Ryan L. Gianatassio

Retrosynthetic Analysis - Vol. 1

Baran GM
1/28/2012

Pre-lecture exercise: Please think about building a house backward.

To be covered:
1. Topological strategies
2. Discussion of terminology
3. Bond disconnection algorithms
4. Introduction to the polar bond theory (consonance/dissonance)
5. Basic Symmetry
6. Examples of application

You will obtain: the ability to rapidly identify strategic bond disconnections using topological strategies.

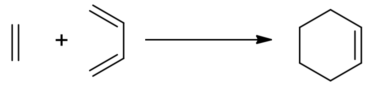
Potential topics for future meetings:
1. SM Goal, functional group, and stereochemical strategies
2. Structural Pattern Recognition in Natural Products
3. In depth discussion of polar bond (and consonance dissonance) theory
4. Multistrategic Analysis
5. Creative reaction development and T-Goal

*Suggestions for future strategy meetings are welcome: ryangi@scripps.edu

*Most strategies discussed in this meeting can be found in *The Logic of Chemical Synthesis and Elements of Synthesis Planning*

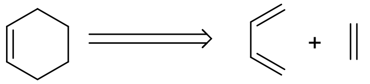
Retrosynthetic Analysis (Antithetic Analysis): synthesis planning - backward.

Reaction = forward



starting materials — product

Transform = backward



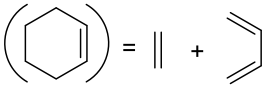
product — starting materials

Corey's Philosophy - Two General Categories

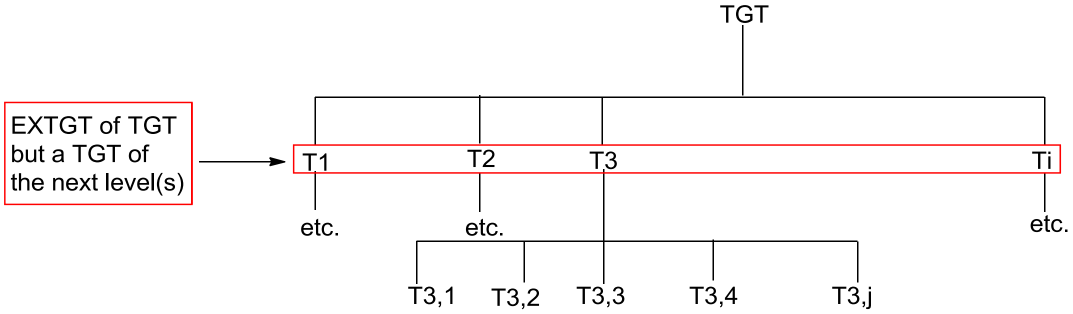
1. Topological, functional group, stereochemical strategies
2. Structure Goal (S-Goal) Transform Goal (T-Goal)

A robust organic transform can be thought of as a Mathematical Function (only one answer). That is, it is not desirable to invent or invoke the use of transforms that give mixtures, several byproducts, poor selectivity etc..

Diels-Alder transform expressed as a function

Diels-Alder


Targets and the Ex-target tree



≅

TGT tree = infinite extension of branches

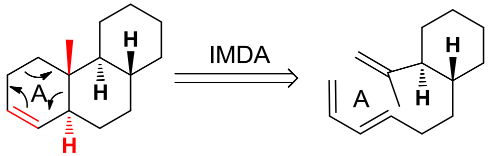
Ryan L. Gianatassio

Retrons, Supra-Retrons and Synthons

Corey:

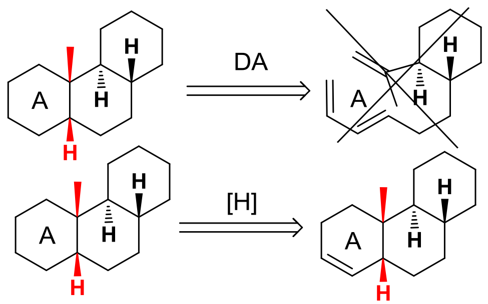
retrons: products of a reaction that are present in a molecule but may not indicate the strength of the transform.
supra-retrons: products (usually advanced intermediates) of a reaction that are usually the result of a powerful transform (highly selective, cascades, highly effective - form multiple rings etc.)
synthons: starting material(s)
partial retron: not the product of a reaction but close (can be converted to the full retron).

Example 1. A Retron with clearable stereocenters.



The intramolecular Diels-Alder transform with keying elements highlighted in red.
"Clearable" means that you will get the correct product (correct stereochemistry).
Tip: If you think a IMDA will work, draw the retro-DA transform product. Also, pushing arrows helps to generate the synthon(s).

Example 1a. IMDA transform fails; NOT AN IMDA RETRON.



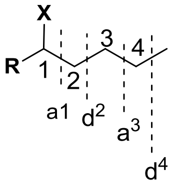
*But addition of olefin makes it a full retron.

*now it is an IMDA retron.

"Polar Bond" Theory: An Intro. to theories of Evans and Seebach: theories are similar; based on FG's; great for functional group relationship analysis.

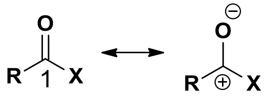
*classified by donor (d)/(nucleophile) and acceptors (a)/(electrophile)

Seebach



The set of "natural synthons" where C1 bears a positive charge affinity.

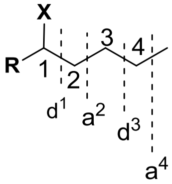
e.g.



acceptor at C1 = a^1 synthon

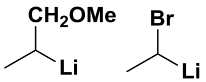
*Seebach: removal or addition of a proton can accentuate the reactivity pattern

ACIEE. 18, 239-258 (1979)



The set of non-natural or "umpoled" synthons where C1 bears a negative charge.

e.g.

