N,N-diisopropylaminocarbonyl)cubane 7 (67 mg): mp 197-199°C (dec); PMR (500 MHz, CDCl₃) δ 1.15-1.50 (24H, m); 3.38 (2H, heptet, J = 6 Hz); 3.57 (2H, heptet, J = 6 Hz); 4.60 (1H, dd, J = 2, 3 Hz); 4.60-4.65 ppm (2H, ddd, J = 2, 3, 6 Hz).

2,3,6,7-Tetraiodo-1,4-bis(N,N-diisopropylaminocarbonyl)cubane 8 (11 mg): mp 250-260°C (dec); PMR (500 MHz, CDCl₃) δ 1.31 (12H, d, J = 6 Hz); 1.41 (12H, d, J = 6 Hz); 3.39 (2H, heptet, J = 6 Hz); 3.56 (2H, heptet, J = 6 Hz); 4.74 ppm (2H, s).

Preparation of dicadmium intermediate from cubane bisamide.

Finely powdered cubane-1,4-bisamide (50 mg, 0.14 mmol) and finely ground dry CdCl₂ (Aldrich, not dried further; 104 mg, 2 equivalents per amide group) were added to 2.5 mmol of LiTMP (9 equivalents of base/amide group) in THF at 0°C. After 10 min, the ice bath was removed and the reaction mixture was stirred an additional 45 min as it warmed to room temperature. The successful formation of the bisamide-dicadmium intermediate was demonstrated by quenching the reaction mixture with I₂ (0.5 g) at 0°C and allowing the mixture to stir overnight. On work-up (see procedure for the mercury case above) there was obtained a mixture of bisamide-moniodide and bisamide-diiodide in the ratio of about 1:10 as determined by PMR.

Preparation of Grignard derivative of cubane bisamide.

Finely powdered cubane-1,4-bisamide (20 mg 0.06 mmol) and $\text{MgBr}_2 \cdot \text{OEt}_2$ (Aldrich, 57 mg, 0.22 mmol) were added to the usual THF solution of LiTMP (0.9 mmol) at room temperature. The reaction mixture was stirred for 1.5 h, then quenched with elemental iodide. After stirring an additional few minutes the reaction mixture was worked-up as described for the mercury case. Bisamide monoiodide was the major product, obtained along with a few percent each of diiodide 4 and the starting material.

1,4-Bis(N,N-diisopropylcarboxamido)-2,7-dibenzoylcubane 10

A. Preparation of Anhydrous ZnCl_2 .

Commercial "anhydrous" ZnCl_2 was placed in a sublimator and heated under high vacuum (<10 mtorr) with a Bunsen burner for 15 min. The gray melt solidified to a hard gray mass on cooling. This process was repeated twice more, after which an appreciable amount of material had collected on the water-cooled cold finger. For the present purpose, either the bulk material or the sublimed ZnCl_2 can be used; both are dry. Dry ZnCl_2 is exceedingly hygroscopic and even brief exposure to atmospheric moisture must be carefully avoided. The sublimator, closed off under vacuum, was therefore transferred to a dry box before opening. An appropriate quantity of ZnCl_2 was weighed out and transferred to an amber bottle. The bottle was then tightly stoppered with a rubber septum and removed from the dry box. At the bench, dry THF was added via syringe to make a nearly saturated solution (ca. 0.35M). The dissolution of ZnCl_2 was greatly facilitated by sonication. (The punctured septum was covered by another septum when not in use.) Such solutions, stored at room temperature in double septum capped bottles under a positive pressure of a argon, showed no noticeable change in their performance over a period of two months.

