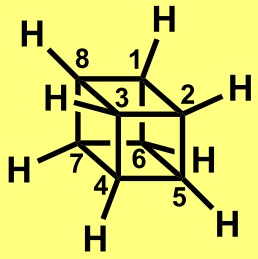
Chemistry around Cubane And its Derivatives

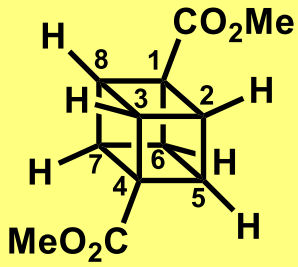
2016.09.10 Hideyuki Sawada

Contents

1-1. Cubane



Cubane
pentacyclo [4.2.0.0.0] octane



Cubane-1,4-dimethyl ester
Often used as intermediate
of cubane derivatives

Chemical properties of cubane [1]	
C-C distance	1.5727 Å
C-H distance	1.118 Å
Color	transparent
Toxicity	nontoxic
Stability	inert to light, water, air
Decomposition	>220 °C
Density	1.29 g cm^{-3}
Vapor pressure	1.1 mm
Boiling point	161.6 °C
Melting point	133.5 °C
Solubility	18 wt% (hexane)
Heat of formation	144 kcal mol^{-1}
Strain energy	166 kcal mol^{-1}

Total synthesis of cubane

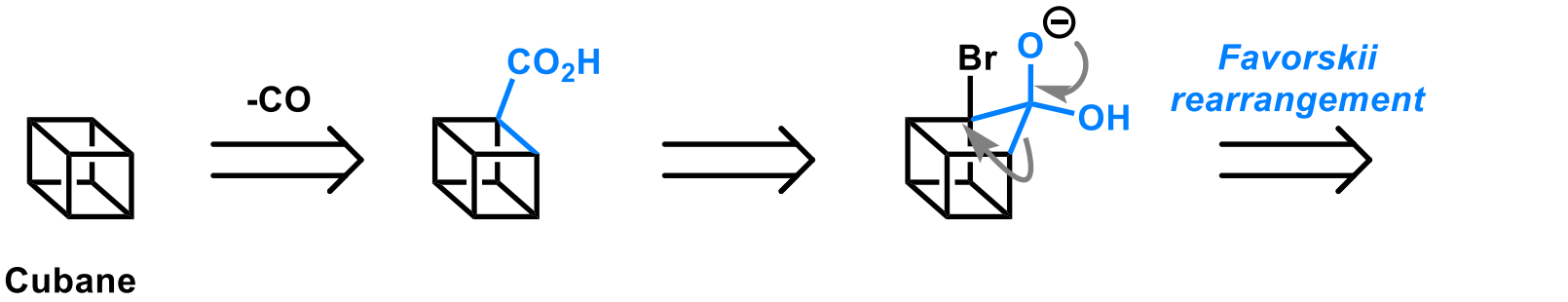
Eaton, P. E. et al. *JACS* 1964, 86, 3157.

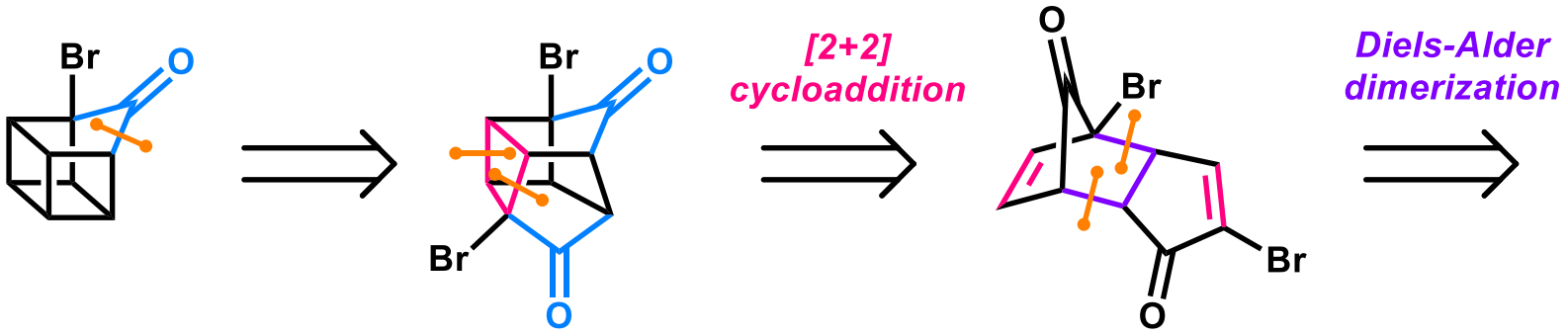
Synthesis of cubane system

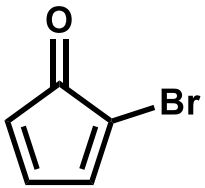
Barborak, J. C. et al. *JACS* 1966, *88*, 1328. (1,3-dicarboxylic acid)
Chapman, N. B. et al. *JOC* 1970, *35*, 3860. (1,4-dimethyl ester)
Tsanaktsidis, J. et al. Aust. J. Chem. 1997, 35, 4969. (1,4-dimethyl ester)

1) Eaton, P. E. *ACIE* **1992**, *31*, 1421.

