Exploring Cubanes as Bioisosteres of Benzene Rings: Towards the Synthesis of 1,3-Disubstituted Cubanes

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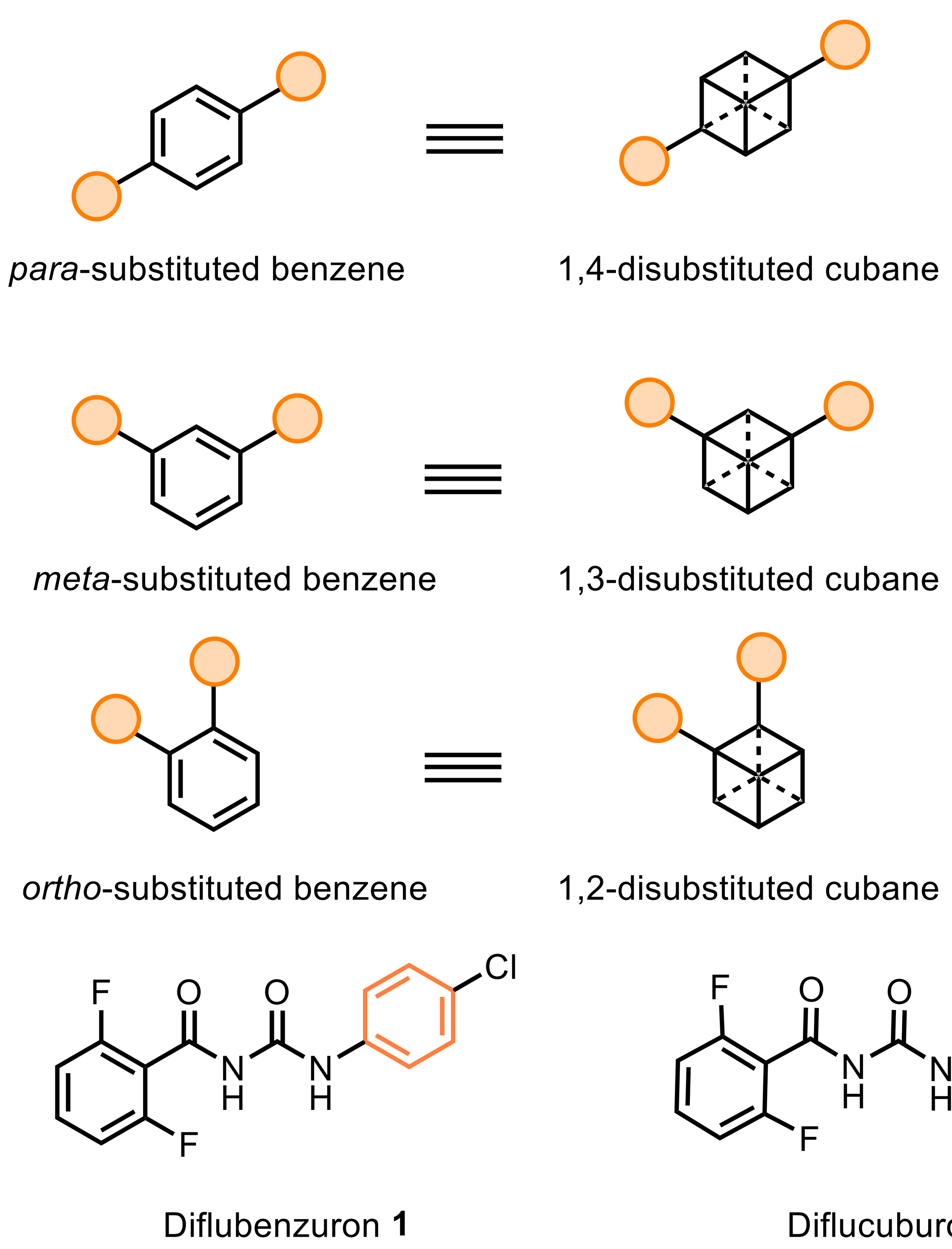
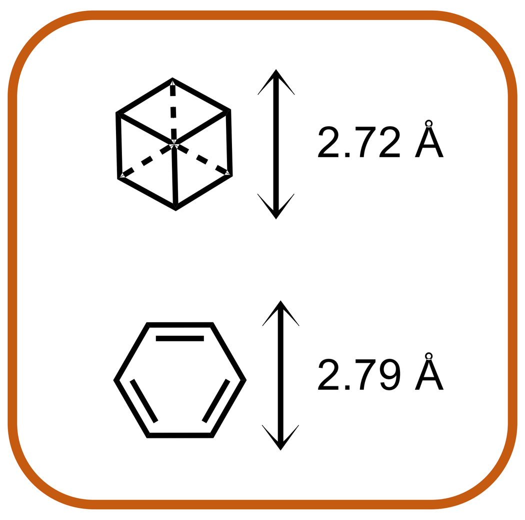
Cubane: A 3D Scaffold of Interest