B. Zincation of cubane-1,4-bisamide. Formation of 10

A 250 ml, 3-necked flask containing a magnetic stirrer and equipped with a septum inlet, gas inlet and thermometer was flame dried in vacuo, filled with argon, and then cycled several times between vacuum and the argon atmosphere. The flask was maintained under a positive argon pressure for the remainder of the experiment. THF (distilled from benzophenone ketyl; 40 ml) and tetramethylpiperidine (Aldrich, redistilled under N_2 ; 12.75 ml, 75.4 mmol) were added via syringe, and the stirred solution was cooled to ca $-40^\circ C$ (internal) in an acetonitrile/dry ice bath. *n*-BuLi (Aldrich, 29.5 ml of 2.55 M solution in hexanes, 75.4 mmol) was added dropwise over about 7 min, such that the exothermic reaction did not drive the internal temperature about $-20^\circ C$. After the addition was completed, the cooling bath was removed. The temperature rose to ca. $0^\circ C$ over 10 min; the flask was then immersed in an ice/ H_2O bath for an additional 10 min to complete the formation of LiTMP. The solution of LiTMP thus prepared was cooled to below $-15^\circ C$ in an ice/MeOH bath. A solution of anhydrous $ZnCl_2$ (prepared as described, 20 ml of 0.35 M solution in THF, 7 mmol) was added via syringe, followed by finely powdered cubane-1,4-bisamide (1.50 g, 4.19 mmol). The bisamide dissolved within 15 min. After 20 min, another equal-sized portion of $ZnCl_2$ solution was added. The reaction mixture was stirred a further 20 min at $-15^\circ C$. The ice/MeOH bath was then replaced with an ice/ H_2O bath, and the homogeneous solution was stirred 4-6 h at $0^\circ C$. (The metalation does not proceed correctly if the reaction mixture is warmed to room temperature.) The metalation was monitored by the iodination of aliquots as described for the mercury case. Conversion to the bisamide-dizinc intermediate 9 was complete within 6 h at $0^\circ C$. The reaction mixture was then cooled to $-40^\circ C$. Benzoyl chloride (freshly distilled from CaH_2 ($85^\circ/40$ torr, 13.1 ml, 110 mmol) was added dropwise over 10 min. This addition was very exothermic and was done slowly enough that the temperature

of the reaction mixture remained below -20°C . Palladium(0) tetrakis(triphenylphosphine) 1.2 g, 1.0 mmol) was then added. The resulting dark slurry was allowed to come to room temperature and stirred overnight. The reaction mixture was diluted with CHCl_3 (250 ml) and washed (2 x 50 ml) with 10% aq NaOH, 1F H_2SO_4 , and finally once with saturated aqueous $(\text{NH}_4)_2\text{SO}_4$. The dried (Na_2SO_4) organic layer was stripped in vacuo to a dark, viscous oil which was applied to a column of silica gel (4 x 13 cm, 70-270 mesh). Elution with 400 ml of CH_2Cl_2 gave a red band containing benzoyl chloride and TMP derivatives; this was discarded. Elution with 600 ml of 20:5:75 (v/v) EtOAc:MeOH: CH_2Cl_2 gave a dark brown eluate of benzoylated cubyl bisamide. The brown solid residue after removal of solvents was crystallized from THF/pentane (1:1) to give the dibenzoylcubane 10 (710 mg, 31%). The mother liquor was chromatographed on silica gel (4 x 13 cm, 230-400 mesh) using a gradient elution from neat CH_2Cl_2 to 20% EtOAc in CH_2Cl_2 giving first the monobenzoyl compound (100 mg, dark oil homogeneous by TLC, but not purified further), followed by additional dibenzoylcubane 10 (240 mg, total 950 mg, 40%) and finally starting bisamide (70 mg, 5%). After recrystallization from the THF/pentane, dibenzoylcubane 10 had mp $197-202^{\circ}\text{C}$ (dec); PMR (CDCl_3 , 500 MHz) δ 7.83 (dd, $J = 8, 1$ Hz), 2H), 7.53 (tt, $J = 8, 1$ Hz), 7.46 (t, $J = 8$ Hz, 2H), 4.80 (s, 4H), 3.29 (heptet, $J = 6$ Hz, 2H), 3.09 (heptet, $J = 6$ Hz, 2H), 1.50 (d, $J = 6$ Hz, 12H), 1.20 ppm (d, $J = 6$ Hz, 12H); CMR (CDCl_3) δ 195.3, 166.3, 134.1, 133.7, 128.8, 128.5, 61.7, 60.8, 49.0, 47.1, 45.9, 21.3, 19.8 ppm; IR ν 1657 (s), 1621 cm^{-1} (s); MS (CI, isobutane) m/e 567, $\text{P} + \text{H}^+$ for $\text{C}_{36}\text{H}_{43}\text{N}_2\text{O}_4$. 1,4-Bis(N,N-diisopropylcarboxamido)cubane-2,7-dicarboxylic acid, diphenyl ester 11 and derivatives.