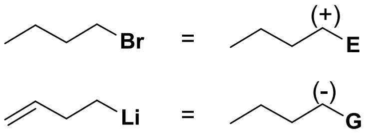


*Typically not strategic - add 2 steps b/c convert back to natural.
**But can be made strategic with aid of a catalyst.

What is the problem with this approach?

*uses (+) or (-) to denote positional polar reactivity

Evans

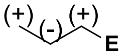


E is a FG that has a greater electronegativity than C = induces positive charge on C.

G induces negative charge.

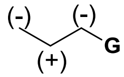
Further elaborated into 3 classes (Functions)

E function



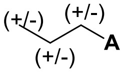
E Functions: -OR,NR_2,=NR, =O, halogens

G function



G Functions: -MgBr, -Li, halogens

A function



no charge preference

A functions: $-NO_2$, =NOR
$=NNR_2$, =N(O)R, $=N_2$, CN,
-SR, -S(O)R, $-SO_2R$, $-\overset{+}{S}R_2$,
$-PR_2$, $-P(O)R_2$, $-\overset{+}{P}R_3$

Ryan L. Gianatassio

Transform Selection and Molecular Complexity

Baran GM
1/28/2012

I. The Overall Goal of Antithetic Analysis: Decrease Complexity

Reduce: size cyclic connectivity or topology, element or functional group content, stereocenter content/density

Remove: centers of high chemical reactivity, centers of kinetic (thermal) instability

II. Characteristics of Powerful Transforms (most powerful)

Disconnect molecular skeleton (chains or rings).

a. *Keep in mind*: Diels-Alder, Robinson Annulation, aldol, Dieckmann, cation-π cyclization, internal S_N2 transforms

Remove or disconnect functional groups and stereoenters

Replace functional groups with hydrogen (e.g. C-H activation, C-H oxidation, C-H functionalization etc.)

*cascades, tandem, and domino strategies fall into this category

Non-Simplifying Transforms (moderate)

molecular skeleton: connect or rearrange (e.g. oxy-cope, pinacol)

functional groups: interchange or transpose (e.g. masking (Nef reaction), isomerization, [2,3] rearrangements)

stereocenter: invert or transfer (e.g. epimerization)

*try to use in a tactical combination with a powerful transform when possible

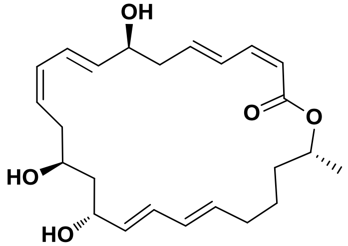
Transforms that Increase Molecular Complexity (lowest)

add: rings, functional groups, stereocenters, protecting groups, activating and/or deactivating groups and temporary bridges

"Fundamental to the wise choice of transforms is the awareness of the position each transform on the heirarchical scale of importance with regard to simplifying power and the emphasis on applying those transforms which produce the greatest molecular simplification."
-Logic of Chemical Synthesis

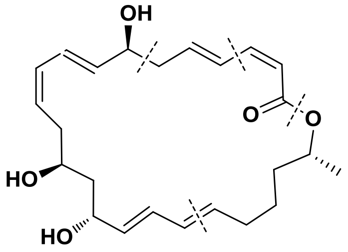
FYI: Reactions lower in the heirarchy become more powerful when they possess elements (or are combined with) of reactions that are higher in the heirarchy. In a sense, you can move a reaction up in the heirarchy. e.g. aza-cope mannich = very powerful

Macrolactin A:

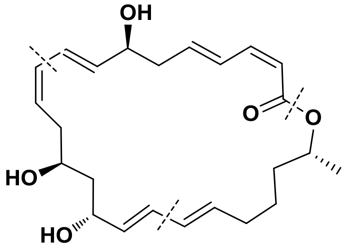


Break into fragments of equal complexity

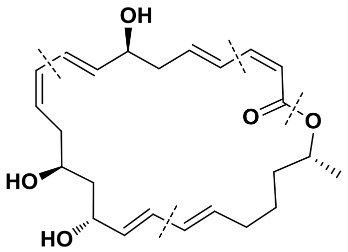
Which reaction should we avoid?



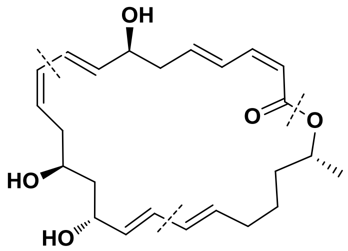
J.P. Marino, *JACS,* 1977,99,5439-5450.



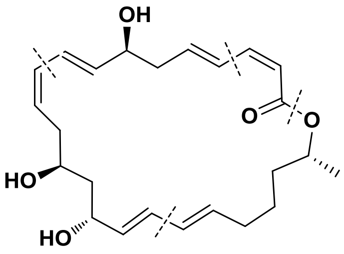
A. B. Smith, *JACS*, 1998, 120, 3935-3948.



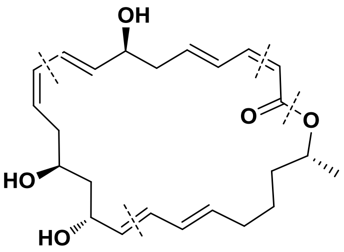
J. Pattenden, *TL*, 1996, 37, 3501-3504.



E. Carreira, *ACIEE*, 1998,37, 1261-1263.



J. Villarasa, *TL* 1996, 37, 8949-8952.



S. Tanimori, *Synthetic Commun.* 1996, 26, 559-567.

How would you disconnect? Need structural complexity and rxn robustness balance.

Acyclic Systems

Topological Strategies: These are single bond or bond pair disconnections that are signaled by the structure of the molecule.

Caveat: Disconnect means that the bond may (not must) be selected for disconnection. Strategic bonds will be denoted with blue arrows, (SB), and bonds.

