Institut für Organische Chemie der Justus-Liebig-Universität

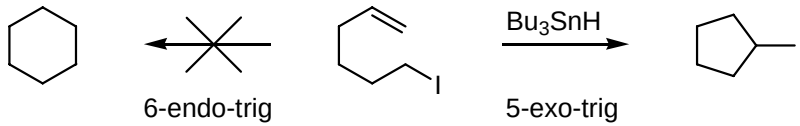
Interconversions of Cages: Fragmentations and Transannular Cyclizations

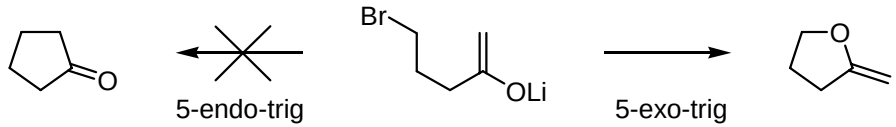
by Dr. Boryslav Tkachenko

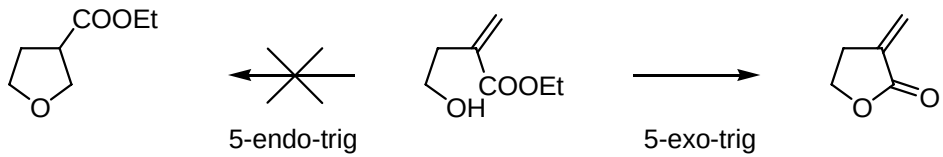
28.04.2006

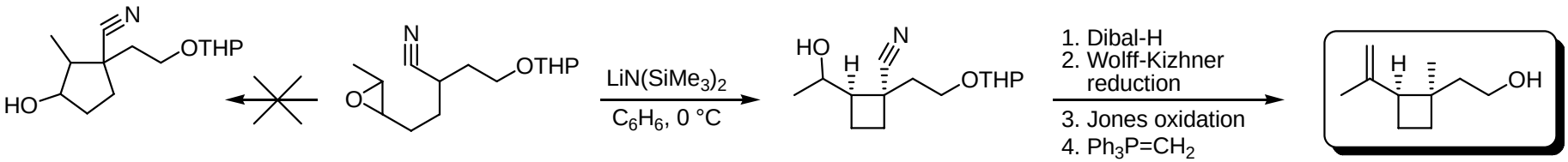
Giessen

Examples of Simple Cyclizations









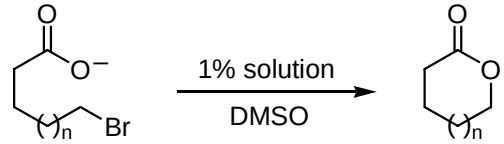
ca. 95:5 mixture of diastereomers in favour of *trans*

grandisol

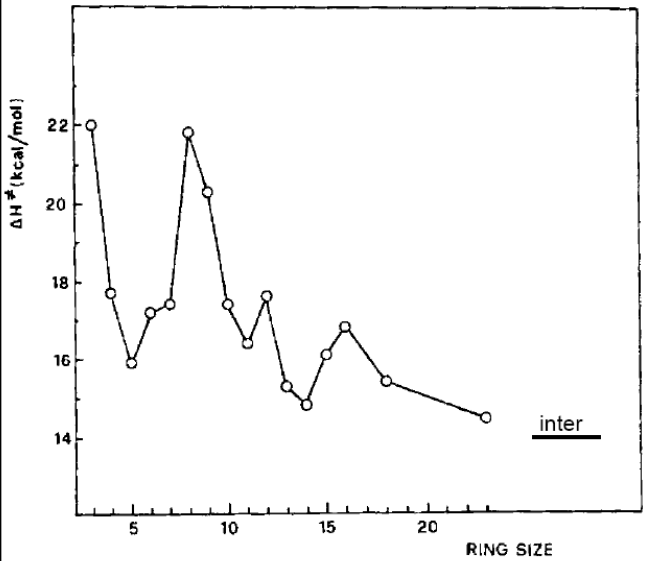
a constituent of the aggregation pheromone of the cotton boll weevil

House, C. F. *J. Org. Chem.* **1978**, *43*, 700.
Baldwin, J. E.; Kruse, L. I. *J. Chem. Soc., Chem. Commun.*, **1977**, 233-235.
Stork, G.; Cohen, J. F. *J. Am. Chem. Soc.* **1974**, *96*, 5270-5272.

The Problem of Medium Ring Synthesis
Energetics of Ring Closure Reactions



ΔH of Cyclization

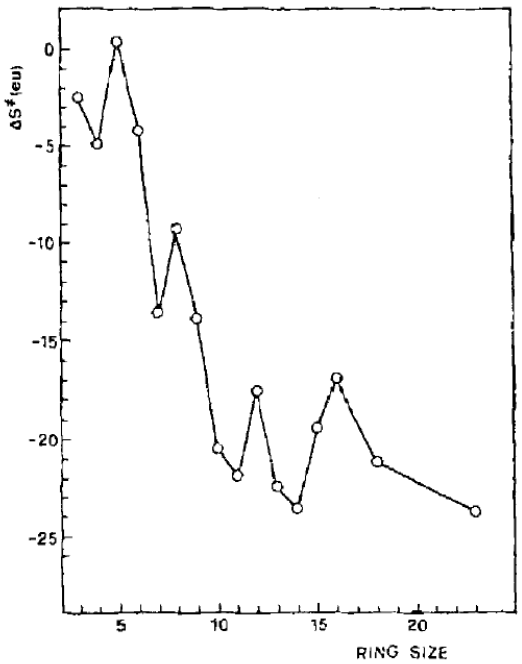


• an indicator of ring strain

Sources of Strain:
1) Imperfect staggering (Pitzer)
2) Deformation of bond <'s (Baeyer)
3) Transannular strain

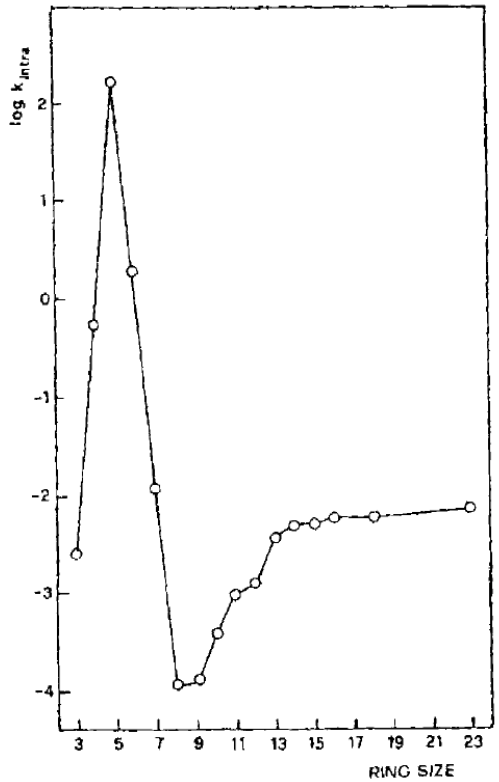
#1 and #3 are especially important for medium rings

ΔS of Cyclization



• a measure of the probability of end-to-end encounters

Rates of Cyclization



• a million-fold decrease in rate from 5- to 10-membered cyclization reaction

Illuminati and Mandolini *Acct. Chem. Res.* **1981**, 95.

Baldwin's rules, Conclusions and Caveats

Baldwin's rules

A set of empirical rules for certain formations of 3- to 7-membered rings. The predicted pathways are those in which the length and nature of the linking chain enables the terminal atoms to achieve the proper geometries for reaction. The disfavored cases are subject to severe distortions of bond angles and bound distances.

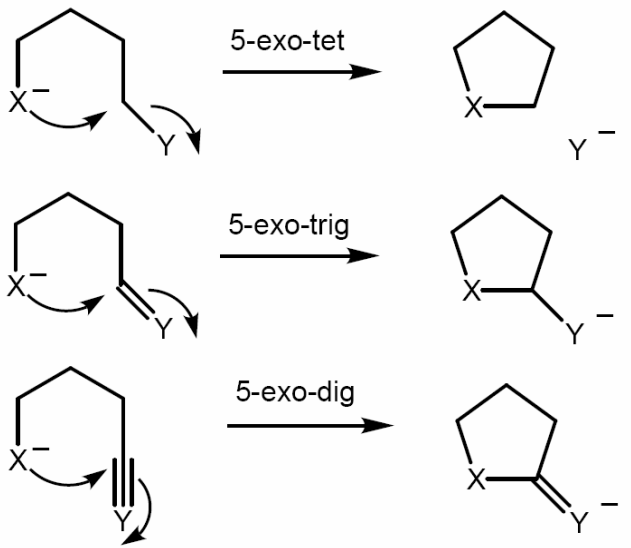
- Baldwin's Rules are an effective first line of analysis in evaluating the stereoelectronics of a given ring closure
- Baldwin's Rules have provided an important foundation for the study of reaction mechanism
- Competition studies between different modes of cyclization only give information about relative rates, and are not an absolute indicator of whether a process is "favored" or "disfavored"
- Structural modifications can dramatically affect the cyclization mode; beware of imines and epoxides

Ring Closure Basics

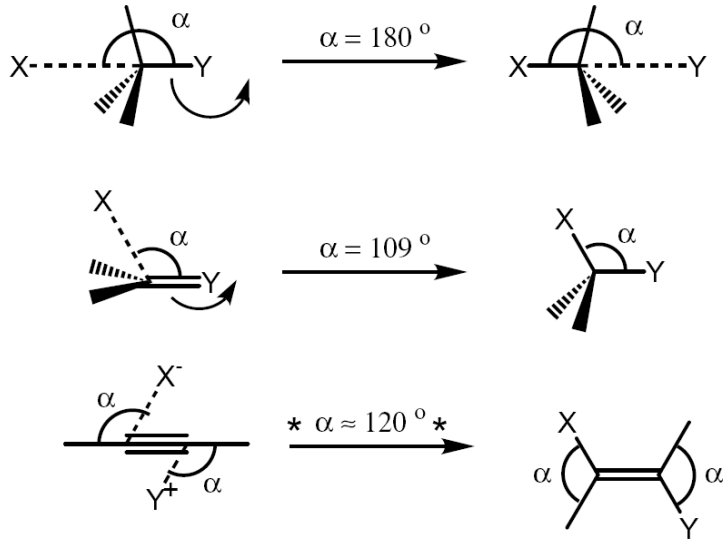
General definitions/underlying concepts:

Cyclization modes:

Hybridization at atom undergoing attack:



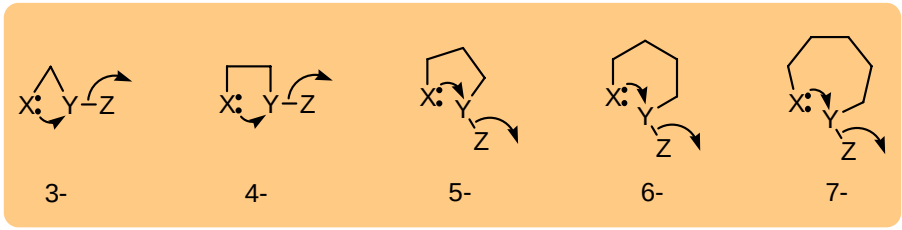
Required trajectories:



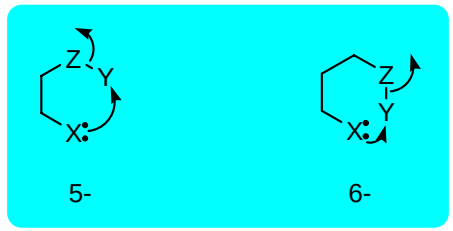
Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976**, 734-736.
Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976**, 738-741.