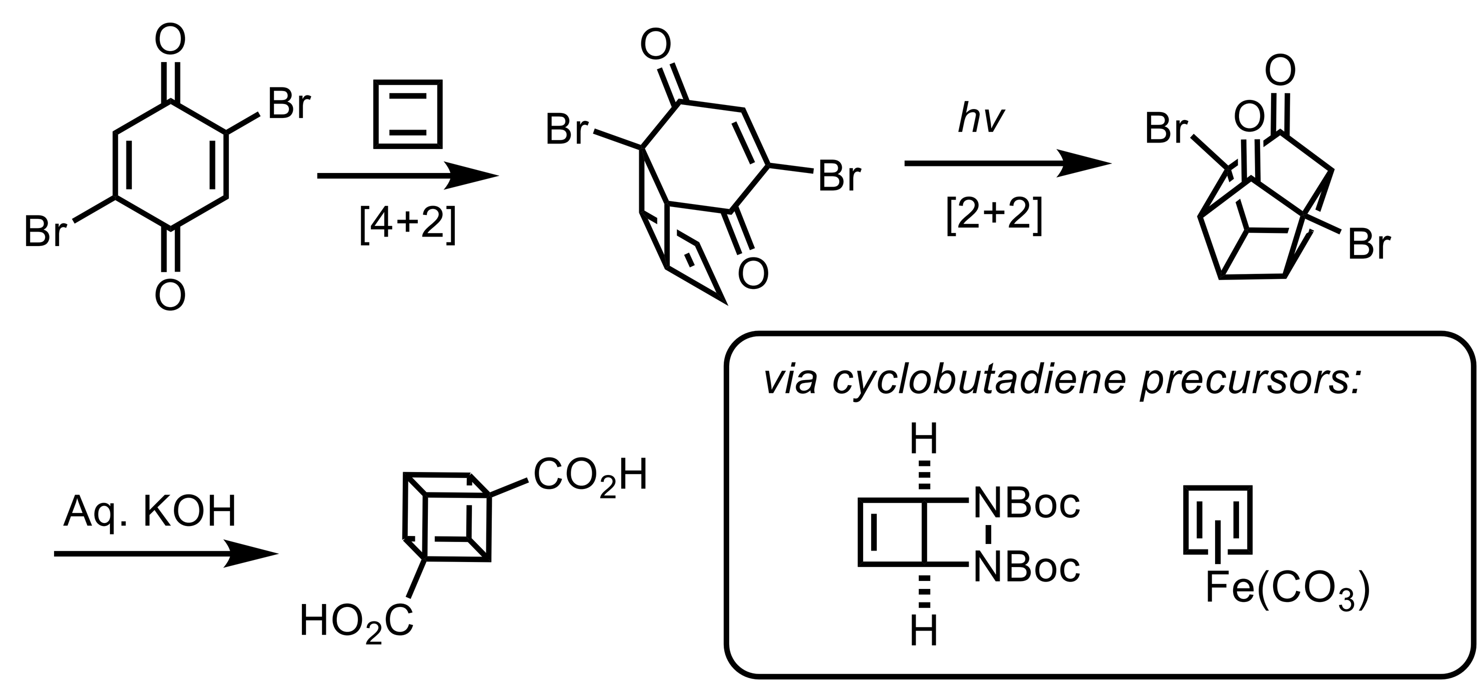


- ***Caged polycyclic carbocycles that are highly strained, but remarkably stable.***
- ***Potential bioisosteres for benzene rings, with diflucuburon 2 being more potent than diflubenzuron 1.[1]***
- ***Greater three-dimensionality allows access to more chemical space than flat, aromatic systems.***
- ***Only mono- and 1,4-disubstituted cubanes have been explored as terminal and para-benzene bioisosteres.[1,2]***

