This group meeting presents a survey of common strategies and tactics for the synthesis of 5-membered carbocycles in the context of natural products synthesis.

Selected examples of natural products containing 5-membered carbocycles.

**Structural Considerations.**

1) Oxidation state (0 to 10, but > 4 is rare). e.g.

![Oxidation state](image)

Most of these have several redox equivalent structures/hydration levels. For example, when the degree of oxidation = 3:

![Oxidation state example](image)

2) Degree of Substitution, e.g.

![Degree of Substitution](image)

3) Nature of Substitution, e.g.

   - Fused vs. Bridged ring systems
   - Identity of substitution
     - EWGs, EDGs, Ar, Alkyl, Halogen, etc.
   - Stereochemistry
     - Both the absolute and relative stereochemistry of the substituents

4) Physical organic chemistry considerations

   - Cyclization to form 5-membered rings is the fastest of any size (in general, >100x than 6-membered rings). For this reason, 5-membered rings are frequently formed in the construction of adjacent ring systems.
   - 5-membered rings are thermodynamically less stable than 6-membered rings. Be aware of this fact when both cyclization modes are viable and the reaction pathway is reversible.
   - Relay of stereochemical information about a 5-membered ring is often challenging, and far less predictable than in 6-membered rings.

These structural considerations determine which strategies and tactics should be selected retrosynthetically.
Strategies

1) Make 1 bond (most common, by far)

![Diagram 1]

2) Make 2 bonds

![Diagram 2]

3) Make 3 bonds

![Diagram 3]

4) Rearrangements (very common)

![Diagram 4]

Tactics (not exhaustive)

Make 1 bond
- as tethers in the process of making other rings, especially cycloadditions reactions
- intramolecular S_N2/alkylation
- intramolecular Wittig
- classic carbonyl chemistry: aldol, Michael, Claisen, Dieckmann, Mannich, etc.
- Friedel-Crafts
- Nazarov
- Piancatelli
- vinylidine/carbonoid C-H insertions
- radical cyclizations
- cycloisomerizations
- π-philic metal-mediated/catalyzed cyclization (more recent development)
- ring closing metathesis
- Prins/Ene
- many others...

Make 2 bonds
- stabilized dipole and photo [3+2]
- phosphine catalyzed [3+2]
- arene-alkene meta-photocycloaddition
- double alkylation (formal [4+1])
- radical cascades
- [5+2] cycloadditions

Make 3 bonds
- Pauson-Khand

Rearrangements
- 3→5 (vinyl-cyclopropane rearrangement)
- 4→5 (Tiffeneau-Demjanov; pinacol, semi-pinacol, etc.)
- 6→5 (oxidative cleavage, aldol; Favorskii; α-santonin di-π-methane)

α-ketol rearrangement
A) As a tether in the formation of other rings, especially cycloadditions

Since cyclization to form 5-membered rings is kinetically fastest of any cyclization (> 100x faster than 6-membered ring cyclization), 5-membered rings are frequently formed in the process of forming fused and bridged polycyclic systems. (eg. JACS 1984, 106(4), 1051). Cycloaddition reactions are particularly common in this regard.


Kozikowski, A.P.; Stein, P.D. JACS 1982, 104(14), 4023.
B) Intramolecular $S_{N}2$ alkylation

\[
\begin{align*}
\text{LiN}({}^{t}\text{Bu})_{2}, \ -120^\circ\text{C} & \quad \text{kinetically controlled deprotonation} \\
\end{align*}
\]

2 steps

aphidicolin

Corey and co. *JACS* 1980, 102, 1742.