Baldwin's Rules (Suggestions) for Ring Closure

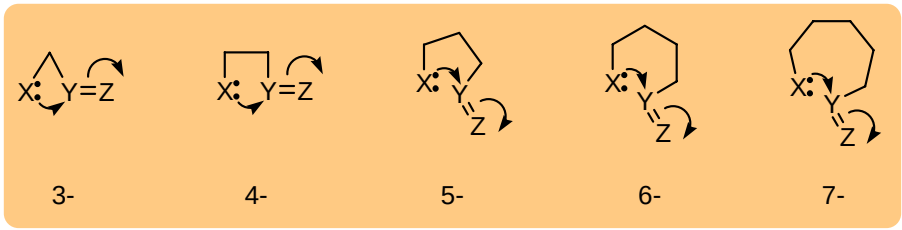
Exo-Tet



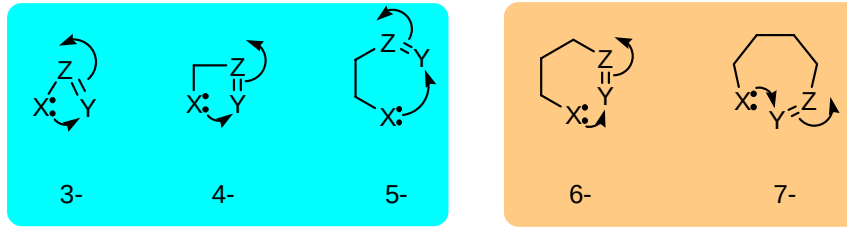
Endo-Tet



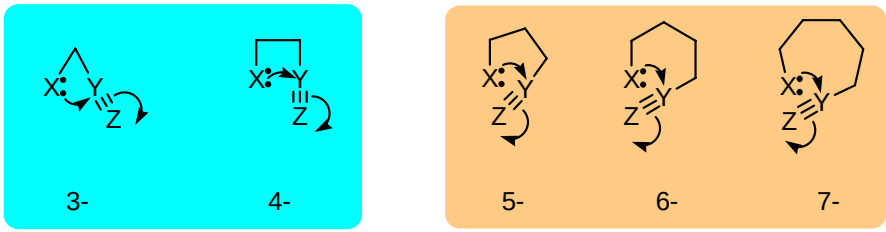
Exo-Trig



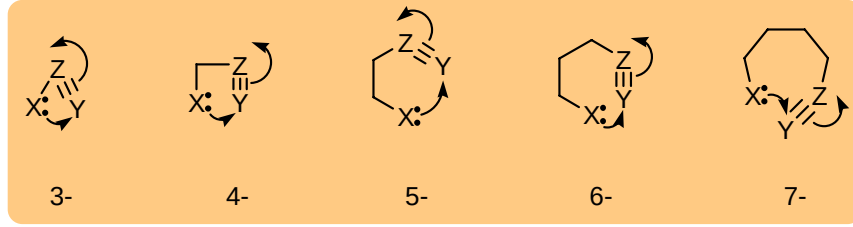
Endo-Trig



Exo-Dig



Endo-Dig

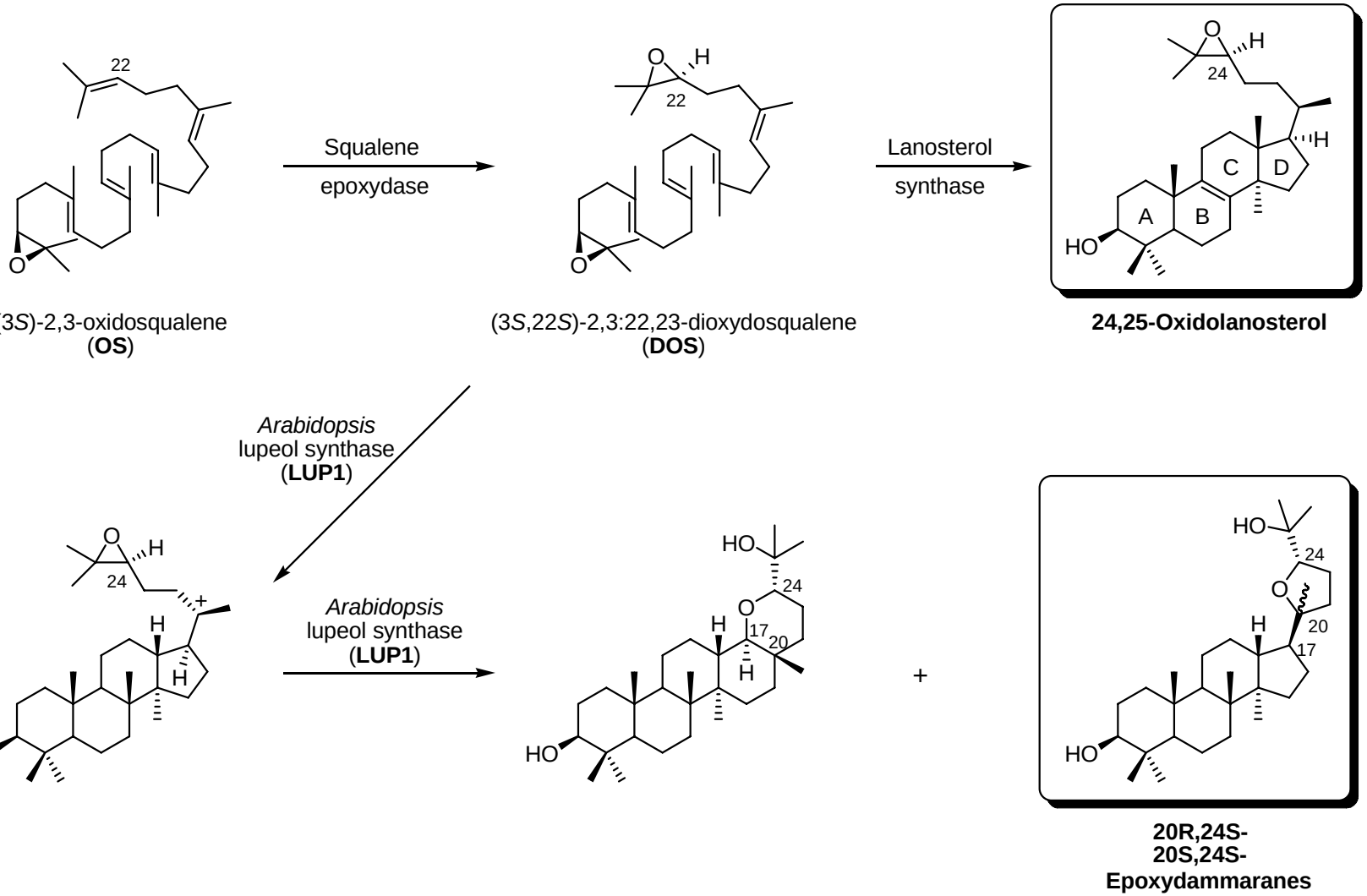


Disfavored does not imply the reaction can't or won't occur – it only means the reaction is more difficult than favored one.

- favored **- disfavored**

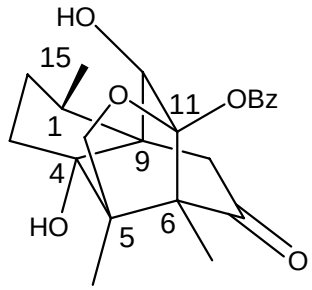
Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. *J. Org. Chem.* **1977**, *42*, 3846-3852.
Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976**, 734-736.

Enzymatic Cyclization in Triterpenoids and Steroids Synthesis



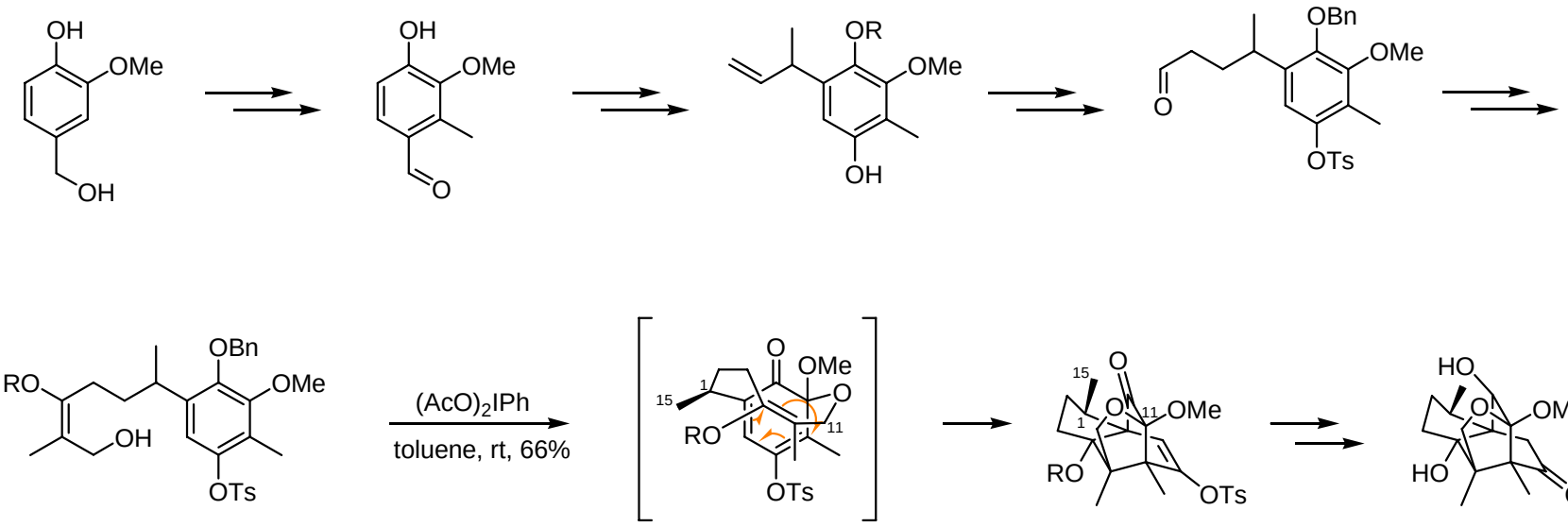
Shan, H.; Segura, M. J. R.; Wilson, W. K.; Lodeiro, S.; Matsuda, S. P. T. *J. Am. Chem. Soc.*, **2005**, *127*, 18008-18009.