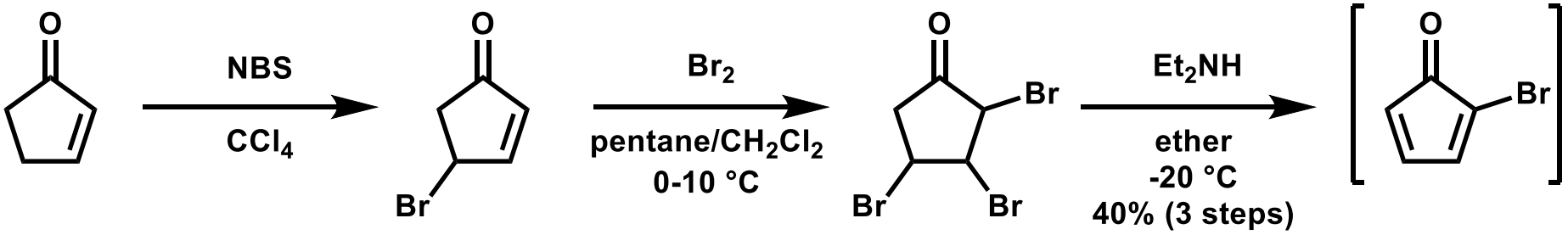
1-2. Eaton's Synthetic plan of Cubane



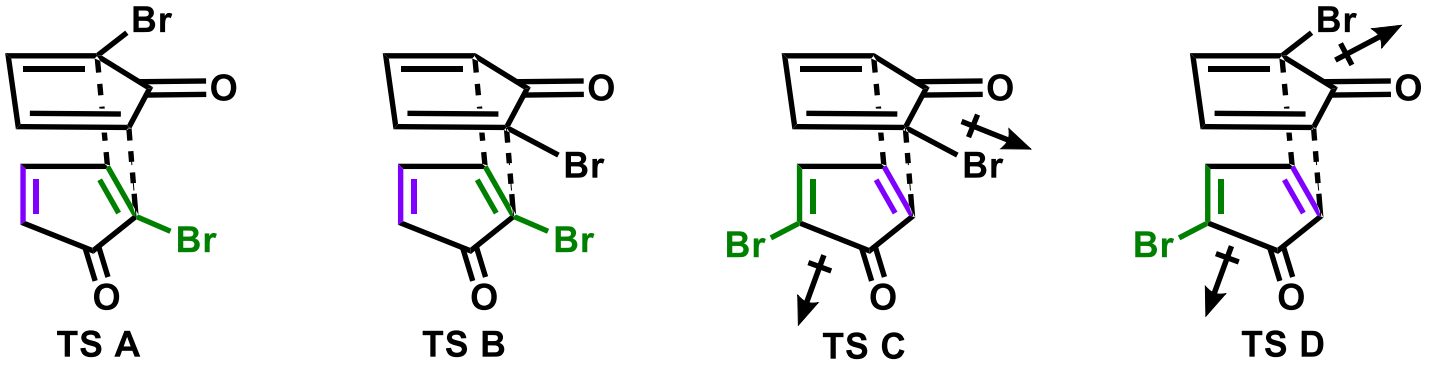




1-3. Synthesis of Precursor of [2+2] cycloaddition

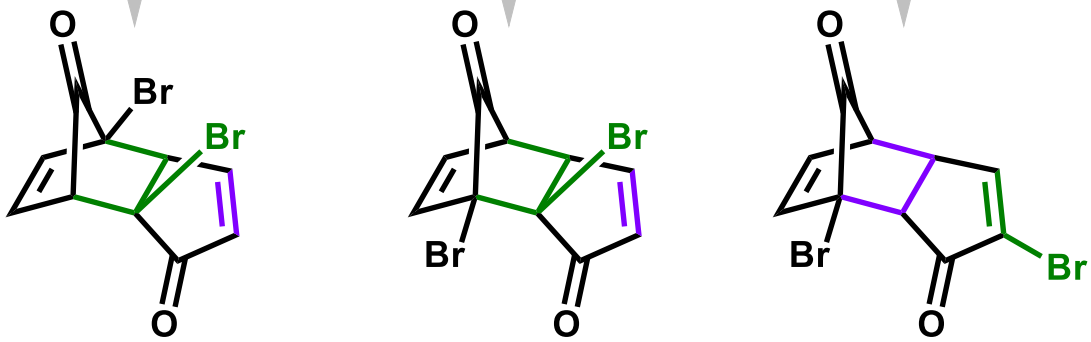


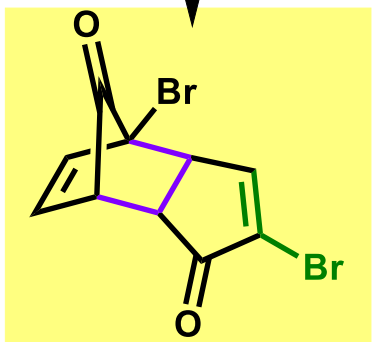
Diels Alder dimerization



Via less reactive dienophile

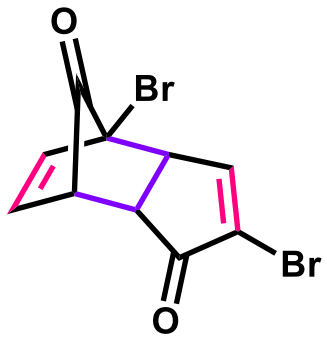
Via more reactive dienophile



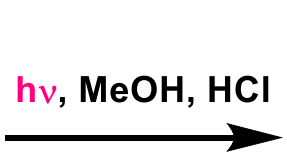


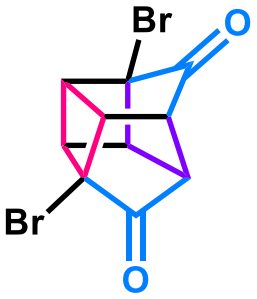
Obtained as single diastereomer

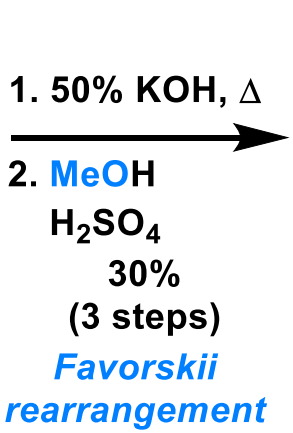
1-4. [2+2] cycloaddition

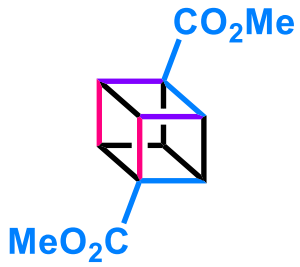


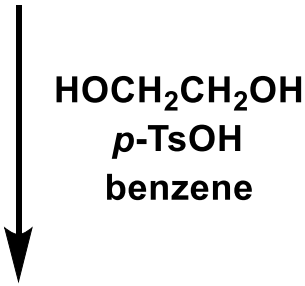
this compound is easy to polymerize

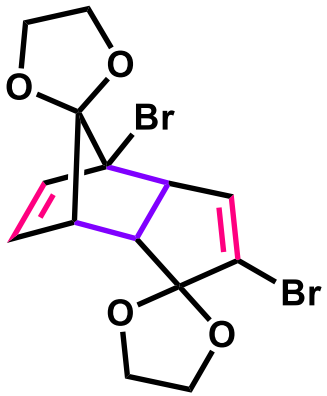


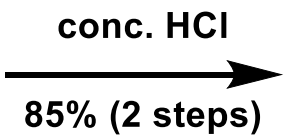


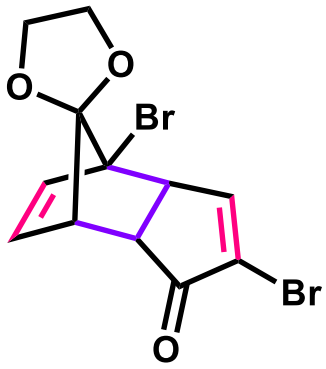


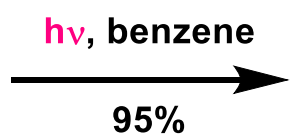


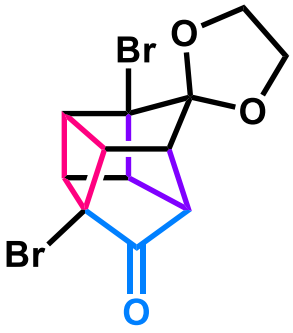




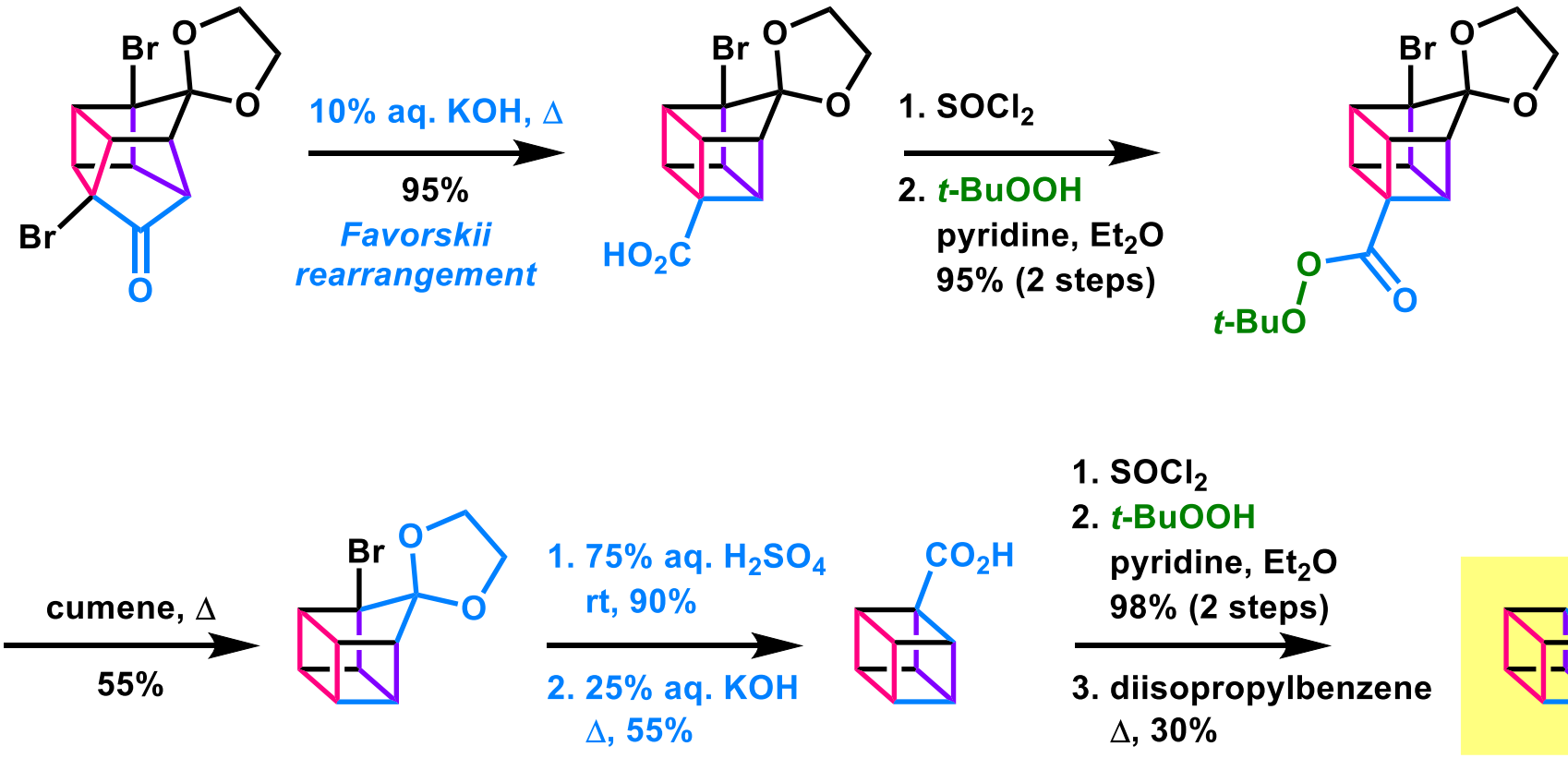






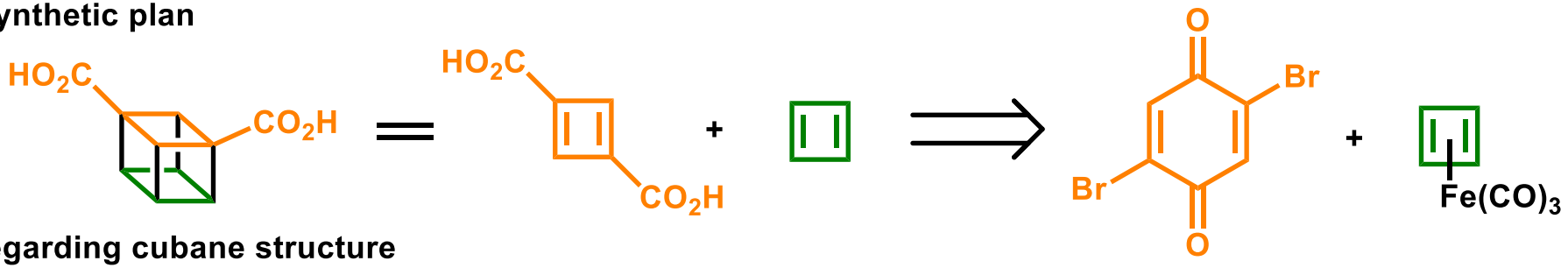


1-4. Completion of Synthesis of Cubane



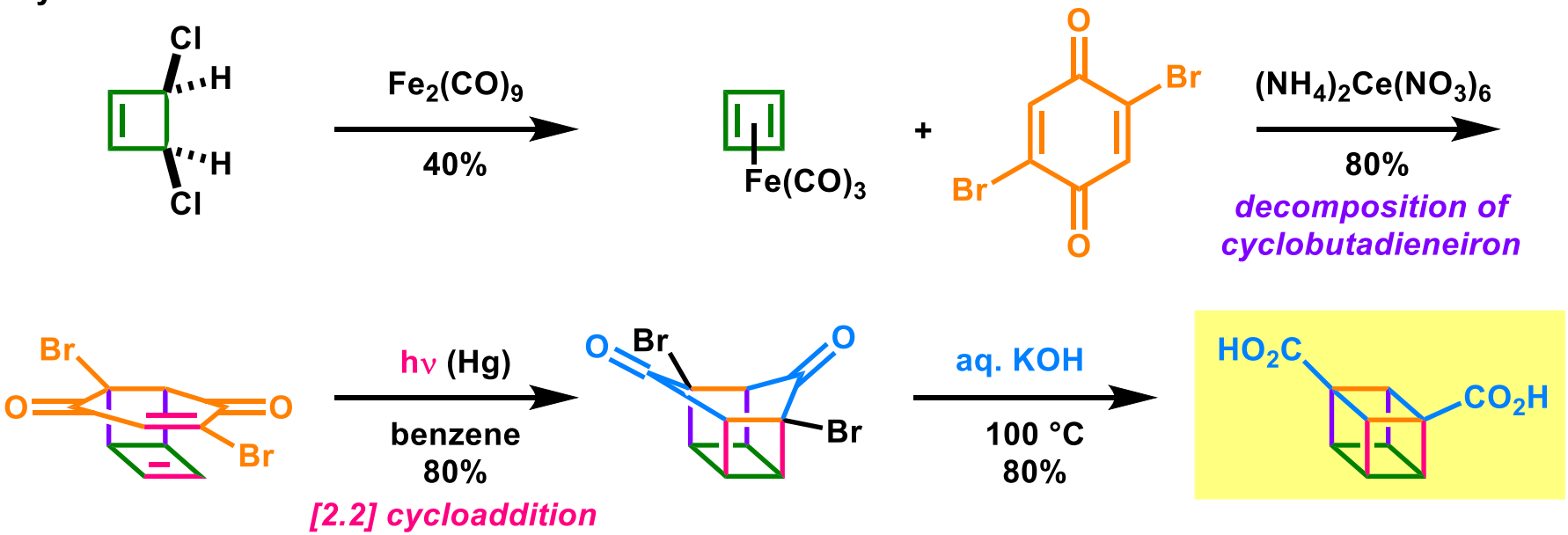
1-5. Pettit's Synthesis of 1,3-Cubanedicarboxylic Acid

♦ Synthetic plan



Regarding cubane structure as dimer of cyclobutadiene

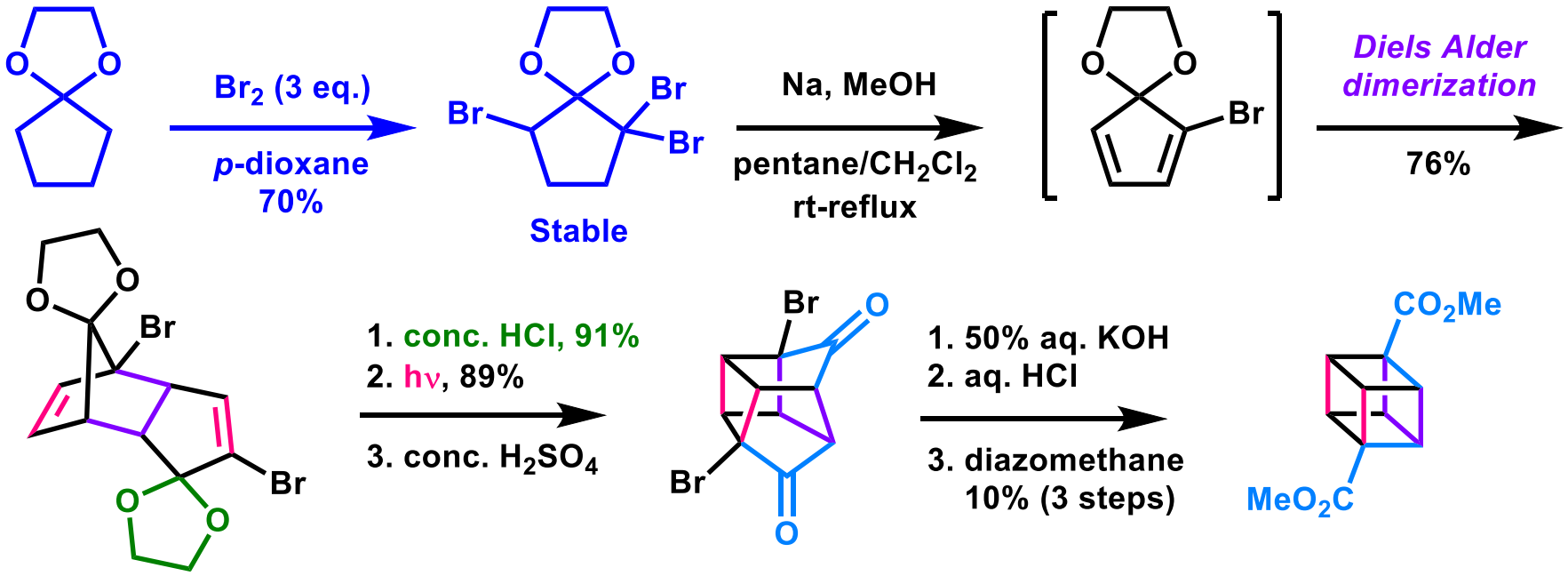
♦ Synthetic scheme



This synthetic route is very short, but it has limitation in the expediency because it needs to use cyclobutadiene iron tricarbonyl.

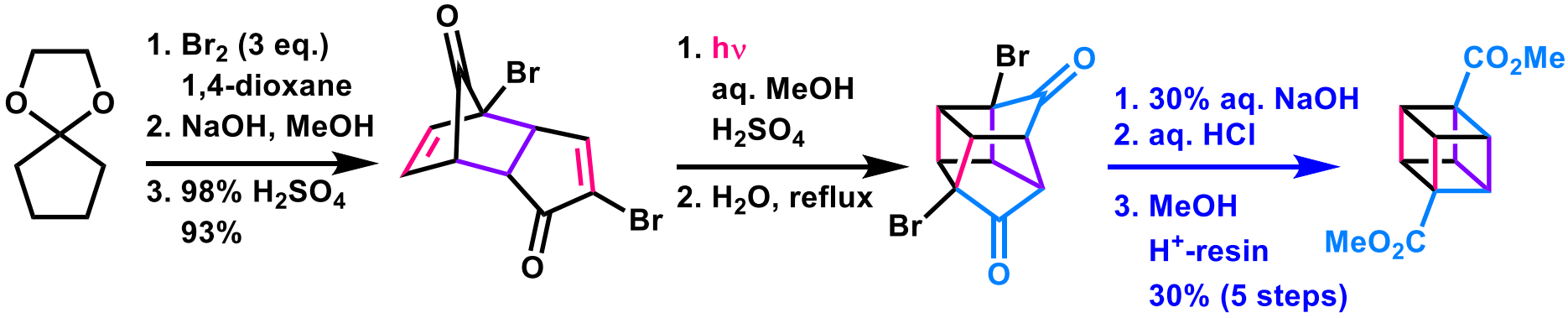
1-6. Modified Synthesis of Dimethyl 1,4-Cubanedicarboxylate

♦ Chapman's approarch (1970) [1)]



♦ Tsanaktsidis' approarch (1997) [2)]

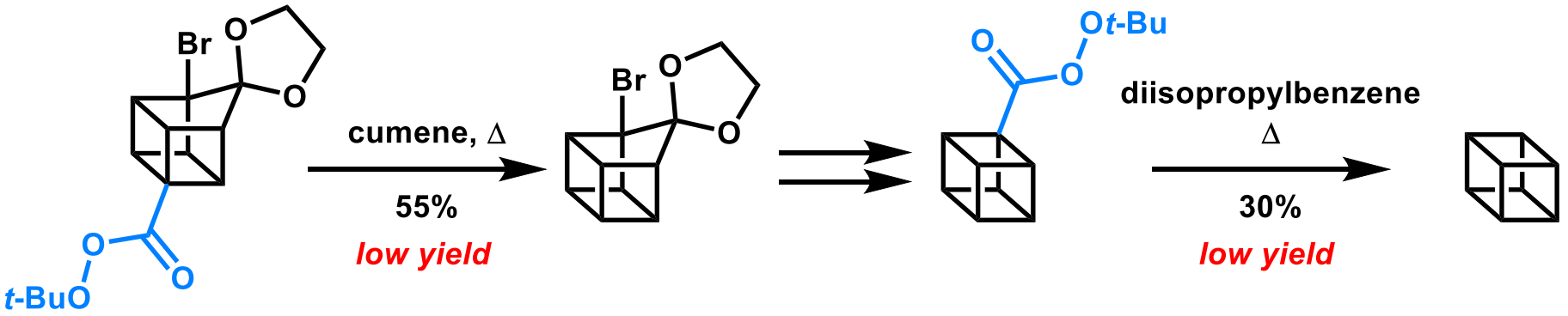
Synthesis able to be conducted in pilot-scale