B) Wittig, HWE, etc. type olefinations

\[
\begin{align*}
\text{NaH, THF, } \Delta & \quad (91\%) \\
\end{align*}
\]

11 steps

(–)-jiadifenin

C) Classic carbonyl chemistry

**aldol condensation**

1) pyrrolidine, PhCO₂H, PhH
2) aq. AcOH, AcONa, CHCl₃, Al₂O₃, PhH
(84.5%)


**aldol addition**

1) O₂, CH₂Cl₂, -78 °C; Me₂S, -78 °C→23 °C
2) NaOMe, THF, 0 °C
(50%, 2 steps)

Make 1 bond

**Aldol addition**

\[ \text{NHCHO} + \text{RCHO} \xrightarrow{1) \text{DBN, CH}_2\text{Cl}_2, 0 \, ^\circ\text{C}} \text{adduct} \xrightarrow{2) \text{Ac}_2\text{O, pyr.}} \text{product} \]

*Made by oxidative cleavage of a DA adduct.*

**Michael/aldol addition**

\[ \text{MeO} + \text{RCHO} \xrightarrow{1) \text{base, 2) HWE}} \text{adduct} \xrightarrow{\text{SnCl}_4, \text{acetone}} \text{product} \]

Corey and co. *JACS* 1968, 90, 3245.

**Michael addition**

\[ \text{MeO} \xrightarrow{i) 2N \text{HCl, EtOH, 100 \, ^\circ\text{C}}} \text{product} \xrightarrow{ii) \text{ethylene glycol, Et}_3\text{N, 225 \, ^\circ\text{C} (10-20\%, 2 steps)}} \text{product} \]


**Final ring closed by an aldol condensation**

Make 1 bond

**Dieckmann**

![Dieckmann reaction diagram]


**Mannich**

![Mannich reaction diagram]


**D) Friedel-Crafts**

![Friedel-Crafts reaction diagram]

E) Cationic
cation-olefin cyclization

Corey and co. *JACS* 1969, 91, 1557; *JACS* 1955, 77, 1072; *JACS* 1961, 83, 3114

**cyclopropanation, then cationic ring opening strategy**

Corey and co. *JACS* 1987, 109, 6187; For a similar strategy in cafestol and kahweol syntheses, see *JACS* 1987, 109, 4717; *Tetrahedron Lett.* 1987, 28, 5403.

E) Pericyclic
metallo-ene


*Bases with K+ as a counterion were optimal for this reaction. Yields and reaction times with Na+ counterions were lower, and Li+ gave no product. (i.e. 71%:57%:0% yields on test substrate.)*
Nazarov

(Use of AIBN/HSnBu₃ was used to form the other 5-membered ring)

Photo-Nazarov

A carbonylative Stille coupling was used to join the left and right halves.

The photo-Nazarov is commonly used when aromatic rings are involved, and can occur at neutral or basic pH.
F) Radical Methods

Tin radical examples

\[
\begin{align*}
\text{MeO} & \quad \text{Me} \\
\text{O} & \quad \text{H} \\
\text{H} & \quad \text{Me} \\
\end{align*}
\]

\[
\begin{align*}
\text{Bu}_3\text{SnH}, \text{AIBN}, \text{PhH}, & \quad 80 ^\circ \text{C}, 22 \text{ h.} \\
& \quad (57\%) \\
\text{Me} & \quad \text{Me} \\
\text{H} & \quad \text{Me} \\
\text{MeO} & \quad \text{Me} \\
\end{align*}
\]

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

\[
\begin{align*}
\text{Bu}_3\text{SnH}, \text{AIBN}, \text{PhH} & \quad \text{(slow addition)} \\
& \quad (69\%) \\
\text{Me} & \quad \text{Me} \\
\text{H} & \quad \text{Me} \\
\text{MeO} & \quad \text{Me} \\
\end{align*}
\]

\[
\begin{align*}
\text{Bu}_3\text{SnH}, \text{AIBN}, \text{PhH} & \quad 80 ^\circ \text{C}, 22 \text{ h.} \\
& \quad (57\%) \\
\text{Me} & \quad \text{Me} \\
\text{H} & \quad \text{Me} \\
\text{MeO} & \quad \text{Me} \\
\end{align*}
\]

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


Both diastereomers give the same distribution of only cis products

Shenvi Lab Group Meeting
June 19, 2017

S. Crossley

Make 1 bond

SmI₂ cyclization

\[
\text{SmI}_2, \text{LiBr, } '\text{BuOH, THF} \\
\text{-78 °C (54%)}
\]