Transannular Diels-Alder Reaction in Tashironin Synthesis



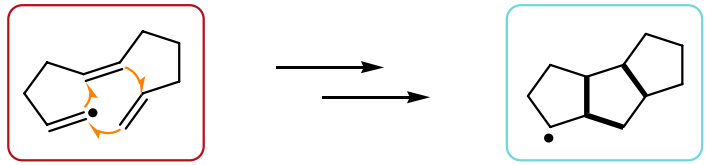
Tashironin

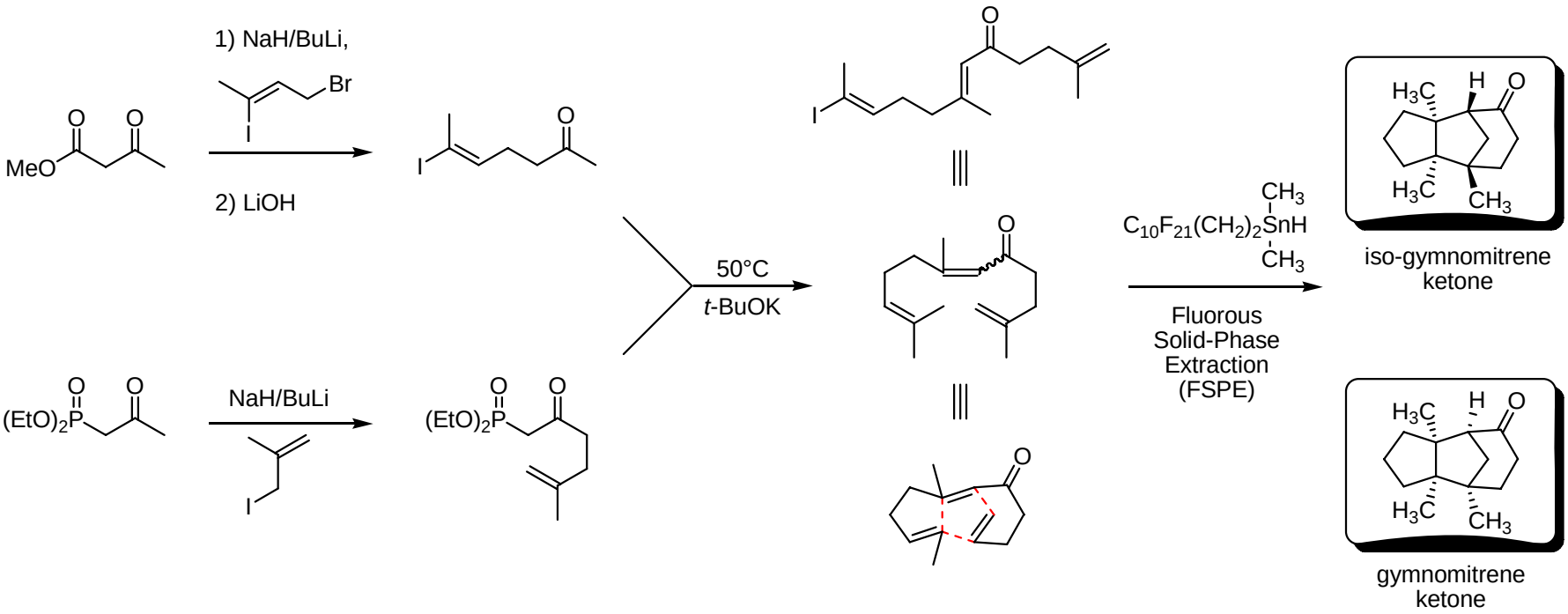
Neurotrophic factors, or neurotrophins, are agents that can prevent neuronal death (neurotrophism) or promote axonal growth (neurotropism).



Cook, S. P.; Gaul, C.; Danishefsky, S. J. *Tetr. Lett.* **2005**, *46*, 843–847.

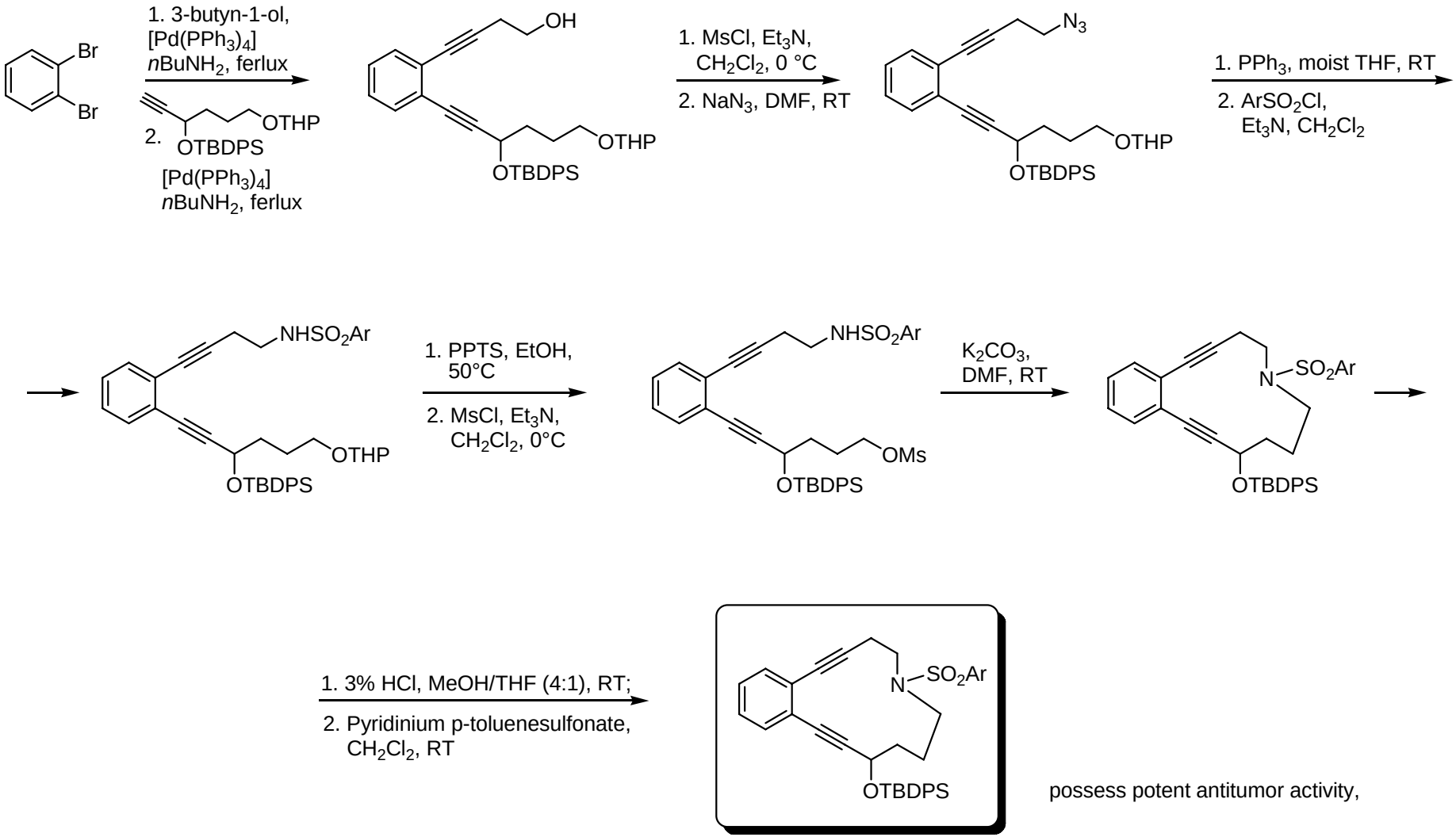
Round-Trip Cyclization Strategy





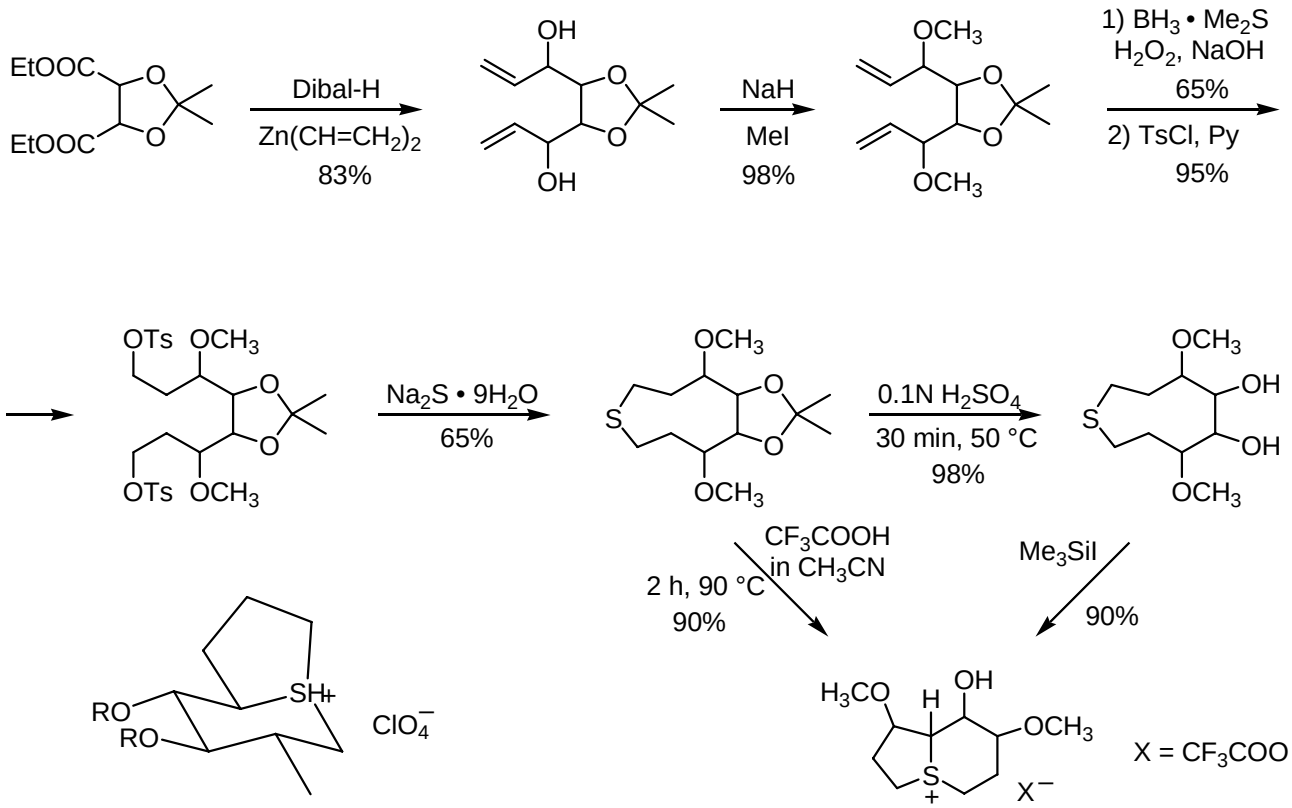
Haney, B. H.; Curran, D. P. R. *J. Org. Chem.*, **2000**, *65*, 2007-2013.