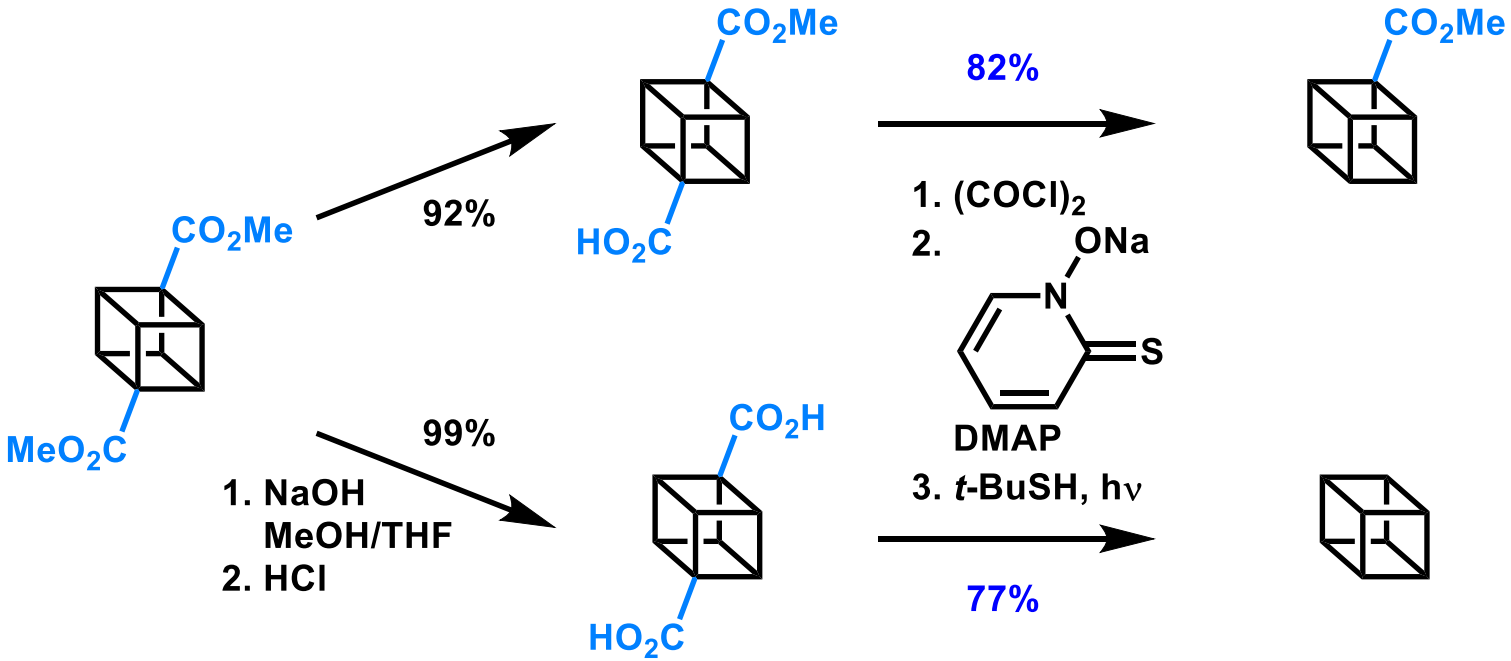
1) Chapman, N. B.; Key, J. M.; Toyne, K. J. *JOC* **1970**, *35*, 3860.
2) Bliese, M.; Tsanaktsidis, J. *Aust. J. Chem.* **1997**, *50*, 189.

1-7. Barton Decarboxylation for Cubane Core

♦ Eaton's original report



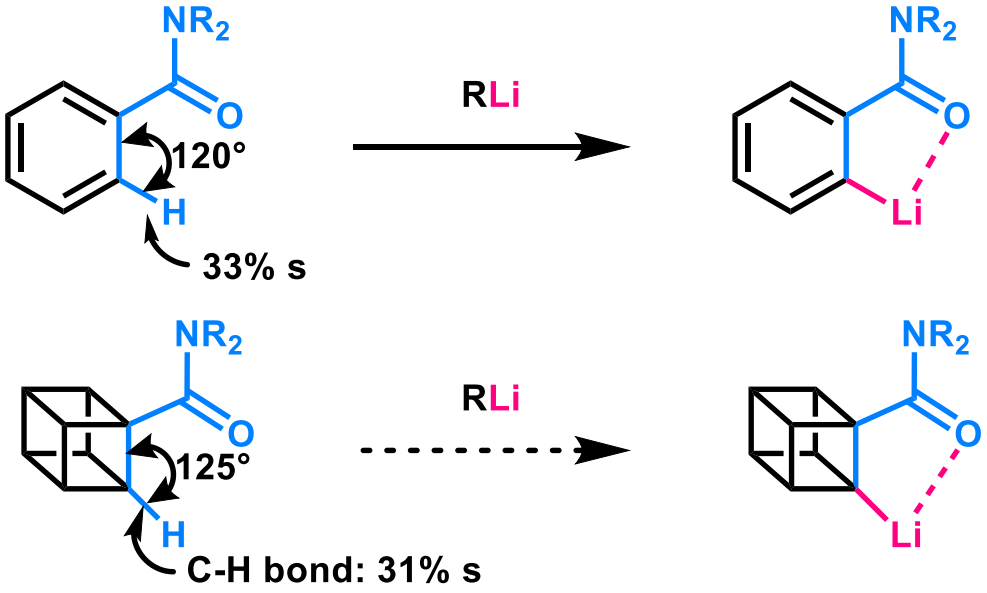
♦ Attempt via Barton Decarboxylation reaction [1)]



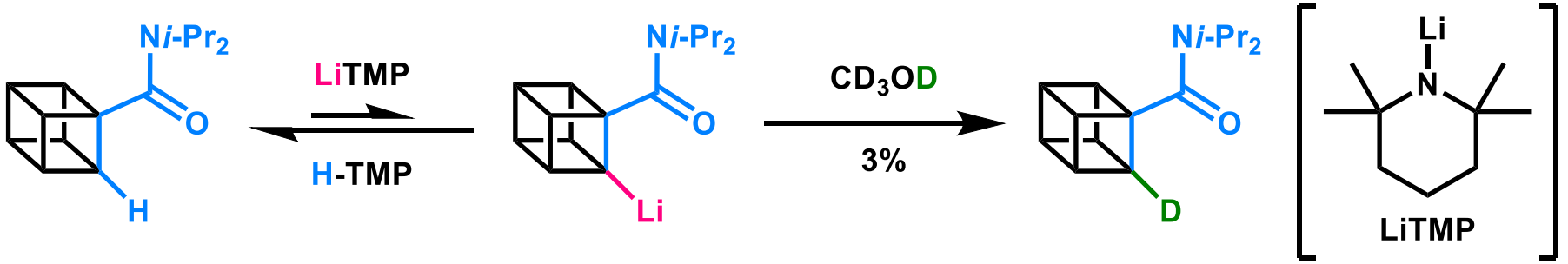
1) Della, E.; Tsanaktsidis, J. *Aust. J. Chem.* **1986**, *39*, 2061.

1-8. *Ortho* Metalation of Cubane (1)

The C-H bond of cubane have high s character, so it might be possible to lithiate cubane by appropriate activator, like arene.

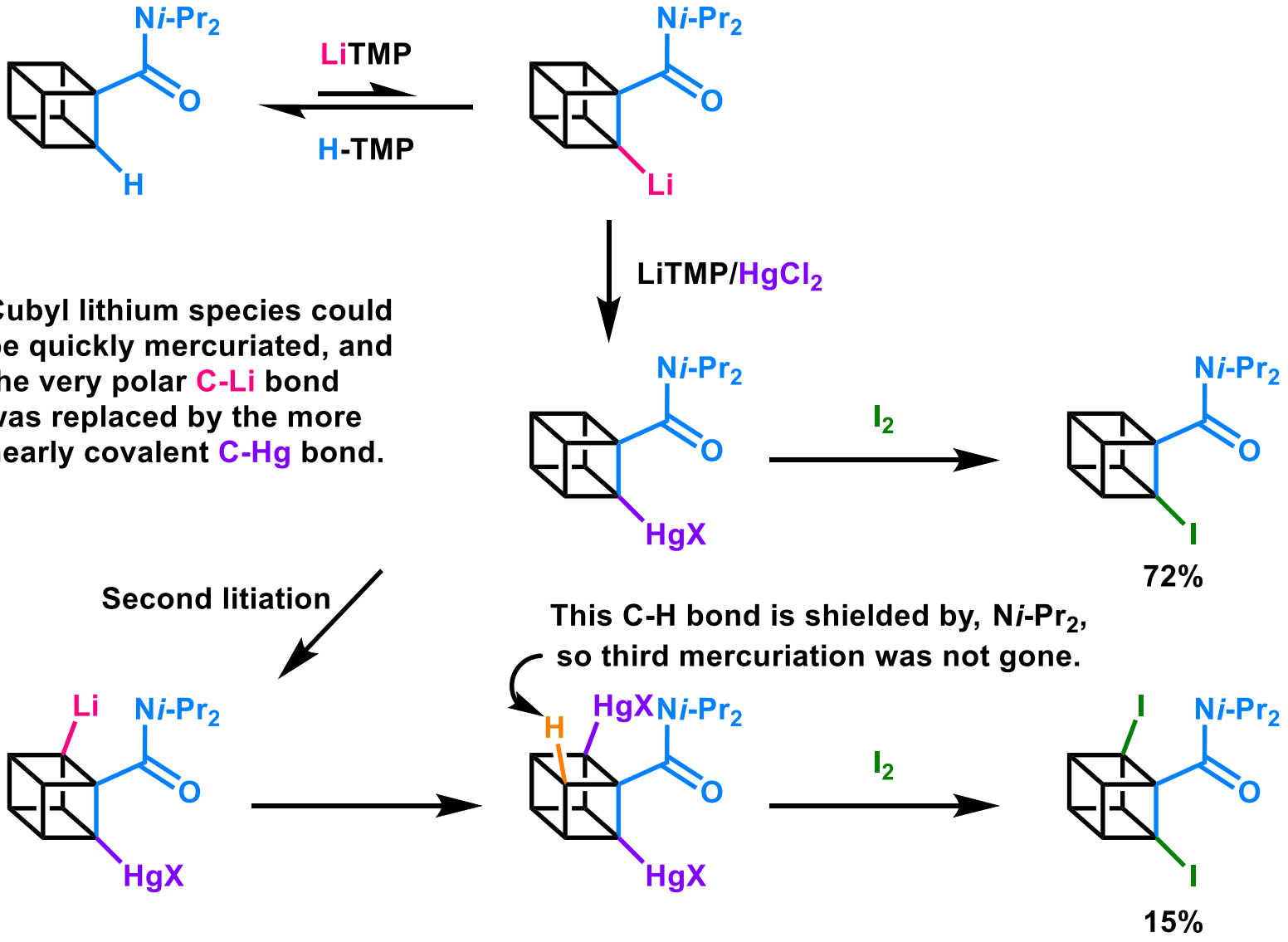


⇒ **To this end, lithiation of cubane below was attempted.**[1)]



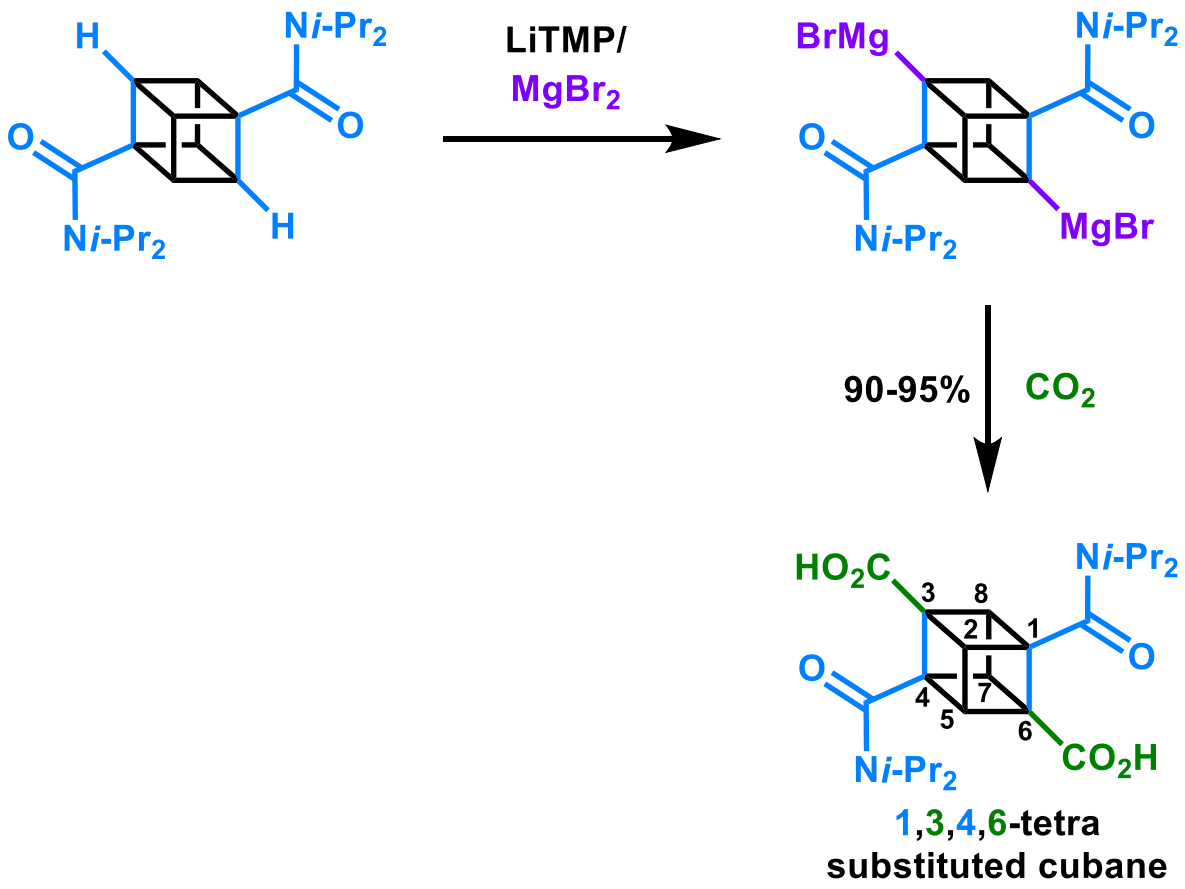
1) Eaton, P. E.; Castaldi ,G. *JACS* **1985**, *107*, 724.