\((-\text{-macocrystal } Z\)

Reisman and co. *JACS 2011, 133, 14964.*

\[\text{SmI}_2 \text{ mediated pinacol coupling. Reduction of the aldehyde to the hydroxyl followed by ketalization is a competitive pathway.}\]

\[
\text{Sml}_2 (5 \text{ equiv.}, \text{THF, HMPA (20 equiv.), 23 °C) (67%)}
\]

\((+\text{-fawcettimine)}

Lei, X. and co. *ACIE 2012, 51, 491.*

\[\text{Ti(III) initiated}\]

\[
1) \text{Cp}_2\text{TiCl}_2, \text{Zn}^0, \text{THF, 60 °C} \\
2) \text{TBSCI, imid., DMF, (42%, 2 steps)}
\]

\[\text{berkeleyone } A\]

Make 1 bond

**Polarity-reversal + asymmetric catalysis**

\[
\text{Et}_3\text{B} (1.25 \text{ equiv.}), \quad \text{TMS}_3\text{SiH} (1.0 \text{ equiv.}), \quad \text{cyclopentane} [0.009 \text{ M}], \text{ air}
\]

```
<table>
<thead>
<tr>
<th>Compound</th>
<th>AcO</th>
<th>Cl2C</th>
<th>H2C</th>
<th>Cl2C</th>
<th>AcO</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBSO</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
</tr>
</tbody>
</table>
```

Thiol catalyst (25 mol%), -10°C

(56% combined yield of all diastereomers)

```plaintext
-10\(^\circ\)C
```

**Polarity-reversal + asymmetric catalysis**

```
\text{Et}_3\text{B} + \text{O}_2 \rightarrow \text{Et}\text{^}\text{•} + \text{Et}_2\text{BOO}\text{^}\text{•} \rightarrow \text{radical initiation}
\text{Et}_2\text{BOO}\text{^}\text{•} + \text{TMS}_3\text{Si-H} \rightarrow \text{Et}_2\text{BOOH} + \text{TMS}_3\text{Si}\text{•}
```

```
\text{R}\text{'S-H}
```

**Plausible mechanism based on literature precedence:**


**Chirality in the final step is enabled by a terminating H^+ abstraction from the chiral thiol by the tertiary carbon radical**

G) Carbene/Carbenoid

Hodgson cyclopropanation.

\[
\text{MOMO} \quad \text{Me} \quad \text{O} \quad \text{O} \quad \text{Me} \\
\text{LTMP, 'BuOMe, -78 °C→23 °C} \\
\text{6 steps} \\
\text{chloranthalactone A}
\]


Carbene: C-H insertion

\[
\text{Me} \quad \text{Me} \quad \text{Me} \\
\text{CHBr}_3 (2 \text{ equiv.}), \text{MeLi (1 equiv.)} \\
\text{Et}_2\text{O, -75 °C→-30 °C; MeLi (1 equiv.), -30 °C→0 °C} \\
\text{(26%)} \\
= \text{ishwarane}
\]


Benzylic C-H insertion of a Rh-carbenoid. An example of enantioselective quaternary carbon formation.

\[
\text{MeO}_2\text{C} \quad \text{N} \quad \text{O} \\
\text{Rh}_2(\text{OAc})_4 (\text{cat.}), \text{CH}_2\text{Cl}_2, 30 \text{ min.} \\
\text{4 steps} \\
\text{α-cuparenone}
\]

Formation of 9-membered enediyne macrocyclic natural products. The high strain of a 9-membered enediyne macrocycle necessitated initial formation of a 12-membered macrocycle (by an Eglinton Cu-mediated alkyne-alkyne coupling), followed by 5-membered ring closure to access the challenging 9-5 fused ring system.


H) Metal catalyzed/mediated anulation methods. The power of metal mediated/catalyzed cyclizations may be attributed to their capacity to form multiple ring systems in a cascade sequence, forge highly substituted stereocenters, effect enantioselective transformations through catalyst control, and exhibit good chemoselectivity.

Heck annulation

Oppolzer's palladium-ene/Heck annulation.