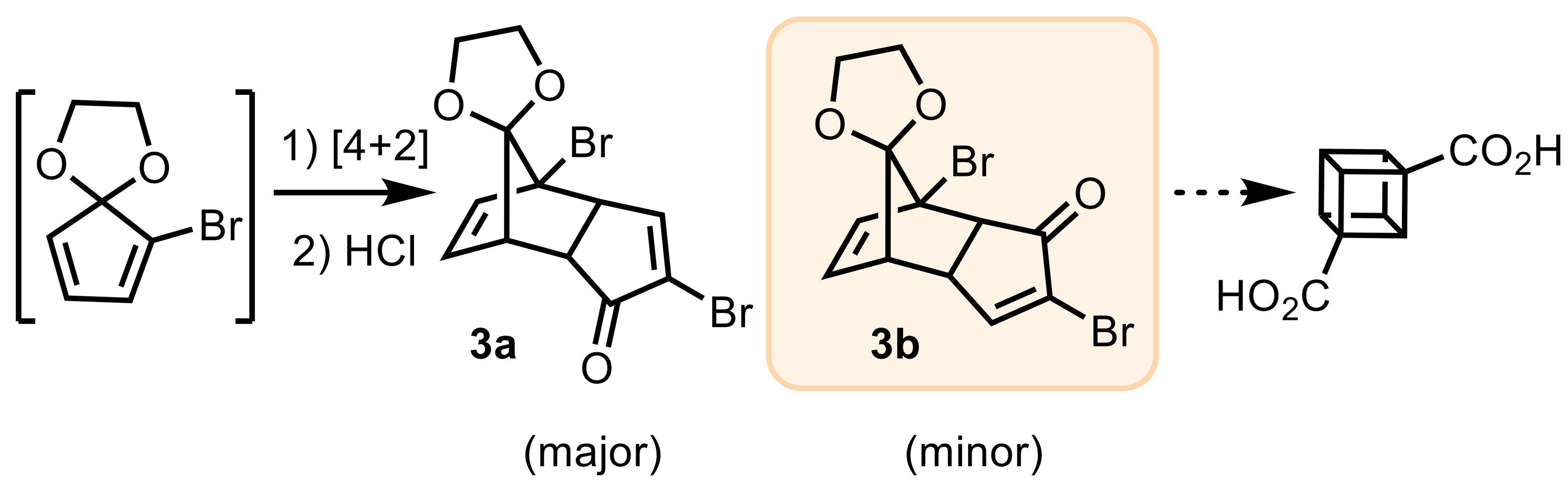


Previous Work

a) Macmillan and Pettit Routes to 1,3-Disubstituted Cubanes.[3,4]