1-9. *Ortho* Metalation of Cubane (2)



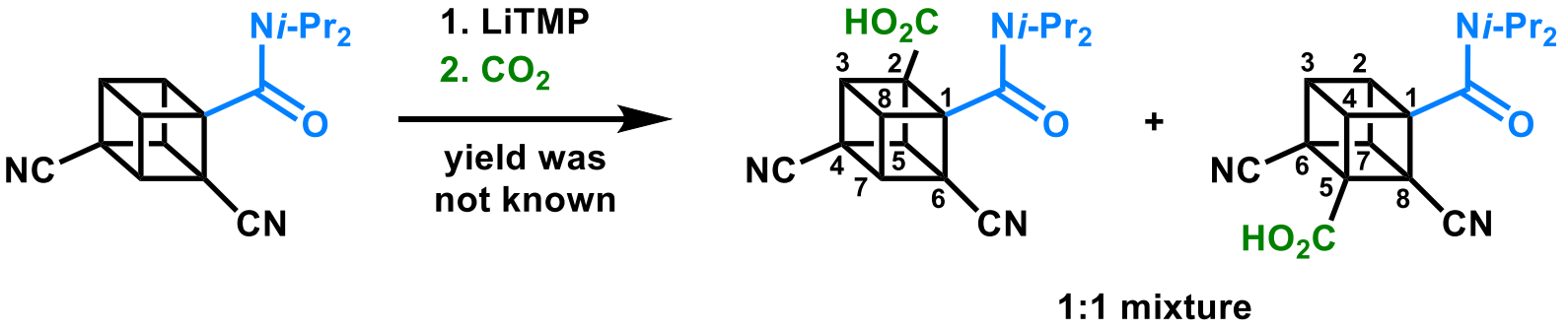
Eaton, P. E.; Castaldi ,G. *JACS* **1985**, *107*, 724.

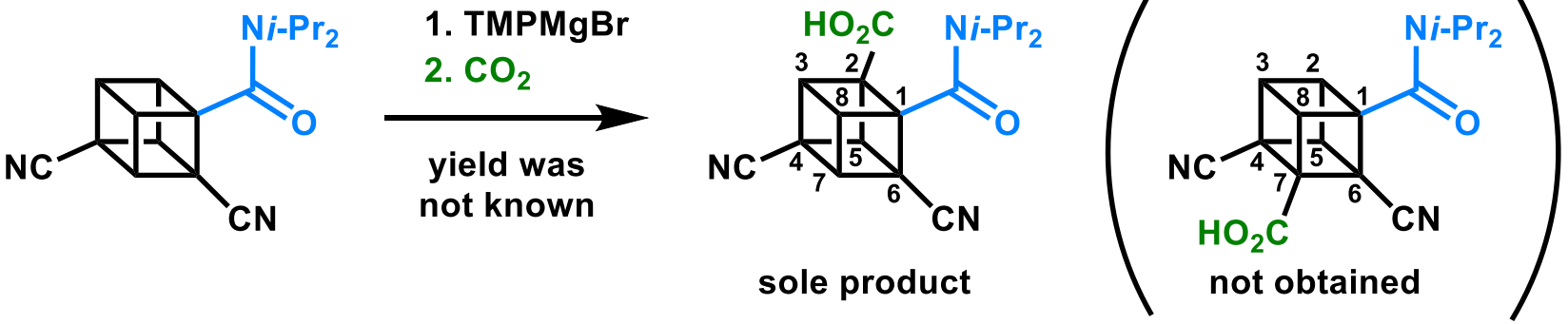
1-10. Trans Metalation and Introduction of Carboxylic acid in Cubane



Bashir-Hashemi, A. *JACS* **1988**, *110*, 7234.

1-11. Different reactivity of metalation



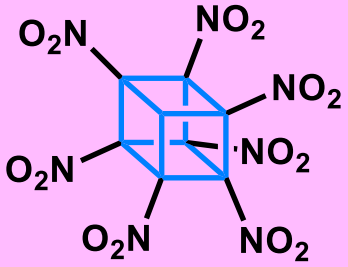


Eaton, P. E. *JACS* **1989**, *111* , 8016.

Contents

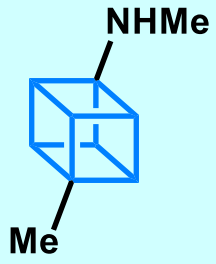
2-1-1. Application of cubyl structure

♦ **Explosive**

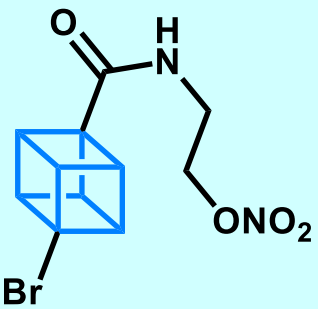


Octanitrocubane (ONC)

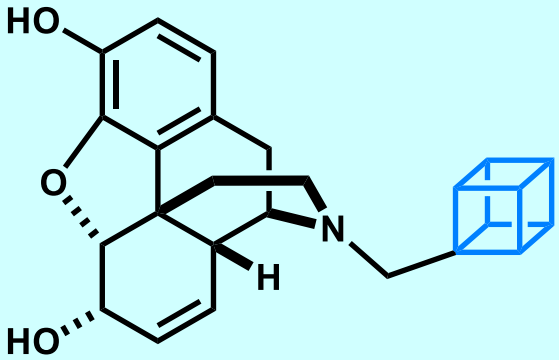
♦ **Medicine**



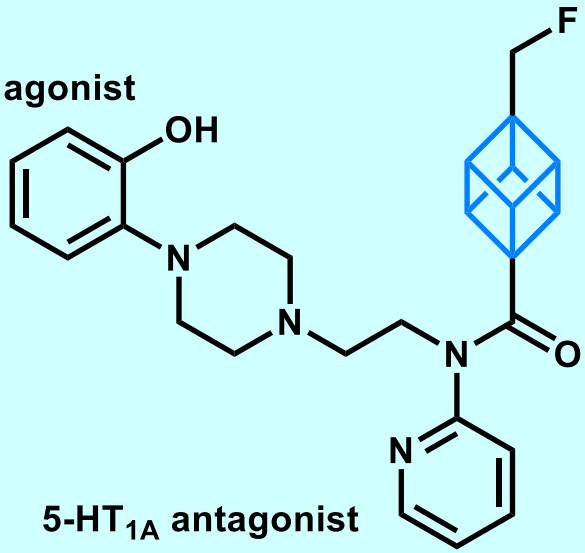
antiviral agent



K+ATP channel agonist

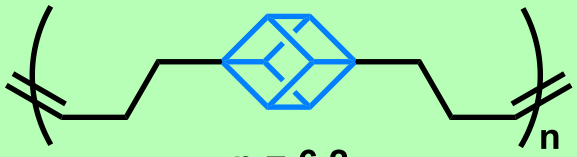


narcotic antagonist

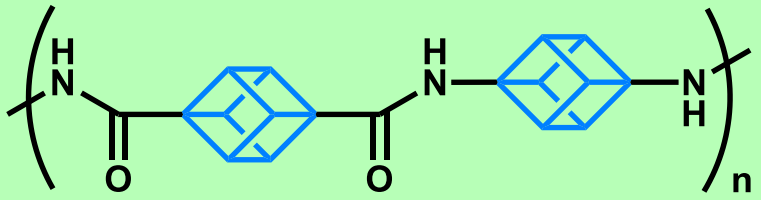


5-HT_{1A} antagonist

♦ **Polymer**



n = 6.2

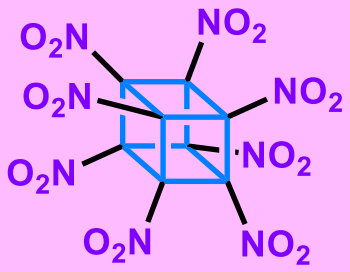


M_n = 12500

units = 43

Biegasiewicz, K. F. et al. *Chem. Rev.* **2015**, *115*, 6719.

2-1-2. OctaNitroCubane



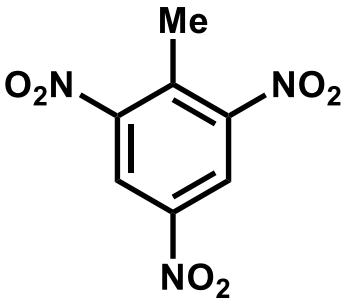
Octanitrocubane (ONC)

- Density: 1.9-2.2 g cm^{-3}
- ΔH_f = 81-144 kcal mol^{-1}
- All of carbon atoms in cubane core were substituted by nitro groups.
- In principle, ONC is the strongest explosive in the world.
- The power is considered to stronger than TNT, HMX, CL-20, one of the strongest explosives.

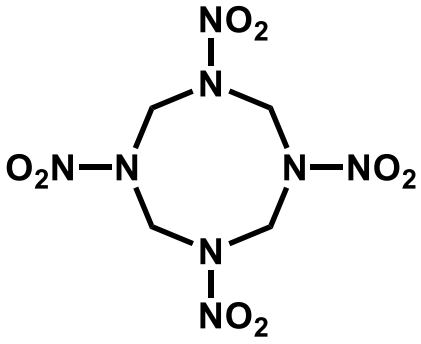
But, the cost to synthesize ONC is too high to be practically used.

- Synthesis of ONC: US Naval Research Laboratory (2000)[1)]

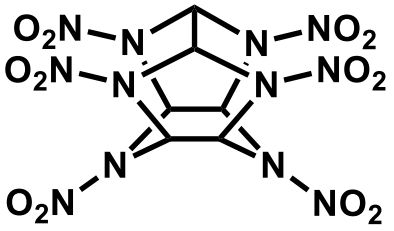
Related explosives



TNT



HMX

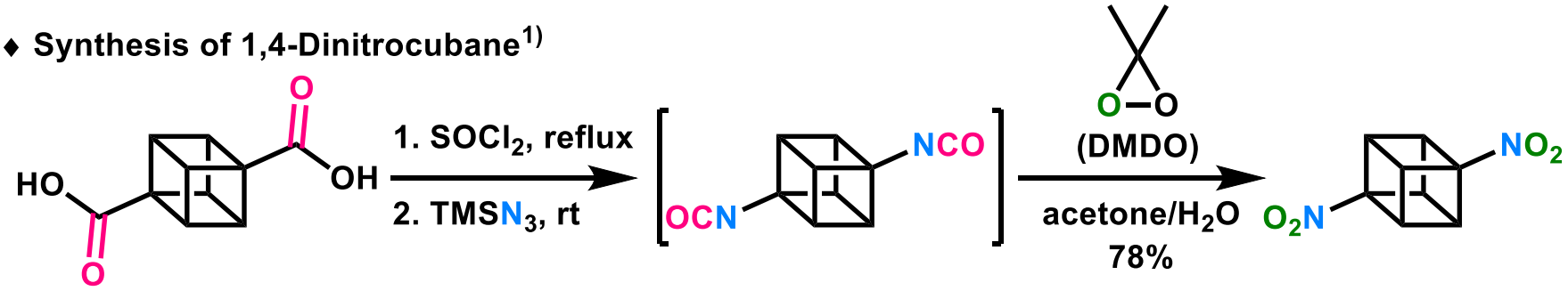


CL-20

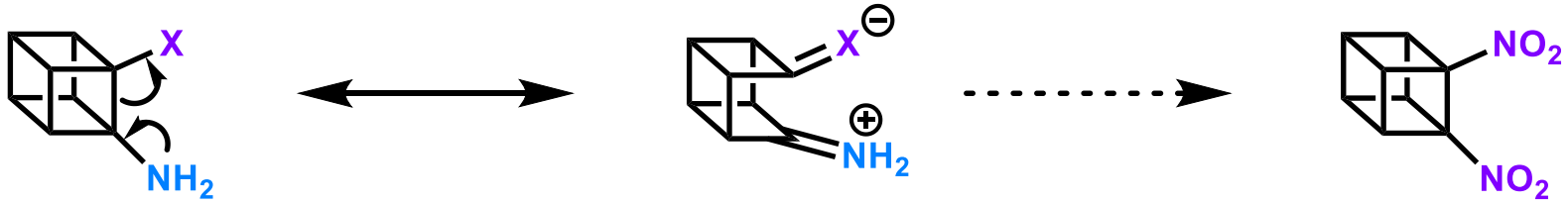
1) Zhang, M. X.; Eaton, P. E. *ACIE* **2000**, *39*, 401.

2-1-3. Synthetic strategy of ONC

♦ Synthesis of 1,4-Dinitrocubane[1)]

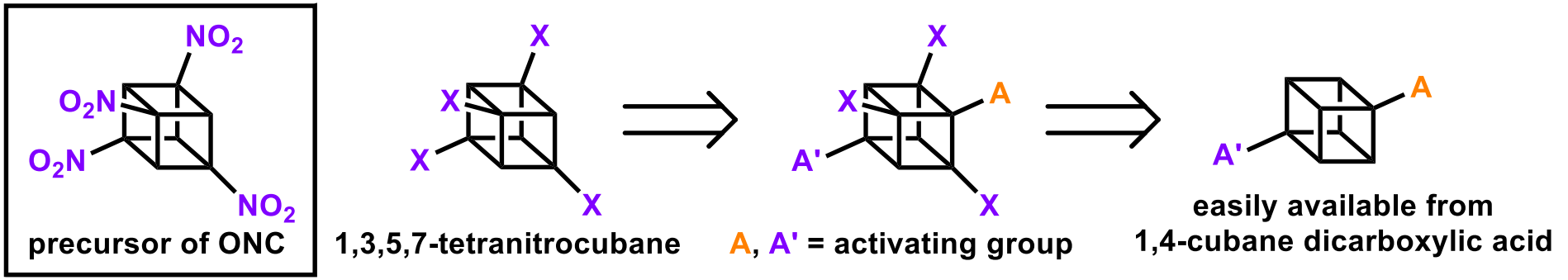


On the other hand, 1,2-disubstituted cubane is difficult to synthesize because of the hyperconjugative destabilization of the cubane nucleus (below)[2)].