Trost's Pd-catalyzed Alder-ene reaction effectively forges the cis-fused 5-6 ring system of picrotoxinin.

(M. Krische's graduate work) Trost and co. *JACS* 1996, 118, 233; *JACS* 1999, 121, 6183

Ring closing metathesis

Make 1 bond

Enyne RCM

Grubbs I, ethylene, CH₂Cl₂, 23 ºC
(86%)

9 steps

valerenic acid


electrophilic Pt-catalyzed cycloisomerization

Wender's use of a zirconium-mediated enyne ring closure.


Pd-catalyzed isomerization.

"Considering that the basicity and leaving ability of β-ketoester enolate are similar to those of phenoxide, we rationalized that a transition metal complex that promotes the substitution of a phenyl ally ether would fit the requirement."

Li, A. and co. *JACS* 2012, 134, 920.

[4+1] double alkylation strategy

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June 19, 2017

Make 1 bond

S. Crossley
A Claisen-Michael cascade

\[
\text{LDA (2 equiv.), HMPA (3 equiv.), THF; }\]

(72%)

5-endo-dig


Phosphine catalyzed [3+2]. Not (yet) commonly used in total synthesis, but is an active area of research. See G. Fu's work for extensive developments.

Stabilized cation-olefin [3+2]

Biosynthetically, many 5-membered ring containing terpenes and terpenoids arise from tail-to-head cation-olefin cyclization cascades. This paper demonstrates that these cyclization pathways are viable in a flask by sequestration of the counterion away from the propagating cation to make a number of highly strained terpenes, including cedrenes, funebrenes and cumacrenes.
Make 2 bonds

[3+2] photocycloaddition

\[
\text{Ph} = \text{CO}_2\text{Me} \quad \text{hv, CH}_2\text{Cl}_2/\text{PhMe} \quad -70 \degree \text{C} (66\%)
\]

via:

\[
\text{OMe} \quad \text{OH} \quad \text{MeO}_2\text{C} \quad \text{Ph}
\]

\[
\text{OMe} \quad \text{OH} \quad \text{Ar}
\]

\[
\alpha\text{-ketol rearrangement}
\]

4 steps

\[
\text{(-)-silvestrol (87% ee)}
\]

[5+2] cycloadditions can be used to form 5-membered rings

\[
\text{HO} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Pb(OAc)}_4, \text{CHCl}_3 \quad -40 \degree \text{C} (61\%)
\]

\[
\alpha\text{-cedrene}
\]

\[
\alpha\text{-pipitzol}
\]

\[
\text{sec-cedrenol}
\]


Alkene-arene meta photocycloaddition. The alkene-arene meta-photocycloaddition is one of the most powerful reactions for building up complexity (3 bonds and up to 6 stereocenters formed), but has numerous subtleties which make it difficult to modulate. The reaction has generally been used to rapidly construct triquinane (linear, angular and propellane) containing natural products. See Belstein J. Org. Chem. 2011, 7, 525; Chem. Rev. 2016, 116(7), 9816 for details.

Paul Wender has shown the utility of this reaction in the synthesis of numerous natural products, including this seminal synthesis of α-cedrene. Through use of an intramolecular tether and judicious selection of aromatic substituents, Wender is able to effect the desired meta cycloaddition with the desired regiochemistry over competing ortho- and para- cycloaddition pathways.
**Pauson-Khand reaction, a [2+2+1] annulation**

- this reaction results in the formation of two ring systems when employed intramolecularly

Make 3 bonds


Rearrangements

A) 3→5 ring expansion

*vinyl-cyclopropane rearrangement.* Normally required $T > 300$ °C, but can occur under lewis acidic conditions if there are charge stabilizing functional groups.

\[
\text{MeO} \quad \text{CO}_2\text{Me}
\]

1) Cu cat, PhMe, $\Delta$ (84%)
2) Br$_2$, 0 °C, CCl$_4$/Et$_2$O
3) DBU, DMF, 50 °C (48%, 2 steps)

\[
\text{MeO} \quad \text{CO}_2\text{Me}
\]