A. Preparation of Trifluoroperoxyacetic Acid

A standard procedure was adapted. To a dry 25 ml, round-bottomed flask equipped with a magnetic stirrer and septum covered side arm was added a solution

of trifluoroacetic anhydride (freshly distilled, middle cut, 4.67 g, 22.7 mmol) in methylene chloride (12.0 ml). The flask was immersed in an ice water bath. To the stirred, cold solution was added 90% hydrogen peroxide (FMC, 0.50 ml, 18.4 mmol) via syringe in one portion. The reaction mixture was stirred in the ice bath for 10 min, during which time it became homogeneous. The ice bath was then removed, and the solution was stirred an additional 10 min to complete the formation of peracid. The clear, colorless solution of trifluoroperoxyacetic acid thus produced (ca. 1.2 M, nearly anhydrous) was kept at ice temperature until use.

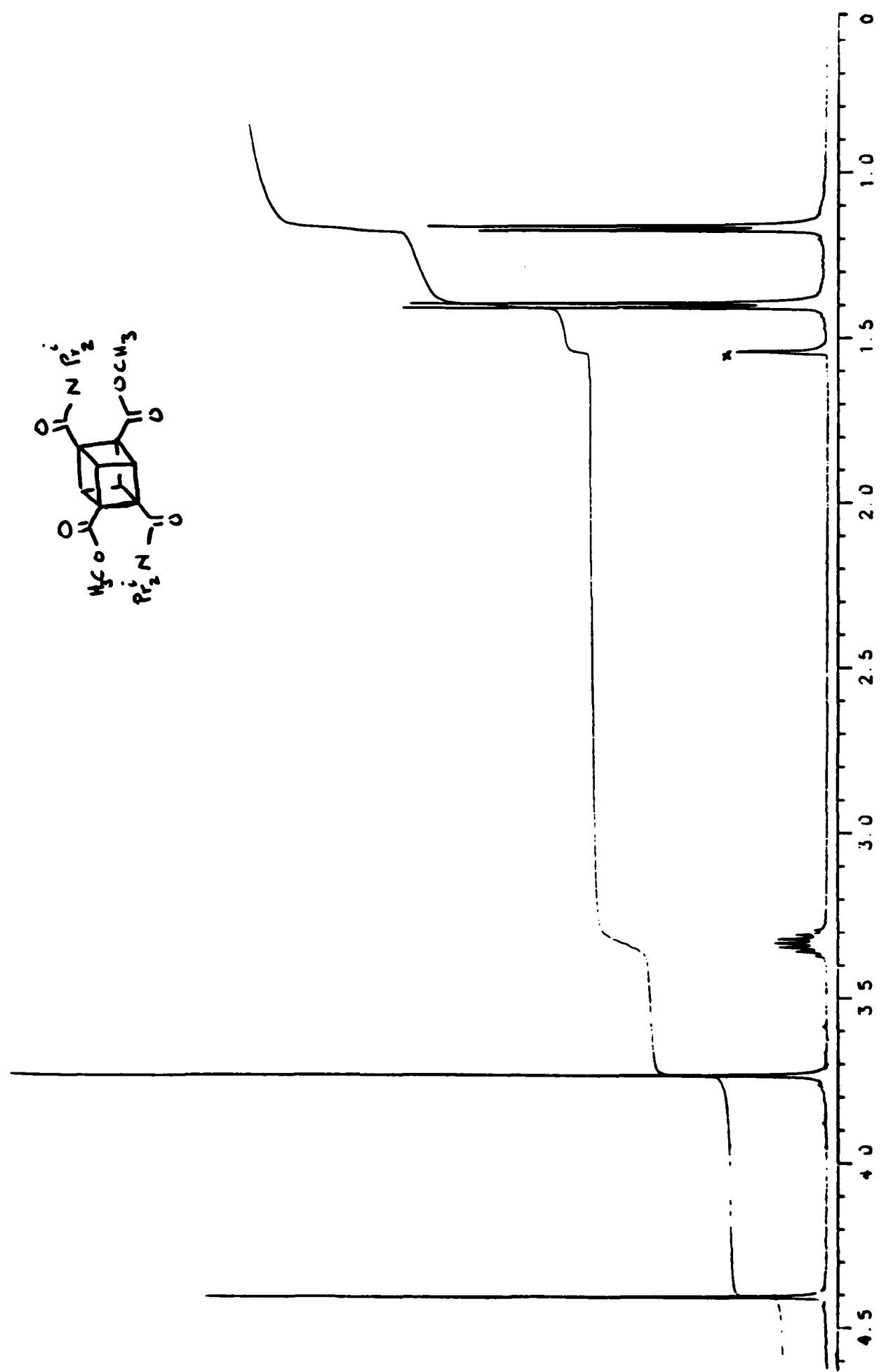
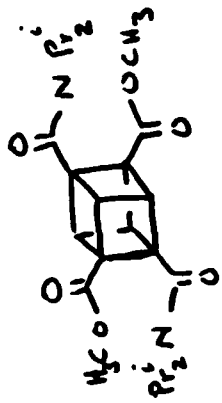
B. Baeyer-Villiger Oxidation

