Cyclobutanes:
- exist in puckered conformation where eclipsing interactions of C-H bonds are minimized.

\[
\begin{align*}
\text{Me} & \\
\text{Me} & \\
\text{Me} & \\
\text{Me} & \\
\end{align*}
\]

strain \[27.5 \text{ kcalmol}^{-1}\]

- its inherent ring strain makes formation of cyclobutanes difficult, yet it is this strain that makes cyclobutanes extremely useful in organic synthesis.

pentacycloanammoxic acid

- ladderane with 5 fused cyclobutanes
- 3 times the strain of a single cyclobutane
- found in bacteria-anammox process
- protects organisms from NH2OH/H2NNH2 formed in production of N2 and H2O from nitrates and nitrates
- cyclobutanes are the basic structural unit in bacteria, fungi, plants and marine invertebrates
- many biological activities: cpds like amino acids, peptides and nucleosides with cyclobutane often exhibit protective properties against UV.

* Nature 2002, 419, 708

Useful reviews on this topic:

* Cyclobutanes in Catalysis * Cramer, ACIE 2011, 50, 7740.
* Photochemical Reactions as Key Steps in NP Synthesis * Bach, ACIE 2011, 50,1000
* Photocycloaddition in NP Synthesis * Greaney, EJOC 2007 4801

Some methods to form cyclobutanes:

[2+2] cycloaddition of olefins:
- photochemically with \( \pi, \pi \)-unsat. substrates (mostly cyclic)
- C=O cpds
- ring closure via 1,4-diradical
- common sensitzers (for population of triplet state) are acetone/benzophenone
- OR TM-catalyzed [2+2]

Most naturally occuring NP containing cyclobutanes were synthesized using [2+2] cycloadd. of olefins.
Cyclobutanes in Organic Synthesis

*Punctaporonin C*
Bach, *ACIE* **2008**, 47, 6189

(+)-*Solanascone*

(-)-*Biyouyanagin A*

(JACS **2008**, 130, 11114)

(-)-*Littoralisone*

(+)-pentacycloammonoxic acid

*JACS* **2006**, 128, 3118

- use of 1,5-dienes in intramolecular [2+2] photocycloaddition leads to crossed regioselectivity

α-trans-**Bergamotene**
Corey, *JACS* **1971**, 93, 7016

(+)-**Paeonilbin**
Takano, *JACS* **2002**, 124, 4081

-4 studies towards the skeleton core
-3 of which involves a [2+2] photocycloaddition
-11 stereocenters

Lear, *TL* **2009**, 50, 1731

Sulikowski, OL **2006**, 8, 903


- use of 1,5-dienes in intramolecular [2+2] photocycloaddition leads to crossed regioselectivity

Nicolaou

Noyori cat. A

(84%, 92% ee)

MeO₂C

OH

CAN, MeOH

(58% dr 1:1)

1. Grubbs I

2. NaBH₄

(75%)

- use of 1,5-dienes in intramolecular [2+2] photocycloaddition leads to crossed regioselectivity

-4 studies towards the skeleton core
-3 of which involves a [2+2] photocycloaddition
-11 stereocenters

Lear, *TL* **2009**, 50, 1731

Sulikowski, OL **2006**, 8, 903

**Baran Group Meeting**

**Cyclobutanes in Organic Synthesis**

### Nishikama - radical cyclization

\[
\text{Hajos-Parrish ketone} \rightarrow \text{Cyclobutane} (77\%)
\]

### Other development of [2+2]-cycloaddition:

- [2+2] cycloaddition between 2 acyclic enones

\[
\text{Ph} + \text{Ph} \rightarrow \text{Cyclobutane} (84\%, dr >10:1)
\]

### C-H activation to form cyclobutanes

- R" has to be ester
- R' alkyl
- 10g scale (81\%) for R" = Me and R'=COOMe
- examples with more aromatic substitution

\[
\text{Baudoin, JACS 2008, 130, 15157}
\]

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**Solanececpin A**

**Hiemstra** - via [2+2] photocycloaddition

**Miyashita** - cyclization of epoxynitrile


**Nishikama, CL 2012, 287**

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**Bray, TL 2006, 47, 3937**
**Direct ring closure to cyclobutanes - some recent examples**

CuX (5mol%), Ligand (5mol%), B(pin) (1eq) rt, [B(pin)]2 (2 eq) base (1eq) rt

- bigger rings (5 or 6) can be made by increasing alkyl chain length (93%, 99:1 trans) Ito, JACS 2010, 132, 5990

