







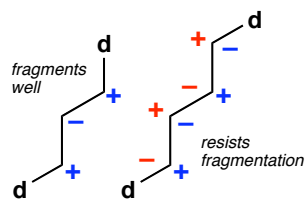
### Fragmentation

- **Heterolytic** - governed by "polarity alternation" (Lapworth, *A. J. Chem. Soc.* **1898**, 73, 495); predictable based on these concepts, also by consonance/dissonance (Evans), conjointment/disjointment (Ho), resonance (see Coulson, C. A., O'Leary, B., Mallon, R. B. "Hückel Theory for Organic Chemists" **1978**, Academic Press, p.132-33.)
- **Homolytic** - less predictable, governed by different rules, energy differences less directing (see below).

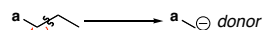
$E_{\text{DISS}}$ (kcal/mol)		4.2		~0	
	95.8	<	100	<	100
$E_{\text{DISS}}$ (kcal/mol)		17.3		27.5	
	231.9	<	249.2	<	276.7

### Distribution of charge

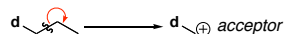
- Hydrocarbon chains are essentially homopolar, therefore the introduction of polar groups affects the chain profoundly.
- Polar groups can be situated in consonant/dissonant (conjoint/disjoint) patterns.



d = OH, OR, OCOR, NRR', NR(COR), SH, SR, F, Cl, Br, I  
a = CHO, COR, CO<sub>2</sub>H, CO<sub>2</sub>R, CN, SO<sub>2</sub>R, NO<sub>2</sub>, SiR<sub>3</sub>  
Attaching an acceptor gives the adjacent carbon donor characteristics.



Attaching a donor gives the adjacent carbon acceptor characteristics.

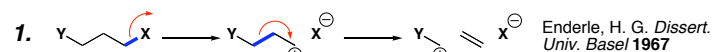


- Resources for further reading on polarity alternation:

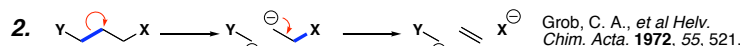
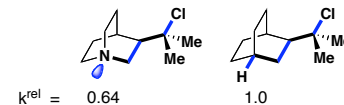
Lapworth, *A. J. Chem. Soc.* **1898**, 73, 495; Ho, T.-L. *Rev. Chem. Intern.* **1988**, 9, 117; Ho, T.-L. *Rev. Chem. Intern.* **1989**, 11, 157. Ho, T.-L. "Polarity Control for Synthesis" **1991**, Wiley, New York. Ho, T.-L. "Heterolytic Fragmentation of Organic Molecules" **1993**, Wiley, New York; Evans, D. A. "An Organizational Format for the Classification of Functional Groups. Applications to the Construction of Difunctional Relationships." **2001**, Chemistry 206 Handout (Harvard).

### Requirements of Fragmentation

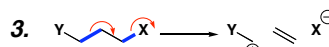
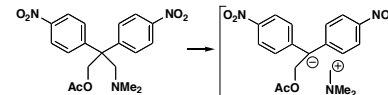
- Each member of atomic chain engages in exchanging an electron pair (stereo-electronic implications).
- Three predominant mechanisms operational



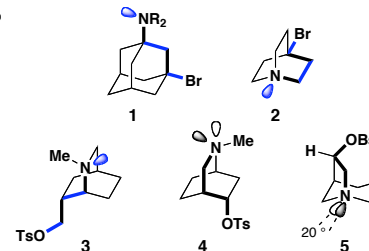
Operative in substrates where 3° cation is formed; product ratios (fragmentation, solvent capture, elimination, cyclization) insensitive to leaving group; non-participation of Y in the rate-determining step.



Operative where there is low nucleofugality of X and stability of intermediate anion: 1<sup>st</sup> order rate constants for X are very similar.



Required antiperiplanarity (see Prelog, V. and co-workers, *Experientia* **1960**, 16, 521), must be able to adopt a zig-zag (1) or  $\square$  (2) chain conformation. Thus, tosylate 3 fragments readily, while tosylate 4 does not. Minor deviations in angle prevent fragmentation, as in brosylate 5, where the nitrogen lone pair deviates only 20° from the desired angle.