Diketone 10 (200 mg, 0.35 mmol) was dissolved in 5 ml of dry methylene chloride. Trifluoroperoxyacetic acid (1.2 ml of 1.2 M solution in CH_2Cl_2 , 2-fold excess) was added in one portion via syringe. (This solution is exceptionally corrosive; a clean, gas-tight syringe with teflon plunger fitted with a new 22 gauge needle was used; the syringe and needle were rinsed with a small portion of the peracid solution, which was discarded, prior to taking up the reagent for use. The syringe and needle were cleaned promptly.) The reaction mixture was stoppered tightly, stirred briefly, and allowed to stand at room temperature for 1 h. The solution was then cooled in an ice bath. 10 ml of aqueous phosphate buffer (pH 7) were added, followed by the dropwise addition of aq. Na_2SO_3 until the reaction mixture gave a negative starch/iodine test. The mixture was transferred to a separatory funnel. The organic layer was separated, and the aqueous layer extracted once with CHCl_3 . The combined organic phase was then washed once with brine, dried over Na_2SO_4 and stripped in vacuo to leave crude 11 as a pale yellow solid: PMR (CDCl_3 , 500 MHz) δ 7.38 (t, J = 7 Hz, 2H) 7.23 (t, J = 7 Hz, 1H), 7.22 (d, J = 7 Hz, 2H), 4.59 (s, 4H), 3.51 (heptet, J = 6 Hz, 2H), 3.35 (heptet, J = 6 Hz, 2H), 1.45 (d, J = 6 Hz, 12H), 1.22 ppm (d, J = 6 Hz, 12H); IR: ν 2967 (m), 1740 (complex), 1615 (complex), 1319 (s), 1261 (s), 1195 cm^{-1} (s).

C. Hydrolysis

The crude bisamide-diphenyl ester was taken up in 10% aq. NaOH (10 ml) along with a few ml of THF, and the mixture stirred at 70° for 6 h. The mixture was then cooled to below 10°C and acidified to pH 1 with conc. HCl. The precipitated bisamide-dicarboxylic acid was collected as an off-white powder, sparingly soluble in CHCl_3 . (Salting the filtrate and extraction with CHCl_3 did not give additional product). A small sample was purified by column chromatography on a minimum amount of silica gel. Elution with CHCl_3 gave the non-polar impurities. Further elution with 10:2:0.5 CH_2Cl_2 :EtOAc:MeOH gave the desired bisamide-diacid as a white solid; mp 220°C; PMR (CDCl_3) δ 4.59 (heptet, J = 6 Hz, 2H), 4.51 (s, 4H), 3.50 heptet, J = 6 Hz), 1.43 (d, J = 6 Hz, 12H), 1.37 ppm (d, J = 6 Hz, 12 H); IR ν 1709 (s), 1563 (s), 1306 cm^{-1} (s). The bisamide-diacid was esterified in methanol with ethereal diazomethane and the ester crystallized from THF/hexanes (1:1); see attached PMR.