Topological Strategies (LCS p.38):
Strategies for Acyclic Systems

1. Do not disconnect building-block type groups.
   Tip: If a building block group is present, then work backward to it.

2. Disconnect to obtain symmetrical precursors.

3. Disconnect bonds between carbon and heteroatoms (e.g. O,N,S,P).

4. Disconnect bonds that attach rings to chains (can be 1,2, or 3 bonds away from the ring).

5. Do not disconnect skeletal bonds that are attached directly to remote stereocenters.

6. Do not disconnect stereocenters that are far (more than 3C away) from functional groups.

8. Disconnect bonds between (1,2, or 3C between) functional groups

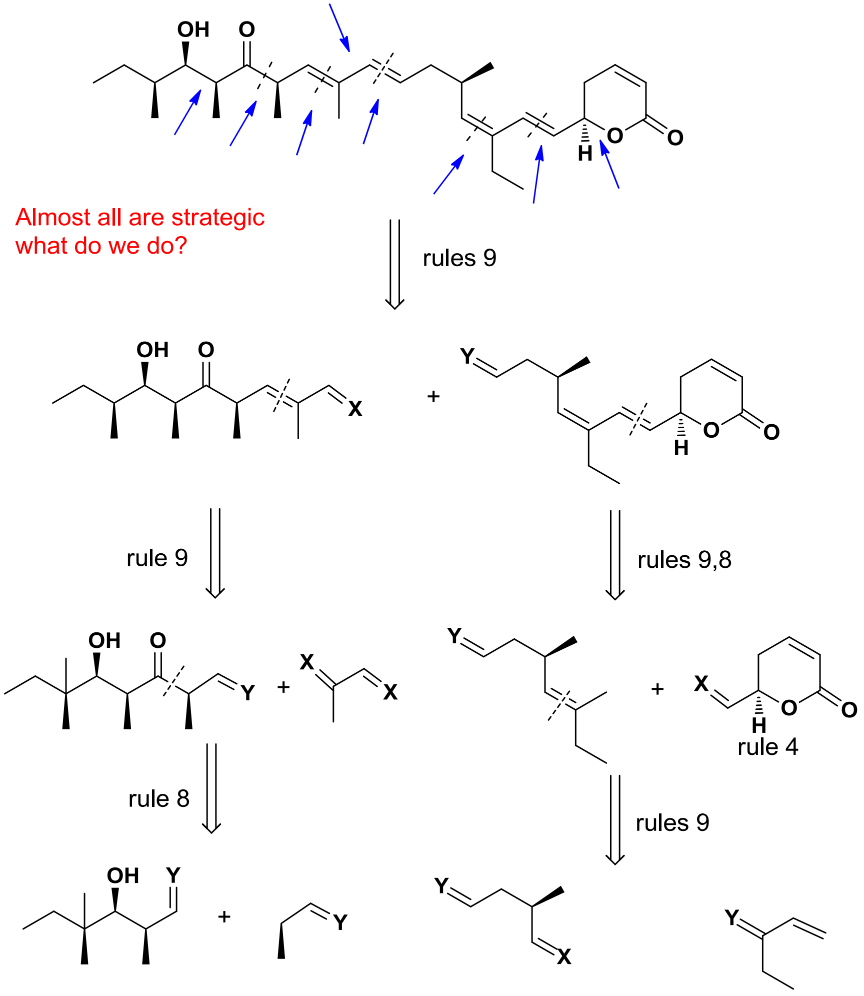
9. Disconnect bonds that are 1,2, or 3 bonds away from a functional group.

10. Disconnect double bonds or double bond equivalents.

Keep in Mind: It is difficult to make bonds between FG's and to install stereocenters when they are more than 3C's apart.

Callystatin A.

*Blue arrows indicate strategic bond



*X and Y are undefined atoms which will be defined in later panning stages.

What other two initial disconnections are strategeic (hint: want equal size SM pieces)?

*Adapted from *Elements of Synthesis Plannning*.

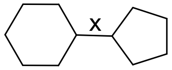
Ryan L. Gianatassio

Intro. to Ring Systems

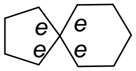
Types of Ring Systems: directly joined (no common atoms but directly linked), spiro (one and only one common atom), fused (one and only one common bond,f), bridged bicyclic (more than one common bond)

bond nomenclature; e=exendo, oe=offexendo, f=fusion

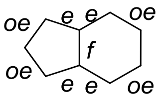
directly joined



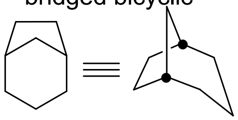
spirocyclic



fused



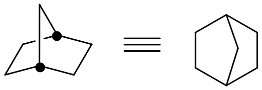
bridged bicyclic



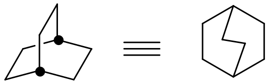
bicyclo[3.2.1]octane

The 5 and 6 membered rings in the fused and bridged rings are the primary rings and the peripheral rings correspond to the deletion of the fusion bond and the bridged atom.

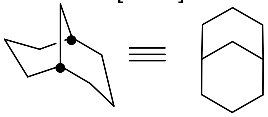
Some Common representations of Bridged Bicycles



[2.2.1]



[2.2.2]



[3.3.1]

***Bridgehead atoms are incated as bold bullets.**

*FYI: There must be at least one carbon (outside the ring in question) between the carbon under consideration and another carbon in the ring in question for it to be a bridgepoint.
Ref: Organic Synthesis Lecture Notes (D. Boger)

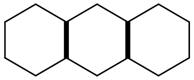
Naming Bicycles: "The X,Y,Z" Method

the general expression is:

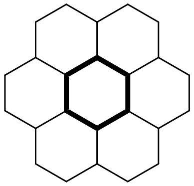
bicyclo[x.y.z]alkane

where **x,y,** and **z** are the intervening carbons on the 3 paths between the two bridgehead atoms in decreasing order; **alk** is the total number of carbons in the ring system(s). (check; alk = x+y+z+2)

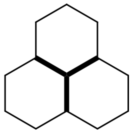
Different types of fused rings



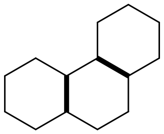
not directly linked



cyclocontiguous



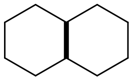
contiguous



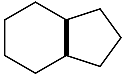
directly linked

Which bonds are most stategic? why?