Cyril A. Grob (1917–2003)

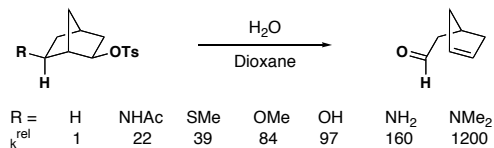
Born in London, studied chemistry at ETH Zürich (PhD, 1943, Leopold Ruzicka); synthetic studies at Universität Basel on biotin, lysergic acid, the steroid framework, and sphingosin. An investigation of the reductive elimination of bromine from 1,4-dibromides in the presence of zinc led in 1955 to the recognition of heterolytic fragmentation as a general reaction principle. The structural and stereochemical prerequisites for a fragmentation to occur were investigated with model compounds, and the fundamental mechanisms of this reaction type were elucidated. In public Cyril Grob was reserved and he did not particularly enjoy socializing. Only in intimate circles did he shine as a relaxed, witty, cultured, and kind person. *He fulfilled his social duties efficiently, reliably, and without a fuss.* - Excerpted from Schiess, P. *Angew. Chem. Int. Ed.* **2004**, 43, 4392.

Representative publications:

C. A. Grob, W. Baumann, *Helv. Chim. Acta* **1955**, 38, 94; C. A. Grob, *Angew. Chem. Int. Ed. Engl.* **1969**, 8, 535; C. A. Grob, *Chimia* **1971**, 25, 87; C. A. Grob, *Angew. Chem. Int. Ed. Engl.* **1976**, 15, 569; C. A. Grob, *Helv. Chim. Acta* **1985**, 68, 882. C. A. Grob, *Angew. Chem. Int. Ed. Engl.* **1982**, 21, 87.

**Frangomeric Effect**

Ratio of the fragmentation and ionization rate constants -  $k_{frag} : k_{ion}$ ; estimated by comparing hetero-substituted and homosubstituted analogues (with adjustments made for induction).



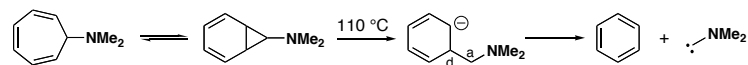
Grob, C.A. *Angew. Chem. Int. Ed.* **1976**, 15, 569

**0-carbon separation: (a-d and d-a)**

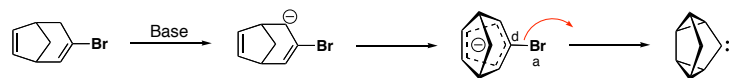


Hoffmann, R. W. *et al. Liebigs Ann. Chem.* **1981**, 581.

Prinzbach, H. *et al. Angew. Chem. Int. Ed. Engl.* **1965**, 4, 435.

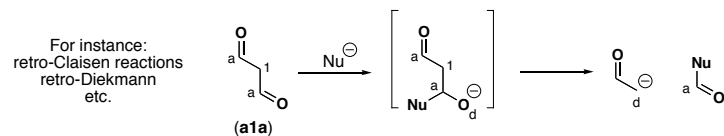


Nefedov, O. *et al. Liebigs Ann. Chem.* **1967**, 707, 217.

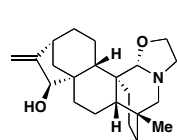
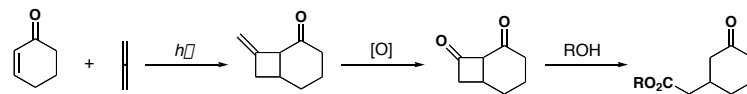


Bergman, R.G. *et al. J. Am. Chem. Soc.* **1970**, 92, 2163.