Et$_2$AlCl, CH$_2$Cl$_2$, 0 °C (80%)

15 steps

\[
\text{MeO} \quad \text{CO}_2\text{Me}
\]


B) 4→5 ring expansion

*Often effected from a [2+2] cycloaddition adduct by generation of cation or similarly activated leaving group.*

\[
\text{MeO} \quad \text{CO}_2\text{Me}
\]

LDA, THF, HMPA; -105 °C→-50 °C

\[
\text{MeO} \quad \text{CO}_2\text{Me}
\]

FVP (585 °C) 10$^{-4}$ mmHg

(27% β-H (shown) + 24% α-H)

4 steps

\[
\text{MeO} \quad \text{CO}_2\text{Me}
\]

Hudlicky and co. *JACS* 1989, 111, 6691.
**Rearrangements**

**semi-pinacol rearrangement**

\[
\text{Me} \quad \text{Me} \\
\downarrow \quad \uparrow \\
\text{Me} \quad \text{Me}
\]

1) hv, -10 °C, pentane

\[
\text{Me} \quad \text{Me} \quad \text{H} \quad \text{H} \quad \text{Me} \quad \text{Me} \\
\downarrow \quad \uparrow \quad \downarrow \quad \uparrow \\
\text{Me} \quad \text{Me} 
\]

40% H$_2$SO$_4$

THF, -5 °C → 25 °C

\[
\alpha\text{-caryophyllene alcohol}
\]


**acid-induced ionization**

\[
\text{Me} \quad \text{Me} \quad \text{O} \\
\downarrow \quad \uparrow \\
\text{Me} \quad \text{Me}
\]

1) hv, (350 nm) hex. (77%)

\[
\text{Me} \quad \text{Me} \\
\downarrow \quad \uparrow \\
\text{Me} \quad \text{Me}
\]

2) Ph$_3$P=CH$_2$, DMSO, 70 °C

Isocomene can also be obtained by a mechanism involving an initial shift of the b bond and a second Wagner-Meerwein shift, see Ch. 14 of Classics in Total Synthesis.

Pirrung, M.C. *JACS* 1979, 101, 7130; 1981, 103, 82.

**Tiffeneau-Demjanov ring expansion**

\[
\text{Me} \quad \text{Me} \\
\downarrow \quad \uparrow \\
\text{Me} \quad \text{Me}
\]

1) NaBH$_4$

\[
\text{Me} \quad \text{Me} \\
\downarrow \quad \uparrow \\
\text{Me} \quad \text{Me}
\]

2) Cr(ClO$_4$)$_2$

2) CH$_2$N$_2$

another 4 steps gives hirsutene

Rearrangements

C) 6→5 ring contraction

Oxidative cleavage of alkenes, followed by aldol condensation is the classic way in which to effect a 6→5 ring contraction. This tactic is useful for several reasons:

a) Stereocontrolled formation of highly substituted cyclohexenes is well studied, and oxidative cleavage/aldol addition/condensation is robust and highly FG tolerant.

b) Allows one to use the chiral centers found in the numerous and cheap chiral pool 6-membered terpenes and terpenoids.

c) The transformation retains the olefin and adds an exocyclic carbonyl handle, both of which may be utilized for subsequent transformations.

Use of a Diels-Alder transform enables construction of 3 stereocenters of the stereochemically dense massidine/palau’amine cyclopentane core. Oxidative cleavage and aldol addition sets the other 2 stereocenters, with stereocontrol set by the former 3 stereocenters.

