Varian VXR 300S instrument operated in the pulsed Fourier transform mode and locked on solvent deuterium. Samples were prepared as 10–15% solutions in $CDCl_3$ (**4b** in DMSO-d_6) with 0.1% of TMS as internal reference in 5-mm-o.d. tubes.

One- and two-dimensional spectra were recorded under the following conditions. ^1H NMR: spectral width, 7500 Hz; acquisition time, 3.742 s; number of scans, 16/32/128; pulse width, 7 μs (35°); weighting function, line broadening of 0.8–1.0 Hz and gaussian apodization of 0.543 s; zero filling of 64 K; digital resolution, 0.23 Hz/point. ^{13}C NMR: spectral width, 16500 Hz, acquisition time, 0.8 s; delay time between pulses, 1 s; pulse width, 4 μs (30°); number of scans, 1024–4096; weighting function, line broadening of 0.6–1.0 Hz; decoupler, Waltz-16 modulated; zero filling of 64 K; digital resolution, 0.5 Hz/point. DEPT spectra: spectral width, 3614 Hz; acquisition time, 0.8 s; delay time between pulses, 1.5 s; pulse width, 12 μs (90°); pulse width of decoupler, 18 μs (90°); number of scans, 128/256/512; decoupler, Waltz-16 modulated; weighting function, line broadening of 1.0 Hz. Two-dimensional ^1H–^{13}C heteronuclear correlation spectra, ^{13}C dimension: spectral width, 3766 Hz; acquisition time, 0.8 s; pulse width, 12 μs (90°); delay time between pulses, 1.5–2.0 s; number of scans, 512/1024; number of increments; 32/64. ^1H dimension: pulse width, 18 μs (90°); decoupler gated on during acquisition and off during delay; decoupler, Waltz-16 modulated. Data processing, zero filling: ^1H dimension, 2 K and ^{13}C dimension, 0.5 K. Weighting functions: ^1H dimension, sine bell of 0.034 s, and ^{13}C dimension, sine bell of 0.020 s.

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Registry No. **1a**·HCl, 135625-93-3; **1b**·HCl, 135625-94-4; **1c**·HCl, 135625-95-5; (*R,S*)-**2a**·HCl, 135625-96-6; (*R,S*)-**2b**·HCl, 135625-97-7; (*R,S*)-**2c**·HCl, 135625-98-8; (*R,R*)-**3a**·HCl, 135626-02-7; (*R,R*)-**3b**·HCl, 135626-03-8; (*R,R*)-**3c**·HCl, 135626-04-9; **4a**·HCl, 135625-99-9; **4b**·HCl, 135626-00-5; **4c**·HCl, 135626-01-6.

Supplementary Material Available: Tables S1 (dihedral angles), S2 (calculated vicinal coupling constants for compounds **1a–4a** from the Altona and Osawa equations), S3 (^{13}C equatorial substituent parameters in 3-(alkylthio)-substituted *N*-methylpiperidinium chlorides), and S4 (^{13}C induced shift contributions of a ring quaternary nitrogen in substituted cyclohexanes) (4 pages). Ordering information is given on any current masthead page.

Systematic Substitution on the Cubane Nucleus: Steric and Electronic Effects

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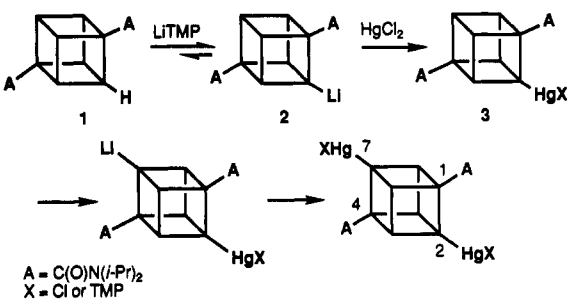
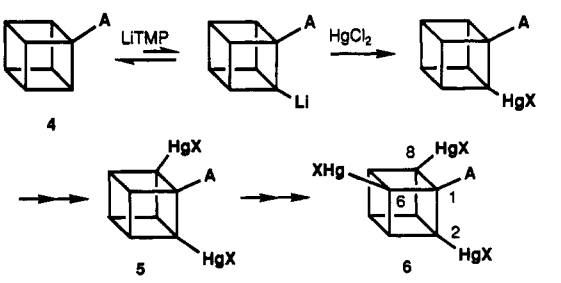
Effective methodology for the synthesis of cubanes with novel substitution patterns is presented. The use of an electron-withdrawing group to accelerate ortho-metalation of amide-activated cubanes is described, as is the effect of the steric bulk of the activating group on the degree of ortho-metalation.