500 MHz
CDCl₃



1-(N,N-Disopropylcarboxamido)-4-methylcubane

Thionyl chloride (35 ml) was carefully added to 2.0 g (12 mmol) of 4-methylcubane carboxylic acid.⁵ The reaction mixture was stirred at reflux for 3 h. The excess thionyl chloride was distilled from the reaction mixture under reduced pressure leaving an orange oil. The oil was dissolved in 15 ml of methylene chloride and then added dropwise under nitrogen to a -10°C solution of 5 ml diisopropylamine in 50 ml methylene chloride. The reaction mixture was stirred at -10° for 1 h and then at room temperature for 12 h; 20 ml of water was then added and the organic phase was separated and washed with 5% aqueous sulfuric acid, water, sat. aqueous copper sulfate, then water. Drying of the methylene chloride solution over sodium sulfate followed by solvent removal left the amide as a wet solid. Purification was accomplished by sublimation (90-100°C (0.1 torr)), then crystallization from hexane: mp 141.5-143.5; ¹H NMR (500 MHz, CDCl₃); δ 4.02 (br t, J = 5 Hz, 3H), 3.58 (b t, J = 5 Hz, 3H), 3.55 (heptet, J = 6 Hz, 1H), 3.28 (heptet, J = 6 Hz, 1H), 1.42 (d, J = 6 Hz, 6H), 1.28 (s, 3H), 1.18 ppm (d, J = 6 Hz, 6H); ¹³C NMR (50.3 MHz CDCl₃): δ 171.3 (s), 60.0 (s), 54.7 (s), 48.0 (d, J = 131 Hz), 46.4 (d, J = 154 Hz), 45.7 (d, J = 131 Hz), 46.4 (d, J = 154 Hz), 45.7 (d, J = 120 Hz), 45.6 (d, J = 154 Hz), 45.7 (d, J = 120 Hz), 20.6 (q, J = 126 Hz), 19.4 ppm (q, 127 Hz); IR (CCl₄) ν 1600 (s, CO), 1445 (s), 1370 (s), 1350 cm⁻¹ (s). MS (CI, isobutane) m/e 246, P+H⁺ for C₁₆H₂₃NO.

1-(N,N-Diisopropylcarboxamido)-2-iodo-4-methylcubane 13

A solution of lithium tetramethylpiperidide was made as follows: to a -70°C solution of 2.0 ml (11.6 mmol) distilled tetramethylpiperidine in 20 ml dry THF stirred under argon was added 8.2 ml (11.5 mmol) 1.4 M n-BuLi in hexanes dropwise at such a rate that the temperature of the solution did not rise above -60°C. After the addition, the reaction flask was placed in an ice bath and stirred at

0°C for 25 min. To this freshly made lithium tetramethylpiperidide solution was added 0.44 g (1.6 mmol) anhydrous mercuric chloride and 0.30 g (1.2 mmol) of the 4-methylcubane diisopropyl amide in one portion as the powdered solids. The dark brown solution was stirred at 0° for 10 min. The ice bath was removed; stirring was continued for 20 min as the mixture slowly warmed to room temperature. The reaction mixture was rechilled to 0° and quenched with 20 ml sat. aqueous ammonium chloride solution. The phases were separated, and the aqueous phase was extracted with 2 x 10 ml chloroform. Drying of the combined organic phase over sodium sulfate and concentration afforded 0.9 g of a dark brown, viscous oil which was partially purified by passing through a 3" column of silica gel with 15% v/v ethyl acetate in hexane. The resulting light brown oil was dissolved in 10 ml pyridine; 0.36 g (1.4 mmol) iodine was added, and the reaction mixture was stirred for 12 h. The pyridine was removed under reduced pressure; the residual black oil was diluted with 50 ml chloroform and then washed successively with 10% aqueous sodium sulfite, 10% aqueous hydrochloric acid, and water. Drying over sodium sulfate, concentration, and then filtration through a 3" plug of silica gel with 10% ethyl acetate in hexane gave 0.40 g of a pale yellow oil which was then chromatographed using a chromatotron (silica gel, 7% ethyl acetate in hexane) to yield 0.31 g of a clear oil which solidified after standing for 3 days. NMR analysis shows that this is the desired iodide contaminated with about 5% starting material: ¹H NMR (500 MHz, CDCl₃) δ 4.27 (brt, J = 5 Hz), 2H), 3.98 (m, 2H), 3.71 (m, 1H), 3.58 (heptet, J = 6 Hz, 1H), 3.37 (heptet, J = 6 Hz, 1H), 1.46 (d, J = 6 Hz, 6H), 1.40 (s, 3H), 1.31 ppm (d, J = 6 Hz, 6H).