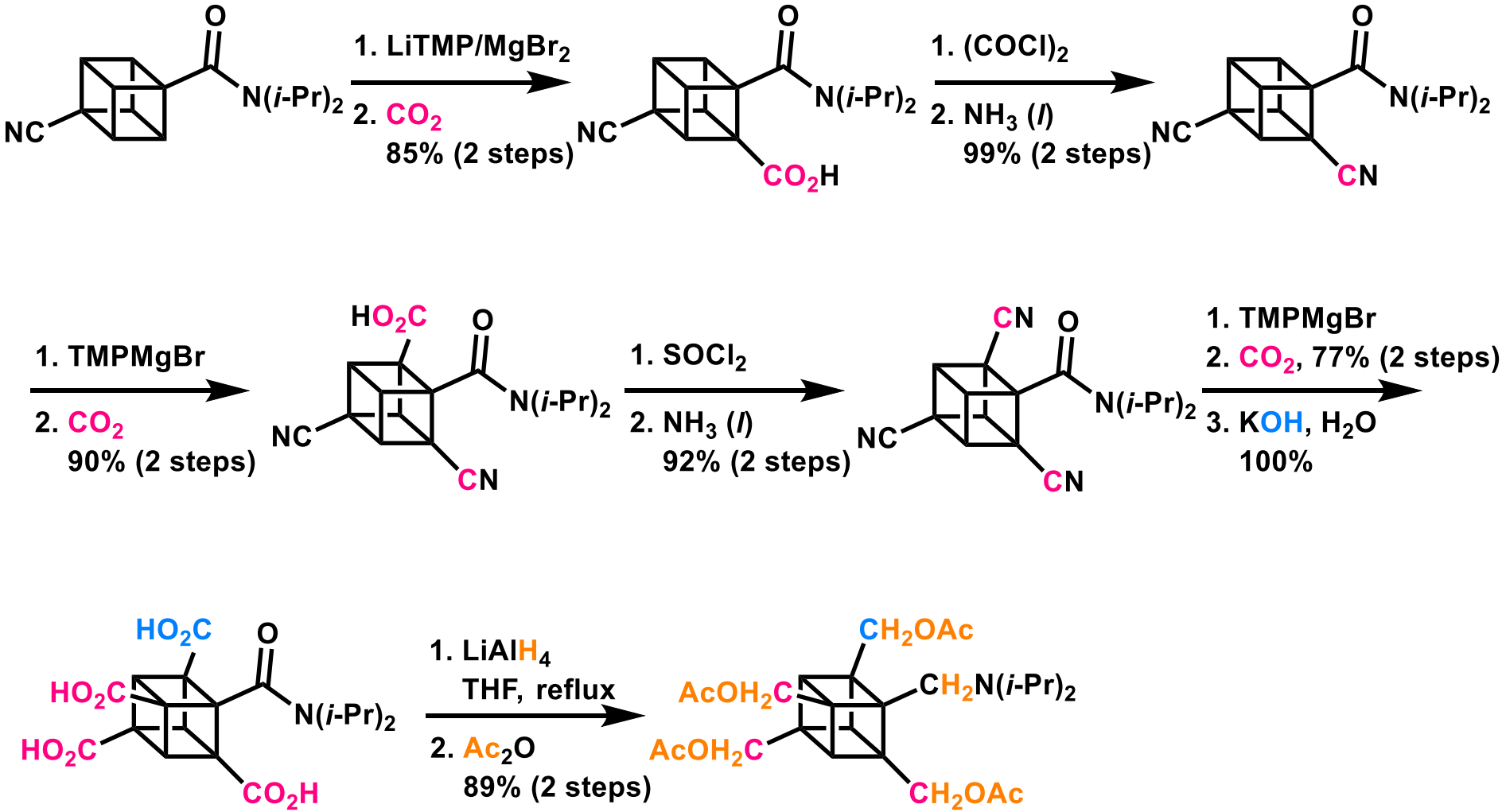
X = electron acceptor

⇒ 1,3,5,7-tetrasubstituted cubane was designed.

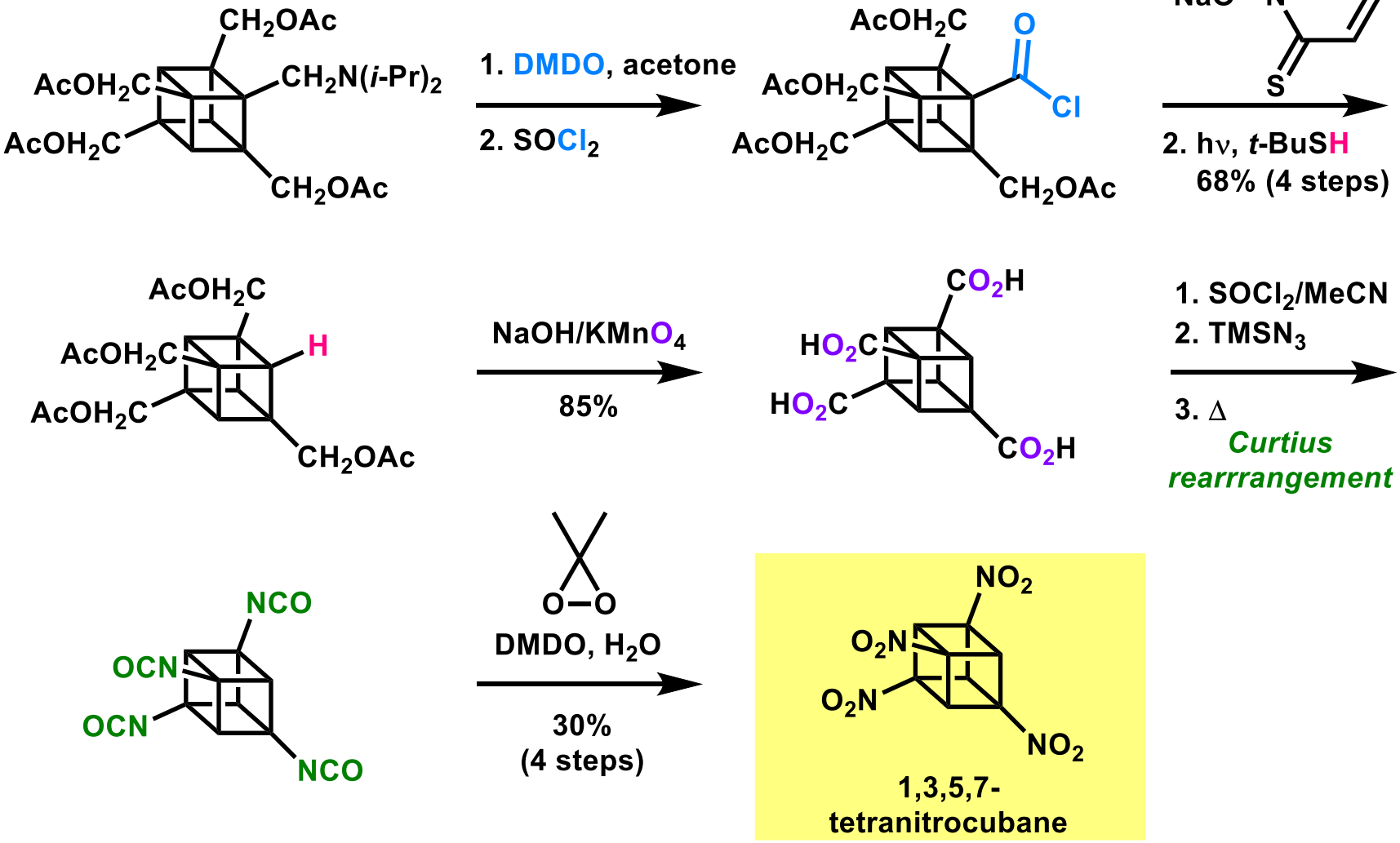


1) Eaton, P. E.; Wicks, G. E. *JOC* **1988**, *53*, 5353.
2) Murray, J. S.; Seminario, J. M.; Politzer, P. *Struct. Chem*. **1991**, *2*, 153.

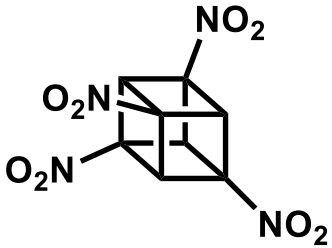
2-1-4. Synthesis of 1,3,5,7-tetranitrocubane (1)



2-1-5. Synthesis of 1,3,5,7-tetranitrocubane (2)

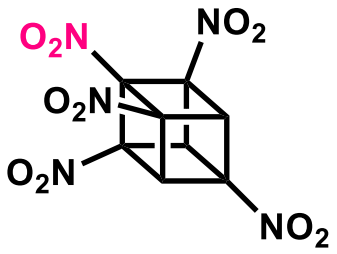


2-1-6. Synthesis of ONC (1)
~Preparation of heptanitrocubane~

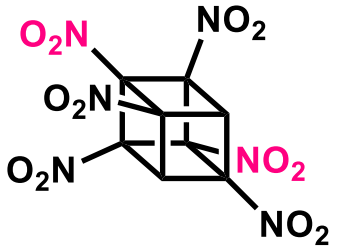


SM (tetranitro)

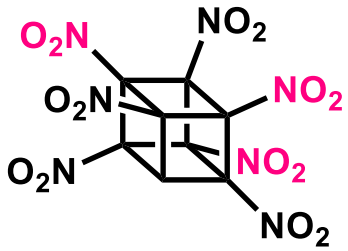
1. $NaN(SiMe_3)_2$ (*X* eq.)
   THF/MeTHF, -78 °C
2. cool to ca. -130 °C
3. add N_2O_4
   in cold isopentane
4. quench with H^+
   in cold Et_2O



A (pentanitro)



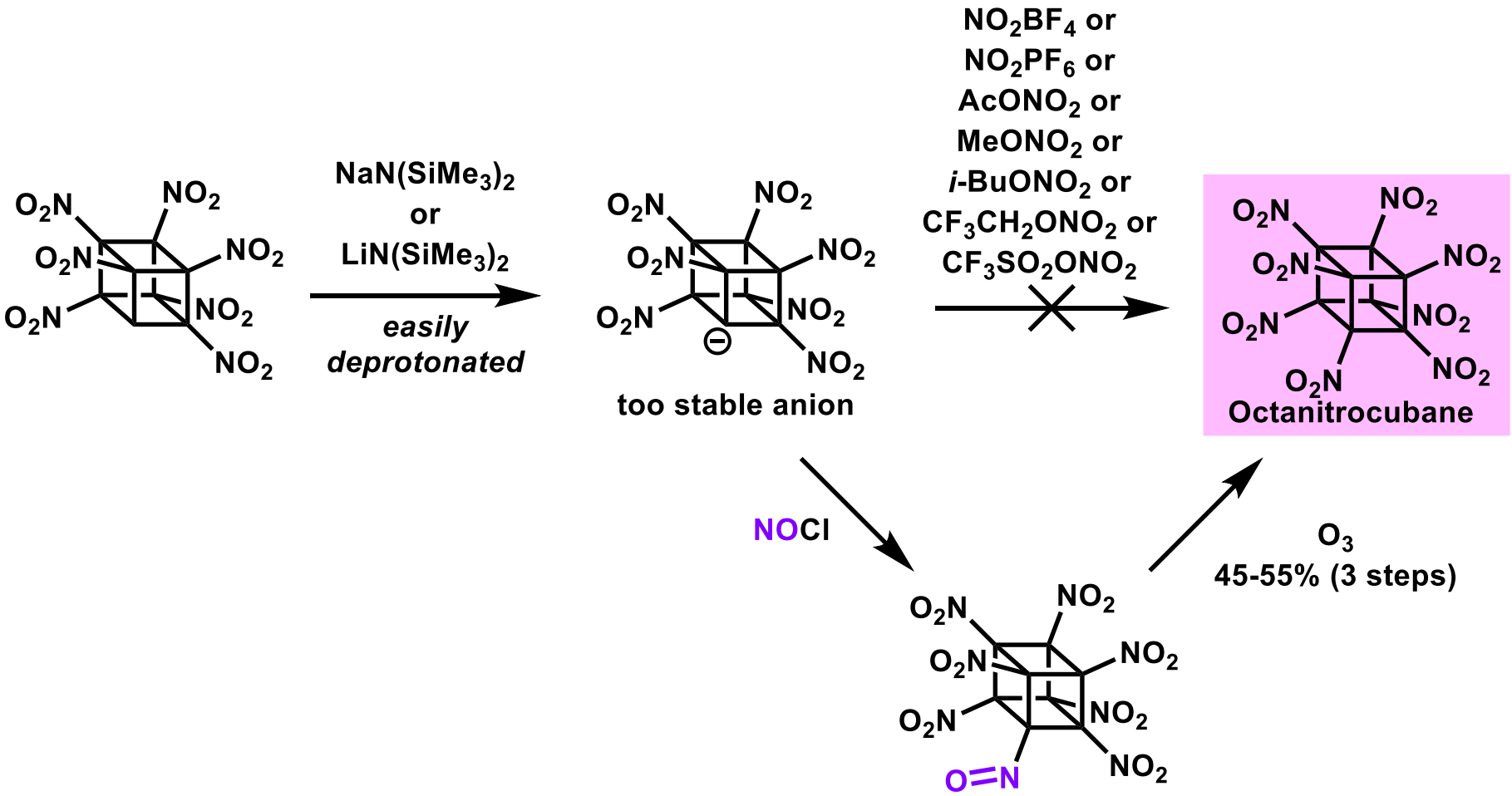
B (hexanitro)



C (heptanitro)

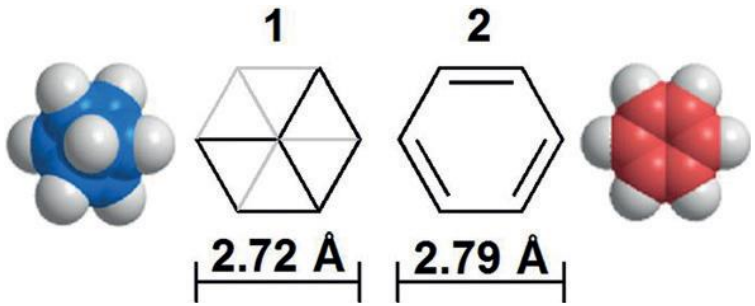
	ratio (by NMR)			
X	SM	A	B	C
1.5	12	70	18	-
3.0	11	3	57	29
4.0	-	-	5	95

2-1-6. Synthesis of ONC (2)
~Completion of ONC~



Contents

2-2-1. Bioisoster of benzene



The size of cubane and benzene

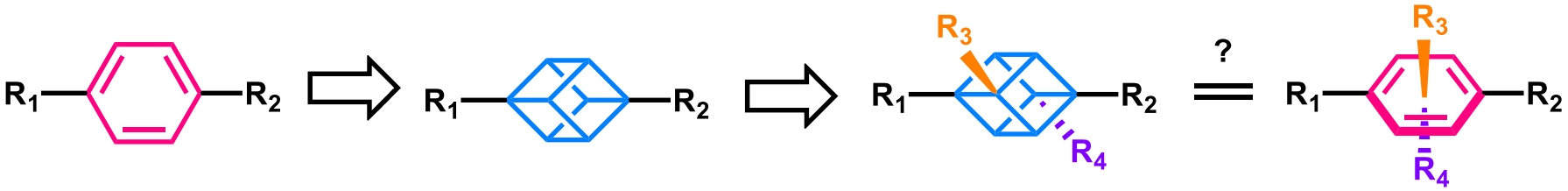
♦Cubane may be attractive bioisoster because...

The distance across the cube is almost the same as that between the para positions of benzene.

The cubane system is not inherently toxic.

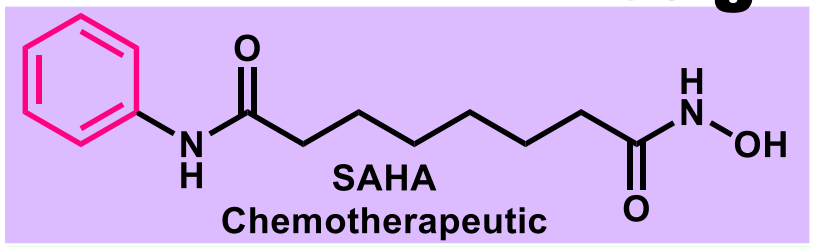
The cubane core is a poor substrate in cytochrome P_{450} metabolic pathways, so metabolically stable.

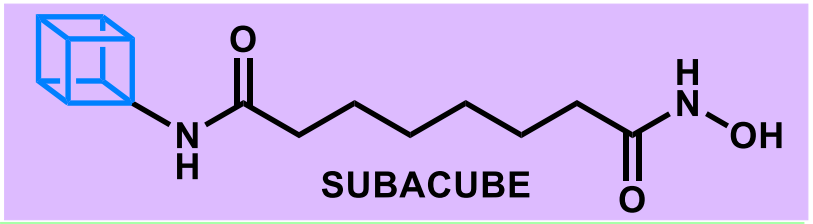
One can add substituents on "the benzene plane" (see below).

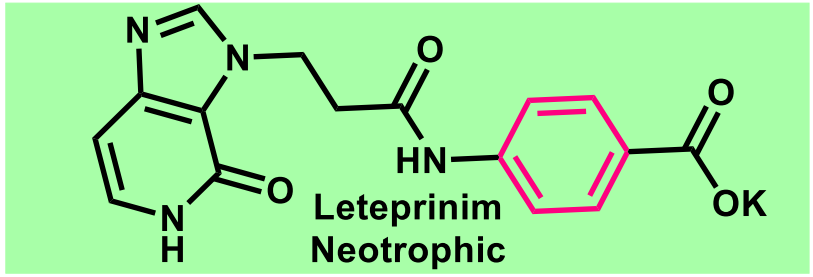


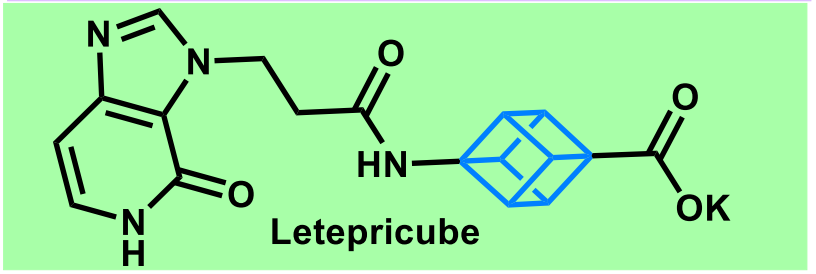
Despite above points, cubane has found only limited use in medicinal chemistry, presumaly due to the assumption that cubane compounds are esoteric, unstable, or synthetically intractable.