Activation of Macrocyclic Enediynes by Transannular Cyclization



possess potent antitumor activity,

Stereo- and regiospecific transannular cyclization reaction in synthesis of bicyclic sulfonium salts



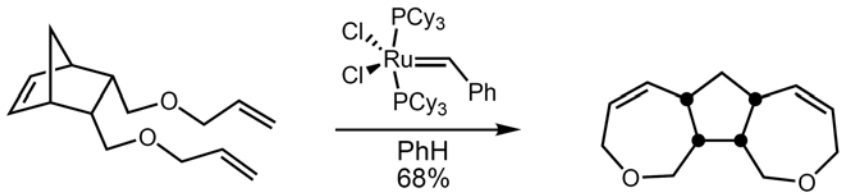
Castanospermine

Mimic of Castanospermine

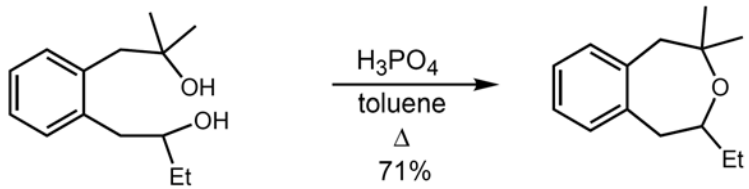
Castanospermine is among the most important therapeutic agents used as glycosidase inhibitors. Glycosidase enzymes play an important role in the biochemical processes,1 and their abnormal activity leads to serious diseases.

Cerè, V.; Pollicino, S.; Ricci, A. *J. Org. Chem.*, **2003**, *68*, 3311-3314.

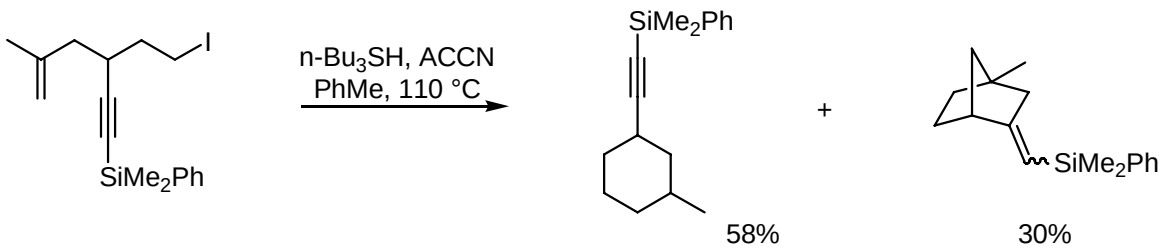
Ring Opening - Ring Closing Metathesis



Protic Acid Cyclization

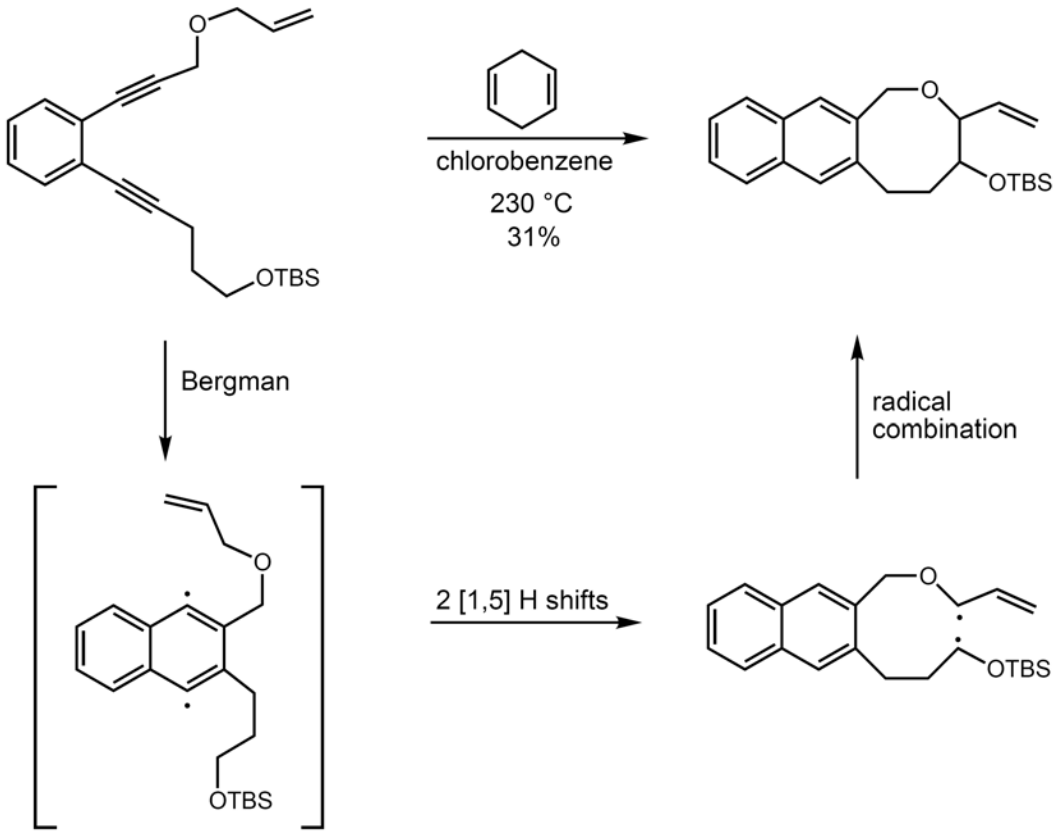


Radical Cyclization to Bicyclo[2.2.1]heptane Framework



Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. Grubbs *J. Am. Chem. Soc.*, **1996**, 118, 6634-6640.
Brown, D. S.; Elliott, M. C.; Moody C. J.; Mowlem T. J. *J. Chem. Soc., Perkin Transactions 1*, **1995**, 1137-1144.
Pianowski, Z.; Rupnicki, L.; Cmoch, P.; Stalinski, K. *Synlett* , **2005**, 6, 900-904.

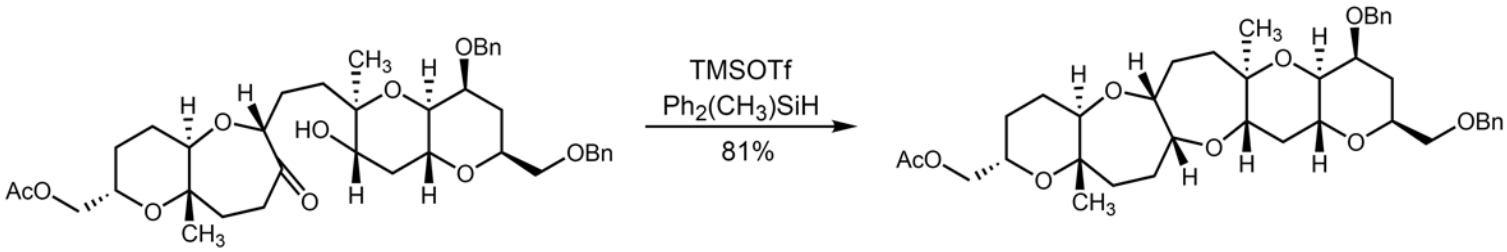
Bergman Cyclization



Grissom, J. W.; Calkins, T. L.; Huang D.; McMillen, H. *Tetrahedron*, **1994**, 50, 4635-4650.

Reductive Cyclization

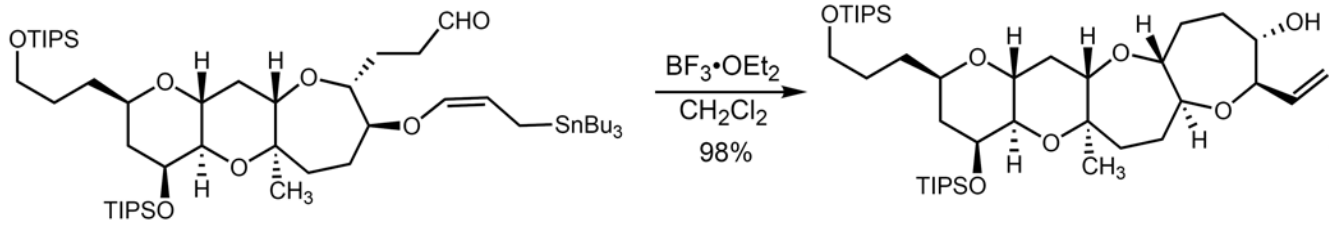
Both the synthesis of Hemibrevetoxin B and 7-epi-Hemibrevetoxin B have utilized this reaction:



not universally applicable

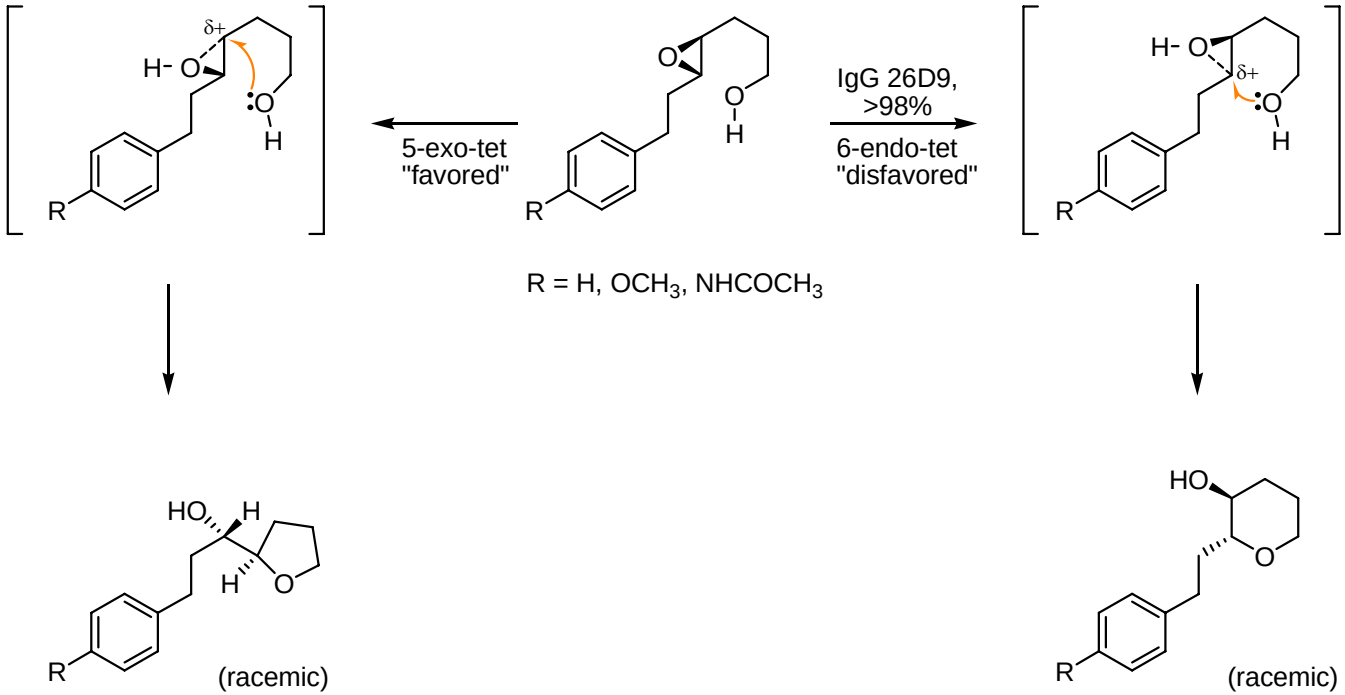
A Complex Allyl Stannation

Both 7-membered rings of hemibrevetoxin B
formed using this method; The latter is shown here:



Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, X. Y.; Hwang C. K. *J. Am. Chem. Soc.*, **1993**, 115, 3558-3575.
Kadota, I.; Jung-Youl, P.; Koumura, N.; Pollaud, G.; Matsukawa, Y.; Yamamoto Y. *Tetrahedron Lett.*, **1995**, 36, 5777-5780.

Catalytic antibodies Mediated Cyclization (Anti-Baldwin cyclizations)

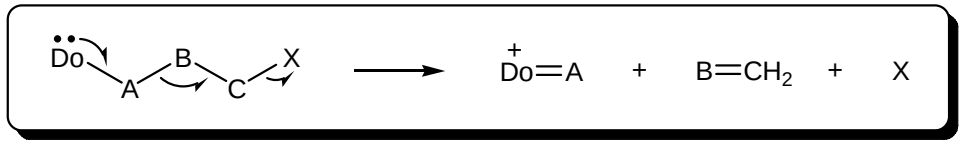


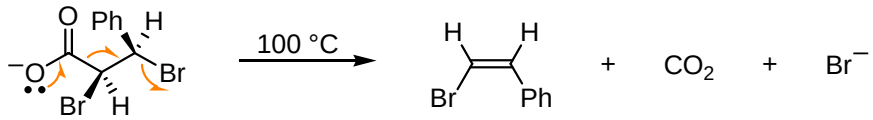
absent ⇦ **regioselective antibody stabilyzing element (catalityc antibodies)** ⇨ **present**

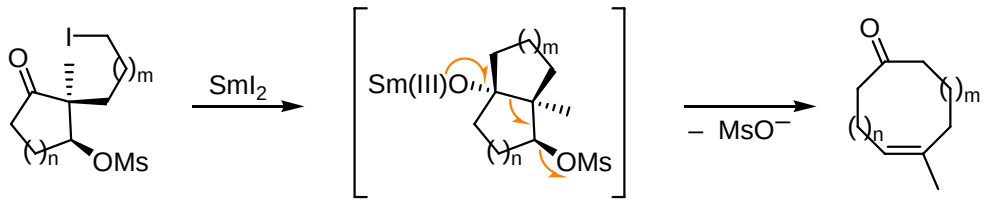
has no enzymatic or synthetic catalyst equivalent

Janda, K. D. *Pure & Appl. Chem.*, **1994**, *66*, 703–708.

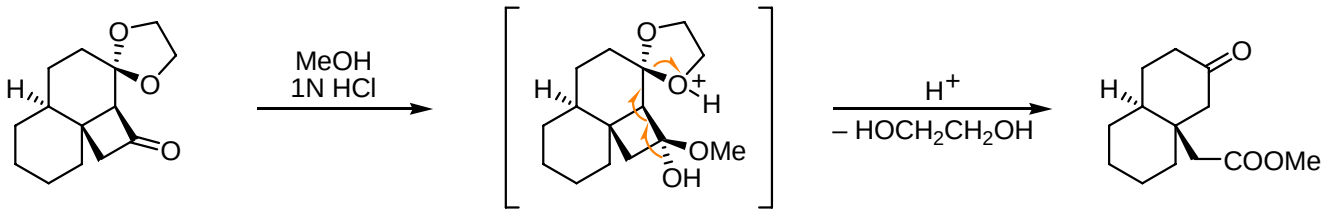
Grob-type Fragmentations





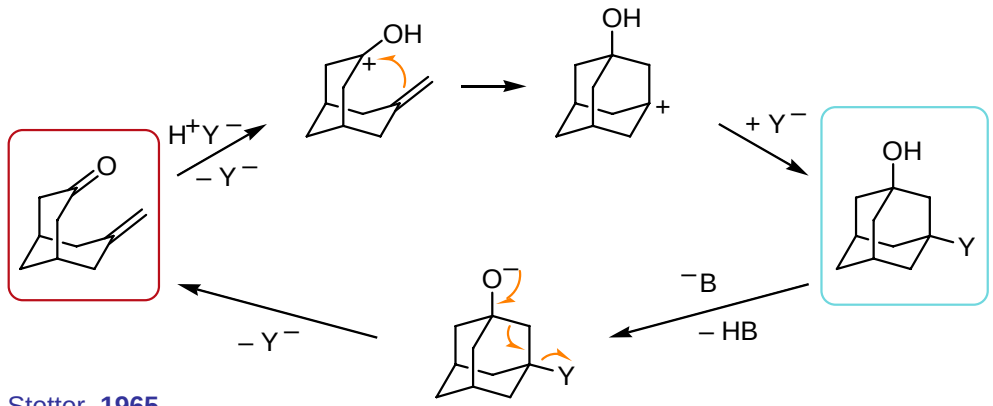


n = 1, 2
m = 1, 2, 4

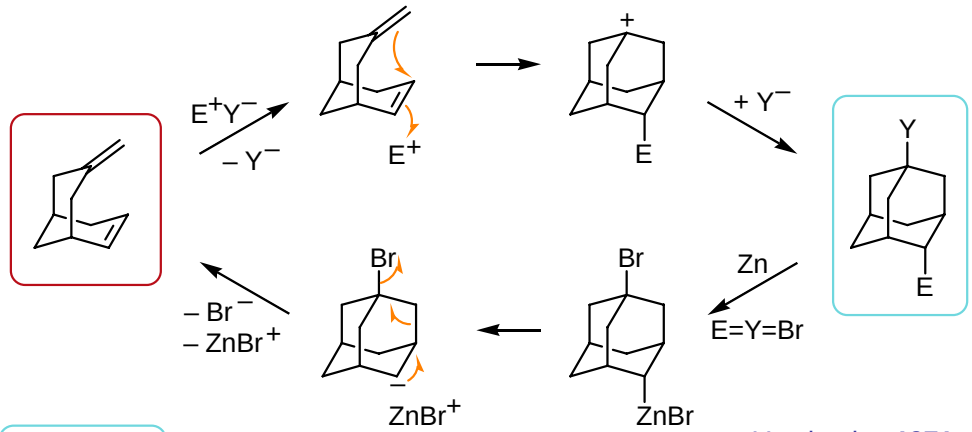


De Giacomo, M.; Bettolo, R.M.; Scarpelli, R. *Tetrahedron Lett.*, **1997**, *38*, 3469-3470.
Molander, G. A.; Le Huérou, Y.; Brown, G. A. *J. Org. Chem.*, **2001**, *66*, 4511-4516.