In Hu and Synder’s synthesis of (−)-presilphiperfolan-8-ol, a Wolff rearrangement proved optimal to effect the 6→5 ring contraction. Like epoxydictymene, palau’amine and the funebrenes, (syntheses of which are all featured in this group meeting) presilphiperfolan-8-ol contains a strained 1,2-trans ring fusion. In cases like these, direct formation of the 5-membered ring directly is often avoided in favor of the more facile 6-membered ring formation, followed by a ring contraction.
Rearrangements

Wolff rearrangement

\[
\text{MeO} \quad \text{OMe} \quad \text{Me} \\
\text{Me} \quad \text{Me} \quad \text{Me} \\
\text{H} \quad \text{O}_2 \quad \text{N}_2 \\
\text{MeO} \quad \text{OMe} \quad \text{Me}
\]

\[
\text{collidine, BnOH, 160 °C} \quad \text{(56%)} \\
\]

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

\[
\text{6 steps}
\]

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

taiwaniaquinol B


Favorskii rearrangement

\[
\text{OTBDMS}
\]

\[
\text{NaOH, EtOH, rt.} \quad \text{(70%)} \\
\text{Herz-Favorskii}
\]

\[
\begin{align*}
\text{EtO}_2 & \quad \text{C} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

\[
\text{17 steps}
\]

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

trichodermol


α-santonin rearrangement

\[
\text{hv, AcOH} \quad \text{(50%)} \\
\]

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

di-\(\pi\)-methane and o xo-di-\(\pi\)-methane rearrangements can convert [2.2.2] (bridged) bicycles to [3.3.0] (fused) tricycles:

\[
\text{O} \quad \text{Me} \quad \text{OPv} \quad \text{OPv} \quad \text{hv} \quad (300 \text{ nm}), \quad \text{acetone, r.t.} \quad (91\%)
\]


\[
\text{Me} \quad \text{H} \quad \text{CO}_2 \text{Me} \quad \text{O} \quad \text{pentaleneolatone P methyl ester}
\]

**D) Other**

5-membered ring formation from 8 membered macrocycle

\[
\text{OH Me} \quad \text{OBn} \quad \text{OH Me} \quad \text{1) Pb(OAc)}_4 \quad (95\%) \quad \text{19 steps}
\]

\[
\text{OH Me} \quad \text{OBn} \quad \text{OH Me} \quad \text{2) LiHMDS, THF, } -100 \text{ °C} \quad (85\%) \quad \text{merrilactone A}
\]

Multiple Strategies

**Pinacol coupling, followed by a 6→5 ring-contraction**

![Chemical structure diagram showing the transformation of pinacol into a compound with a 6-membered ring followed by a 6→5 ring contraction.](image)

1) Ti (from TiCl₃+K), THF (55%)
2) MeOH; aq. K₂CO₃
3) Swern
4) MEMCl, base

1) OsO₄, NMO, acetone, H₂O
2) Pb(OAc)₄, PhH, 5 °C
3) CF₃CO²⁻·Bn₂NH⁺, PhH, 50 °C

→ giberellic acid

**Favorskii, Nicholas/Prins/Prins/Sakurai, Pauson-Khand, conjugate addition**

![Chemical structure diagram showing the conversion of a cyclic diene into a trans-fused 5-5 ring system.](image)

1) Br₂
2) NaOMe, MeOH

→ radical conditions gave the 6-membered ring

1) tBuLi (2 equiv.), Et₂O, -78 °C (74%)
2) K, 18-c-6, PhMe (82%)

→ epoxydictymene

→ Co(CO)₈
1) Co₂(CO)₈
2) AlEt₂Cl, CH₂Cl₂
-78 °C (20:1 dr, 82%)

→ via:

- CH₃CN, air, reflux, 15 min. (85%, 5:1 at C12)
- NMO, CH₂Cl₂ (70%, 11:1 dr)
- CH₃CN, ultrasound 40 °C (45%, 3:1)

installation of the trans-fused 5-5 ring system required considerable manipulation

Multiple Strategies

**Prins, 4→5 ring expansion, 6→5 ring contraction**

1) EtAlCl₂, PhH

(99%)

2) Et₃N, PhH

14 steps

via:

via:

n-BuLi, THF, -78 °C

5 steps

1) CuOTf, Et₃N, PhH

2) NaIO₄, aq. dioxane

3) Al/Hg, THF/H₂O

1) OsO₄, pyr.; NaHSO₃

2) Pb(OAc)₄, CH₂Cl₂

3) neutral Al₂O₃, mol. sieves, CH₂Cl₂

NaClO₂, NaH₂PO₄

H₂O/BuOH

retingeranic acid