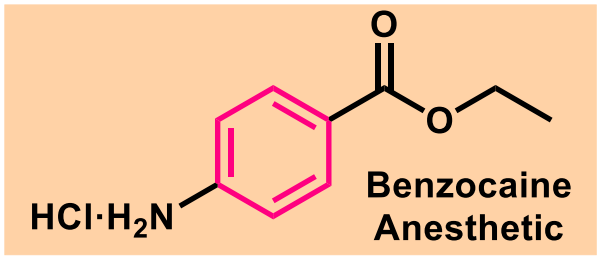
2-2-2. Design of cubane derivatives



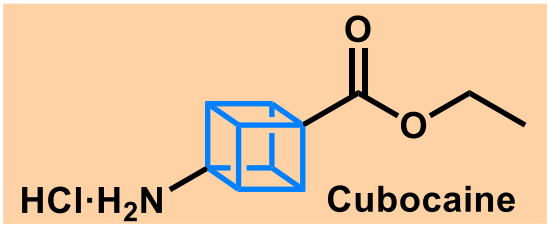


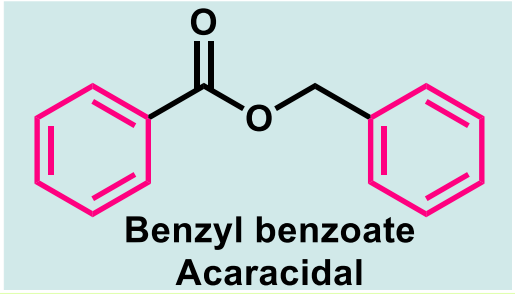


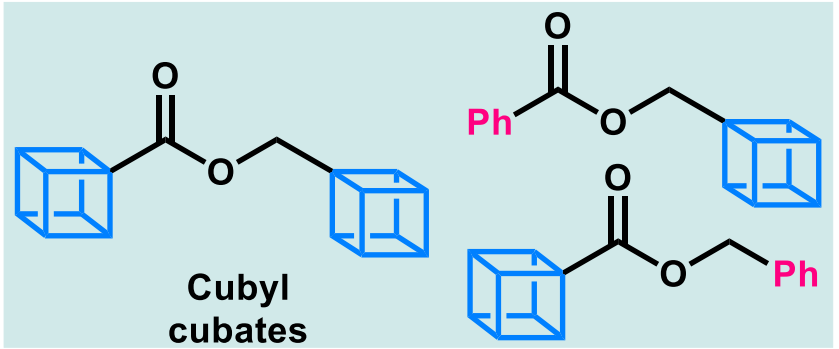


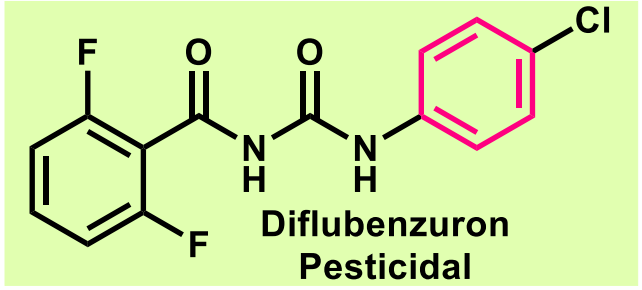


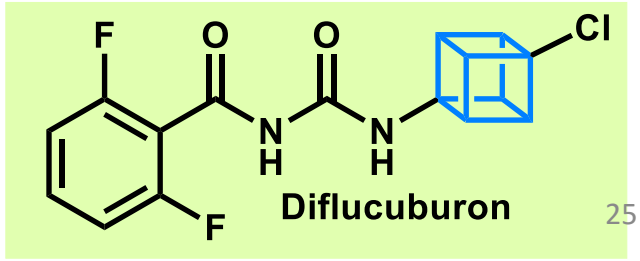
Conversion of benzene to cubane



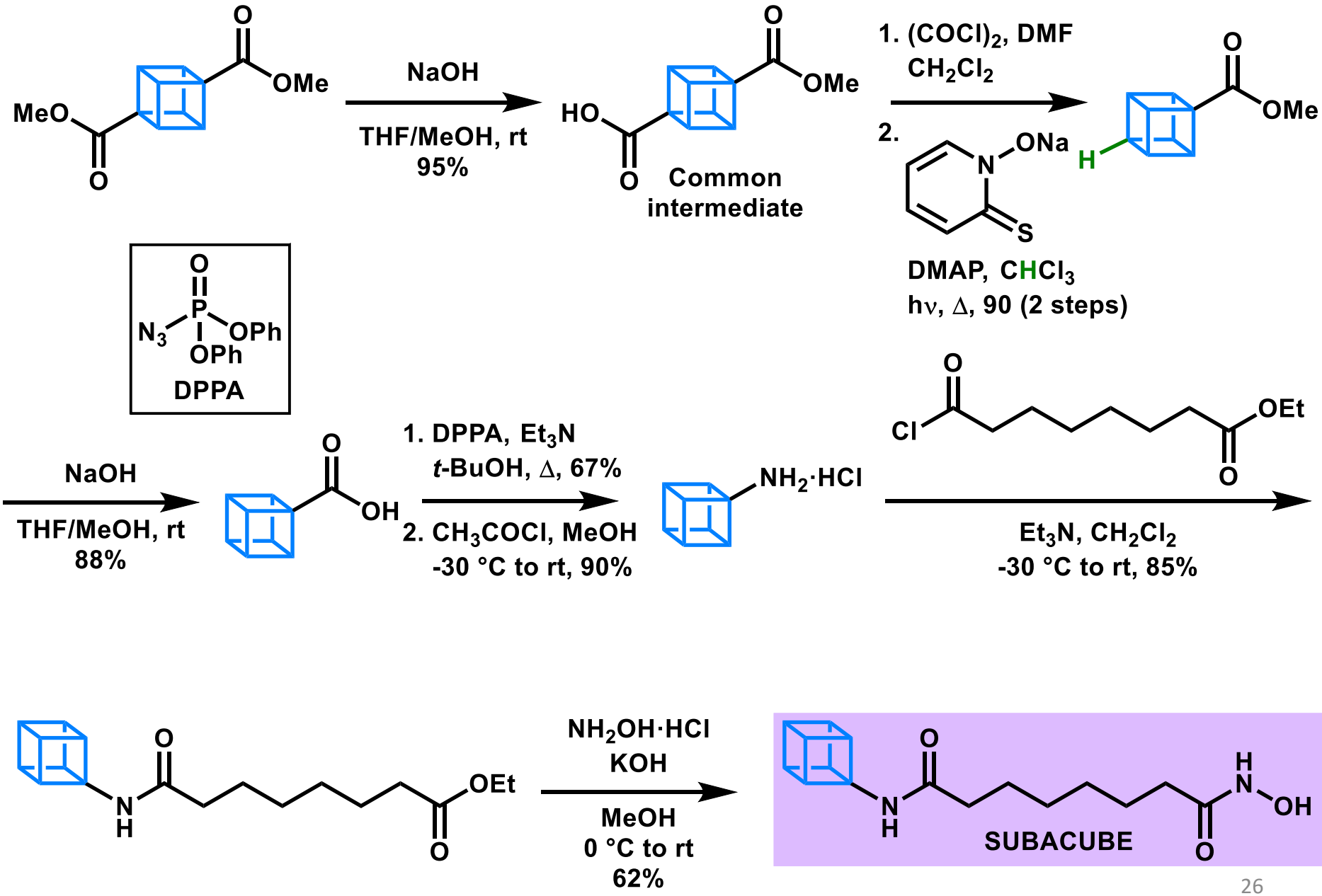




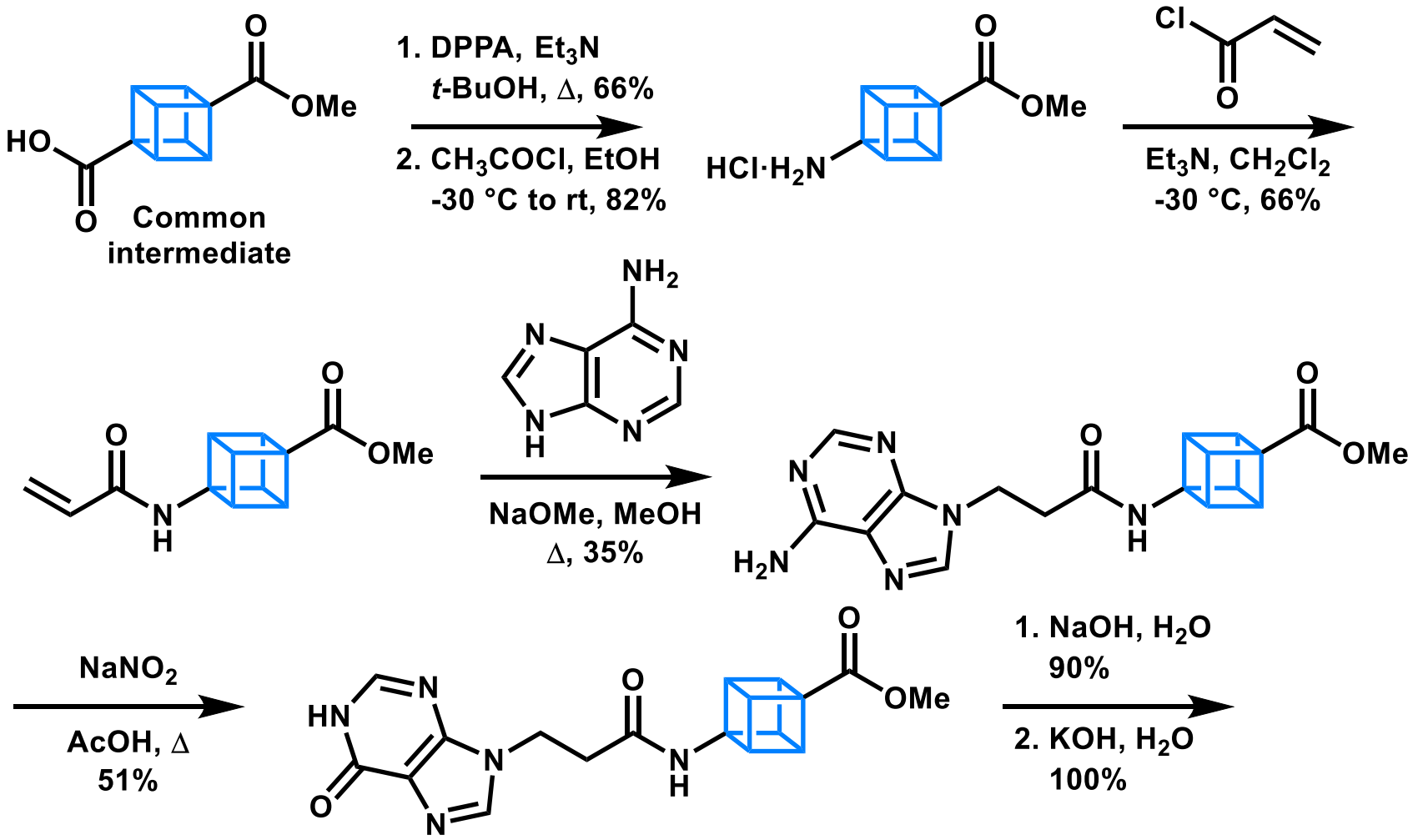




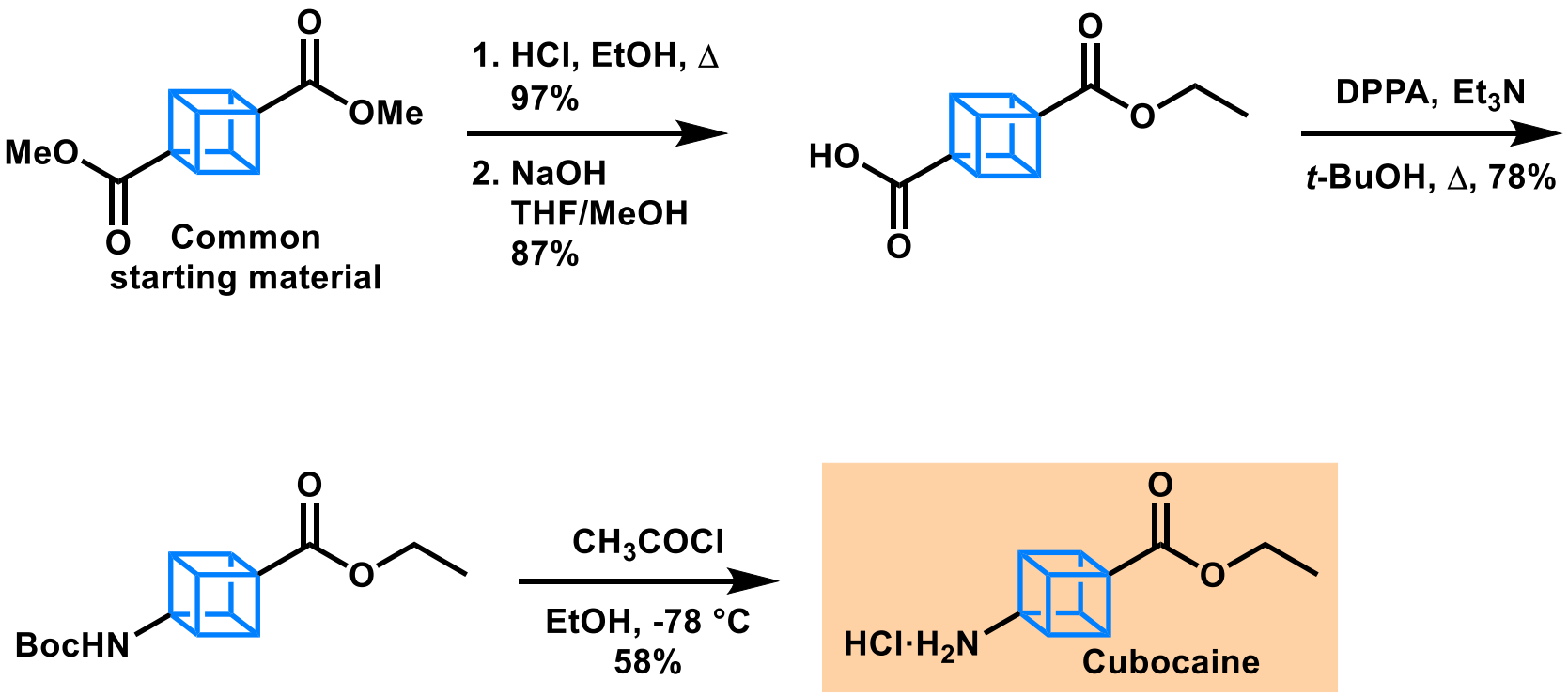
2-2-3. Synthesis of SUBACUBE



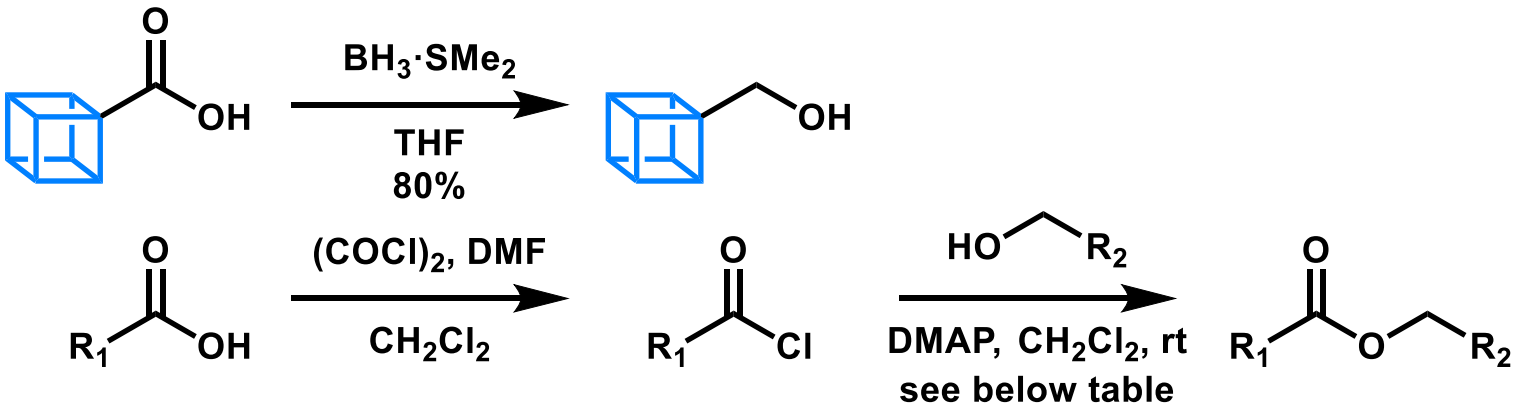
2-2-4. Synthesis of Letepricube

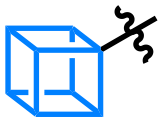
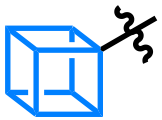
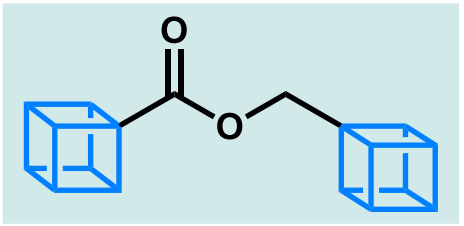
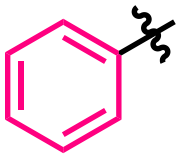
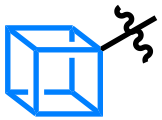
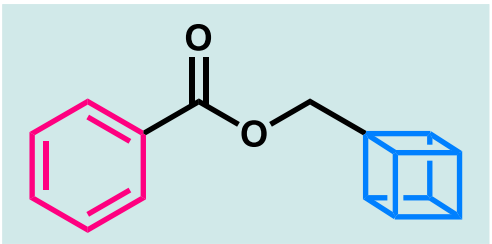
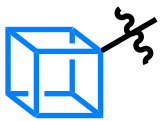
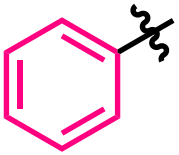
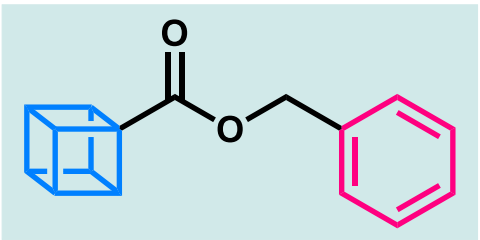


2-2-5. Synthesis of Cubocaine

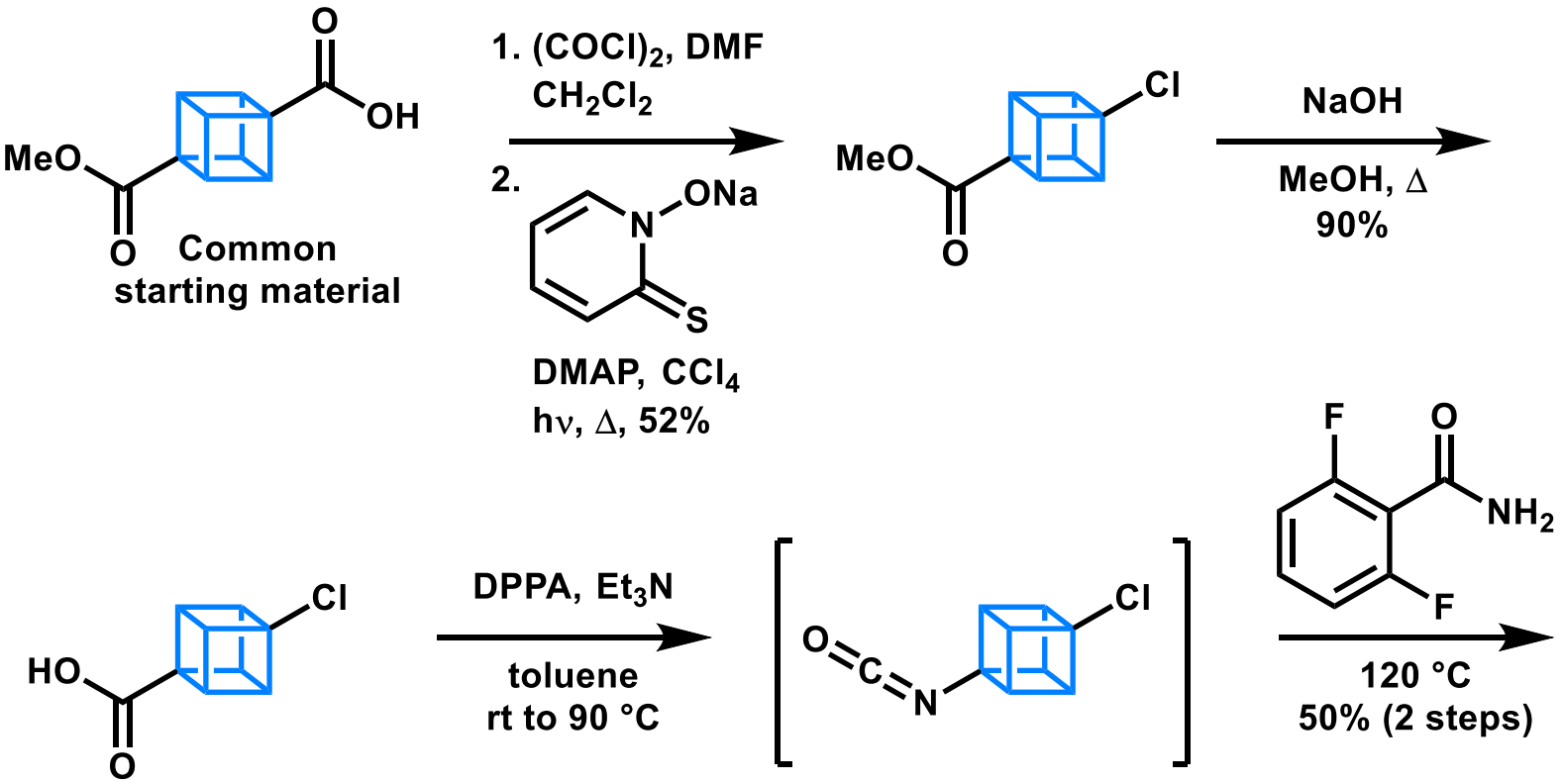


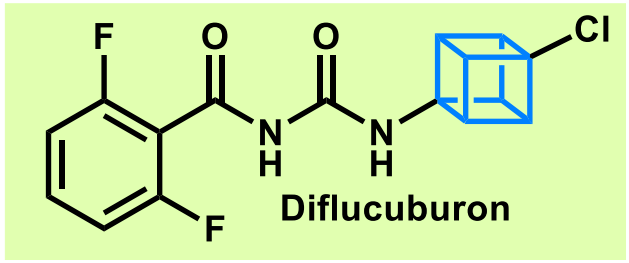
2-2-6. Synthesis of Cubyl cubates



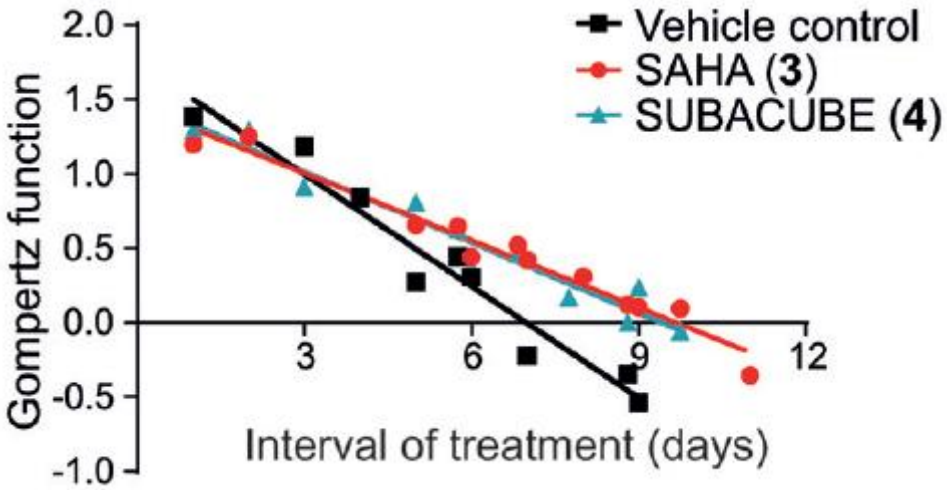
R_1	R_2	Product	Yield
			85%
			87%
			86%