1-(N,N-Diisopropylcarboxamido)-2-(m-chlorobenzoxy)-4-methylcubane 15

To a solution of 0.0526 g (0.14 mmol) cubyl iodide 13 in 7 ml of tetrachloroethane (filtered through a plug of activity 1 alumina) was added 0.050 g (0.20 mmol) of purified m-chloroperbenzoic acid. The reaction was stirred under

nitrogen for 2 h (+ 14) and then slowly heated to 80° over a 90 min period and held there for 5 h during which time an iodine color developed. The solvent was removed under reduced pressure to leave a oily solid which was thoroughly titrated with 5 ml of carbon tetrachloride. Concentration of the carbon tetrachloride solution gave 0.05 g of an oily solid which was purified by preparative TLC (silica, 15% ethyl acetate in hexane). The band at R_f 0.45 afforded 0.020 g (37%) of the m-chlorobenzoate 15: PMR (270 MHz, $CDCl_3$) δ 7.97 (m, 1H), 7.86 (br d, $J = 5$ Hz, 1H), 7.51 (m, 1H), 7.35, (t, $J = 5$ Hz, 1H), 4.07 (m, 4H), 3.60 (heptet, $J = 6$ Hz, 1H) 3.51 (m, 1H), 3.31 (heptet, $J = 6$ Hz, 1H) 1.43 (d, $J = 6$ Hz, 6H) 1.41 (s, 3H), 1.13 ppm (d, $J = 6$ Hz, 6H); (500 MHz, C_6D_6 , upfield region only) 4.03, (br t, $J = 5$ Hz, 2H) 3.98 (m, 2H), 3.53 (heptet, $J = 6$ Hz, 1H), 3.20 (m, 1H), 3.04 (heptet, $J = 6$ Hz, 1H), 1.60 (d, $J = 6$ Hz, 6H), 1.30 (s, 3H), 0.91 ppm (d, $J = 6$ Hz, 6H).

1-(N,N-Diisopropylcarboxamido)-2-chloro-4-methylcubane 17

Method A. - To a 0°C solution of 0.013 g (0.035 mmol) cubyl iodide 13 in 0.5 ml $CDCl_3$ in an NMR tube was added 0.015 g (0.054 mmol) of iodobenzene dichloride. Within a few second a purple color developed which slowly faded over 5 min to leave a pale orange solution. By NMR, the solution contains at least two new cubyl derivatives with the major one (16) displaying cubyl resonances of δ 4.85 (m, 2H), 4.37 (m, 2H), and 4.21 ppm (m, 2H). The reaction mixture was kept in the dark for 12 h at 0° and then 6 h at room temperature, then all the volatile material was removed under reduced pressure to leave primarily the cubyl chloride 17 as an orange oil: PMR (500 MHz, $CDCl_3$) δ 4.24 (br t, $J = 5$ Hz, 2H), 3.90 (m, 2H), 3.69 (m, 1H), 3.64 (heptet, $J = 6$ Hz, 1H), 3.50 (heptet, $J = 6$ Hz, 1H), 1.45 (d, $J =$ Hz, 6 H), 1.37 (s, 3H), 1.32 (d, $J + 6$ Hz, (6H); mass spec (CI^+ , isobutane) m/e (relative intensity) 280 (100), 281 (18), 282 (34) for $C_{16}H_{22}ClNO + H^+$.

Method B - To a room temperature solution of 0.0164 g (0.044 mmol) of the cubyl iodide 13 in 0.5 ml CDCl_3 was added 1 drop (excess) of t-butyl hypochlorite (Frinton). After standing at room temperature in the dark for 3 h the reaction mixture was diluted with 20 ml of chloroform and washed with 5% aqueous sodium sulfite. Drying (Na_2SO_4) and concentration of the chloroform solution gave 0.0124g (100%) of the title cubyl chloride, pure by PMR.

SECTION 4

References

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