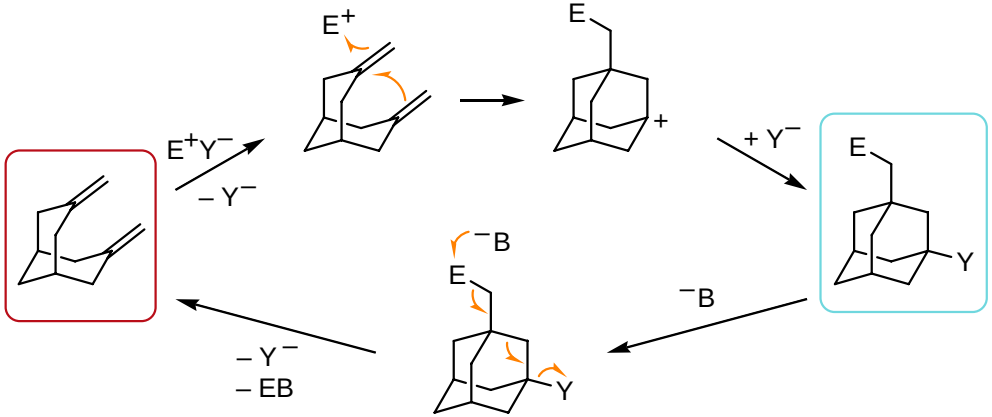
“Reversable” Cyclizations and Fragmentations of some Adamantane Derivatives



Stetter, **1965**

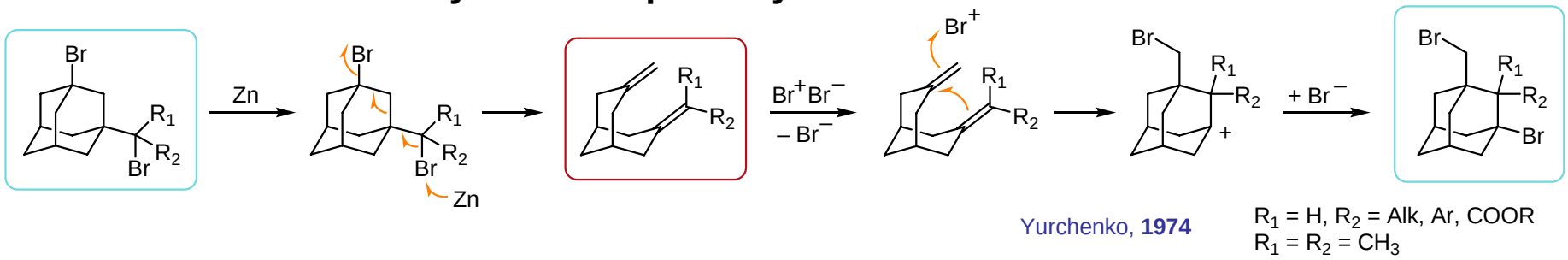


Yurchenko, **1971**



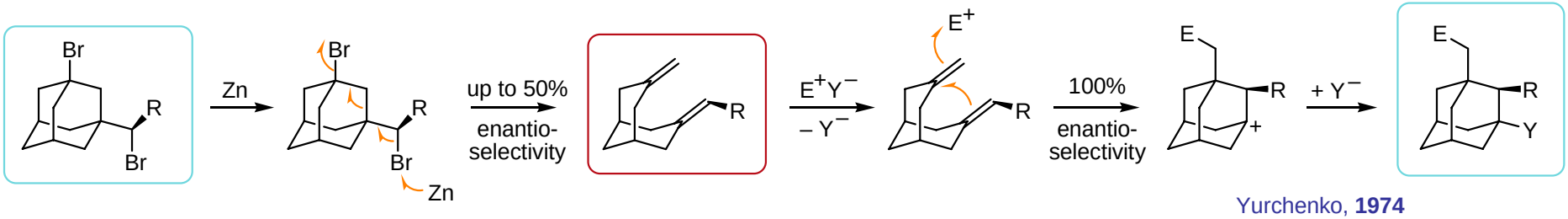
Stetter, **1966**

“Irreversable” Cyclizations pathways of some Adamantane Derivatives

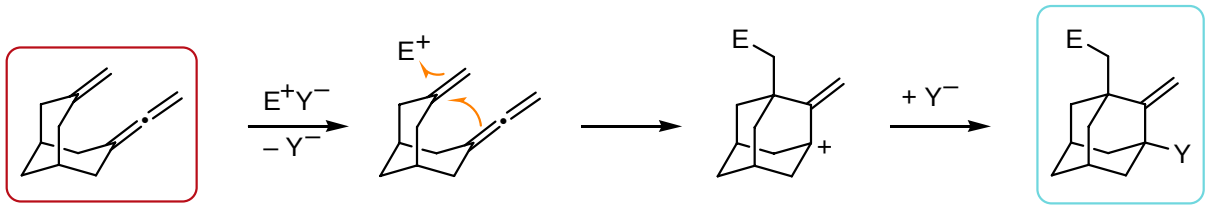


Yurchenko, **1974**

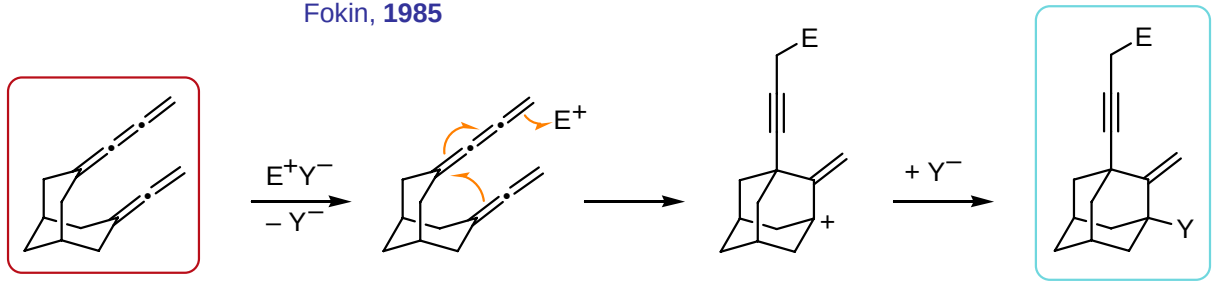
R_1 = H, R_2 = Alk, Ar, COOR
R_1 = R_2 = CH_3



Yurchenko, **1974**

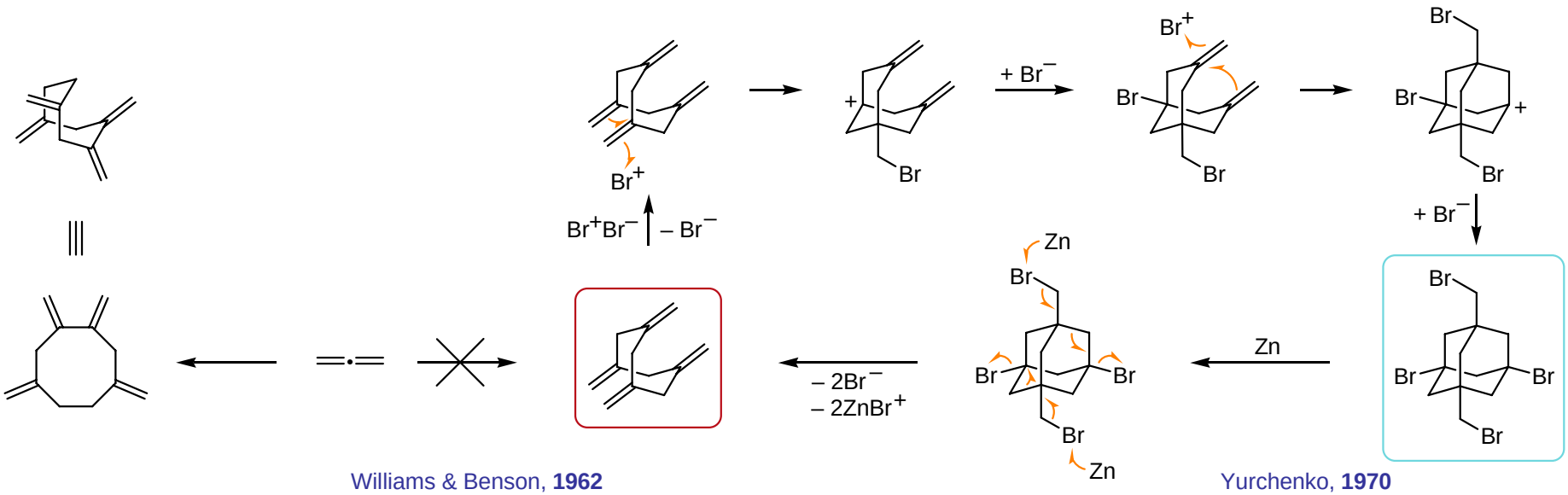


Fokin, **1985**



Fokin, **1985**

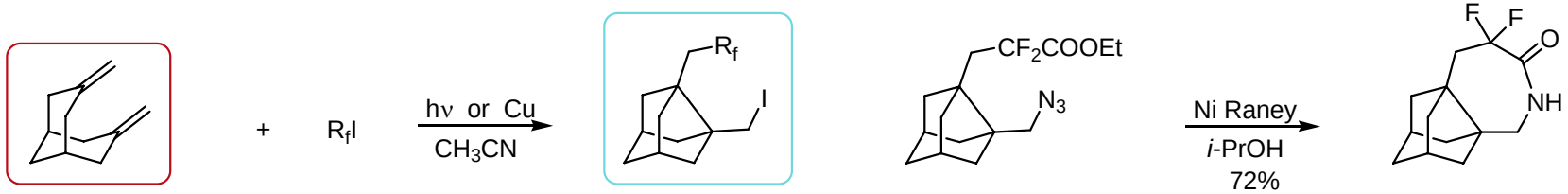
1,3,5,7-tetramethylenecyclooctane structure resolving



Williams & Benson, **1962**
(wrong structure)

Yurchenko, **1970**

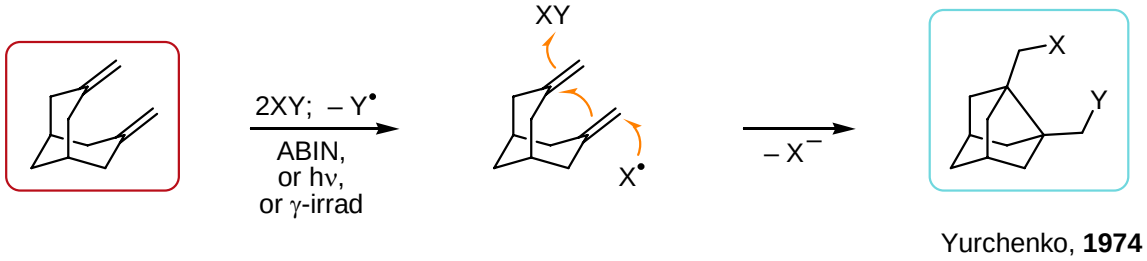
Cyclizations of 3,7-Dimethylenebicyclo[3.3.1]nonane with Polyfluoroalkyl Radicals



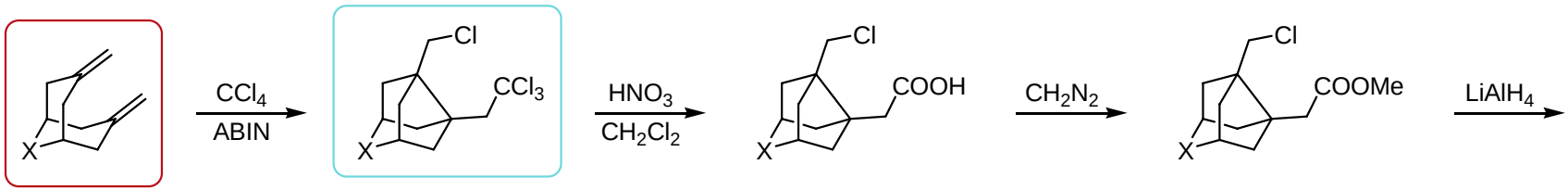
R_f = CF_3, *n*-C_3F_7, CF_2COOEt, $CF_2PO(OEt)_2$

