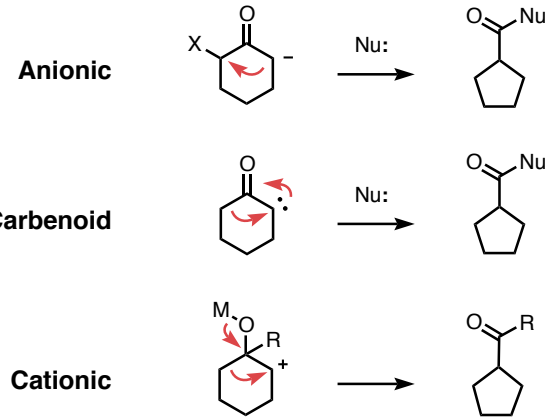
Recent Reviews:

Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556.
Silva, Jr. L. F. *Tetrahedron* **2002**, *58*, 9137–9161.

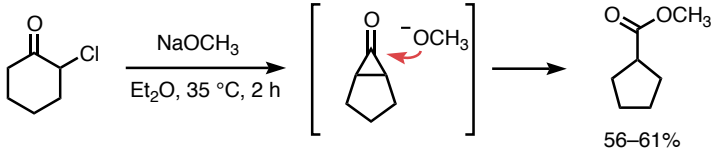
- Ring contraction reactions can be grouped into three general categories based on mechanism:



Anionic Ring Contractions

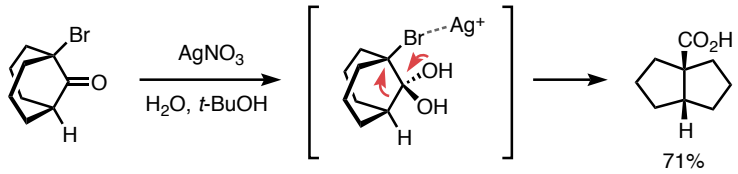
Favorskii Rearrangement

- The Favorskii reaction leads to the rearrangement of an α-halo cycloalkanone upon treatment with base. This reaction proceeds through a cyclopropanone intermediate that is opened by nucleophilic attack.



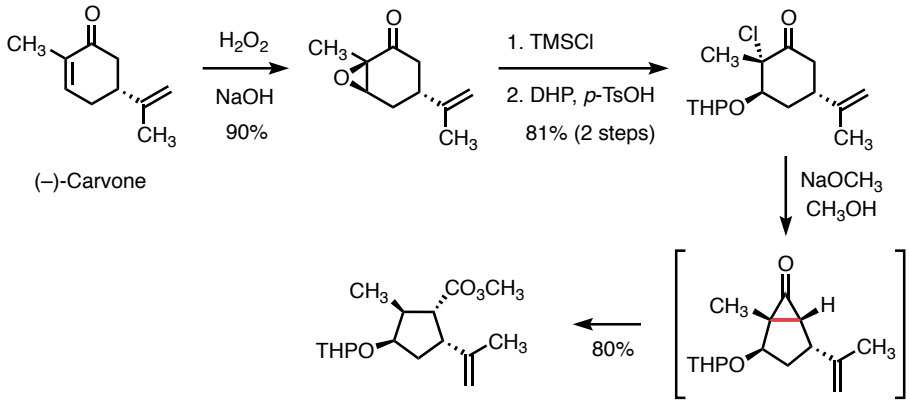
Organic syntheses; Wiley & Sons: New York, **1963**; Coll. Vol. No. 4, pp. 594.

- In some cases, enolization is not possible, precluding cyclopropanone formation. An alternate mechanism involves formation of a tetrahedral intermediate that promotes alkyl migration.



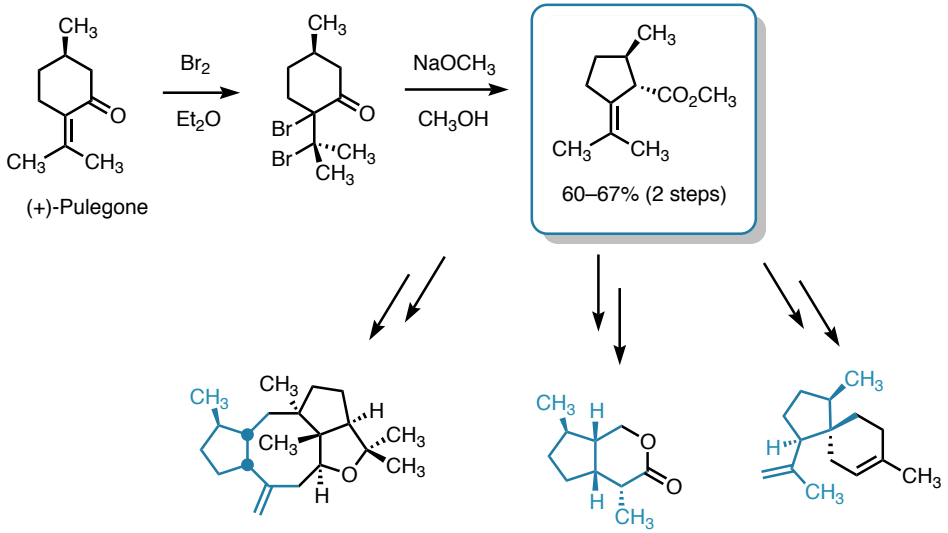
Cope, A. C.; Graham, E. S. *J. Am. Chem. Soc.* **1951**, *73*, 4702–4706.
Loftfield, R. B. *J. Am. Chem. Soc.* **1951**, *73*, 4707–4714.

- Chiral-pool starting materials have been much used as substrates for the Favorskii reaction, affording functionalized, optically active cyclopentanes.



Lee, E.; Yoon, C. H. *J. Chem. Soc., Chem. Commun.* **1994**, 479–481.

- For example, the ring contraction of a (+)-pulegone derivative has been used in the synthesis of several terpenoid natural products.



Common intermediate: Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry.* 5th ed. Longman: London, 1989.
(+)-Epoxydictymene: Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4353–4363.
(–)-Iridomyrmecin: Wolinsky, J.; Gibson, T.; Chan, D.; Wolf, H. *Tetrahedron* **1965**, *21*, 1247–1261.
(+)-Acoradiene: Kurosawa, S.; Bando, M.; Mori, K. *Eur. J. Org. Chem.* **2001**, 4395–4399.

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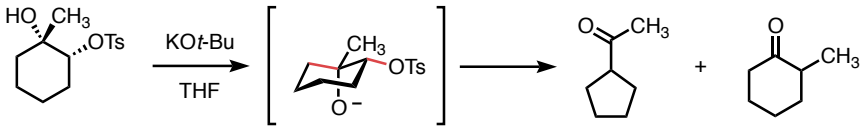
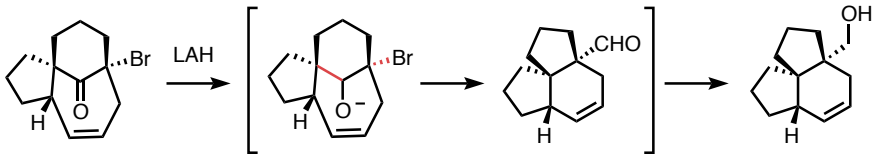
Quasi-Favorskii Rearrangement

- Also referred to as the negative-ion pinacol rearrangement, the quasi-Favorskii rearrangement involves an alkyl shift with concomitant nucleophilic displacement of an aligned leaving group.
- These fragmentations are generally accelerated by oxyanion formation.