Commonn Fused Rings



decalin

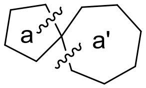


hydrinane

Hint: 2 bond disconnections are better than 1.

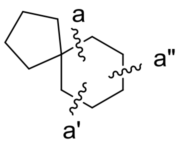
Disconnection of Spiro Rings

1. Disconnect one *e* bond.
2. Disconnect e bond and one cocyclic bond beta to it.

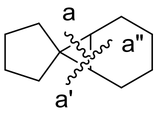


rule 1

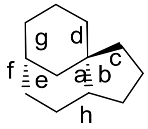
What rxns can we do if only a is disconnected? (hint: you're not limited to this retron)



rule 2
options: aa', aa"



rule 2
options: aa', aa"



Can use rule 1 or rule 2.
One bond disconnections: e and f
bond pair disconnections: ag and ge

Ryan L. Gianatassio

Ring Bond Disconnections - Isolated Rings

Baran GM
1/28/2012

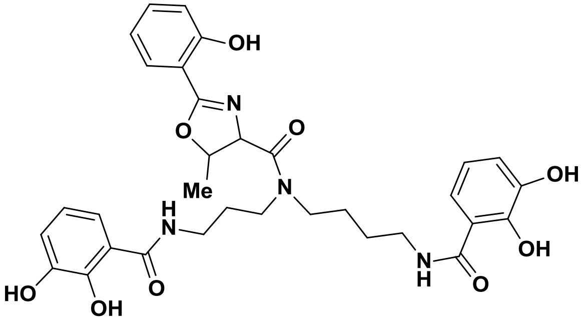
Ring-Bond Disconnections - Isolated Rings (not spiro, fused, or bridged)

1. Disconnect non-building block rings which are embedded in a skeleton and centrally located; break one bond or pair of bonds.
   a. bonds between C, N, O, or S
   b. bonds that create symmetrical, locally symmetrical, or linear skeleton.

2. Disconnect easily formed rings such as lactone, hemiketal, hemiacetal embedded in the skeleton but in a non-central location.

Tip: If several isolated rings are present, the most strategic ring for disconnection will be the one that is most centrally located, especially if it allows a two bond disconnection (typically 3,4, or 6 membered). (2) Think back (ahead): acyclic rules still apply.

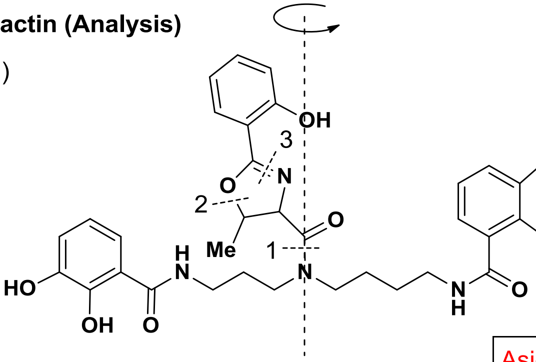
(+) - Parabactin



Bergeron, JACS, 1982, 104, 4489

(+) - Parabactin (Analysis)

(Re-drawn)

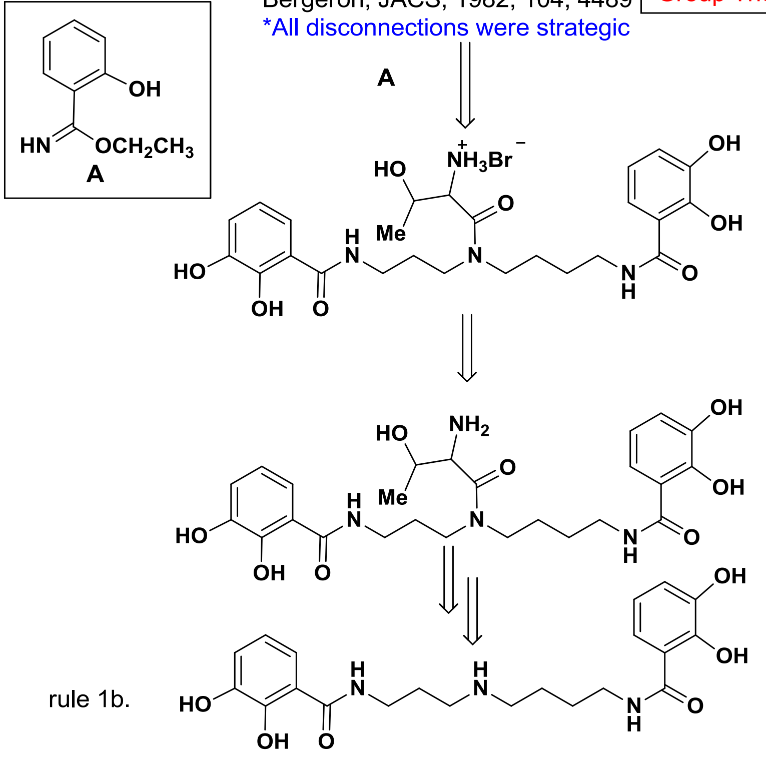


pseudo-C$_2$ axis

Bergeron, JACS, 1982, 104, 4489

*All disconnections were strategic

Aside: Can you "see" the σ plane?
-Group Theory Helps!