Ponomarenko, M. V.; Serguchev, Y. A.; Ponomarenko, B. V.; Röschenthaler, G.-V.; Fokin, A. A. *J. Fluor. Chem.*, **2006**, accepted

Transannular reaction in [3.3.3]propellane synthesis



Yurchenko, **1974**

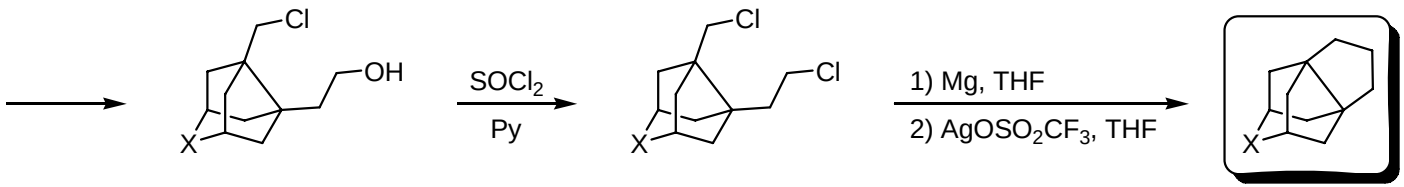


X = H_2
X = CH_2

X = H_2, 63%
X = CH_2, 47%

X = H_2
X = CH_2

X = H_2, 77%
X = CH_2, 87%



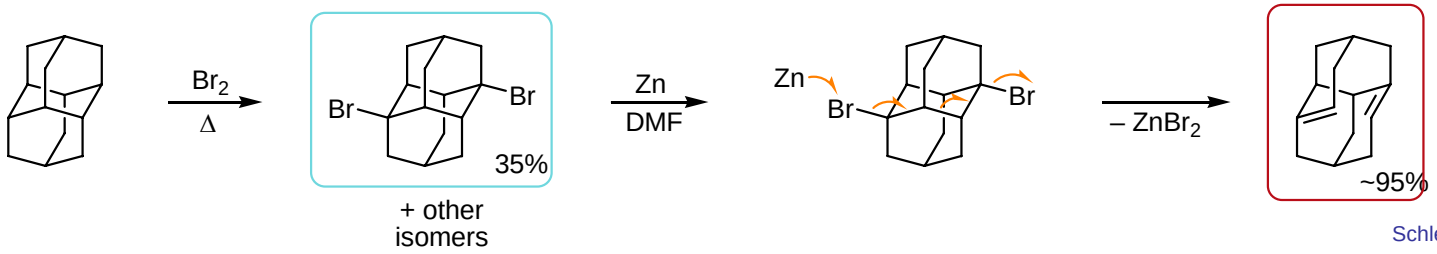
X = H_2, 95%
X = CH_2, 94%

X = H_2, 92%
X = CH_2, 76%

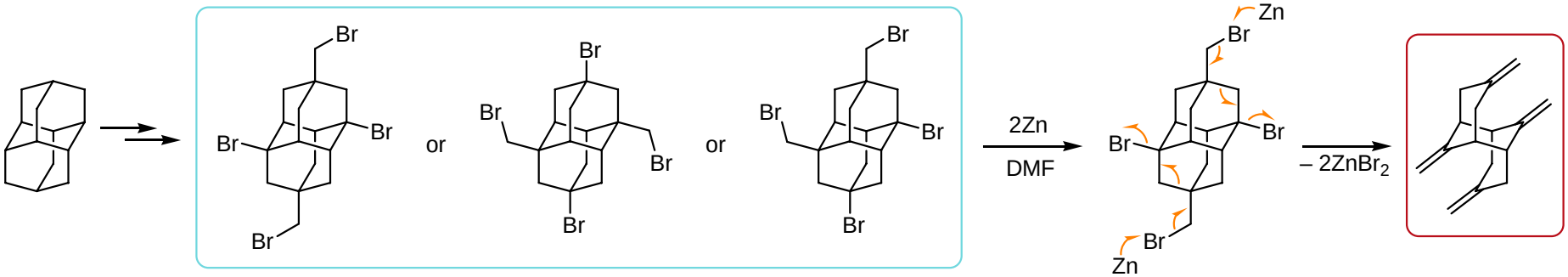
X = H_2, 74%
X = CH_2, 66%

Gunchenko, P. A.; Vygovska, T. S.; Fokin, A. A.; Yurchenko, A. G. *Ukr. Khim. Zhurn.* **2003**, *69*, 113-115.

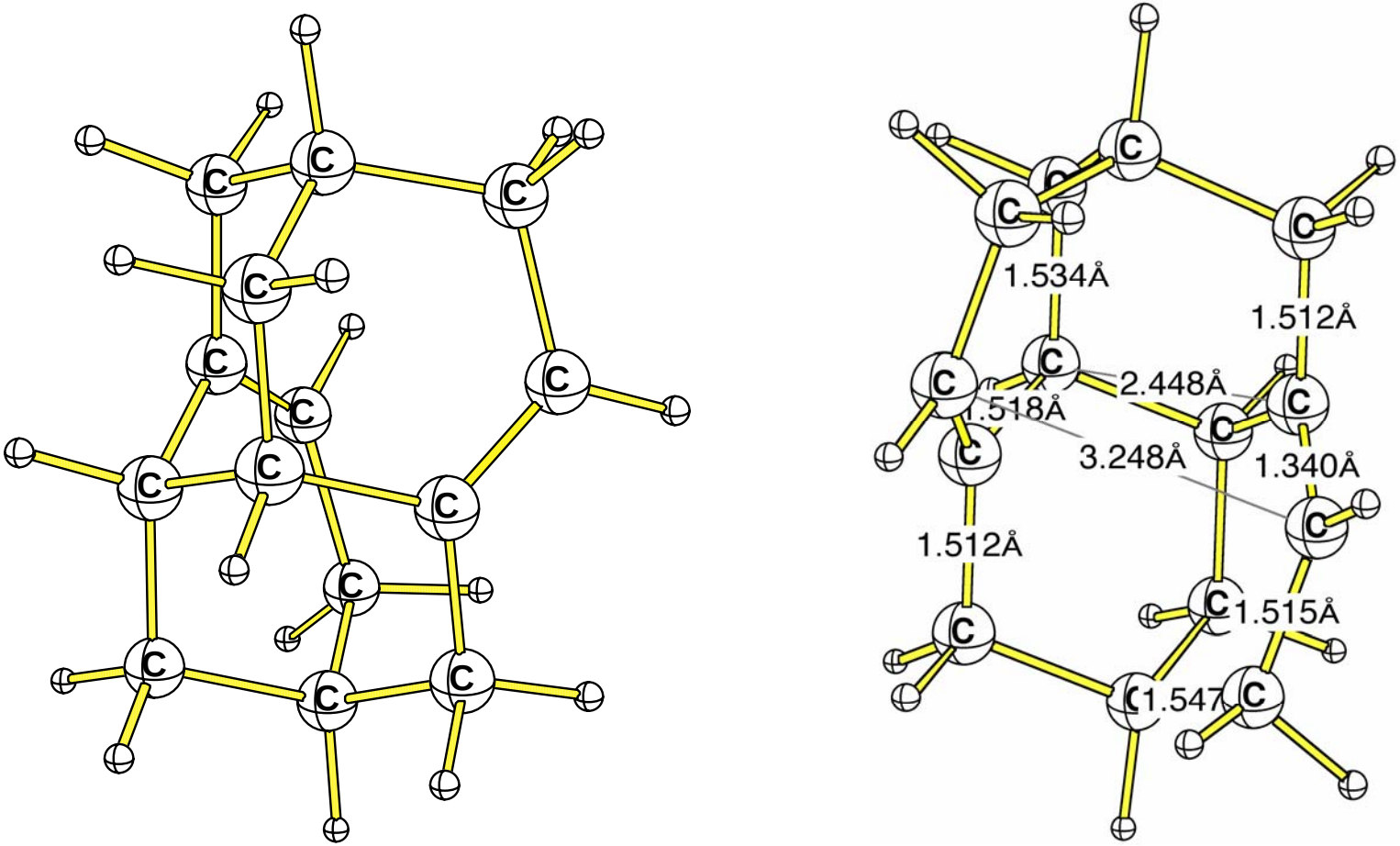
Fragmentations of Diamantane Derivatives