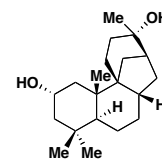
**1-carbon separation: (a1a)**



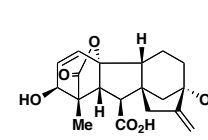
**1. Examples in natural product synthesis: [1]methelenecarboxylation**



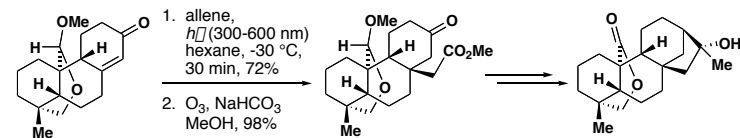
veatchine  
Wisener, K. *et al. Tetrahedron Lett.* **1968**, 6279.



stemodin  
Piers, E. *et al. Chem. Commun.* **1982**, 80.

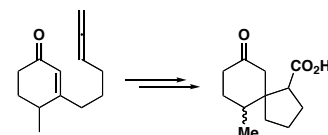


gibberellic acid  
Yamada, Y. *et al. Tetrahedron Lett.* **1989**, 30, 971.

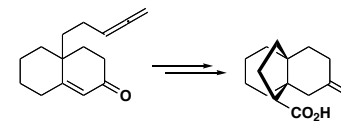


neotripterifordin  
Corey, E.J. *et al. J. Am. Chem. Soc.* **1997**, 119, 9929

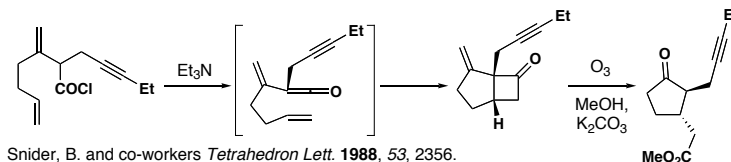
**2. Variations on a theme**



Becker, D. *et al. Chem. Commun.* **1975**, 377.

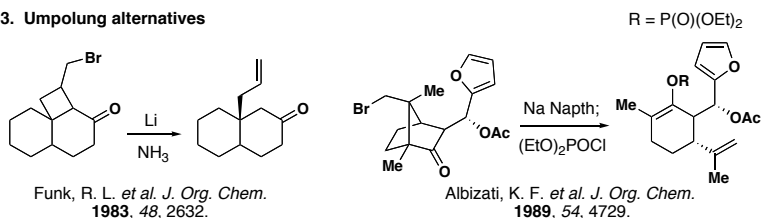


Becker, D. *et al. J. Org. Chem.* **1980**, 45, 570.

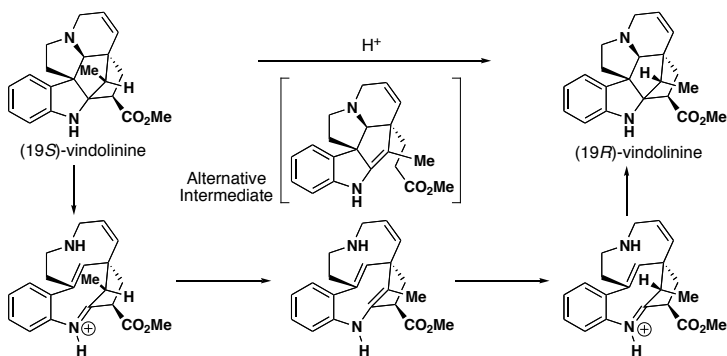
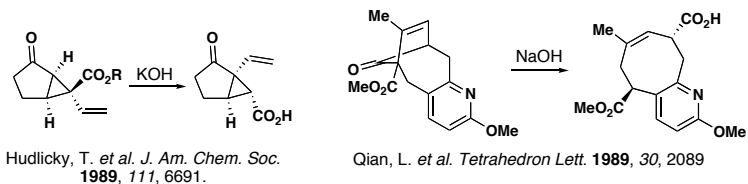


Snider, B. and co-workers *Tetrahedron Lett.* **1988**, 53, 2356.