Disconnection of Fused Rings

Fused Rings: Goal is to get pieces of equal size and/or complexity

1. Disconnect 2 cocyclic bonds that are attached to a fusion bond and opposite to each other (especially O,N,S bonds).

2. Disconnect a cocyclic pair of bonds in a central ring *(tip: think cycloaddition)*.

3. Do not disconnect building block rings (benzenoid).

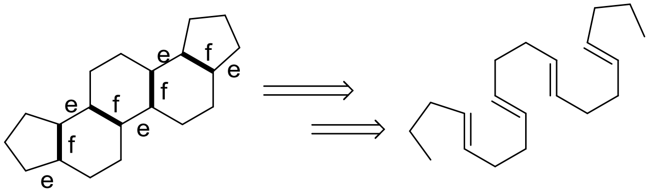
4. Disconnect [2+1] and [2+2] retrons.

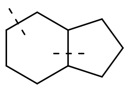
5. Do not disconnect fusion bonds that create ≥7 membered rings. For cyclopentanes and cycloheptanes intramolecular enolate alkylation and Dieckmann cyclizations; [4+3] and [3+2] not as well developed.

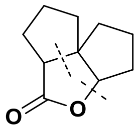
6. Disconnect directly linked *e* bonds in rings that contain alternating *e* and *f* bonds (think:cation-π cyclization).

7. Disconnect heterorings (tip: lactone, ketal, lactam, and hemiketal).

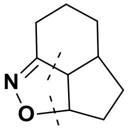
8. Do not disconnect bonds that create stereocenters unless they can be removed with stereocontrol.



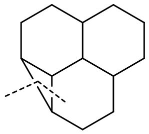

a



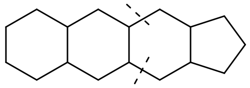
b

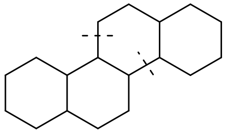


c


d

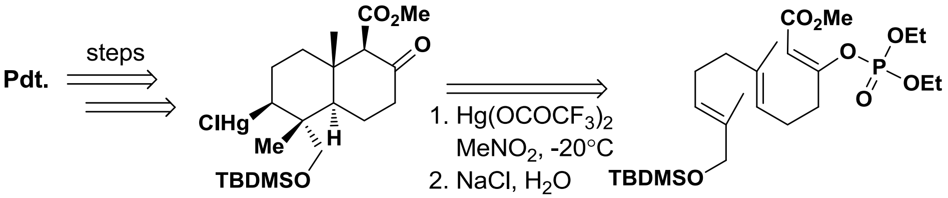
*Bonds must be cis in b-d. why?


e


f

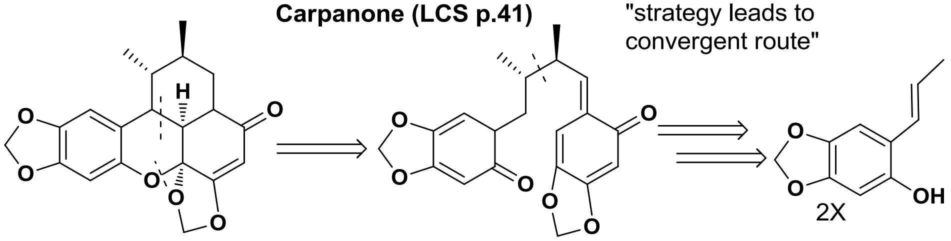
* Disconnections in e and f can signal the use of annulations - broken bonds may involve heteroatoms

Corey in Amphidicolin, Stemodinone, and Stemodin (p.188,191)

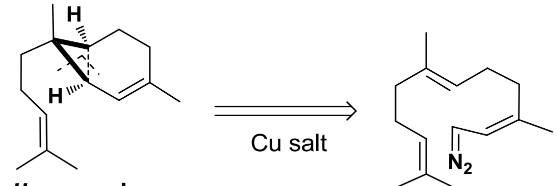


Carpanone (LCS p.41)

"strategy leads to convergent route"



Corey and the [2+1] intramolecular cycloaddition retron (LCS p.165-169)



dl - sesquicarene

*similar reaction used in *dl*-serenin

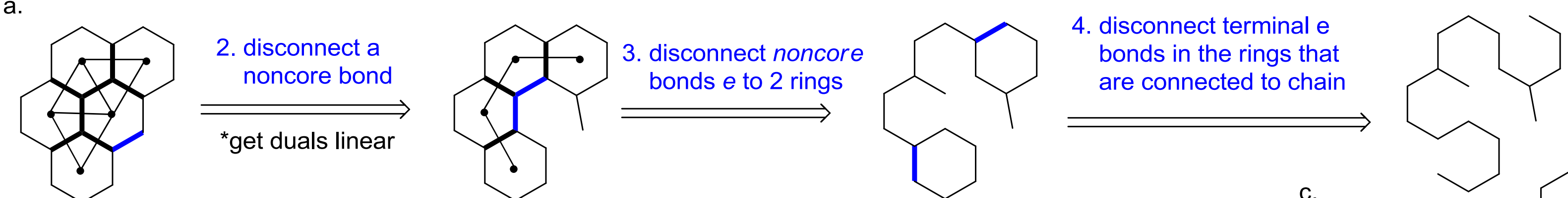
Fused Rings - Graph Theory Approach

Fused Ring Systems: goal is to reduce to chains with minimal branches (simple rings = o.k.)

Graph Theory Aproach - Good for seeing cation-π cyclization and Robinson polyannulation retrons

Remember:
Stork-Eschenmoser hypothesis

a.