90%, 89 : 11

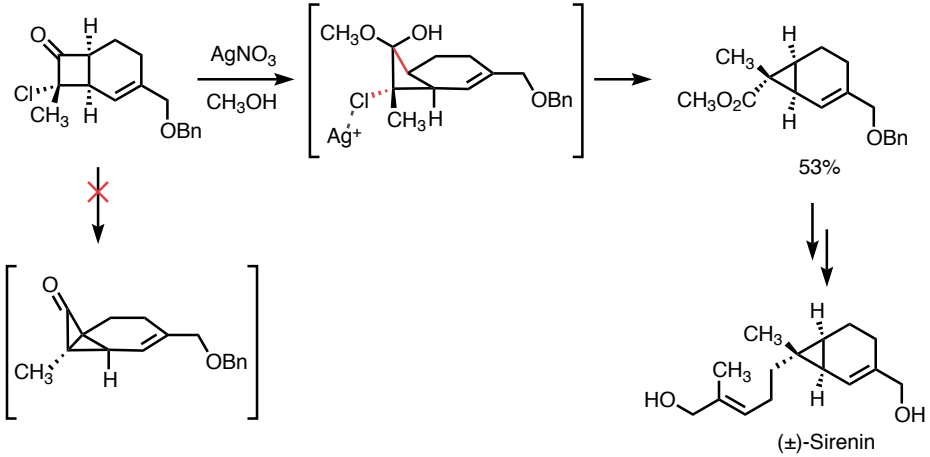
Hamon, D. P. G.; Tuck, K. L. *Chem. Commun.* **1997**, 941–942.



98%

Harmata, M.; Bohnert, G.; Kürti, L.; Barnes, C. L. *Tetrahedron Lett.* **2002**, *43*, 2347–2349.

- A quasi-Favorskii ring contraction was employed by Harding in the synthesis of (±)-sirenin. The stereochemical outcome of this rearrangement suggests formation of a tetrahedral intermediate that undergoes alkyl shift with halide displacement, rather than cyclopropanone formation as in the classic Favorskii rearrangement.

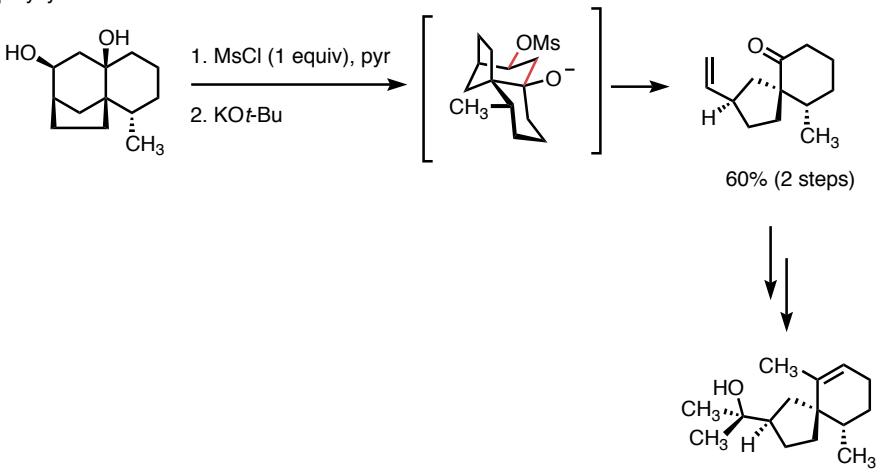


53%

(±)-Sirenin

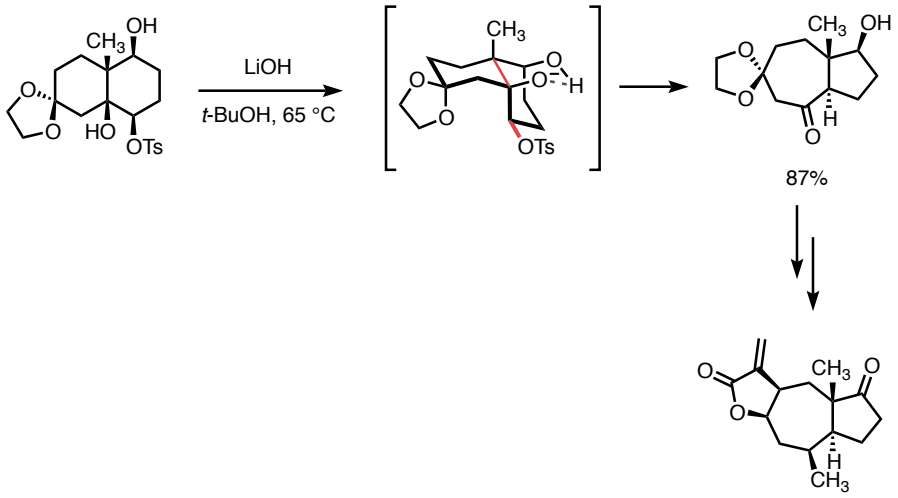
Harding, K. E.; Strickland, J. B.; Pommerville, J. *J. Org. Chem.* **1988**, *53*, 4877–4883.

- A common application of the quasi-Favorskii rearrangement is in the rearrangement of fused polycycles.



Marshall, J. A.; Brady, S. F. *J. Org. Chem.* **1970**, *35*, 4068–4077.

(±)-Hinesol



(±)-Confertin

Heathcock, C. H.; DelMar, E. G.; Graham, S. L. *J. Am. Chem. Soc.* **1982**, *104*, 1907–1917.

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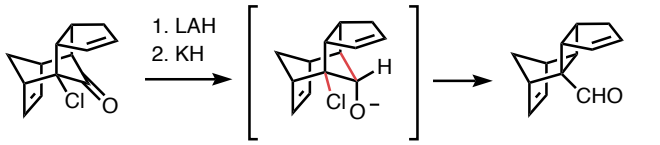
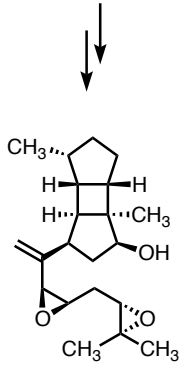
Quasi-Favorskii Rearrangement

- Harmata has showcased the power of the quasi-Favorskii rearrangement in the synthesis of several terpenoid natural products.



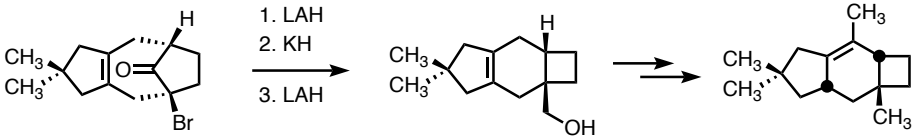
Stereochemistry established by X-ray

76% (2 steps)



(±)-Spatol

Harmata, M.; Rashatasakhon, P. *Org. Lett.* **2001**, *3*, 2533–2535.



91% (3 steps)

(±)-Sterpurene

Harmata, M.; Bohnert, G. J. *Org. Lett.* **2003**, *5*, 59–61.