In previous work from this laboratory it was shown that the ortho-metalation process so well-known in aromatic chemistry could be extended to certain strained, saturated systems like cubane and cyclopropane.[1] This discovery has led to novel and useful methodology for systematic substitution on such compounds. For example (Scheme I), the activation provided by the *N,N*-diisopropylcarbamoyl groups on the 1,4-disubstituted cubane **1** permits a strong base like lithium tetramethylpiperidide (LiTMP) to remove a proton ortho to one amide group, giving the lithiated cubane **2**. When there are no amide groups (cubane itself) only very little deprotonation occurs.[1a] The amide adjacent to the lithiated position assists ortho-metalation, presumably as it does in aromatic cases.[2] The remote amide group (position 4) stabilizes the lithiated cubane significantly via its general electron-withdrawing inductive effect; without it the equilibrium is much less (about $^1/_{25}$) to the right.[1a] The reaction can be drawn

Scheme I



Scheme II



completely over to a metalated species by coupling the first equilibrium step with a transmetalation process in which the cubyl lithium is converted into a far less polar and

(1) (a) Eaton, P. E.; Castaldi, G. *J. Am. Chem. Soc.* **1985**, *107*, 724. (b) Eaton, P. E.; Daniels, R. G.; Casucci, D.; Cunkel, G. T. *J. Org. Chem.* **1987**, *52*, 2100. (c) Eaton, P. E.; Cunkel, G. T.; Marchioro, G.; Martin, R. M. *J. Am. Chem. Soc.* **1987**, *109*, 948. (d) Eaton, P. E.; Higuchi, H.; Millikan, R. *Tetrahedron. Lett.* **1987**, *28*, 1055.

(2) (a) For use of a tertiary amide as a directing group in aromatic ortho-metalations, see: Beak, P; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34 and references cited therein. (b) The role of the directing group is complex. Both inductive and coordinating effects are relevant. For a recent review and key references, see: Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. See also refs 5 and 6.

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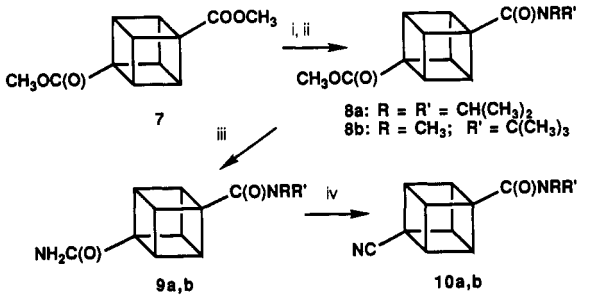
Scheme III[a]



[a] Key: (i) NaOH, THF, 95% yield; (ii) $(COCl)_2$, CH_2Cl_2; for **8a**, $(i\text{-Pr})_2NH$, CH_2Cl_2, 99%; for **8b**, Me(*t*-Bu)NH, CH_2Cl_2, 98%; (iii) NH_4OH, 95%; (iv) $SOCl_2$/DMF/TMEDA, $CHCl_3$, 95%.

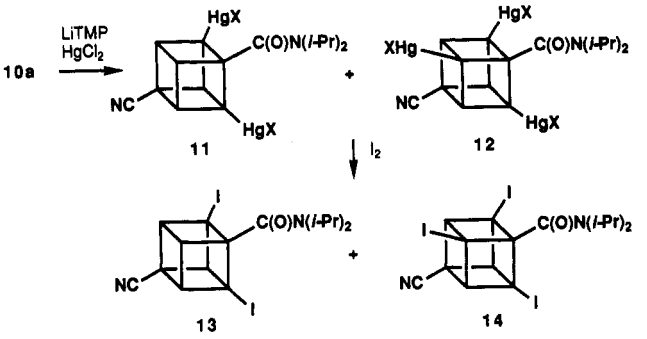
more stable species; e.g., the cubyl mercurial **3**. Once this has occurred a second lithiation/transmetalation is possible. Simple electrostatic considerations dictate its positioning. Thus, the disubstitution process on cubanes with two *equivalent* activating groups placed 1,4 on the nucleus always leads to 1,2,4,7-tetrasubstituted cubanes.

A different disubstitution pattern is obtained when there is only one activating group. Reactions (Scheme II) of monoamide **4** give, in addition to monometalated product, about 15% conversion to the 2,6-dimercuriated cubane **5** and a trace of the 2,6,8-trimercuriated compound **6**.[1a] (These mercurials, as well as those mentioned later, were converted to the corresponding iodides for characterization; the ^{1}H-NMR couplings clearly establish the substitution pattern.) Increasing the reaction time or the severity of reaction conditions is ineffective in increasing conversion to these desirable polysubstituted cubanes; unfortunately, the base (LiTMP) and the solvent (THF) are not mutually compatible over longer periods or higher temperatures.[1d] The reactions of 1,4-diamide **1** are much faster than those of monoamide **4**, reflecting the activating/stabilizing effect of the additional electron-withdrawing group. But the second amide redirects the course of substitution, and the new groups are introduced at the 2 and 7 positions.

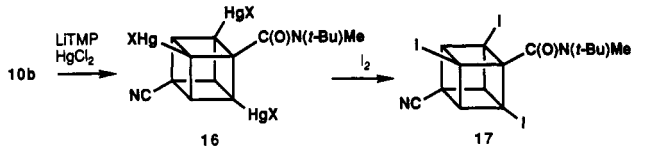
We sought a method to enhance the 2,6-di- and 2,6,8-trisubstitution processes. These should be preferred if there were a group at position 4 which was powerfully electron-withdrawing but less effective than an amide at activating/stabilizing metalation at a vicinal ortho position. Thinking that the linear cyano group might fit these requirements reasonably well,[3] we examined the metalation chemistry of 4-cyano-1-(*N*,*N*-diisopropylcarbamoyl)cubane (**10a**). This was prepared from 1,4-dicarbomethoxycubane (**7**) in 85% overall yield (Scheme III). Only the dehydration of the primary amide merits comment here. Reaction of **9a** with refluxing thionyl chloride or with thionyl chloride in DMF results in its decomposition, probably by way of the iminium chloride of the tertiary amide group. This is avoided if TMEDA is added in excess. The "protection" mechanism is not understood. TMEDA seems special; if triethylamine is used instead, substantial decomposition occurs.