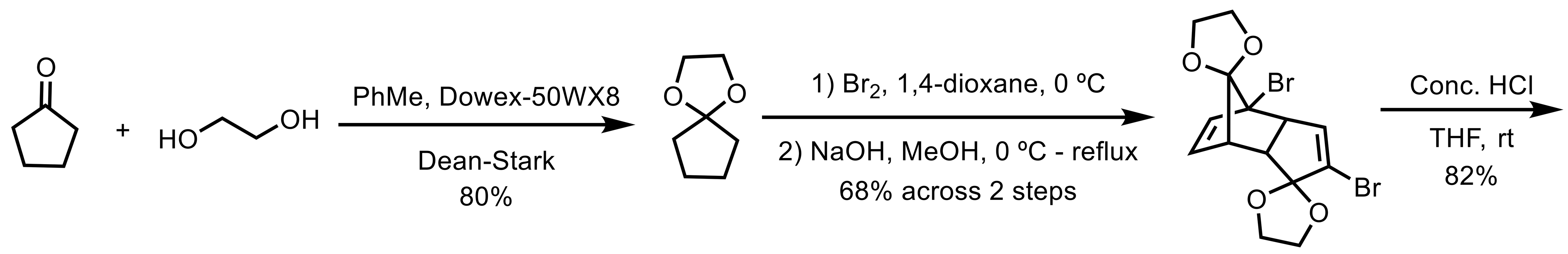


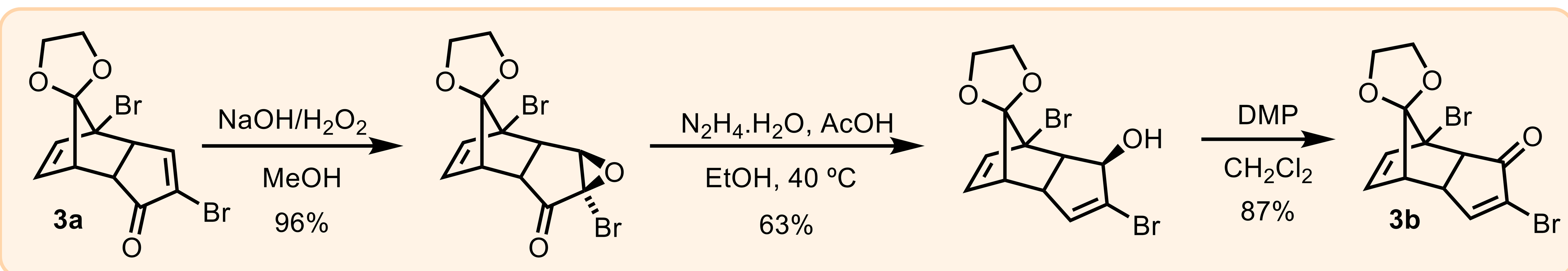
b) Ueda's Route to 1,3-Disubstituted Cubanes.[5]