Carbenoid Ring Contractions

Wolff Rearrangement

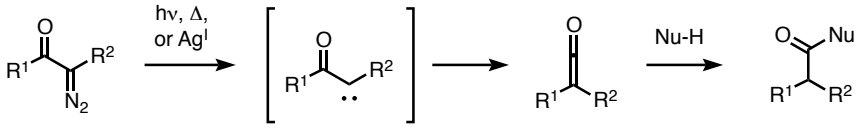
Reviews:

Kirmse, W. *Eur. J. Org. Chem.* **2002**, 2193–2256.

Meier, H.; Zeller, K.-P. *Angew. Chem. Int. Ed.* **1975**, *14*, 32–43.

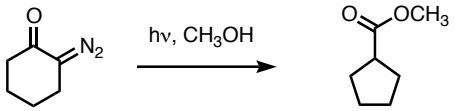
- The Wolff rearrangement involves the transformation of an α-diazo ketone via carbene or carbenoid to a ketene, which undergoes further transformation to form a stable adduct.

- The Wolff rearrangement may be induced by heat, Ag(I) salts, or light.



Nu = -OCH_3, -OBn, -OH, -NR_2, SR, etc.

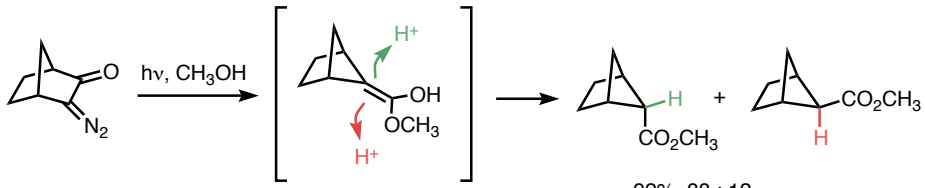
- In the prototypical case depicted below, the Wolff rearrangement proceeds in higher yield relative to the analogous Favorskii system.



> 99%

Tomioka, H.; Okuno, H.; Izawa, Y. *J. Org. Chem.* **1980**, *45*, 5278–5283.

- The stereochemistry of the α position can be kinetically controlled, determined by the relative rates of protonation of the enol or enolate intermediate.



92%, 88 : 12

Kirmse, W.; Wroblowsky, H.-J. *Chem. Ber.* **1983**, *116*, 1118–1131.

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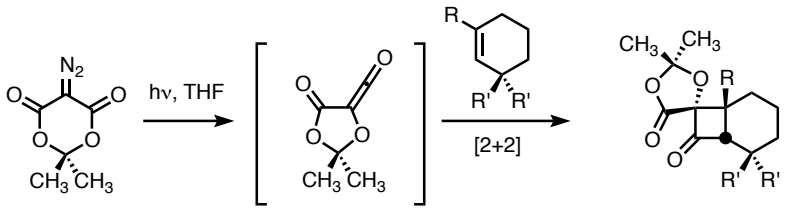
Wolff Rearrangement

- Ketene intermediates produced in the Wolff rearrangement can also be trapped in [2+2] cycloaddition reactions.

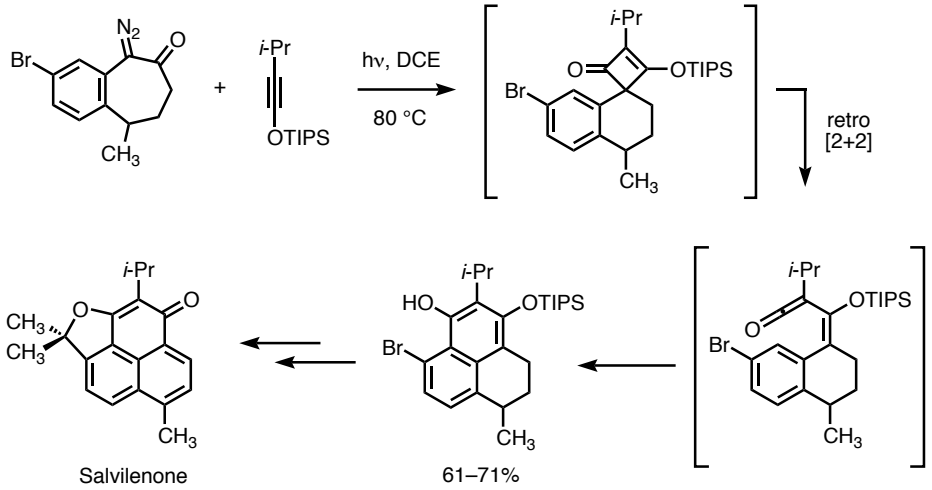


R	R'	Yield
H	H	84%
CH_3	CH_3	64%
CH_3	H	76%
Ph	H	54%

Stevens, R. V.; Bisacchi, G. S.; Goldsmith, L.; Strouse, C. E. *J. Org. Chem.* **1980**, *45*, 2708–2709.

Livinghouse, T.; Stevens, R. V. *J. Am. Chem. Soc.* **1978**, *100*, 6479–6482.

- Danheiser and Helgason used such a strategy in the synthesis of salvilenone. The [2+2] cycloadduct in this case underwent retro-[2+2] ring opening followed by electrocyclization.



Salvilenone

61–71%

Danheiser, R. L.; Helgason, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 9471–9479.

Synthesis of diazo ketones

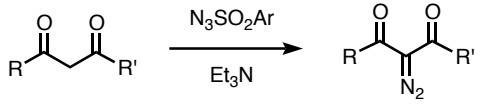
Review

Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds.* Wiley-Interscience, New York, **1998**, pp. 1–60.

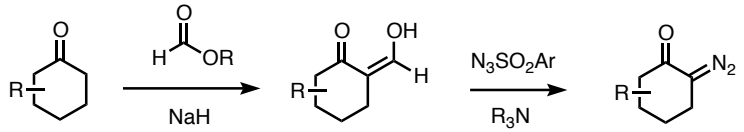
See course handout "C–O Bond-Forming Reactions" for further discussion of the synthesis of diazo compounds.

Direct Diazotization

- Compounds such as 1,3-dicarbonyls can be diazotized directly using arenesulfonyl azide reagents.

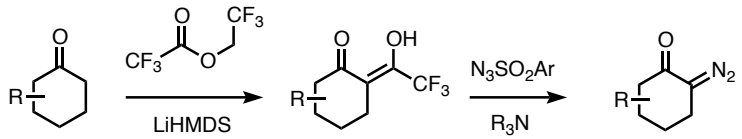


- In the absence of a β activating group, α-diazo ketones can be formed by formylation-diazotization-deformylation, in a procedure known as Regitz diazo transfer.



Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, New York, **1986**, pp. 199–543.
Regitz, M. in: *The Chemistry of Diazonium and Diazo Groups, Part 2* (Ed.: Patai, S.), Wiley-Interscience, Chichester, **1978**, pp. 751–820.

- Similarly, in the Danheiser procedure, reversible α–trifluoroacetylation activates the substrate toward diazotization.



Danheiser, R. L.; Miller, R. F.; Brisbois, R. B.; *Org. Synth.* **1996**, *73*, 134–143.
Danheiser, R. L.; Miller, R. F.; Brisbois, R. G.; Park, S. Z. *J. Org. Chem.* **1990**, *55*, 1959–1964.