Reaction of cyanoamide **10a** with LiTMP/$HgCl_2$ under conditions like those used earlier for the metalations of **1** and **4** produces a mixture of di- and trimercuriated compounds (**11**, **12**, Scheme IV). Treatment of the crude reaction mixture with iodine/water gives the corresponding di- and triiodocubanes **13** and **14**, isolated overall in 56%

Scheme IV

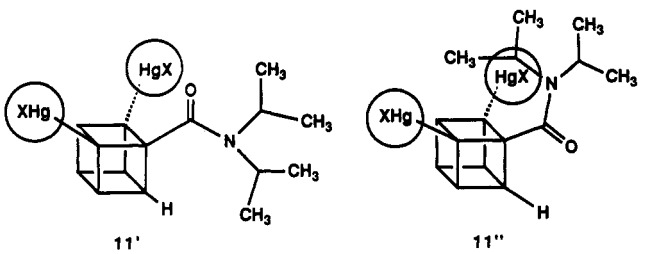


Scheme V



and 15% yield, respectively.[4,9c] Multimetalation of **10a** is quicker and more efficient than that of monoamide **4**. Clearly, as hoped, the cyano group substantially enhances the reaction rate. Nonetheless, the yield of the trisubstituted compound could not be increased above 15%, even when the reaction time was lengthened or the base supply "refreshed" midreaction.

It is useful, as will be seen, to speculate on the geometry of the most stable conformer of **11**, the precursor for the trimetalated intermediate **12** in Scheme IV. In this conformation (something like **11'**) the two big mercury substituents and the bulky isopropyl groups will be well apart; the amide oxygen will be away from the remaining proton ortho to the amide group. Such a conformation is probably exactly wrong; amide-activated metalation is thought to proceed through an arrangement in which the base, the amide oxygen, and the proton-to-be-removed are all nearby.[5] Furthermore, the amide stabilization of the ortho-metalated intermediate would clearly need a conformation in which the amide oxygen was coordinated with the metal.[6] Both roles require a conformation in which the amide oxygen faces the metalation site. Rotation to such a conformer, like **11''**, would bring about a steric clash between an isopropyl group and the mercury substituents.[7]



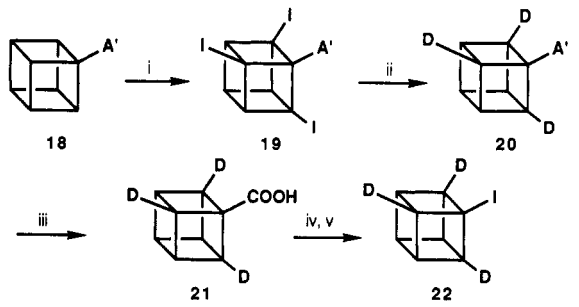
(3) This followed from an early observation of M. Maggini of this laboratory. As has been pointed out, the cyano group lacks lone electron pairs well-situated for coordination (Krizan, T. D.; Martin, J. C. *J. Org. Chem.* **1982**, *47*, 2681).

(4) That substitution had occurred ortho to the amide group, rather than adjacent to the nitrile followed from X-ray structures of derived materials: Eaton, P. E.; Xiong, Y.; Yang, C. 196th ACS National Meeting, Los Angeles, CA, Sept 25–30, 1988; Abstr. ORGN 129. We are grateful to Dr. Richard Gilardi (Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, D.C.) for these X-ray determinations.

(5) The amide oxygen is probably complexed with the incoming base and helps organize an effective arrangement for deprotonation; for analogy, see; (a) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. (b) Hay, D. R.; Song, Z.; Smith, S. G.; Beak, P. *J. Am. Chem. Soc.* **1988**, *110*, 8145.

(6) This has always been taken for granted, and surely rightly; see, Puterbaugh, W. H.; Hauser, C. R. *J. Org. Chem.* **1964**, *29*, 853. Fuhrer, W.; Gschwend, H. W. *J. Org. Chem.* **1979**, *44*, 1133.

Scheme VI[a]



A' = C(O)N(*t*-Bu)Me

[a] Key: (i) BrMgTMP/$HgCl_2$, THF, reflux; I_2/THF/H_2O; (ii) $(n\text{-Bu})_3SnD$/AIBN, benzene, reflux; (iii) 3 N HCl, 70 °C; (iv) $(COCl)_2$; (v) *N*-hydroxy-2-pyridinethione sodium salt/CF_3CH_2I, tungsten light, benzene, reflux.

Undoubtedly the concentration of 11″ would be low, and this would slow the third metalation step.