### 3. Umpolung alternatives

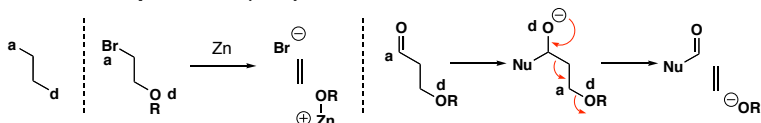


### 4. Other a1a fragmentations

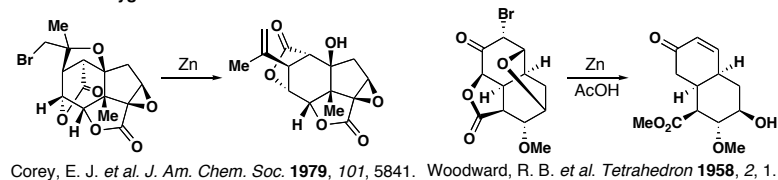


Atta-ur-Rahman, M.; Malik, S.; Albert, K. Z. *Naturforsch* **1986**, *B41*, 386.

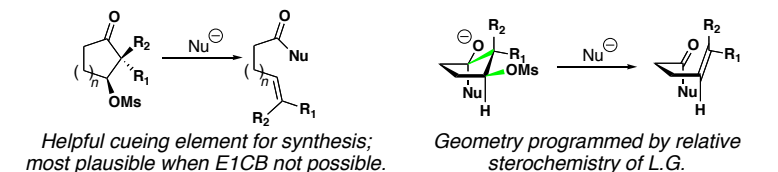
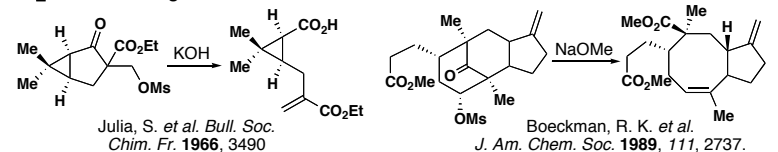
### 2-carbon separation: (a2d)



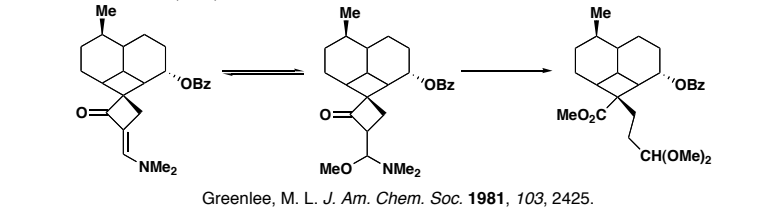
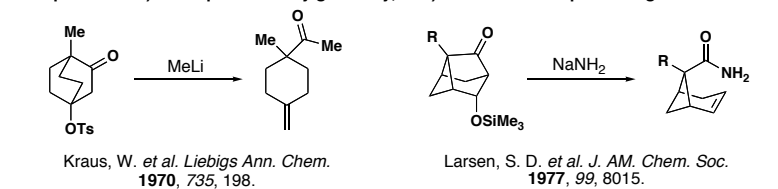
### 1. Halo-deoxygenations



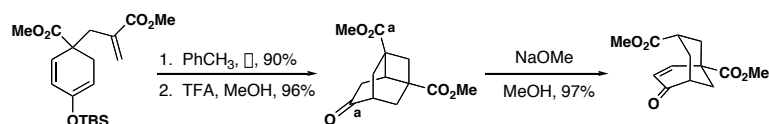
### 2. [1,2]-L.G. ketone fragmentations



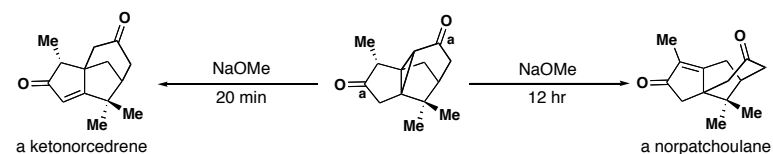
Also possible if i) E1CB prevented by geometry, or ii) elimination is equilibrating



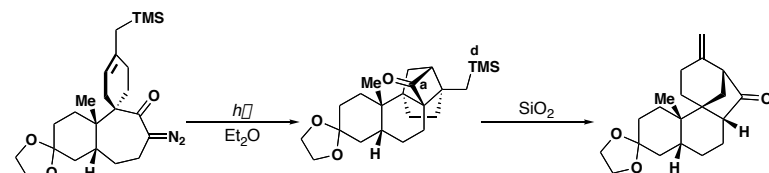
#### 3-carbon separation (a3a, d3d, d3a)



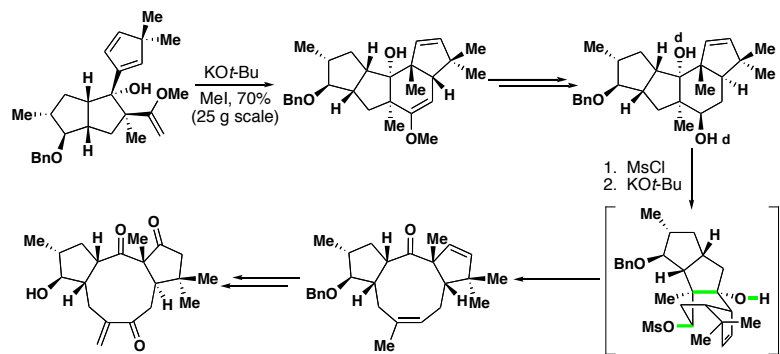
Ganem, B. and co-workers. *Tetrahedron Lett.* **1987**, 28, 6253.



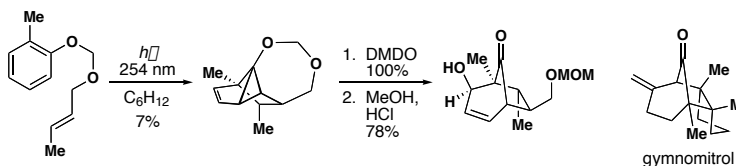
Deslongchamps, P. *Can. J. Chem.* **1977**, 55, 4117.



Ireland, R. E. *et al. J. Org. Chem.* **1984**, 49, 1003.

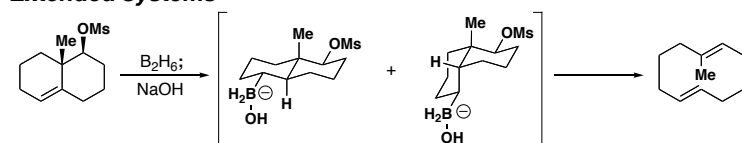


Paquette, L. A. *et al. J. Am. Chem. Soc.* **2003**, 125, 1567.

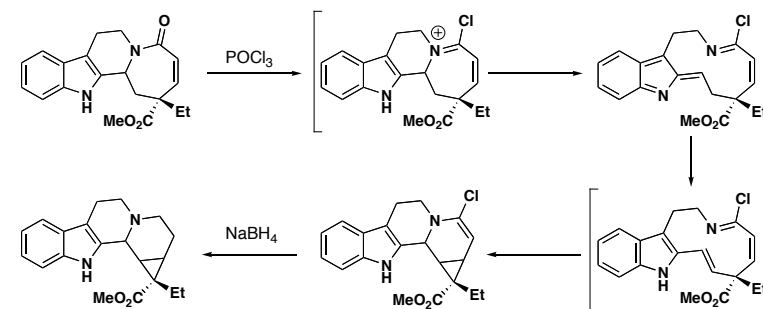


Penkett, C. S. *et al. Tetrahedron* **2004**, 60, 2771.

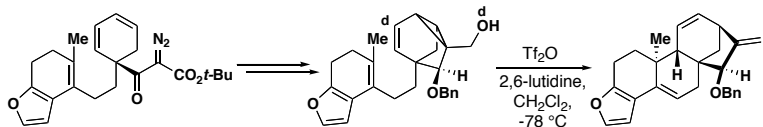
#### Extended systems



Marshall, J. A. *J. Am. Chem. Soc.* **1966**, 88, 4291.

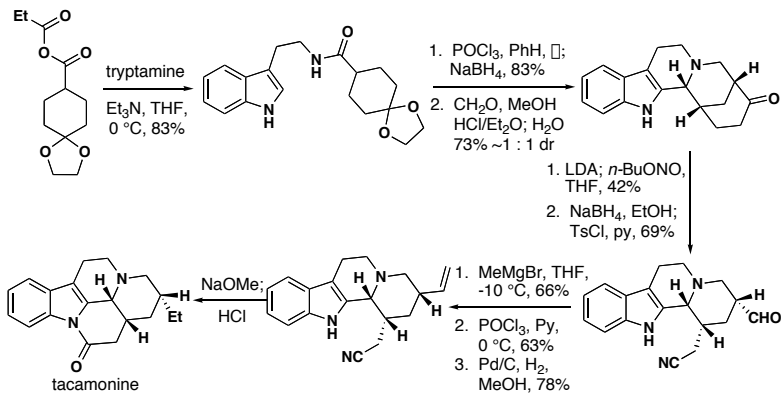


Takano, S. *et al. J. Am. Chem. Soc.* **1979**, 101, 6414.

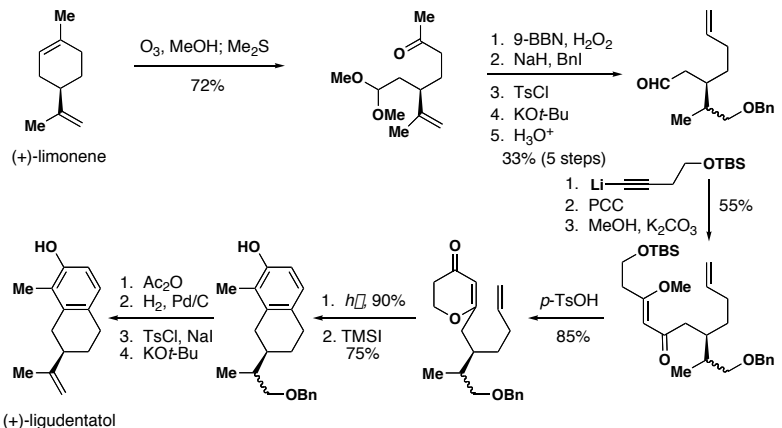


Corey, E. J. *et al. J. Am. Chem. Soc.* **1987**, 109, 4717.

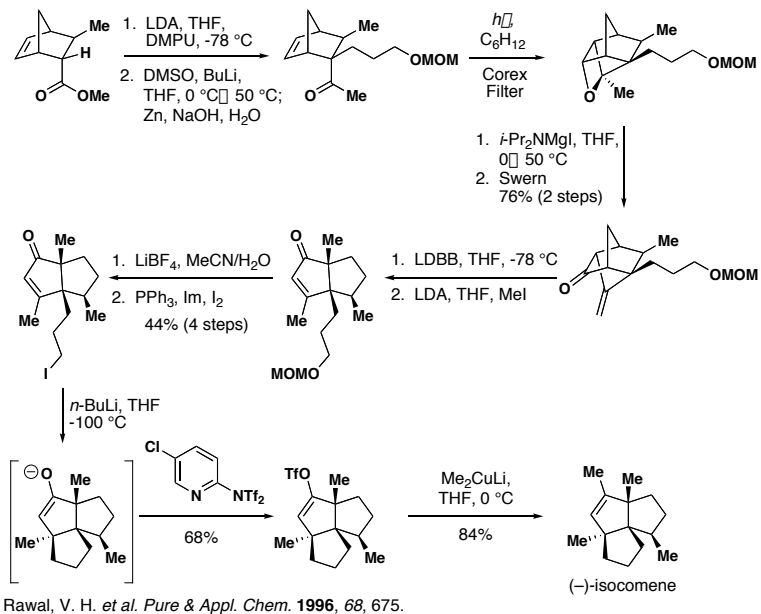
Examples of fragmentation reactions in synthesis



Ho, T.-L. *et al. Tetrahedron*, **2002**, *58*, 4969.



Haddad, N. *et al. Tetrahedron Lett.* **1997**, *34*, 6087.



Rawal, V. H. *et al. Pure & Appl. Chem.* **1996**, *68*, 675.