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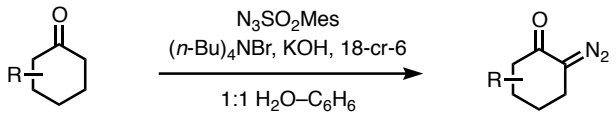
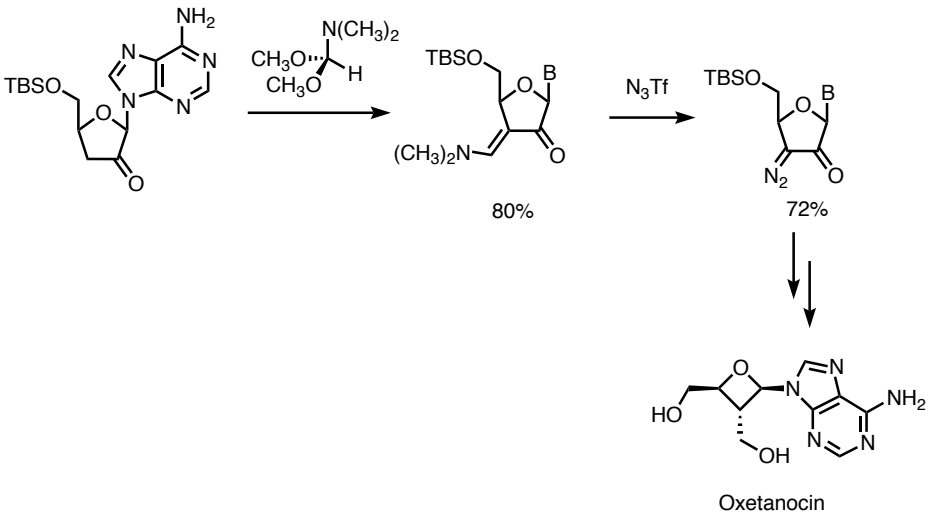
Synthesis of diazo ketones

- In the Mandler procedure, enolized ketones are diazotized without the assistance of an activating group. These reactions are generally run under phase-transfer conditions, and are therefore not ideal for substrates sensitive to aqueous base (e.g., esters).



Lombardo, L.; Mandler, L. N. *Synthesis* **1980**, 368–369.

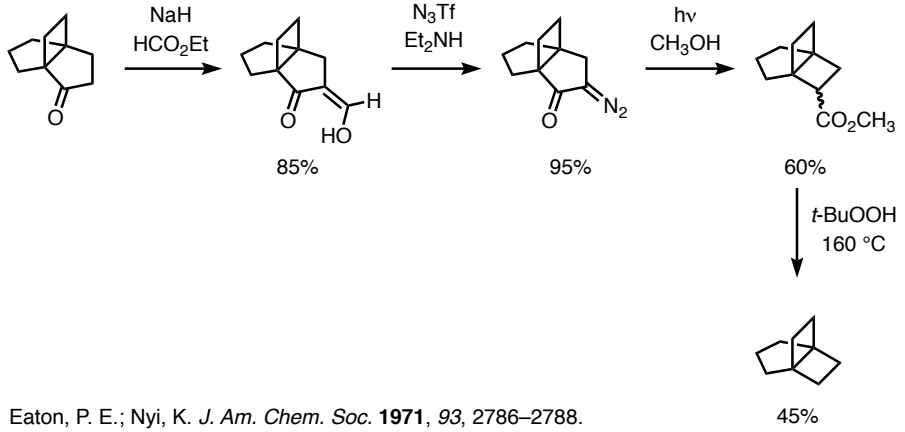
- Mild conditions to activate cyclic ketones using dimethylformamide dimethyl acetal have been developed. The resulting enamine intermediates undergo diazotization with electron-poor diazo transfer reagents such as triflyl azide ($N_3SO_2CF_3$). This approach was used in the synthesis of oxetanocin, a bacterial isolate with anti-HIV activity.



Norbeck, D. W.; Kramer, J. B. *J. Am. Chem. Soc.* **1988**, *110*, 7217–7218.

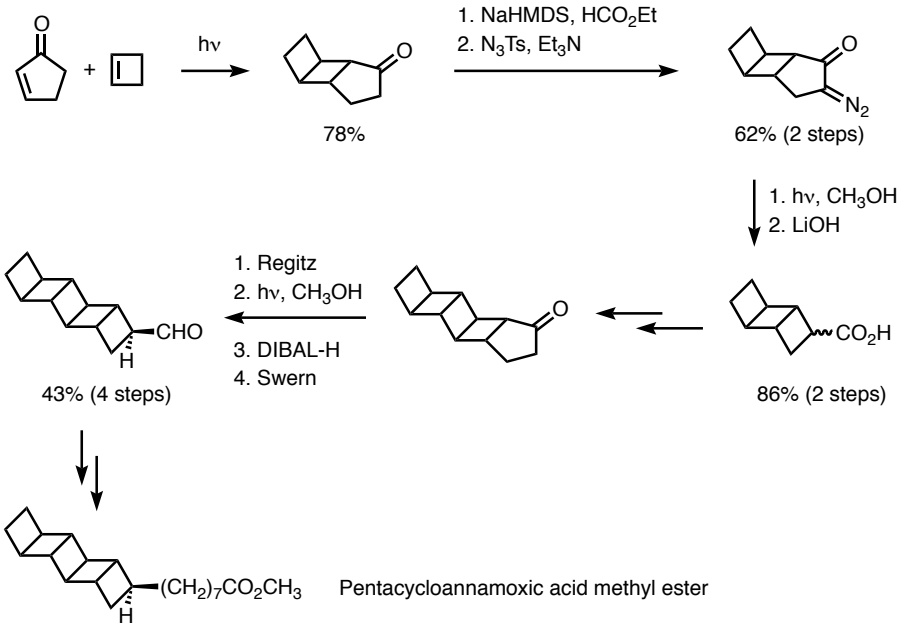
Wolff Rearrangement – Applications in target-oriented synthesis

- Sequential Regitz diazotization–Wolff rearrangement was applied by Eaton and Nyi in their synthesis of [3.2.2]propellane. Thermolytic decarboxylation of a *tert*-butyl perester provides the final product after ring contraction.



Eaton, P. E.; Nyi, K. *J. Am. Chem. Soc.* **1971**, *93*, 2786–2788.

- Similarly, Corey and Mascitti use two Regitz diazotization–Wolff rearrangement reactions in sequence in their enantioselective synthesis of pentacycloannamoxic acid methyl ester.



Mascitti, V.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 3118–3119.

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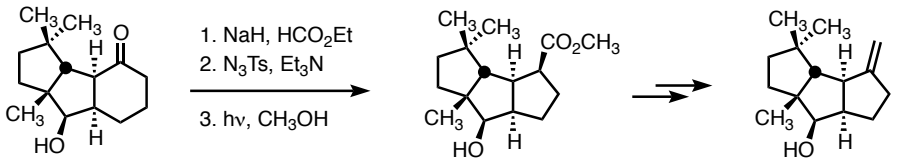
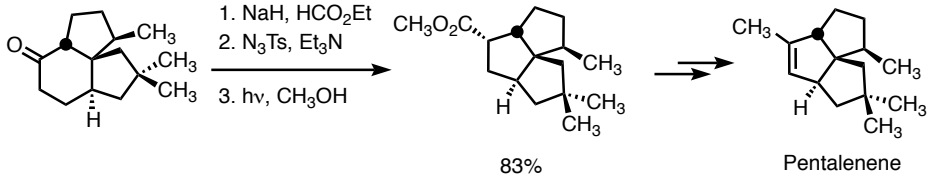
Wolff Rearrangement – Applications in target-oriented synthesis

- The Wolff rearrangement has been employed in the construction of the fused 5,5,5-tricyclic cores of sesquiterpenes.