The steric interactions which interfere with amide activation/stabilization for metalation of **11** would be lessened were one of the *N*-alkyl groups reduced in size. Therefore, we prepared the *N*-methyl-*N*-*tert*-butylcarboxamide **10b** (Scheme III), a less-hindered amide. The methyl group, unlike the larger isopropyl group, can fit comfortably between the two mercury substituents in a conformation like 11″.[8] Treatment of **10b** with LiTMP/$HgCl_2$ under the same conditions used for metalation of **10a** gives the trimercuriated compound **16** (Scheme V). Iodination of the crude reaction mixture gave triiodide **17** in 70% isolated yield! *Once steric congestion is diminished, an amide substituent can effectively assist sequential metalation of all three positions ortho to it on the cubane skeleton.*

Attempts to overcome the steric effects inhibiting triple metalation of the hindered amide **10a** by increasing the reaction temperature and/or time were unsuccessful. LiTMP is unstable in THF above 0 °C. Recently, as discussed in detail elsewhere,[9] we discovered that amidomagnesium bases such as tetramethylpiperidinomagnesium bromide (TMPMgBr) are strong enough to remove (in part) an amide-activated cubyl hydrogen. *Such bases are stable even in refluxing THF.* Indeed, treatment of the *N*,*N*-diisopropylcarboxamide **10a** with TMPMgBr and $HgCl_2$ in refluxing THF results in trimercuriation by way of intermediate Grignards and transmetalation. Iodination of the crude product gives triiodide **14** in 88% yield. Amide **10b** behaves similarly. Even (and most conveniently) monoamides **4** and **18**, *unaided* by an electron-withdrawing group in the 4 position, are easily trimetalated (see Scheme VI).

The *N*,*N*-diisopropylcarbamoyl group has been found to be the best activating group all-around for ortho-metalation of the cubane nucleus.[10] This group is extremely stable to nucleophilic attack and survives treatment with very strong bases. This very property, however, also makes it absolutely unyielding toward hydrolysis after it has served its purpose for ortho-activation. Reitz and Massey have shown that the *N*-*tert*-butyl-*N*-methylcarbamoyl group has sufficient stability toward bases, works well as an ortho-activating group in the synthesis of substituted benzenes, and can be hydrolyzed to the free carboxylic acid.[11a] Bottaro, Penwell, and Schmitt have employed the *N*-*tert*-butyl-*N*-ethylcarbamoyl group similarly for preparation of substituted cubanes and subsequent liberation of the corresponding acid.[11b] This is very convenient.

Our work with Professor Michl on the cubyl radical required the preparation of 2,6,8-trideuteriocubyl iodide.[12] Using the methods and ideas reported here, we have been able to prepare this specifically labeled cubane (Scheme VI). Trimetalation of **18** followed by reaction with iodine gives the triiodoamide **19**. Reduction with $(n\text{-Bu})_3SnD$ introduces the three required deuterium atoms. Hydrolysis of the *tert*-butylmethyl amide at 70 °C with 3 N hydrochloric acid frees the carboxylic acid **21**. Barton radical decarboxylation/iodination,[13] as modified in this laboratory,[14] converts **21** to the desired C_{3v} trideuterioiodocubane **22**: ^{1}H-NMR δ 4.21 (m, 1 H), 4.18 ppm (m, 3 H).

Experimental Section

All experiments involving alkyllithium or magnesium bases were conducted under nitrogen. Flash chromatography was done on Merck silica gel 60 (230–400 mesh). Analytical TLC separations were visualized by immersion in 5% phosphomolybdic acid solution in EtOH followed by heating in air. Additional procedural details are given elsewhere.[14]

Most cubane compounds are quite stable. Nonetheless, as they are all high-energy materials it is prudent and appropriate to run all reactions thereof behind safety shields. Crude reaction products should not be concentrated at elevated temperature, particularly in the presence of acidic contaminants.

1-(*N*,*N*-Diisopropylcarbamoyl)-4-carbomethoxycubane (8a). A solution of methanolic sodium hydroxide (10 mL, 2.5 M, 25 mmol) was added dropwise to a solution of 1,4-bis(methoxycarbonyl)cubane (EniChem Synthesis, 5.6 g, 25 mmol) in THF (150 mL) at room temperature. The mixture was stirred overnight then taken in vacuo without heating to dryness. Water (60 mL) was added and the mixture extracted with chloroform (3 × 25 mL). The extract afforded a little unchanged 1,4-diester (49 mg, ~1%). The aqueous layer was acidified to pH 3 (not lower) with concd hydrochloric acid and extracted with chloroform (3 × 50 mL). The extract was dried ($MgSO_4$) and taken to dryness at room temperature under vacuum to give 4-(carbomethoxy)cubane-1-carboxylic acid as a colorless solid (5.0 g, 95%); mp 182–183 °C.[16] Material was accumulated from additional runs. Oxalyl chloride (14 mL, excess) was added to a suspension of 14.0 g of the half-acid ester in CH_2Cl_2 (120 mL) at room temperature. The mixture was stirred for 50 min. The solvent and excess reagent were evaporated, and the residue was dissolved in CH_2Cl_2 (120 mL). The solution was cooled to 0 °C. Diisopropylamine (20 mL) was added dropwise. The reaction mixture was stirred at room temperature for 1 h and then diluted with $CHCl_3$ (200 mL), washed with 2 N aqueous HCl, saturated aqueous $NaHCO_3$, water,