**Cyclobutanes from cyclopropanes - some recent examples**

Barluenga, ACIE 2009, 48, 7569

**Applications of cyclobutanes**

- many examples covered in previous group meetings

**Cyclobutane from sugar - one example**

Pestalotiopsis A

Paquette, OL 2006, 8, 2429

**BMS-708,163**

- bicyc[1.1.1]pentane motif is a phenyl ring bioisotere
- in this case, observed 4 fold increase Cmax, solubility, activity, RRCK
- such motif easier to functionalize than aromatic system

Klement Foo

Pfizer, J. Med. Chem. 2012, 55, 3414
Cyclobutanes in Organic Synthesis

**Byssochlamic acid**

- attempted synthesis of seychellene
  - eg. of divinyl cyclobutane rearrangement

**CP263114**

- a common strategy to open annelated cyclobutanone

4 to 8 membered ring
- studies towards Taxol skeleton using cyclobutanes: see Wilde GM
  - Winkler, **J 1992**, 34, 7049; Blechert, **TL 1992**, 46, 6953

**Tetramethyldimediterraneol B**

- Mechanism?

**Desdimethyl-dihydroclovene**

- Mechanism?

**Longifolene**

- Winkler's synthesis of ingenol: see **JACS 2002**, 124, 9726
- Winkler's synthesis of saudin: see **JACS 1999**, 121, 7425
- see Cherny GM "Guaianes and Xanthanes" for alismol, dehydrokessans, pelocarpene.

**Snider, JOC 1988, 53, 4508**

**Snapper, JACS 1999, 121, 4534**

**Oppolzer, JACS 1978, 100, 2583**

**Eguchi, JOC 1999, 64, 707**
Cyclobutanes in Organic Synthesis

(+)-Guanacastepene A
Sorensen, JACS 2006, 128, 7025

Linderol A
Yamashita, SL 2004, 1897

Cylindrocyclophane
Danheiser, JOC 1984, 49, 1672

Balanitol
Angela, T 1987, 43, 5537

Mechanism?

- see Foo GM "JACS 1989" for echinospirin
- not covering squarate ester enlargement to phenolic system

Mechanism?

- Sc(OTf)3 is LA for R' = Ar otherwise
- they also attempted a one-pot [(2+2)+2] - form cyclobutane then THP using same LA

Johnson, JACS 2009, 131, 14202
Cyclobutanes in Organic Synthesis

1. PPTS
2. PhSeCl, HCl, NaI04

(49%)

Oxidation, p-TSA (94%)

DMDO, quant.

1. NaH
2. Mel (90%)

-2-aryl-2,3-dihydrobenzofurans
embedded in pterocarpan family
of NPs

Engler, JOC 1999, 64, 2391

Ghera, TL 1987, 28, 709

Gingkolide B

Crimmins, JACS 1999, 121, 10249

-precursor to trichotheconoids

White, Syn. 1998, 619

- ultimate cascade

Filjé, Chem. Ber. 1988, 121, 525

(--)-Merrilactone A

Inoue, ACIE 2006, 45, 4943;
JACS 2003, 125, 10772

-Mehta et al. also used [2+2]
to establish the 2 quaternary
tocenters, but built it
left to right.
Cyclobutanones in Organic Synthesis

\[ \text{Reaction 1:} \quad \text{Br} \quad \xrightarrow{\text{OMe}} \quad \text{TMS} \quad \xrightarrow{\text{Li}} \quad \text{HO} \quad \xrightarrow{\text{TMS}} \quad \text{HO} \quad \xrightarrow{\text{Br}} \quad + \quad \text{HO} \quad \xrightarrow{\text{TMS}} \quad \text{HO} \quad \xrightarrow{\text{Br}} \]

\[ \text{Reaction 2:} \quad \text{Bu}_3\text{Sn} \quad \xrightarrow{\text{SnBu}_3} \quad \text{Pd(PPh)}_3 \quad \xrightarrow{\text{SnBu}_3} \quad \text{HO} \quad \xrightarrow{\text{TMS}} \quad \text{OH} \quad \xrightarrow{\text{TMS}} \quad \text{HO} \quad \xrightarrow{\text{TMS}} \]

\[ \text{Reaction 3:} \quad \text{Ascosalipyrrolidinone} \quad \xrightarrow{\text{X-ray verified}} \quad \text{HO} \quad \xrightarrow{\text{TMS}} \quad \text{OH} \quad \xrightarrow{\text{TMS}} \quad \text{HO} \quad \xrightarrow{\text{TMS}} \quad \text{OH} \quad \xrightarrow{\text{TMS}} \]

Suffert, JACS 2001, 123, 12107