2-2-7. Synthesis of Diflucuburon

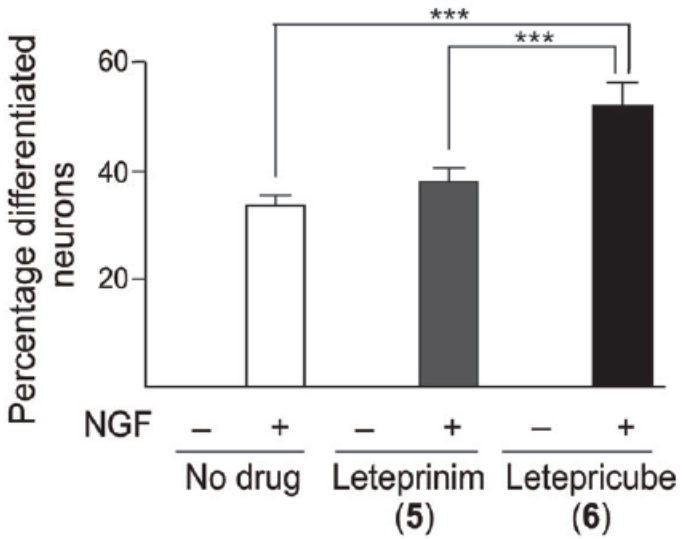




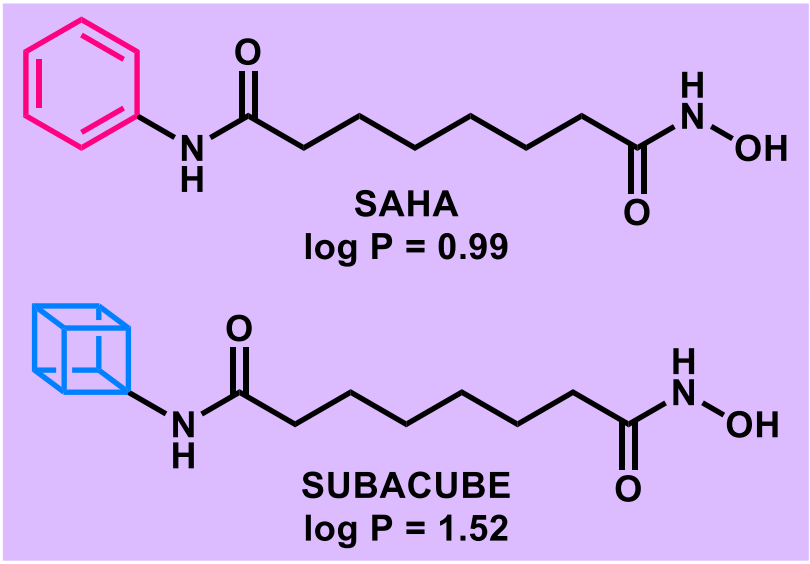
2-2-8. Biological Data for SUBACUBE, Letepricube

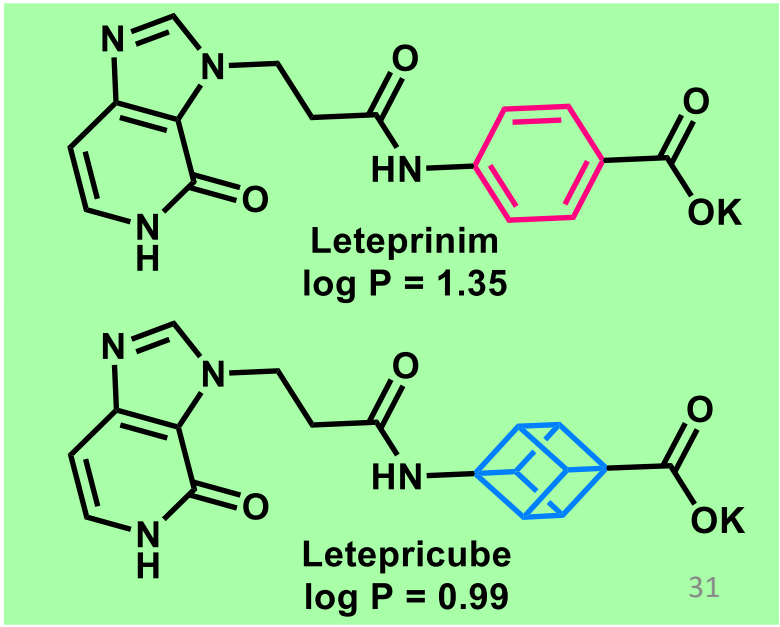


Gompertz plot of tumor growth rates for animals treated SAHA and SUBACUBE versus control animals. Each lines is a representative animal whose tumor growth rate mirrors the average of mice in the relevant treatment group.

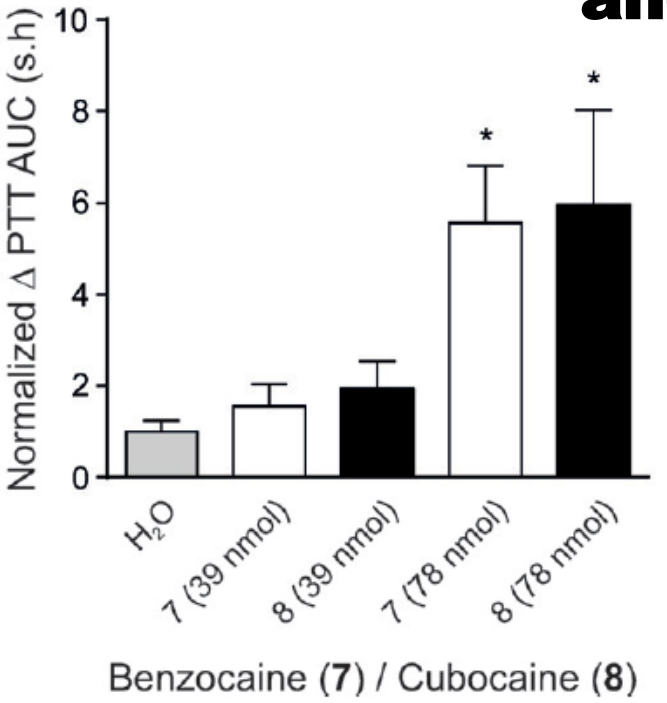


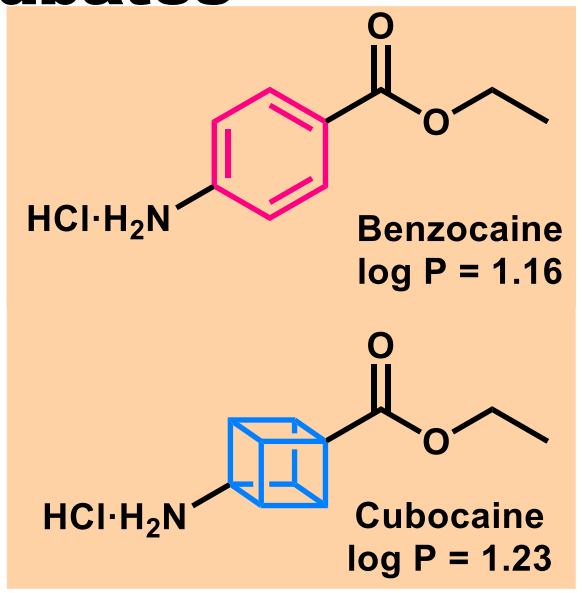
NGF-dependent PC12 cell differentiation was enhanced by letepricube.



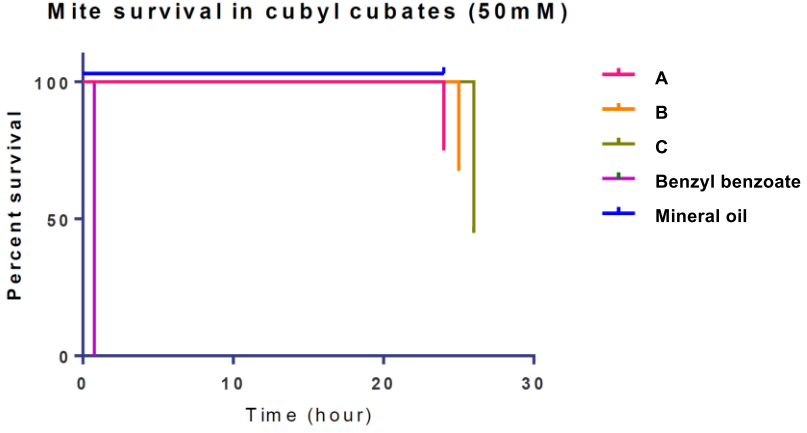


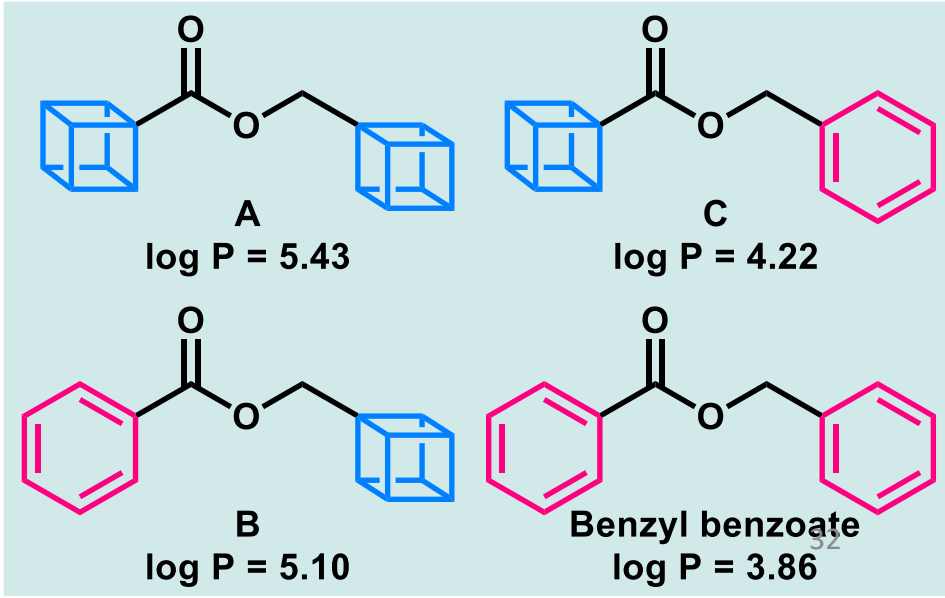
2-2-9. Biological Data for Cubocaine and Cubyl cubates



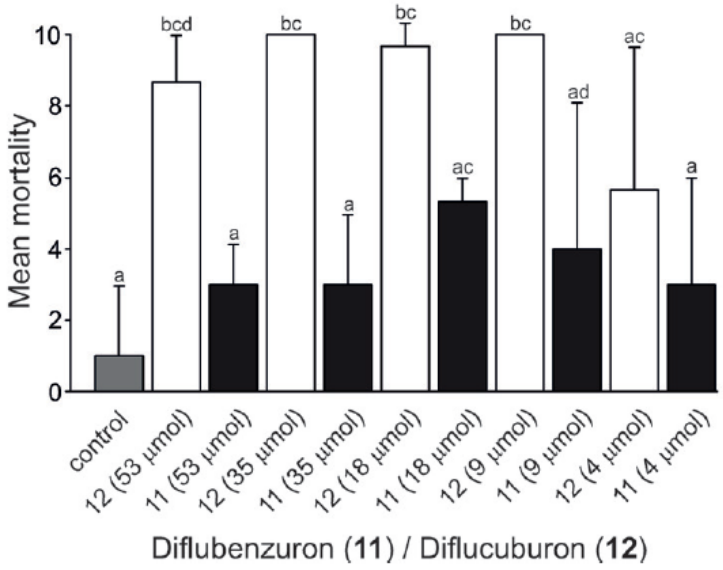


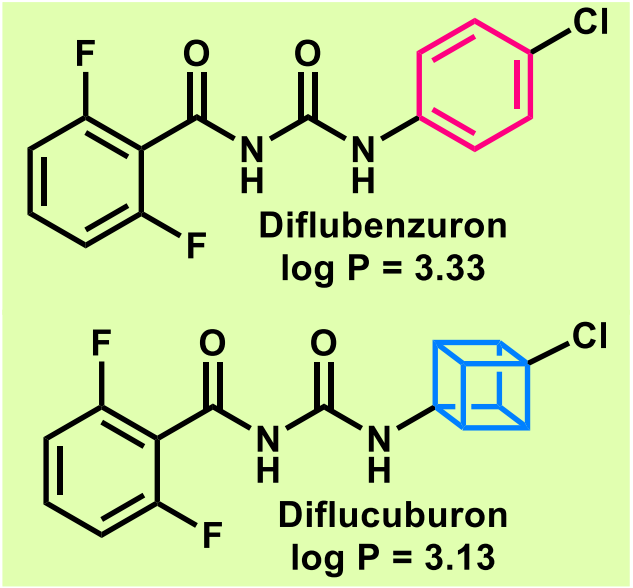
Extent and duration of antinociception (DPTT AUC values) evoked by single intraplantar bolues doses of benzocaine or cubocaine Negative control: water.





2-2-10. Biological Data for Diflucuburon

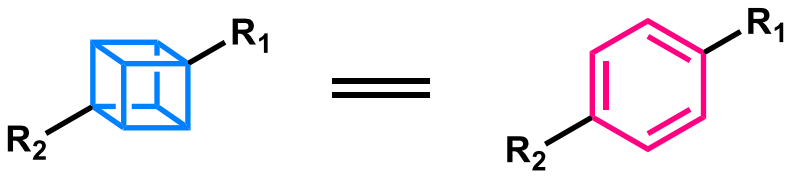




Mean (±SE) mortality of *T. castaneum* caused by different doses of diflucuburon and diflubenzouron.

In summary, cubane derivatives functioned as strong as or stronger than their benzene counterparts in various cerapeutics. This result support the idea that cubane act as isoster of benzene.

Summary



Cubane structure was

1. Tolerant to a wide range of reaction conditions
   - Acid catalyzed transesterification
   - Deprotection
   - Base-mediated hydrolysis
   - Curtius rearrangement
   - Barton decarboxylation
   - Chlorination
   - Diazotization
   - Borane reduction
2. Showed possibility as bioisoster of benzene