(7) Steric interactions like that in 11′ between the bulky isopropyl group and groups ortho to the amide will be somewhat relieved by pyramidalization (rather than planarization) at nitrogen. This should reduce the rotational barrier about the amide C–N bond. This barrier (ΔG^*) in **10a**, **13**, and **14** (in DMSO-d_6) was calculated (see: Sandstrom, J. *Dynamic NMR Spectroscopy*; Academic Press: New York, 1982; p 96) from the measured coalescence temperature of the methyl resonances of 78.5, 62.5, and 38.3 °C, respectively, and indeed decreases with increases in steric crowding: **10a**, 17.4 ± 0.1; **13**, 16.9 ± 0.1; **14**, 15.3 ± 0.1 kcal/mol.

(8) The *tert*-butyl group will then be out of the way in such a arrangement, free of steric problems. Interestingly, the proton and carbon NMR spectra of **10b** show resonances for only one of the two possible amide isomers about the C-N bond. Presumably, the large *tert*-butyl group stays cis to the oxygen and away from the bulky cubane nucleus.

(9) (a) Eaton, P. E.; Xiong, Y.; Lee, C. H. *J. Chin. Chem. Soc.* **1991**, *38*, 303. (b) Eaton, P. E.; Lee, C. H.; Xiong, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8016. (c) Eaton, P. E.; Xiong, Y.; Gilardi, R. Manuscript in preparation.

(10) Martin, R. Ph.D Thesis, The Univesity of Chicago, 1987.

(11) (a) Reitz, D. B.; Massey, S. M. *J. Org. Chem.* **1990**, *55*, 1375. (b) Schmitt, R. J.; Bottaro, J. C.; Penwell, P. E. *Ibid* **1991**, *56*, 1305.

(12) McKinley, A. J.; Michl, J.; Eaton, P. E.; Zhou, J. P. Manuscript in preparation.

(13) (a) Barton, D. H. R.; Larcher, B.; Zard, S. *Tetrahedron* **1987**, *43*, 4321. (b) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron Lett.* **1983**, *24*, 4979.

(14) Tsanaktsidis, J.; Eaton, P. E. *Tetrahedron Lett.* **1989**, *30*, 6967.

(15) Eaton, P. E.; Stössel, D. *J. Org. Chem.* **1991**, *56*, 5138.

(16) This procedure for the half-acid ester was developed by J. Tsanaktsidis and C.-X. Yang.

and brine, and then dried over Na_2SO_4. Removal of solvent left 15.3 g (99%) of white solid **8a**. Crystallization from hexane gave an analytical sample: mp 109–110 °C; ^{1}H-NMR δ 4.19–4.16 (m, 6 H), 3.70 (s, 3 H), 3.46 (sept, J = 7 Hz, 1 H), 3.29 (sept, J = 7 Hz, 1 H), 1.41 (d, J = 7 Hz, 6 H), 1.20 ppm (d, J = 7 Hz, 6 H); ^{13}C-NMR δ 172.20, 170.03, 59.34, 54.64, 51.56, 48.40, 46.91, 46.18, 45.85, 20.94, 20.46 ppm; IR ν 3002 (s), 2981 (s), 2970 (s), 1718 (s), 1617 (s), 1450 (s), 1346 (s), 1255 (s), 1205 (s), 1084 (s) cm^{-1}. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.68; H, 8.04; N, 4.86.

1-(*N*-*tert*-Butyl-*N*-methylcarbamoyl)-4-carbomethoxycubane (8b). The same procedure was used as described for **8a** substituting methyl *tert*-butylamine. Crystalline **8b** was obtained in 98% yield: mp 113–114 °C; ^{1}H-NMR δ 4.17 (s, 6 H), 3.68 (s, 3 H), 2.75 (s, 3 H) 1.40 ppm (s, 9 H); IR ν 2989, 1725, 1620, 1381, 1322, 1200, 1089 cm^{-1}.

4-Carbamoyl-1-(*N*,*N*-diisopropylcarbamoyl)cubane (9a). A suspension of **8a** (15.0 g) in 200 mL of 28% aqueous NH_4OH was stirred at room temperature for 20 h and then filtered. The solid was washed with water and dried under vacuum at 65 °C for 6 h to give 11.0 g of **9a**. The aqueous filtrate was extracted with chloroform (3X). The extract was washed with water (2X) and brine and then dried over Na_2SO_4. Evaporation left another 1.3 g of crystalline **9a**, for a total of 12.3 g (87%). Crystallization from acetonitrile gave an analytical sample: mp 227–228 °C; ^{1}H-NMR δ 5.44 (br s, 2 H), 4.17 (s, 6 H), 3.47 (sept, J = 7 Hz, 1 H), 3.32 (sept, J = 7 Hz, 1 H), 1.43 (d, J = 7 Hz, 6 H), 1.21 (d, J = 7 Hz, 6 H) ppm; ^{13}C-NMR δ 173.93, 169.99, 59.47, 56.15, 48.49, 46.60, 46.29, 45.91, 20.99, 20.49 ppm; IR ν 3354 (s), 3162 (s), 2975 (s), 1677 (s), 1608 (s), 1413 (s), 1348 (s) cm^{-1}. Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.16; H, 8.06; N, 10.27.

4-Carbamoyl-1-(*N*-*tert*-butyl-*N*-methylcarbamoyl)cubane (9b). This was synthesized in 89% yield in the same way as **9a**: mp 200–207 °C (dec; ^{1}H-NMR δ 5.38 (br, 2 H), 4.19 (m, 3 H), 4.15 (m, 3 H), 2.77 (s, 3 H), 1.41 ppm (s, 9 H); IR ν 3345, 3179, 3001, 2978, 1652 (s), 1629 (s), 1618 (s), 1421, 1380, 1364 cm^{-1}.

4-Cyano-1-(*N*,*N*-diisopropylcarbamoyl)cubane (10a). A stirred solution of **9a** (2.78 g, 10.1 mmol) in $CHCl_3$ (100 mL), DMF (10 mL), and TMEDA (7 mL, 47 mmol) was cooled to −10 °C in an ice/acetone bath. Thionyl chloride (2.5 mL, 35 mmol) was added slowly enough so the reaction temperature could be kept below 0 °C. A white precipitate formed immediately. The cooling bath was removed, and the reaction mixture was stirred for 20 min, during which time the temperature rose to 20 °C. The mixture was poured onto 300 mL of cold hydrochloric acid (0.5 N). The mixture was extracted with $CHCl_3$ (3x). The cloudy extract was washed with hydrochloric acid (0.2 N) and brine and then dried (Na_2SO_4). The solvent was removed and the off-white solid residue dried under vacuum. Crystallization from hexane/ethyl acetate (1:1) afforded 2.08 g of white crystals in two crops. The residue from the mother liquor was flash chromatographed (hexane/ethyl acetate (3:1)) to give another 0.38 g, total 2.46 g (95%). An analytical sample was obtained by recrystallization from hexane/ethyl acetate: mp 173–174 °C; ^{1}H-NMR δ 4.30 (m, 3 H), 4.24 (m, 3 H), 2.86 (sept, J = 7 Hz, 1 H), 2.70 (sept, J = 7 Hz, 1 H), 1.40 (d, J = 7 Hz, 6 H), 1.20 (d, J = 7 Hz, 6 H) ppm; ^{13}C-NMR δ 168.92, 118.62, 59.38, 48.70, 47.95, 46.86, 46.01, 39.17, 21.00, 20.44 ppm; IR (KBr) ν 2216 (m), 1619 (s), 1447 (m), 1345 (m), 1215 (m) cm^{-1}. Anal. Calcd for $C_{16}H_{20}N_2O$: C, 74.94; H, 7.86; N, 10.93. Found: C, 75.00; H, 7.97; N, 10.94.

1-(*N*-*tert*-Butyl-*N*-methylcarbamoyl)-4-cyanocubane (10b). This was prepared using the same procedure as for **10a** in 89% yield: mp 189–190 °C; ^{1}H NMR δ 4.30 (s, 6 H), 2.74 (s, 3 H), 1.40 ppm (s, 9 H); ^{13}C NMR δ 170.27 (CO), 118.57 (CN), 60.17 (C), 56.74 (C), 47.84 (CH), 46.53 (CH), 38.93 (C), 30.98 (CH_3), 27.78 ppm (CH_3); IR ν 3005, 2974, 2224, 1618 (s), 1474, 1441, 1387 (s), 1361, 1234, 1207, 1145, 1055 cm^{-1}. Anal. Calcd for $C_{15}H_{18}ON_2$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.03; H, 7.27; N, 11.47.

Metalation/Iodination of 10a. Formation of 2,6-Diiodo-4-cyano-1-(*N*,*N*-diisopropylcarbamoyl)cubane (13) and 2,6,8-Triiodo-4-cyano-1-(*N*,*N*-diisopropylcarbamoyl)cubane (14). A solution of *n*-BuLi in hexanes (Aldrich, 13.4 mL, 33.6 mmol) was added to anhydrous TMPH (5.70 mL, 33.6 mmol) in THF (15 mL) cooled in a dry ice/acetone bath. During the addition the solution temperature (measured directly) was not allowed to exceed −45 °C. After the addition, the solution was warmed to −10 °C, stirred at that temperature for 10–20 min, and then transferred cold via cannula to a stirred mixture of **10a** (286 mg, 1.12 mmol) and $HgCl_2$ (1.93 g, 7.10 mmol) in THF (15 mL) at −13 °C. The resulting dark yellow solution was stirred for 40 min at −13 °C and then 1.5 h at 0 °C to form the mercuriated cubanes **11** and **12**. Iodine (10 g) dissolved in THF (20 mL) and water (5 mL) were added. This mixture was stirred at room temperature for 1 day and then extracted with chloroform. The extract was washed with $Na_2S_2O_3$, 0.1 N HCl, water, and then brine. Flash chromatography over silica gel with increasing amounts (10–25%) of ethyl acetate in hexane afforded first 120 mg (15%) of triiodo compound **14**: mp 210–215 °C dec; ^{1}H-NMR δ 4.66 (s, 3 H), 3.88 (br, 1 H), 3.43 (br, 1 H), 1.48 (br, 6 H), 1.38 (br, 6 H) ppm; ^{13}C-NMR δ 161.44 (CO), 114.86 (CN), 73.42 (C), 62.47 (CH), 48.44 (CH), 47.59 (CH), 39.09 (C), 28.54 (C), 23.43 (CH_3), 20.52 (CH_3) ppm; IR ν 2964 (m), 2924 (m), 2230 (m), 1623 (s), 1440 (m), 1364 (s), 1171 cm^{-1} (s); FAB MS m/e 634 (P^+). Anal. Calcd for $C_{16}H_{17}I_3N_2O$: C, 30.31; H, 2.70; N, 4.42. Found: C, 30.40; H, 2.69; N, 4.32. Later fractions contained 320 mg (56%) of the diiodo compound **13**: mp 220 °C dec; ^{1}H-NMR δ 4.6 (m, 4 H), 3.40 (m, J = 6 Hz, 2 H), 1.45 (d, J =7 Hz, 6 H), 1.34 (d, J = 7 Hz, 6 H) ppm; ^{13}C-NMR δ 163.49, 115.98, 66.20, 62.31, 54.83, 51.85, 48.14, 46.82, 39.93, 29.18, 21.98, 20.52 ppm; IR ν 2984 (m), 2225 (m), 1677 (s), 1445 (m), 1376 (m), 1365 (m), 1339 cm^{-1} (m); FAB MS m/e 508 (P^+). Anal. Calcd for $C_{16}H_{18}I_2N_2O$: C, 37.82; H, 3.57; N, 5.51. Found: C, 37.70; H, 3.41; N, 5.29.

Metalation/Iodination of 10b. The same procedure run with amide **10a** gave **17** in 70% isolated yield: mp 195 °C dec; ^{1}H-NMR δ 4.66 (s, 3 H), 2.97 (s, 3 H), 1.45 ppm (s, 9 H); ^{13}C-NMR δ 162.99, 114.83, 70.01, 62.04, 57.96, 39.50, 36.37, 27.63, 26.42 ppm; IR ν 2979, 2981, 2924, 2231, 1640 (s), 1470, 1375, 1171, 1062, 911, 730 cm^{-1}; MS (CI) m/e 621 (P^+ + 1). Anal. Calcd for $C_{15}H_{15}I_3N_2O$: C, 29.06; H, 2.44; N, 4.52. Found: C, 29.02; H, 2.43; N, 4.33.

2,6,8-Triiodo-4-cyano-1-(*N*,*N*-diisopropylcarbamoyl)cubane (14) via Ortho-Magnesiation. A solution of BrMgTMP in THF (16 mL, 7 mmol) was added to **10a** (59 mg, 0.23 mmol) and $HgCl_2$ (330 mg, 1.22 mmol). This solution was refluxed for 1 h and then cooled to 0 °C. A solution of iodine (4 g) in THF (8 mL) was added cautiously, followed by 5 mL of water. The mixture was stirred at room temperature for 3 days and then extracted with CH_2Cl_2. The extract was washed with 1 N HCl, aqueous Na_2SO_3 solution, and then brine. Flash chromatography on silica gel (ethyl acetate/hexanes (1:10 to 2:10)) gave 128 mg (88%) of **14** as a white solid.

2,6,8-Triiodo-1-(*N*-*tert*-*butyl*-*N*-methylcarbamoyl)cubane (19) via Ortho-Magnesiation. A mixture of (*N*-*tert*-butyl-*N*-methylcarbamoyl)cubane (510 mg, 2.35 mmol) and $HgCl_2$ (3.75 g, 13.8 mmol) was refluxed in a solution of BrMgTMP in THF (120 mL, 69 mmol) for 6 h (after 1 h there was still a substantial amount of dimetalated material). The reaction mixture was cooled to −10 °C; water (3 mL), chloroform (50 mL), pyridine (10 mL), and excess of iodine (30 g) were added. This purple solution was stirred at room temperature for 24 h. Workup as described for **14** gave 960 mg (69%) of triiodide **19** as a white, crystalline solid: mp 153–154 °C; ^{1}H-NMR δ 4.48 (d, J = 5.2 Hz, 3 H), 4.30 (q, J = 5.2 Hz, 1 H), 3.02 (s, 3 H), 1.47 ppm (s, 9 H); ^{13}C-NMR δ 164.03, 71.54, 62.46. 57.65, 46.58, 36.41, 31.40, 27.78 ppm; IR (KBr) ν 2978, 2956, 1621 (s), 1471, 1379, 1371, 1183, 739 cm^{-1}. Anal. Calcd for $C_{14}H_{16}I_3NO$: C, 28.26; H, 2.71; N, 2.35. Found: C, 28.50; H, 2.83; N, 2.29.

2,6,8-Trideuteriocubanecarboxylic Acid (21). Triiodide **19** (380 mg, 0.64 mmol) was refluxed for 6 h with Bu_3SnD (0.64 mL, 2.3 mmol, 99 atom % D) in dry benzene (10 mL) containing a catalytic amount of AIBN. The solvent was removed in vacuo at room temperature. Ethyl acetate (10 mL) and saturated aqueous KF solution (10 mL) were added to the oily residue. The mixture was stirred at room temperature for 12 h, and then the aqueous layer was extracted with ethyl acetate. The extract was dried (Na_2SO_4) and taken to dryness under vacuum. The crude residue was treated with 3 N HCl (20 mL) at 70 °C for 24 h. The mixture was cooled and extracted with CH_2Cl_2 (3 × 10 mL). Aqueous NaOH solution (5%, 20 mL) was added and the basic layer separated and taken at 0 °C to pH 2 with concd hydrochloric acid. The solution was extracted with ether (3 × 10 mL), and the extract was dried over $MgSO_4$ and taken to dryness. The

residue was crystallized from hexane to give 70 mg of **21** as white crystals (72% from **19**): mp 124–125 °C; ^{1}H NMR δ 10.88 (br 1 H), 4.01 ppm (m, 4 H); IR ν 3330–2358 (br), 2997, 2980, 1681 (s), 1423, 1317, 1173 cm^{-1}. The deuterium content at the labeled positions was estimated by NMR integration at >95%.

2,6,8-Trideuteriocubyl Iodide (22). Acid **21** (20 mg, 0.13 mmol) was dissolved in excess oxalyl chloride (0.5 mL) at room temperature and the solution gently refluxed for 1 h and then cooled to room temperature. Excess reagent was removed in vacuo at room temperature. The residue, crude acid chloride, was dissolved in dry CH_2Cl_2 (2 mL) and the solution added to a suspension of the sodium salt of *N*-hydroxypyridine-2-thione (40 mg, 0.26 mmol) in excess CF_3CH_2I (1 mL) containing a catalytic amount AIBN (cf. ref 14). This suspension was brought to reflux, irradiated with a 300-W tungsten lamp for 40 min, and then cooled to room temperature. The solvent and excess CF_3CH_2I were removed in vacuo (do not prolong pumping). The residue was extracted with pentane (3 × 1 mL). The extract was chromatographed on silica gel (70–230 mesh) with pentane to afford pure **22** (R_f = 0.60, 21 mg, 68%) as a white crystalline material: mp 32.0–33.0 °C; ^{1}H NMR δ 4.21 (m, 1 H), 4.18 ppm (m, 3 H); MS (EI) *m/e* 233 (weak), 127 (23), 106 (54), 79 (100), 52 (23). In the observed ^{1}H NMR spectrum the 3-hydrogen mutiplet at δ 4.33 ppm present in the spectrum of nondeuteriated material is missing entirely.

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Registry No. **1**, 94161-36-1; **7**, 29412-62-2; **7** monoester, 24539-28-4; **8a**, 130602-27-6; **8b**, 141807-74-1; **9a**, 141807-75-2; **9b**, 141807-73-0; **10a**, 130640-41-4; **10b**, 141807-72-9; **13**, 141807-76-3; **14**, 141807-77-4; **17**, 141807-78-5; **18**, 141807-79-6; **19**, 141807-80-9; **21**, 141807-81-0; **22**, 141807-82-1.

Notes

Electrophilic Fluorination of Pharmacologically Active 1,3-Dicarbonyl Compounds

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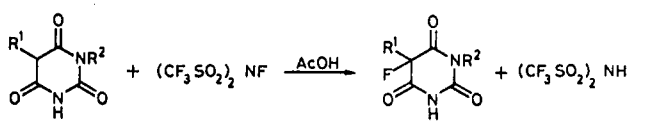
Compounds containing the N–F functionality are attracting increasing interest as stable, nonhygroscopic, and safe reagents for electrophilic fluorinations.

Sulfonimides[2-4] and related compounds[5] are particularly attractive with respect to other structural classes of products containing the N–F moiety[6-13] as they are endowed with a high reactivity, but at the same time they are easy to handle and can be stored for a long time without any deterioration.

The first perfluorinated compounds of this type were the *N*-fluoroperfluoroalkylsulfonimides[14,15] that we have synthesized and shown to work as efficient reagents for the fluorination of several kinds of substrates.[16-18]

Scheme I



2a-i 1 3a-i 4

Starting material	R^1	R^2	Isolated yield (%)
2a	H	H	88 (R^1=F in 3a)
2b	CH_3	H	92
2c	C_2H_5	H	89
2d	n-C_4H_9	H	90
2e	C_6H_5	H	91
2f	OCH_3	H	90
2g	CH_3	CH_3	92
2h	C_2H_5	CH_3	83
2i	C_6H_5	CH_3	91

In order to further study the synthetic potentials of *N*-fluorobis[(trifluoromethyl)sulfonyl]imide (**1**), we have examined the fluorination of several compounds endowed with useful pharmacological and therapeutic properties.

The substrates employed became a severe test of the selectivity and mildness of an electrophilic fluorinating agent, inasmuch as they bear several functional groups susceptible to electrophilic attack, acid- or base-catalyzed hydrolyses, oxidation, and rearrangement. The selectively fluorinated products that were isolated may be of interest in themselves.

Results and Discussion

When a suspension of 2,4,6-trihydroxypyrimidine **2a** was treated at room temperature with 2 equiv of the *N*-fluoroimide **1** a slightly exothermic reaction occurred and the corresponding 5,5-difluoro derivative **3a** was exclusively

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