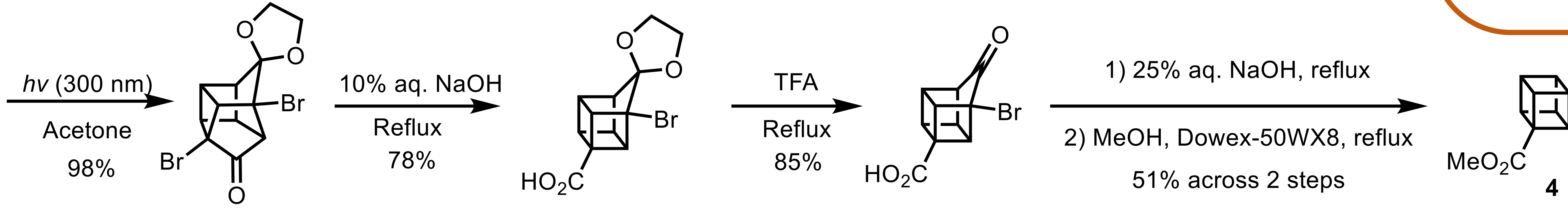


- ***Inaccessible starting materials and/or not suitable for scale-up.***

New Approach to 1,3-Disubstituted Cubanes

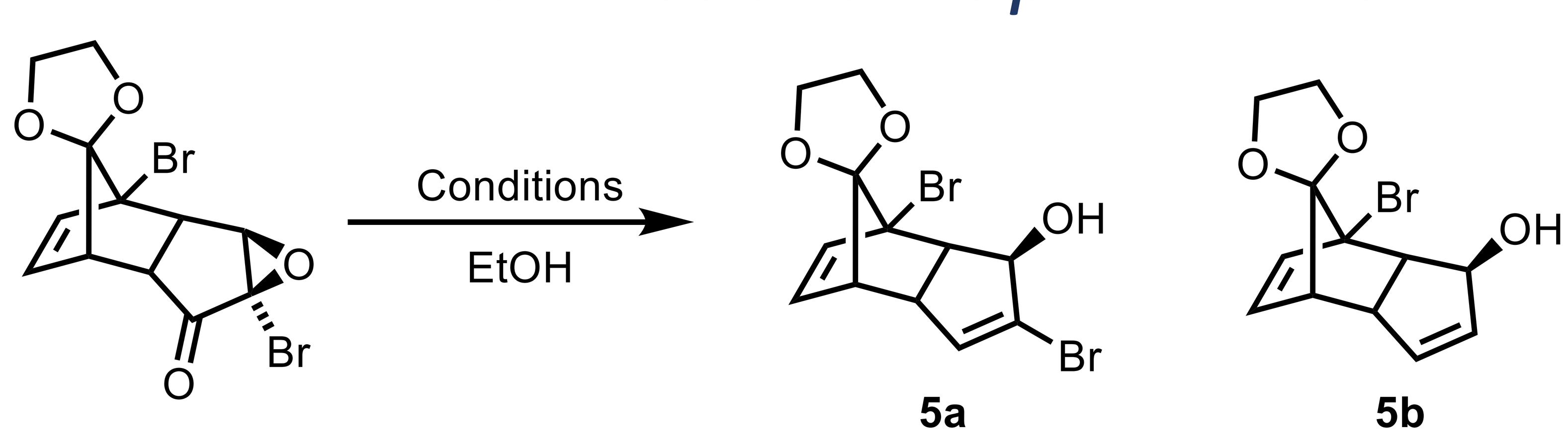






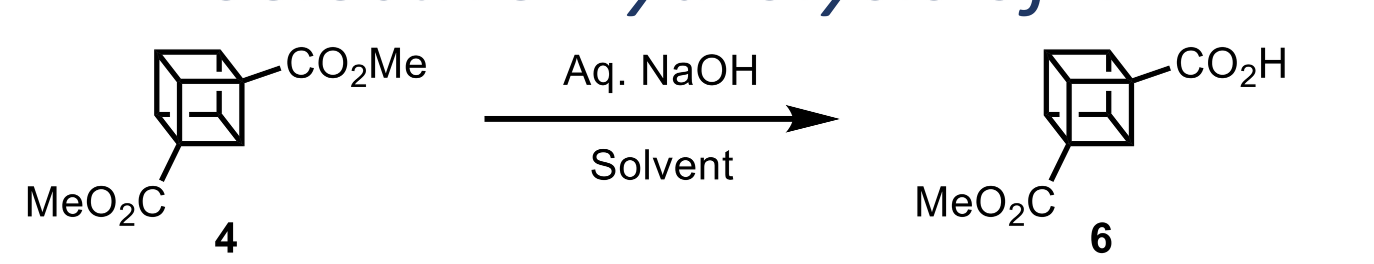
- ***Route focuses on redirecting a key intermediate (3a) in Chapman's synthesis of 1,4-disubstituted cubanes.[6]***
- ***Three-step transformation to access isomeric enone 3b.***
- ***Allows access to cubane 4 on a multigram scale, using limited purifications.***

Wharton Reaction Optimisation



Entry	Reagent (equiv.)	Acid (equiv.)	Temp. (°C)	Time (h)	5a:5b
1	$N_2H_4.H_2O$ (3)	AcOH (2)	rt	5	7.5:1
2	$N_2H_4.H_2O$ (5)	AcOH (3)	rt	4	4.9:1
3	$N_2H_4.H_2O$ (1.5)	AcOH (2)	rt	24	13.0:1
4	$N_2H_4.H_2O$ (1.5)	AcOH (2)	0	24	7.8:1
5	$N_2H_4.H_2O$ (1.5)	AcOH (2)	80	0.25	5.8:1
6	$N_2H_4.H_2O$ (1.5)	AcOH (2)	40	1	11.7:1

Selective Hydrolysis of 4



Entry	Conc. (M)	Solvent	Temp (ºC)	Time (h)	Yield of **6**
1	2.5	THF	rt	24	17
2	2.5	1,4-Dioxane	rt	24	0
3	2.5	MeOH	rt	24	60
4	2.5	MeOH	50	24	37
5	2.5	MeOH	0	24	34
6	1.0	MeOH	0	72	61

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