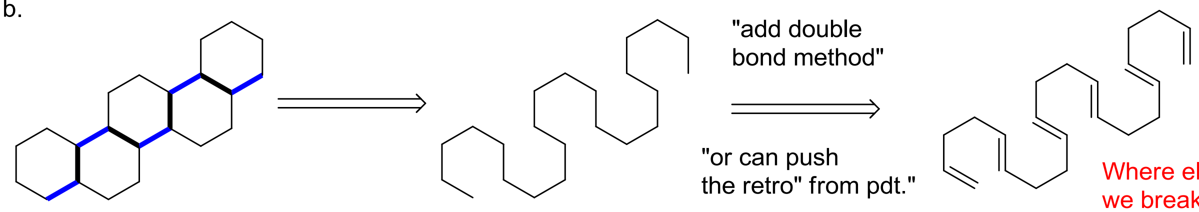
2. disconnect a noncore bond

*get duals linear

3. disconnect *noncore* bonds *e* to 2 rings

4. disconnect terminal e bonds in the rings that are connected to chain

b.



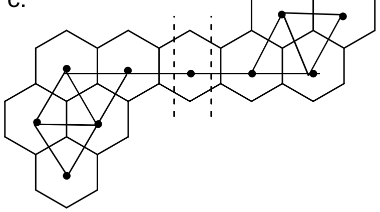
"add double bond method"

"or can push the retro" from pdt."

Where else can we break?

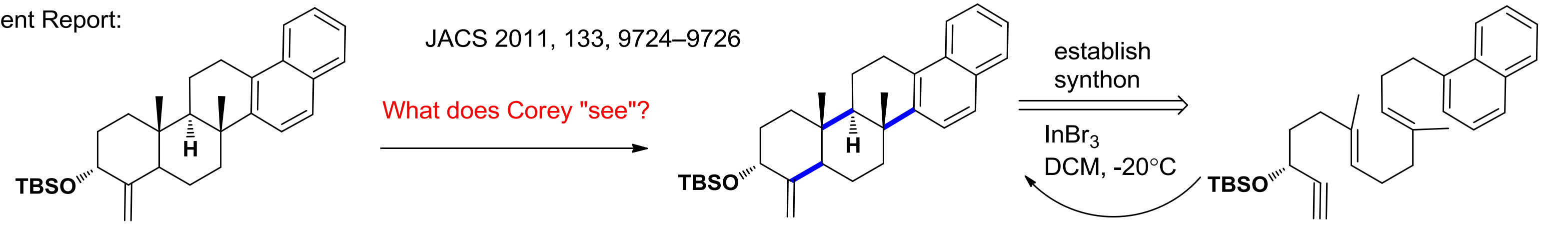
skip to rule 3

c.



1. disconnect bonds on hash
2. treat as in **a**.

Recent Report:

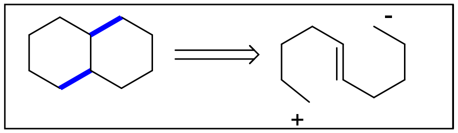


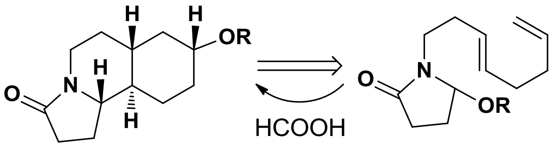
JACS 2011, 133, 9724–9726

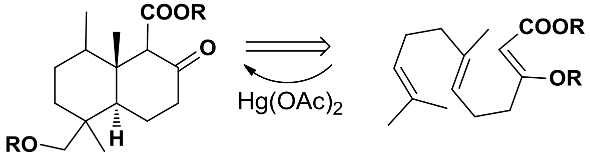
What does Corey "see"?

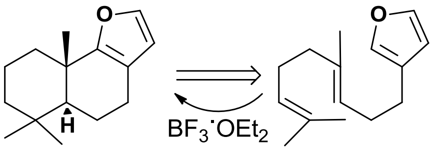
establish synthon

InBr$_3$
DCM, -20°C

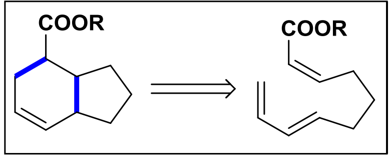


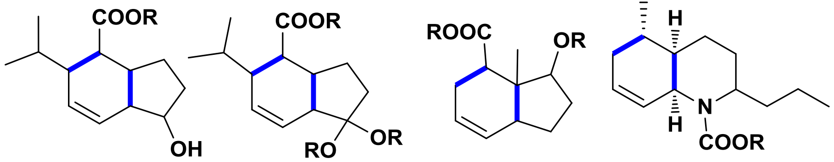






Alternatively, the IMDA as a bicyclization retron (cut fusion and exendo beta to it)





Ryan L. Gianatassio

Bridged Network Analysis

Baran GM
1/28/2012

Bridged Rings:

1. Disconnect e bonds in 4-7 membered rings
   1b. Do not disconnect bonds (in 4-7 membered rings that are exo to 3 membered rings.

2. Do not disconnect bridges that result in rings >7.

3. Disconnect bonds in rings that contain the most bridgehead atoms but that do not violate rule 2.

4. Do not make disconnections that result in stereocenters (o.k. if at point of attachment).

5. Do not disconnect bonds within aromatic and heteroaromatic rings.

6. Disconnect O,N, or S bonds (do not have to be in a ring of max bridging. *Keep in Mind: C-X bonds are usually easier to make than C-C bonds.

7. Disconnect to reduce bridges.

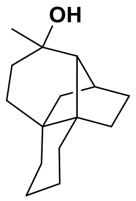
8. Do not disconnect bonds that lead to medium size rings as an intermediate.

9. Do not disconnect bonds that create pendant chains.

*Keep In Mind:
The best disconnections minimize:
1. appendages
2. appendage chiral centers
3. medium or large rings
4. bridged rings

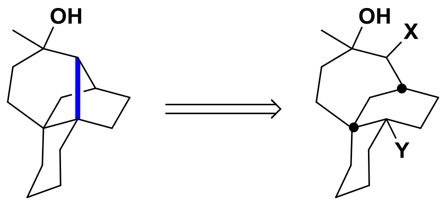
Ref. Organic Synthesis Lecture Notes (D. Boger)

Consider:



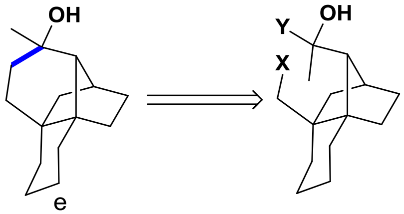
Which bond(s) are most strategic?