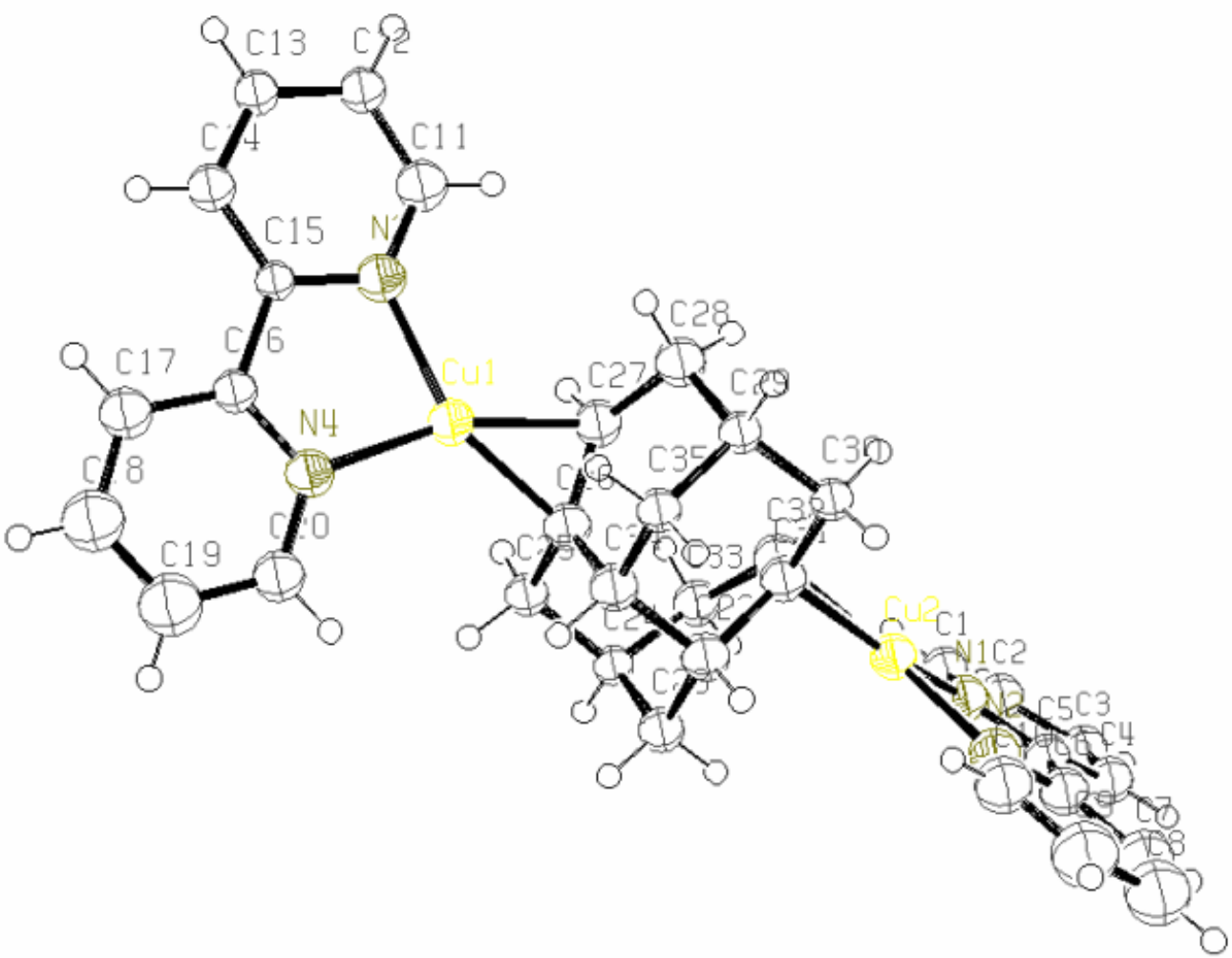
Schleyer, **1973**



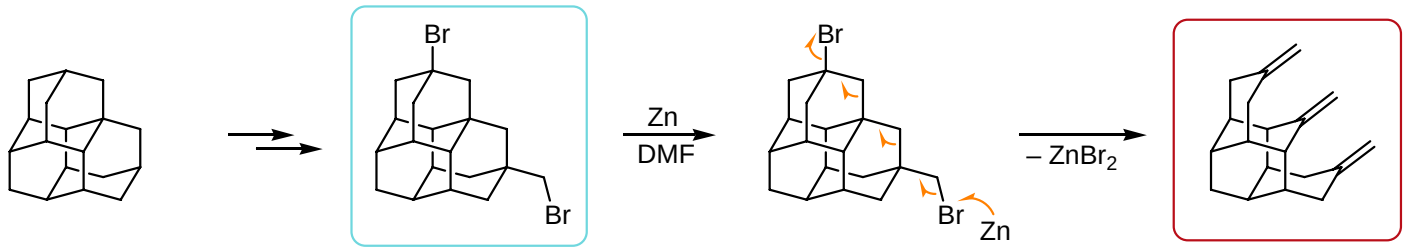
Optimized geometries of tetracyclo[7.3.1.1^{4,12}.0^{2,7}]tetradeca-6,11-diene (B3LYP/6-31G*)

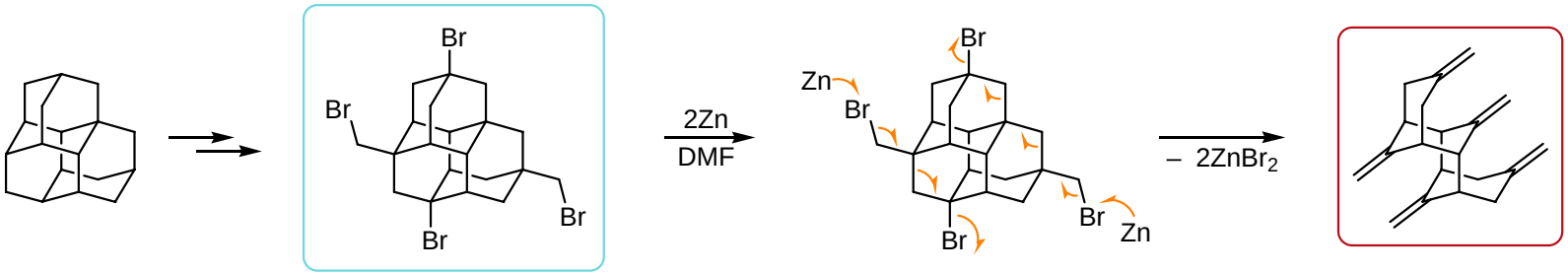


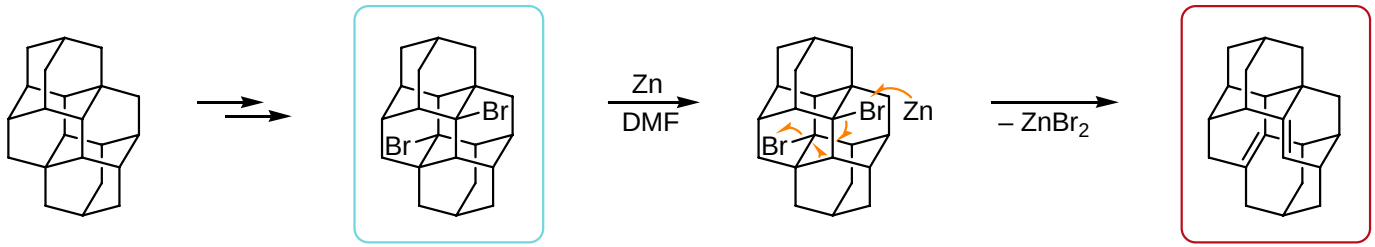
X-ray Structure of bipyCu(I) complex with tetracyclo[7.3.1.1^{4,12}.0^{2,7}]tetradeca-6,11-diene



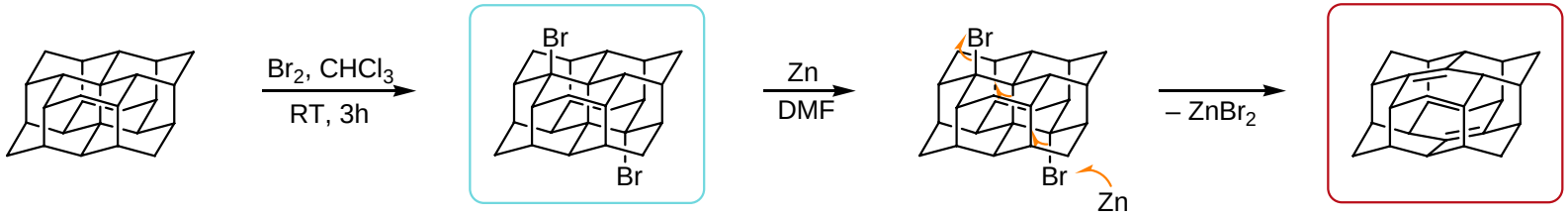
Possible Fragmentation of Triamantane and Tetramantane Derivatives

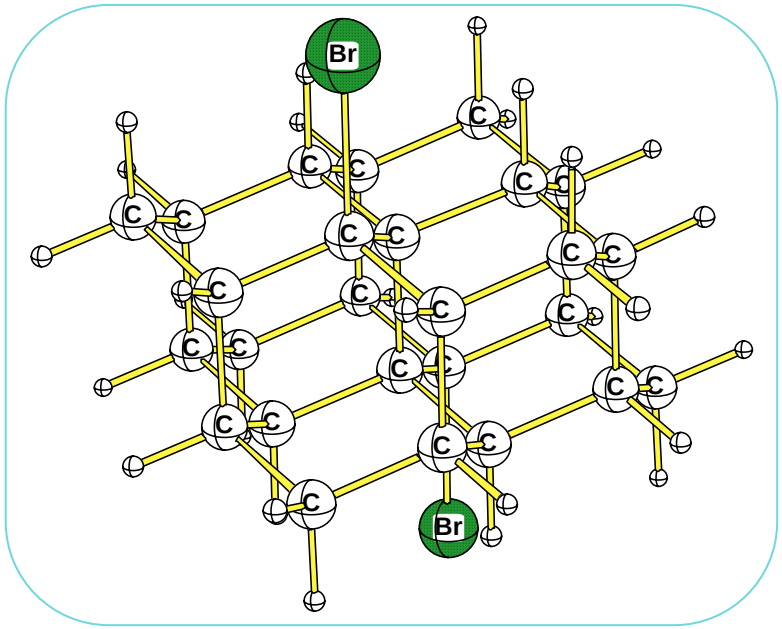




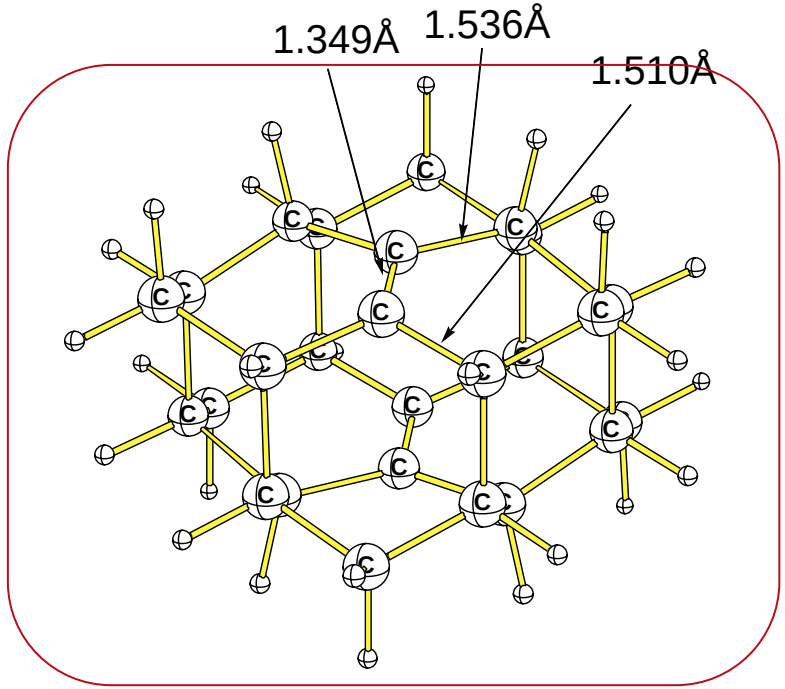


Possible Fragmentation of [12312]hexamantane derivatives





2,15-dihydroxy[12312]hexamantane (B3LYP 6-31G*)



undecacyclo[12.12.0.0^{2,11}.0^{3,8}.0^{4,25}.0^{5,22}.0^{7,20}.0^{9,18}.0^{12,17}.0^{15,24}.0^{16,21}]hexacosa-2,16(21)-diene (B3PW91/6-31+G*)