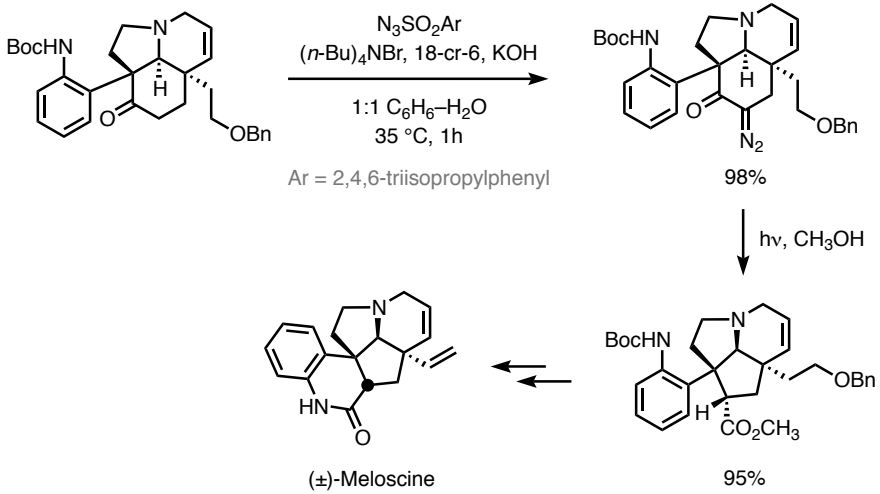


Ihara, M.; Suzuki, T.; Katogi, M.; Taniguchi, N.; Fukumoto, K. *J. Chem. Soc. Perkin Trans. 1* **1992**, 865–873.



Ihara, M.; Katogi, M.; Fukumoto, K. *J. Chem. Soc. Perkin Trans. 1* **1988**, 2963–2970.

- Where other methods failed, the Mandler procedure enabled Overman and co-workers to diazotize a ketone *en route* to (±)-meloscine.



Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Am. Chem. Soc.* **1991**, *113*, 2598–2610.
Overman, L. E.; Robertson, G. M.; Robichaud, A. J. *J. Org. Chem.* **1989**, *54*, 1236–1238.

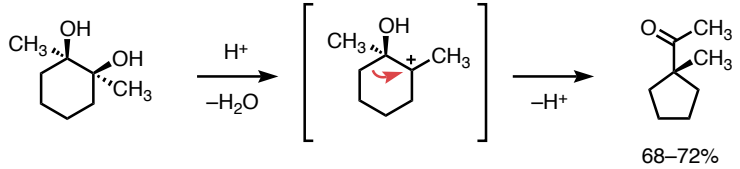
Cation-type rearrangements

Pinacol Rearrangement

Reviews

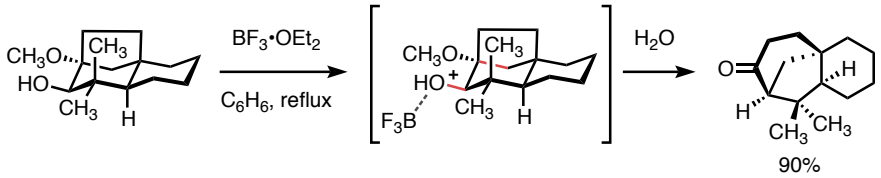
Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523–7556.
Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143–7157.
Overman, L. E. *Acc. Chem. Res.* **1992**, 25, 352–359.

- Vicinal diols, when treated with acid, generate a transient cation that may undergo alkyl shift coupled with carbonyl formation.



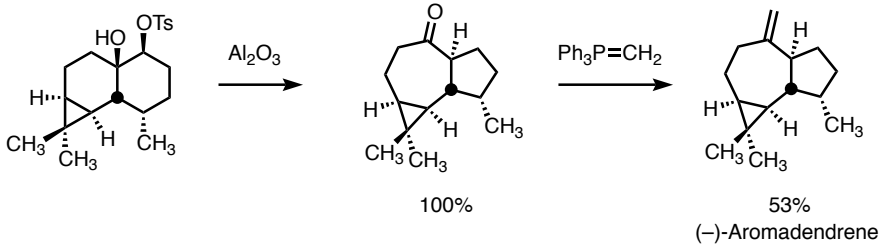
Pavlik, C.; Morton, M. D.; Smith, M. B. *Synlett* **2011**, 2191–2194.

- Cationic rearrangements can proceed through concerted mechanisms as well, particularly when the migrating bond is aligned with the leaving group.



Hariprakasha, H. K.; SubbaRao, G. S. R. *Tetradron Lett.* **1997**, *38*, 5343–5346.

- Halogens and sulfonate esters can also be used, as demonstrated below.

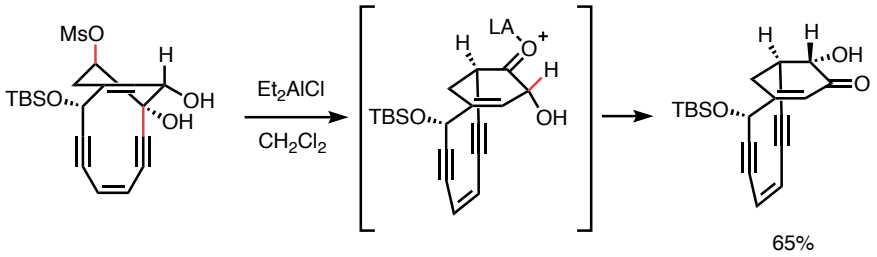


Büchi, G.; Hofheinz, W.; Paukstelis, J. V. *J. Am. Chem. Soc.* **1969**, *91*, 6473–6478.

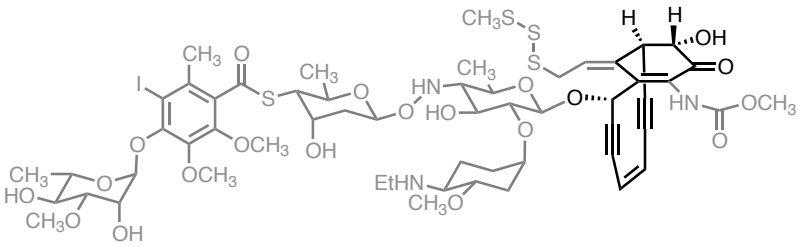
Matt Mitcheltree

Pinacol Rearrangement

- Schreiber's synthesis of the bicyclic core of calicheamicin relied on a pinacol rearrangement. Tautomerization of the resulting α-hydroxy ketone gave the enone product shown.

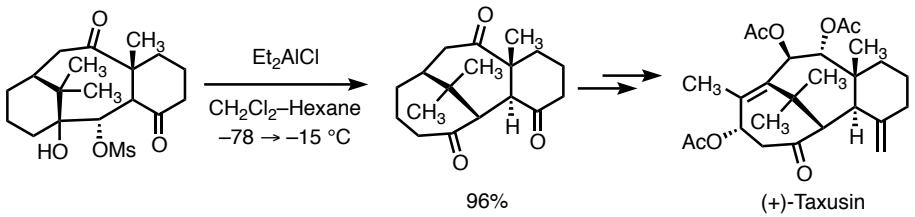


Schoenen, F. J.; Porco, J. A.; Schreiber, S. L. *Tetrahedron Lett.* **1989**, *30*, 3765–3768.



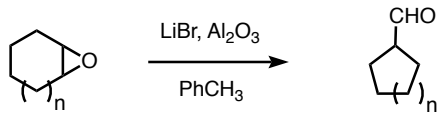
Calicheamicin γ1

- Similarly, Paquette employed a pinacol rearrangement to produce the (+)-taxusin skeleton.



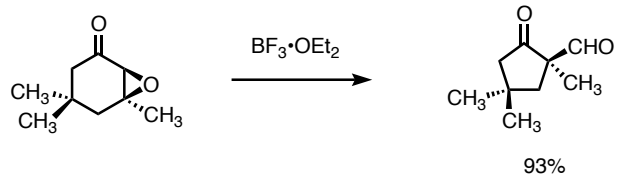
Paquette, L. A.; Zhao, M. *J. Am. Chem. Soc.* **1998**, *120*, 5203–5212.

- The reaction of epoxides with Lewis acids can provide ring-contracted products by a pinacol-type mechanism.



n	Yield
1	77%
2	42%
3	30%

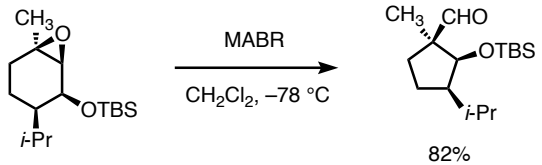
Suga, H.; Miyake, H. *Synthesis* **1988**, 394–395.



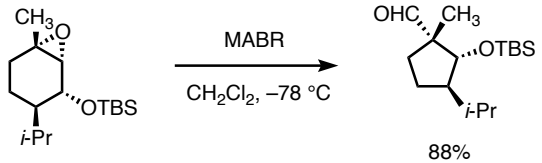
93%

Kunisch, F.; Hobert, K.; Weizel, P. *Tetrahedron Lett.* **1985**, *26*, 6039–6042.

- Yamamoto and co-workers have described an epoxide-opening ring contraction utilizing a methylaluminum diphenoxide Lewis acid that outperforms boron trifluoride in difficult ring contractions.



82%



88%

MABR = $CH_3Al(OAr)_2$

Ar = t-Bu, Br, t-Bu

Maruoka, K.; Ooi, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 6431–6432.

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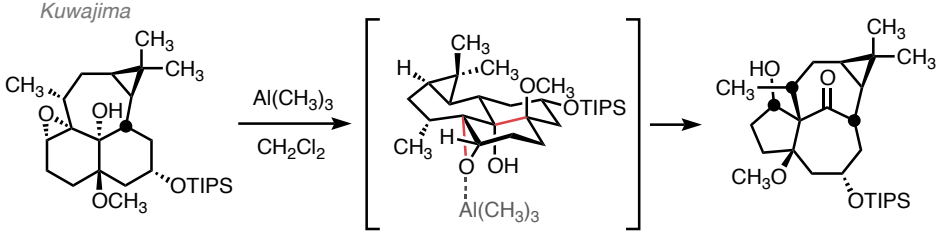
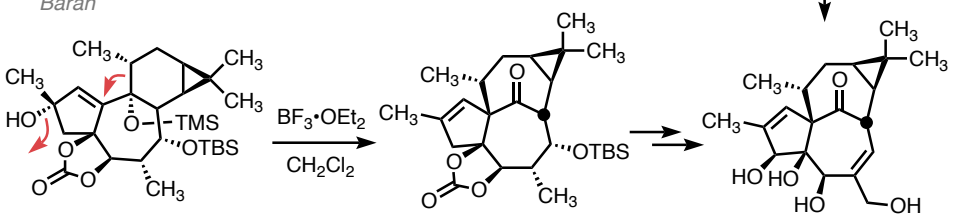
Pinacol Rearrangement

- Kuwajima and Baran both used pinacol-type rearrangements in their syntheses of ingenol.

Kuwajima

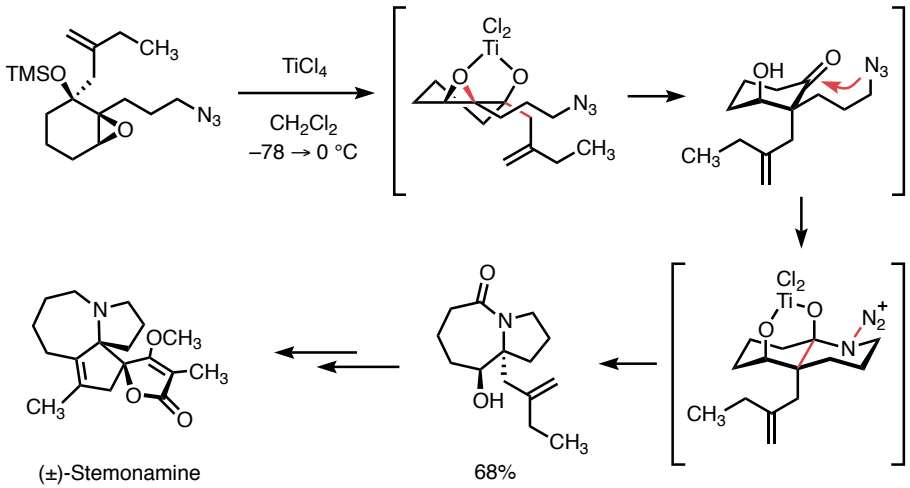


Baran



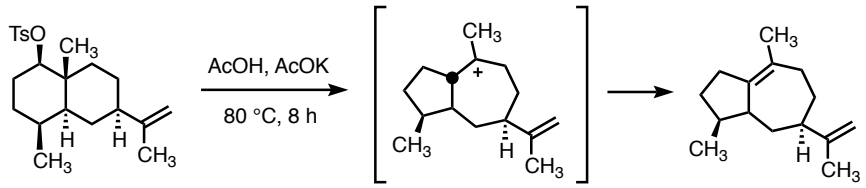
Tanino, K.; Onuki, K.; Asano, K.; Miyashita, M.; Nakamura, T.; Takahashi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **2003**, *125*, 1498–1500.
Jørgensen, L.; McKerall, S. J.; Kuttruff, C. A.; Ungeheuer, F.; Felding, J.; Baran, P. S. *Science* **2013**, *341*, 878–882.

- A tandem pinacol–Schmidt rearrangement was used to synthesize the core of (±)-stemonamine.



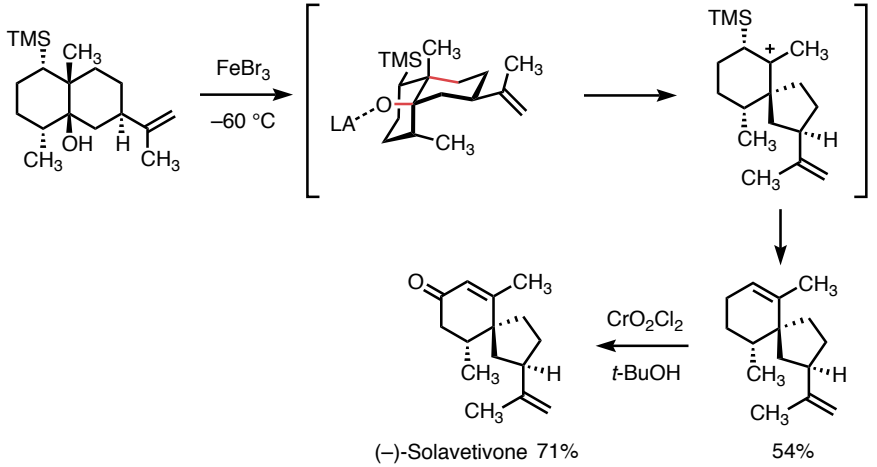
Zhao, Y. M.; Gu, P. M.; Tu, Y. Q.; Fan, C. A.; Zhang, Q. W. *Org. Lett.* **2008**, *10*, 1763–1766.

- After cationic rearrangement, the resulting cation may be intercepted by elimination of an adjacent proton:



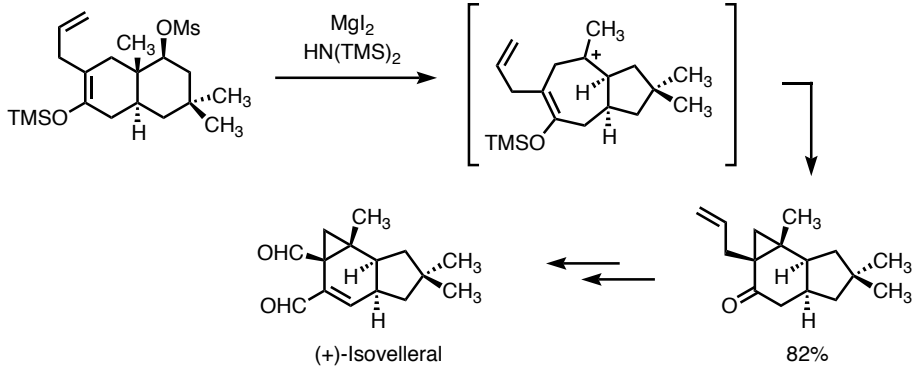
Heathcock, C. H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1971**, *93*, 1746–1757.

- By elimination of a β-silyl group:



Hwu, J. R.; Wetzel, J. M. *J. Org. Chem.* **1992**, *57*, 922–928.

- Or by attack with an endogenous nucleophile.



Bell, R. P. L.; Wjnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **2001**, *66*, 2350–2357.

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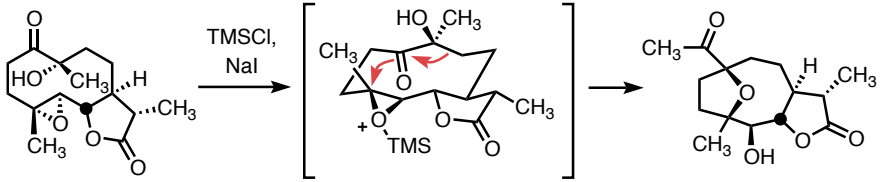
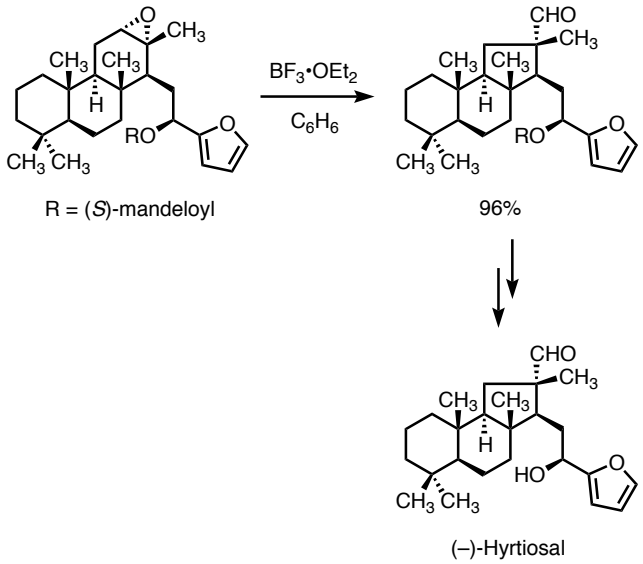
- An example of a pinacol rearrangement initiated by an endogenous electrophile was demonstrated by Oltra:



Rosales, A.; Estévez, R. E.; Cuerva, J. M.; Oltra, J. E. *Angew. Chem., Int. Ed.* **2005**, *44*, 319–322.

- The Imamura synthesis of (–)-hyrtiosal employed an epoxide-opening rearrangement that is proposed to mimic the biosynthetic route to the natural product.

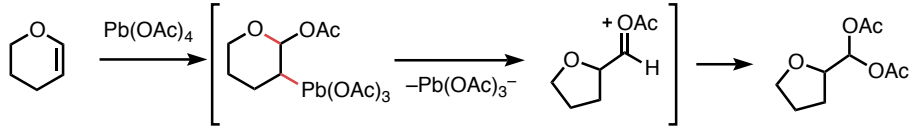


Lunardi, I.; Santiago, G. M. P.; Imamura, P. M. *Tetrahedron Lett.* **2002**, *43*, 3609–3611.

Lead-promoted ring contractions

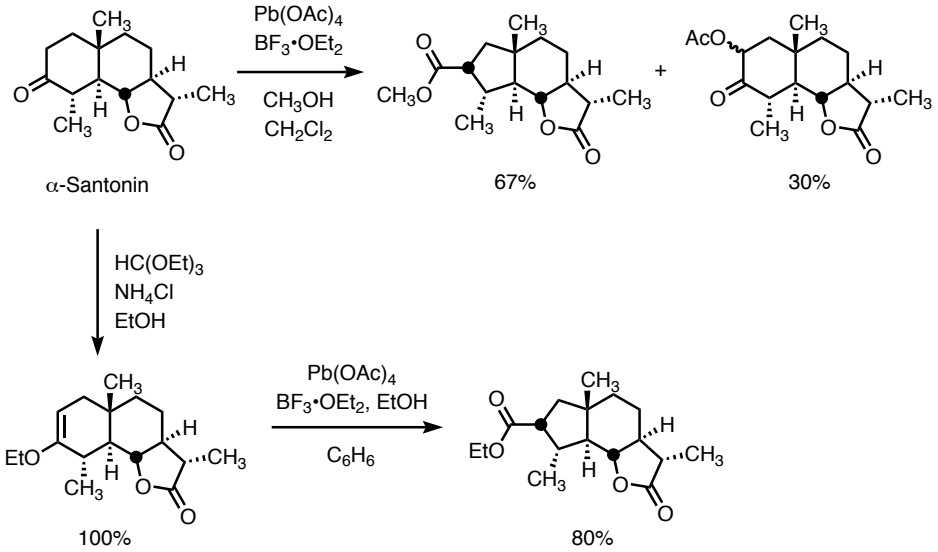
- Lead(IV) salts have been shown to promote ring contractions of ketones and enol ethers. However, these reactions sometimes provide significant amounts of α-acetoxy ketone side-products.

- This reaction is believed to involve Pb–C bond formation followed by pinacol-type rearrangement.



Norman, R. O. C.; Thomas, T. B. *J. Chem. Soc. B.* **1967**, 604–611.

- Lead(IV)-promoted ring contractions have been employed to modify α-santonin. Improved yields were achieved by first converting the substrate to the corresponding ethyl-enol ether.



Miura, H.; Fujimoto, Y.; Tatsuno, T. *Synthesis* **1979**, 898–899.

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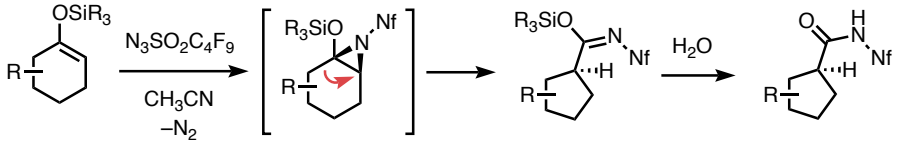
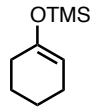
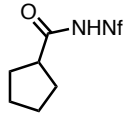
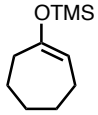
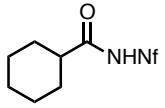
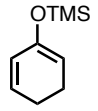
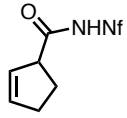
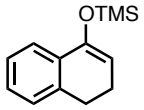
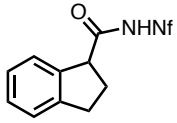
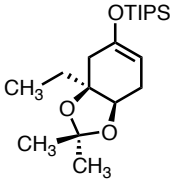
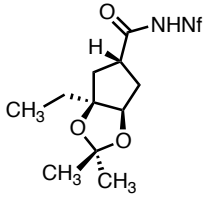
Ring contractions of silyl-enol ethers

- Cyclic silyl-enol ethers undergo ring contraction upon treatment with electron-deficient sulfonyl azides to give trialkylsilyl imidates, which are readily hydrolyzed to *N*-acyl sulfonamides.

- While both triflyl azide (N_3Tf) and nonaflyl azide (N_3Nf; N_3SO_2-*n*-C_4F_9) may be used in the ring contraction of silyl-enol ethers, the latter has the advantage of being a bench-stable, non-volatile liquid that does not detonate spontaneously upon concentration.

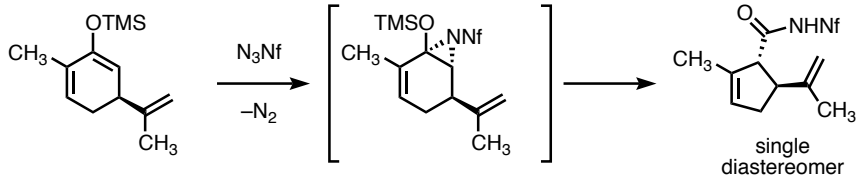


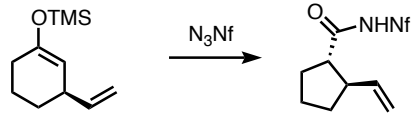
- Alkyl, vinyl, and aryl migrations are all possible. While 6→5 and 7→6 ring contractions are possible, this method does not permit cyclobutane synthesis.

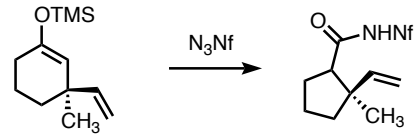
Substrate	Product	Yield
		97%
		67%
		78%
		87%
		65%

Mitcheltree, M. J.; Konst, Z. A.; Herzon, S. B. *Tetrahedron* **2013**, *69*, 5634–5639.

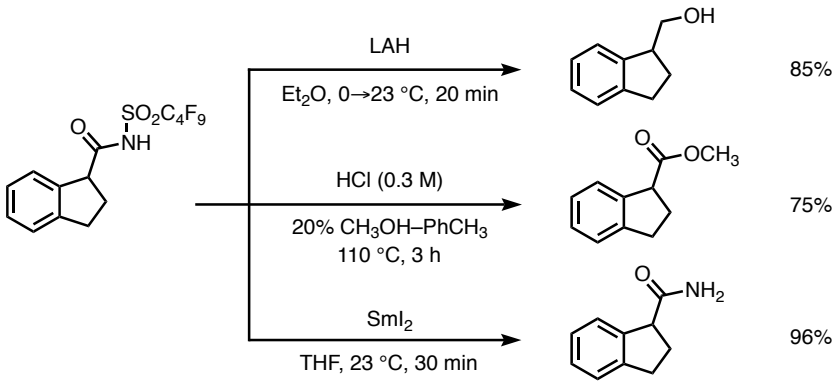
- Because alkyl migration is stereospecific, the stereochemistry of the product is determined by the facial selectivity of sulfonyl-azide addition. Lesser facial differentiation leads to lower diastereomeric ratios, as the following series demonstrates.







- The resulting *N*-acyl sulfonamide can be converted to alcohol, ester, or carboxamide products.



Mitcheltree, M. J.; Konst, Z. A.; Herzon, S. B. *Tetrahedron* **2013**, *69*, 5634–5639.

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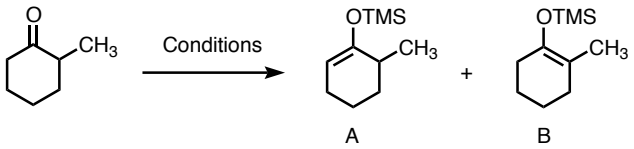
Synthesis of regiodefined silyl-enol ethers

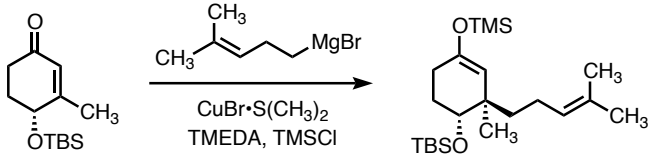
- Silyl-enol ethers are appealing substrates for ring contractions because they can be synthesized regioselectively.



Conditions	Yield	A : B
LDA, TMSCl	74	99 : 1
Et_3N, TMSCl, NaI	92	10 : 90

Negishi, E.-I.; Chatterjee, S. *Tetrahedron Lett.* **1983**, *24*, 1341–1344.
House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324–2336.

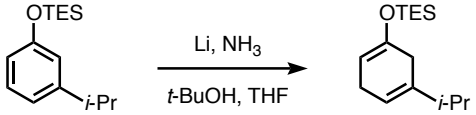
- Silyl-enol ethers can also be formed by 1,4-addition to α,β-unsaturated carbonyls.



100%

Nozawa, D.; Takikawa, H.; Mori, K. *J. Chem. Soc. Perkin Trans. 1*, **2000**, 2043–2046.

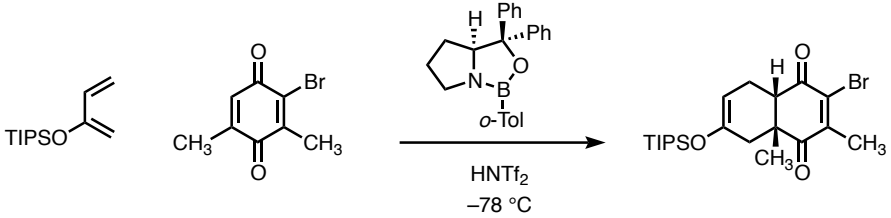
- Birch reduction of substituted silyloxy aryl ethers gives regiodefined substrates for ring contraction.



90%

Macdonald, T. L. *J. Org. Chem.* **1978**, *18*, 3621–3624.

- Silyl-enol ethers can be formed by enantioselective, catalytic Diels–Alder reactions.



96%, 97% e.e.

Ryu, D. H.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 4800–4802.

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