Analysis (X and Y are undefined - just placeholders)



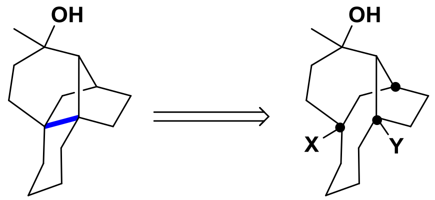
a

X rule 8
-made a bridged med. ring



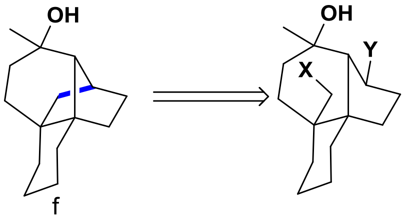
e

X rule 4,9



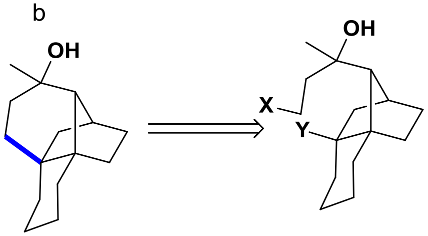
b

X rule 2
- made 10C ring



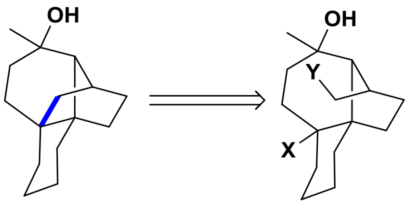
f

X rule 9



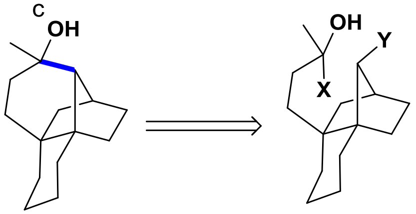
c

X rule 9



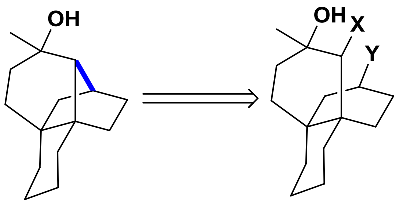
g

X rule 9



d

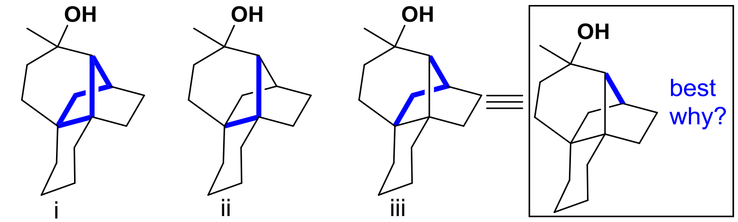
X rule 4,9



h

?

Bridged Network Analysis (Cont'd)



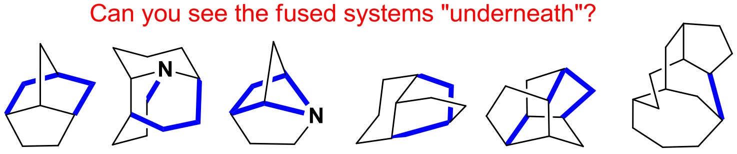
best
why?

i = all bonds exendo; breaking reduces number of rings in core
ii = endoendo, "core" bonds; breaking leads to med. sized ring
iii = ii - i. cut zero atom bridge and get no pendant chains as a result. This is generally most desirable.

Tips:
1. Identify the most highly bridged ring.
2. If one or more bonds are core (endoendo, fusion) then do not disconnect.
3. Of bonds left; identify the exendo bonds.
4. If several bonds still SB, then check if each is in a ring with stereocenters; if yes then do not disconnect.
5. Disconnect a remaining bond.

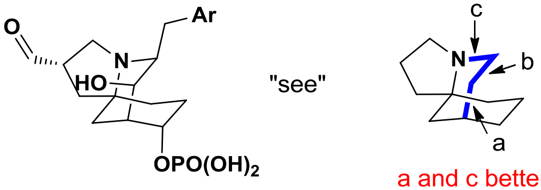
Some strategiec one bond disconnections which induce "top down" approach (from bridged to fused to linear)

Can you see the fused systems "underneath"?



Can you "see" the starting materials yet?

FR901843 - Strategic Bond Analysis

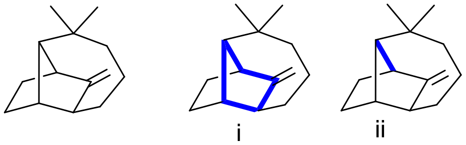


a and c better than b
why?

*5 of 6 total syntheses chose formation of a as key. (A: less appendages)

An analysis of Longifolene

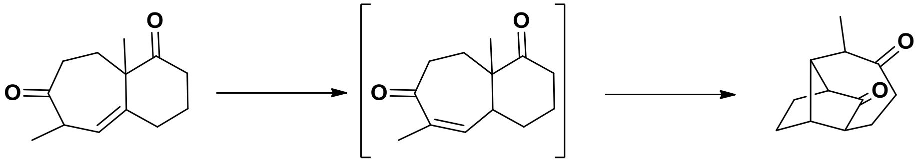
J. Org. Chem., Vol. 58, No. 8, 1993



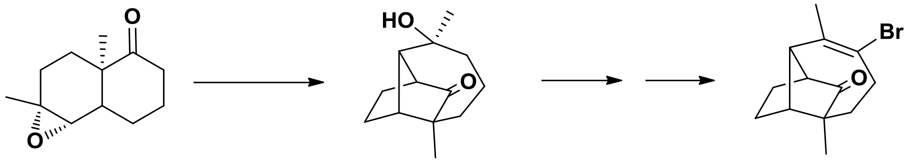
Remember our exercise? It works!

1. i is most bridged
2. ii = zero atom bridge = highest priority

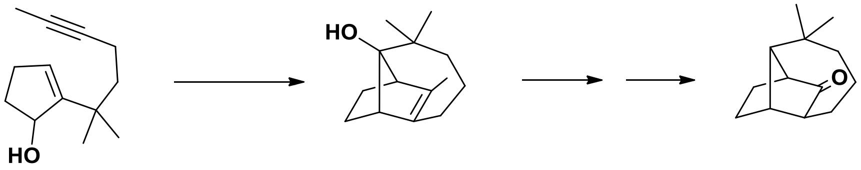
*3 of the 7 successful total syntheses of Longifolone chose the bond in ii as strategic.



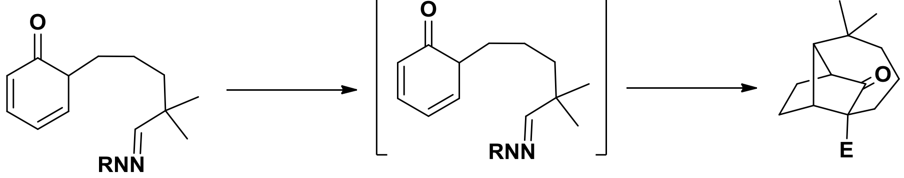
Corey,Ohno, Mitra,Vatakencherry



McMurry, Issler



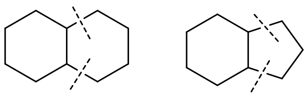
Johnson, Volkmann, Andrews



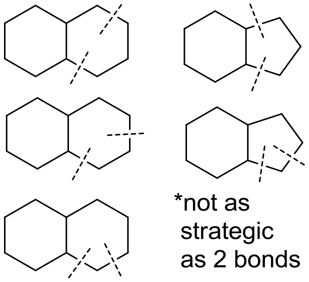
Schultz, Puig

Some Extras

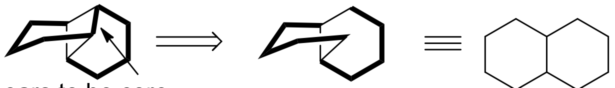
2 bond disconnections



1 bond disconnections



*not as strategic as 2 bonds



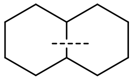
appears to be core but break and get..

but make fused system = can break it

break and get

large ring = X

Envelope Method

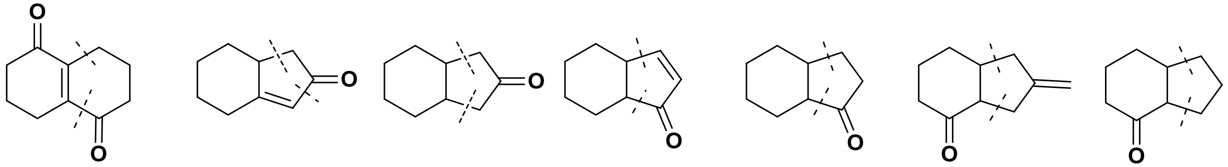


break envelope = large ring (8 or more) then, not strategic!

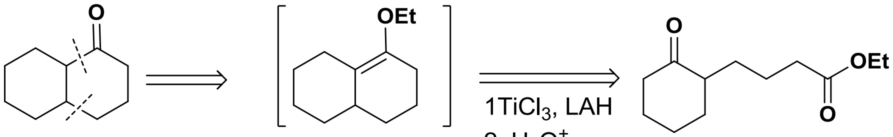
FYI: a ring is not primary if it can be expressed as an envelope of rings.

Bond disconnections for Anellation:

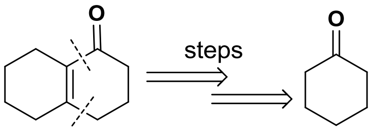
Practice for you: Can you "see" the starting materials?



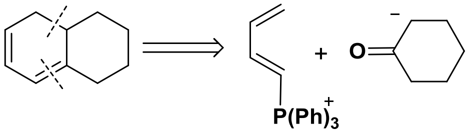
Some Nifty Transforms



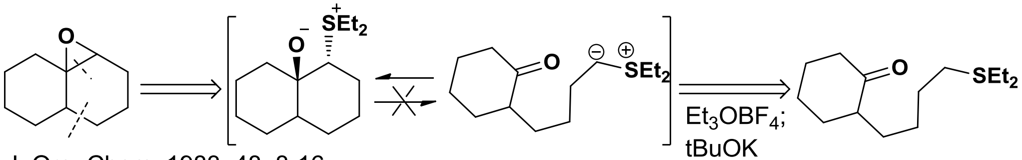
J. Am. Chem. Soc. 1983, 105, 1660-1661



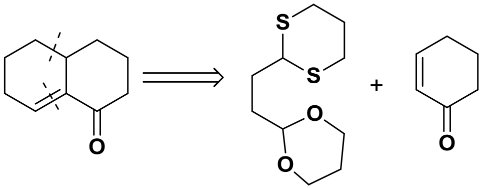
TL. 28, pp 2461 - 2464



JOC, Vol. 40, No. 1, 1975 (101-102)



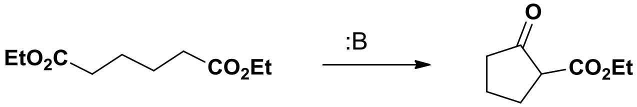
J. Org. Chem. 1983, 48, 8-16



Tetrahedron Letters Vol. 21, pp 5235 - 3236

Don't Forget

Dieckmann:



and

Robinson: