Journal Club

Nick Tappin

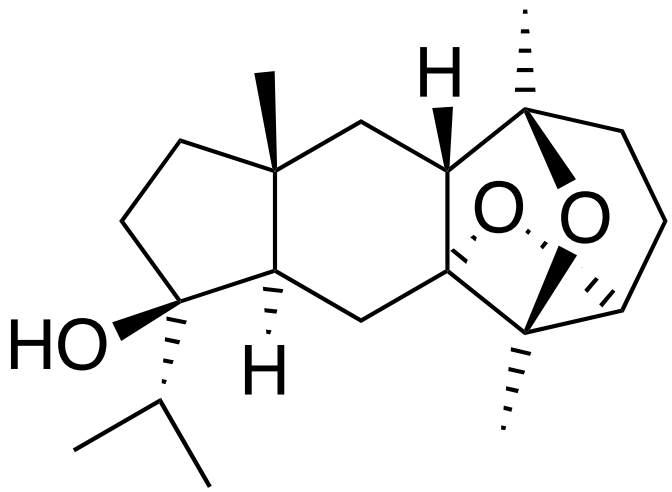
Renaud Group

18 May 2016

A Bioinspired Cyclization Sequence Enables the Asymmetric Total Synthesis of Dictyoxetane

JACS **2016** *138*, 6420−6423

Cedric L. Hugelshofer and Thomas Magauer*

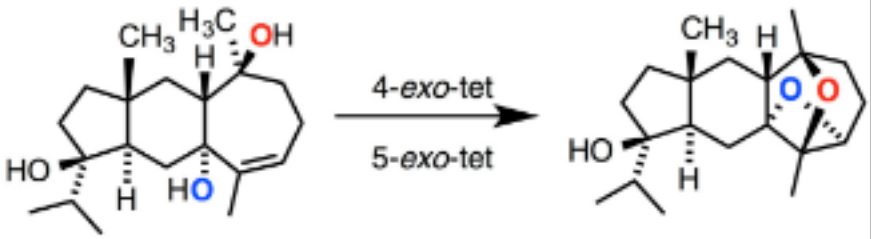


(+)-dictyoxetane
[unknown biological activity]

Thomas Magauer

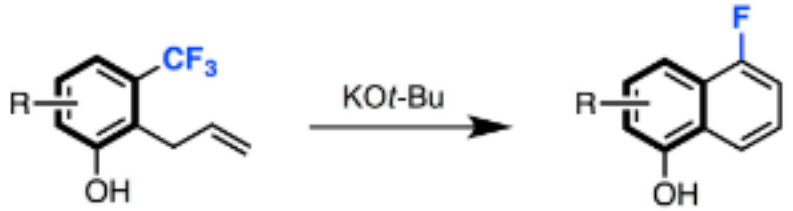
- Born 1983 (only 33-34)
- 2007 Master in chemistry University of Vienna
- 2009 PhD Mulzer in total synthesis (Vienna)
- 2012 PostDoc with A. Myers at Harvard
- 2012- independent at LMU Munchen
- 2015 (Burgenstock)
- Active and upcoming
- 2017 Goering visiting prof. at Wisconsin

Asymmetric Synthesis: *Oxetane Natural Products*



JACS **2016**

Arenes: *C-F activation*



Chem. Eur. J. **2014**

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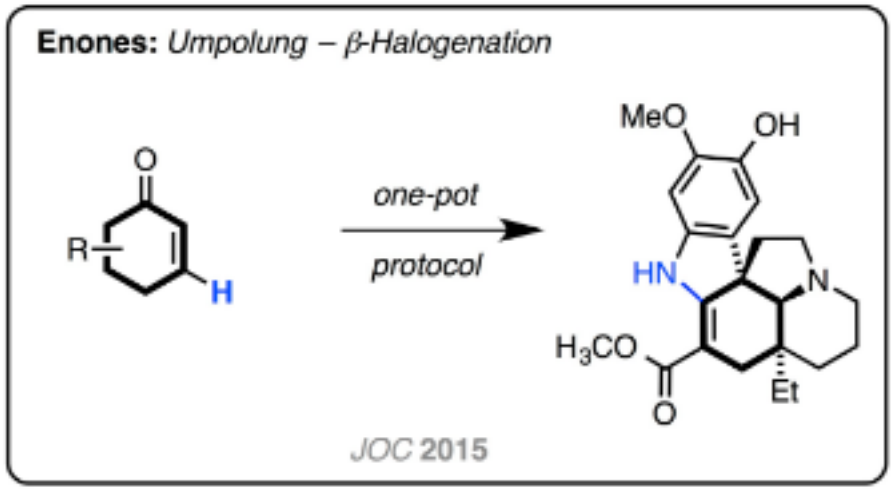

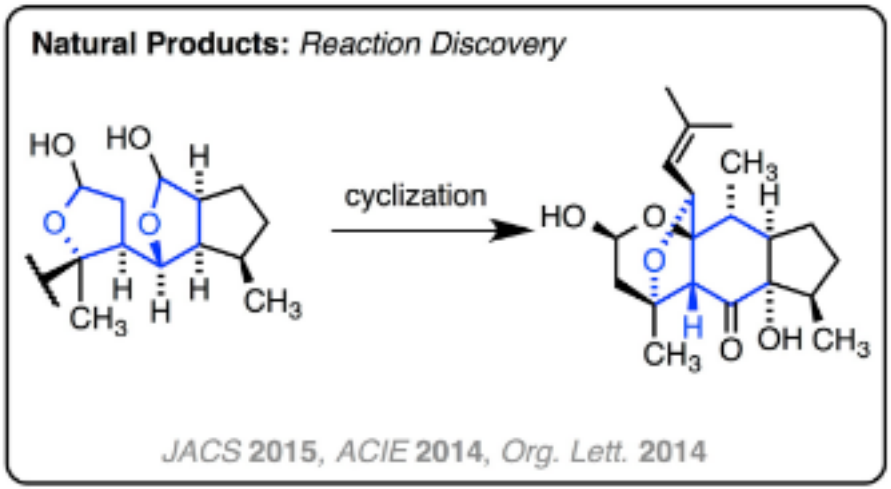

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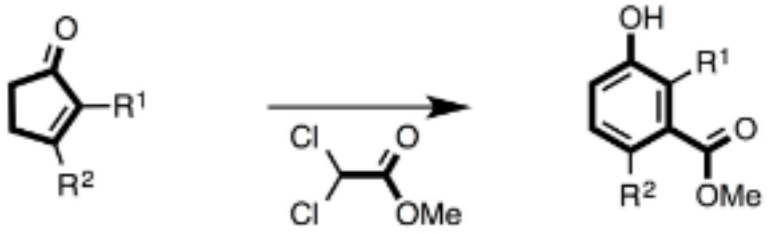
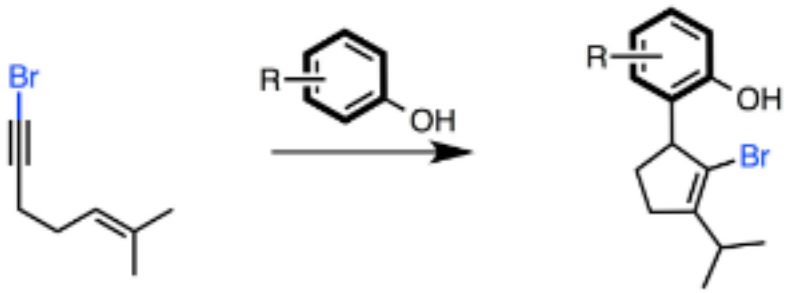
Arenes: *Ring Expansion – Expulsion*



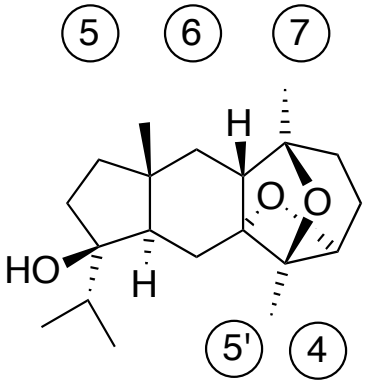
ACIE **2015**

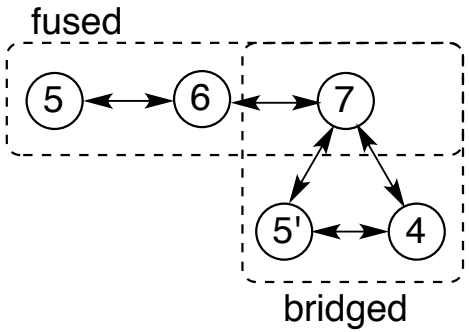
Enynes: *Au(I)-catalysis*



Org. Lett. **2015**

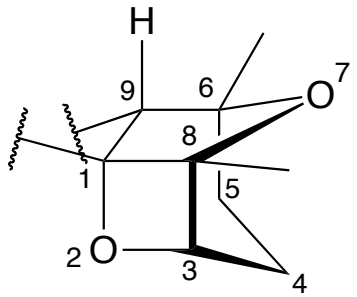
Structural Features



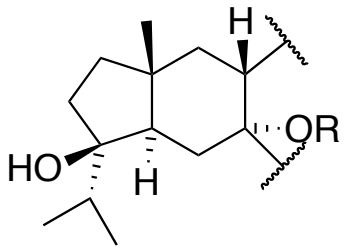


bridged polycyclic systems

iupac rule A-31: http://www.acdlabs.com/iupac/nomenclature/79/r79_163.htm
iupac rule A-32: http://www.acdlabs.com/iupac/nomenclature/79/r79_164.htm



2,7-dioxatricyclo
[4.2.1.$0^{3,8}$]nonane

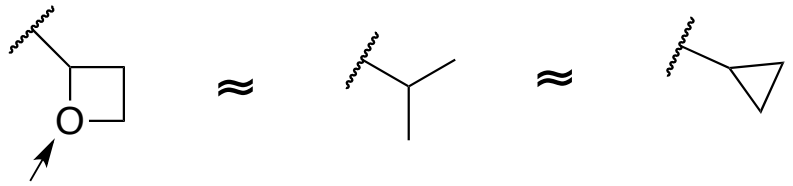


cis-hydrinane

Oxetanes

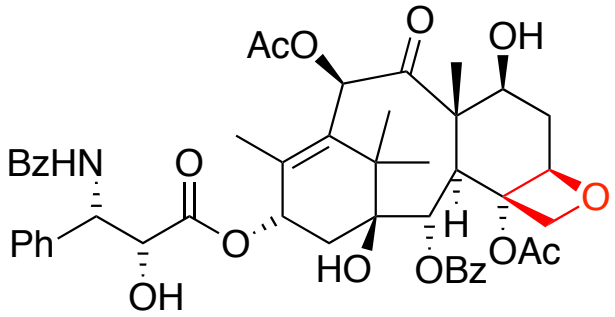
important structural units in drug discovery

oxetanes *gem*-dimethyl cyclopropanes

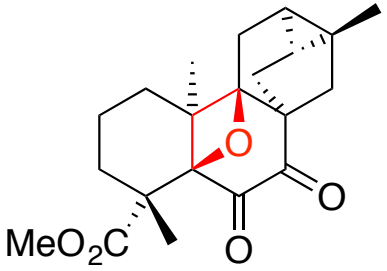


effiecient H-bond acceptor

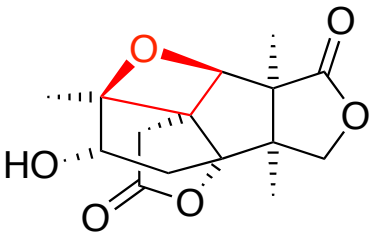
other oxetane-containing natural products



taxol
[anticancer]



mitrephorone A
[anticancer]

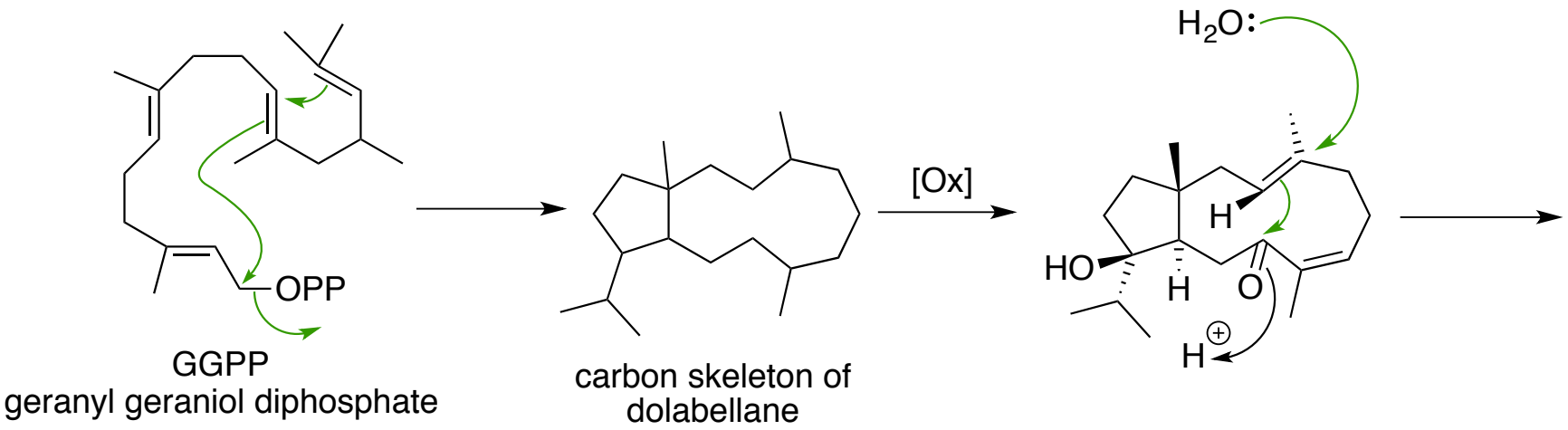


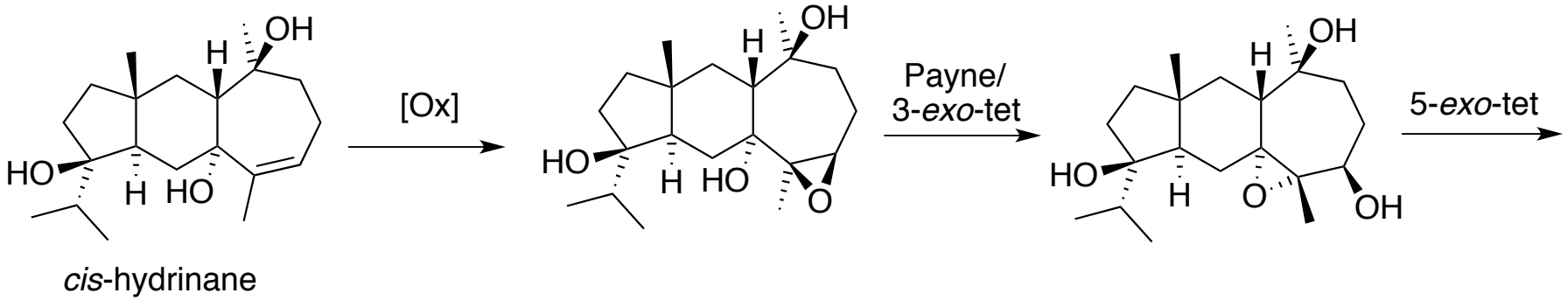
merrilactone A
[neurotrophic agent]

For more info, see:
Wuitschik, Georg. Oxetanes in drug discovery. ETH (2008). http://dx.doi.org/10.3929/ethz-a-005697432

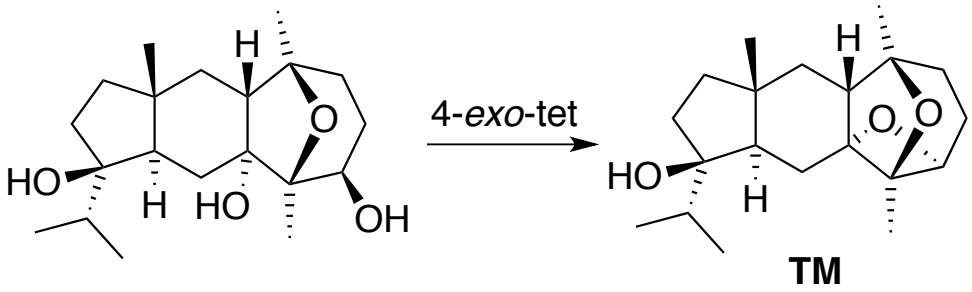
Biosynthesis

Reinecke, J.; Hoffmann, H. M. R. *Chem. Eur. J.* **1995**, *1*, 368–373.

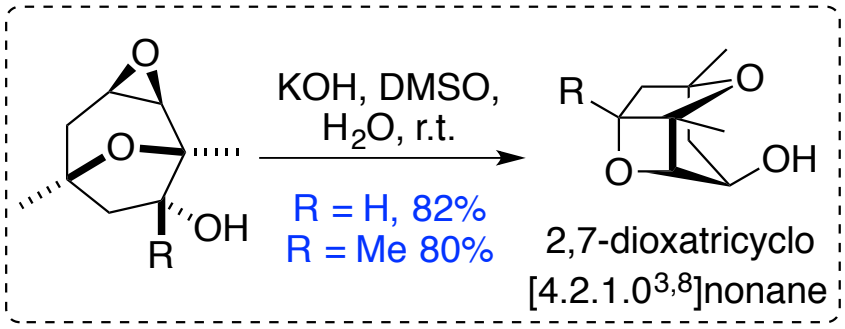




Biosynthesis

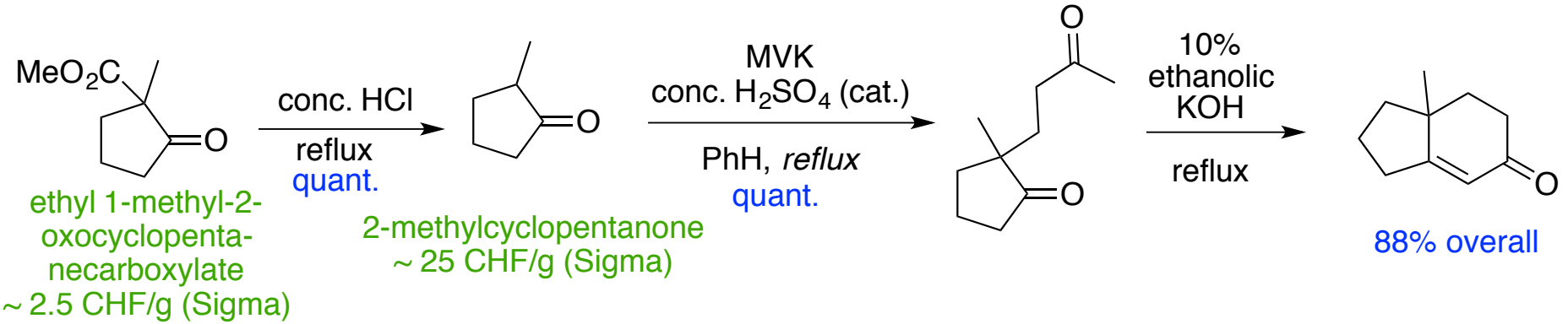


mild conditions, "in vitro"



Synthesis of SM: Grainger's precedent

Robinson annelation

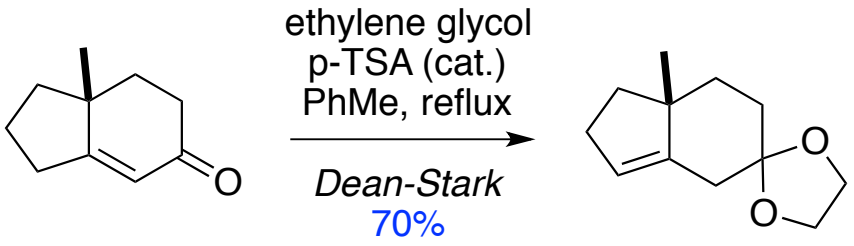


ethyl 1-methyl-2-oxocyclopenta-necarboxylate
~ 2.5 CHF/g (Sigma)

2-methylcyclopentanone
~ 25 CHF/g (Sigma)

88% overall

Rao, H. S. P.; Reddy, K. S. *Org. Prep. Proced. Int.* **1994**, *26*, 491–494.

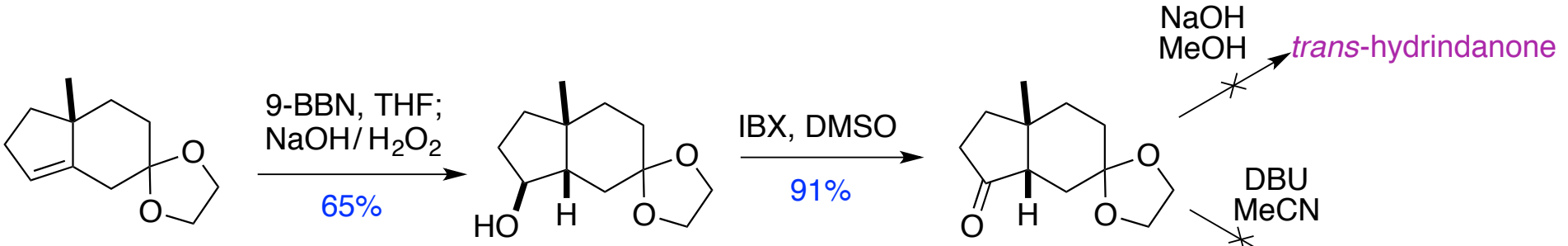


pK_a dependent olefin migration

Acid	pKa	% α.β	% β.γ	% conversion
fumaric acid	3.03	100	0	90
phthalic acid	2.89	70	30	90
oxalic acid	1.23	80	20	93
TsOH	<1.0	0	100	100

T. W. Green, P. G. M. Wuts, *Protective Groups in Organic Synthesis, 4th Ed.,* Wiley-Interscience, New York **2007**, pp 455.
de Leeuw, J. W.; de Waard, E. R.; Beetz, T.; Huisman, H. O. *Recl. Trav. Chim. Pays-Bas* **1973**, *92*, 1047–1052.

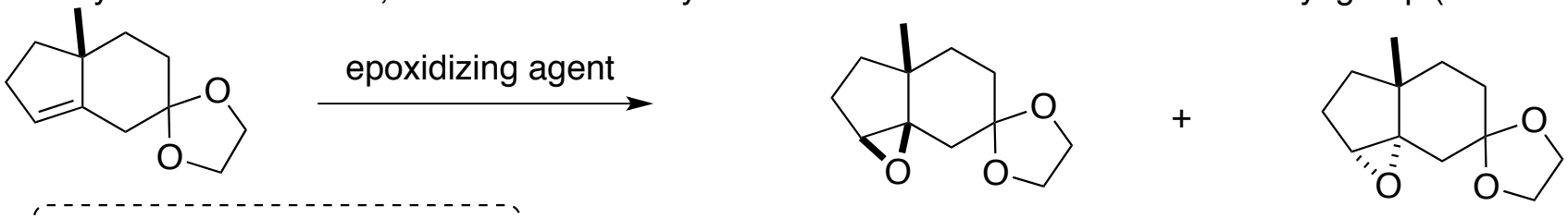
Synthesis of SM: Grainger's precedent

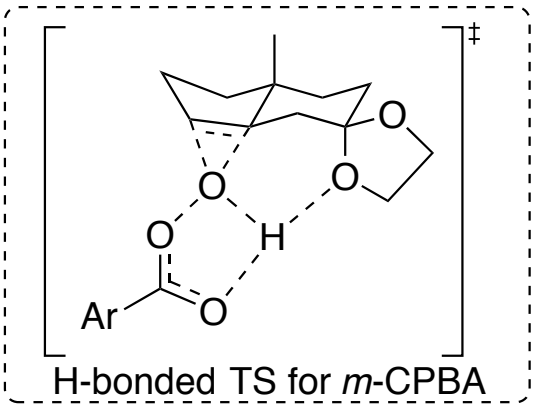


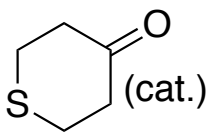
Defaut, B.; Parsons, T. B.; Spencer, N.; Male, L.; Kariuki, B. M.; Grainger, R. S. *Org. Biomol. Chem.* **2012**, *10*, 4926–4932.

angularly-substituted *trans*-hydrindanes thermodynamically less stable than *cis*-hyrdindanes; see Kim, W. H.; Lee, J. H.; Aussedat, B.; Danishefsky, S. J. *Tetrahedron* **2010**, *66*, 6391–6398

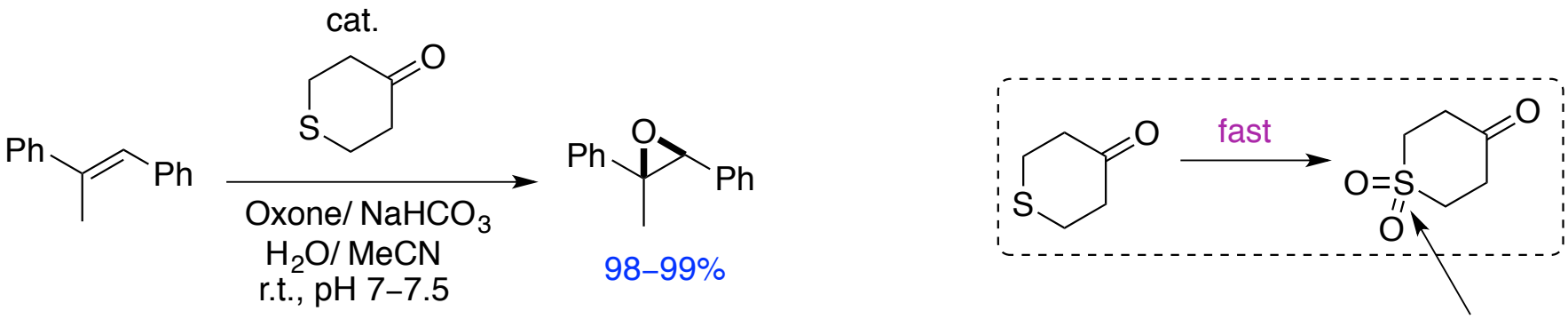
From hydroboration result, the facial selectivity of the alkene should be cis to the methyl group (convex face)





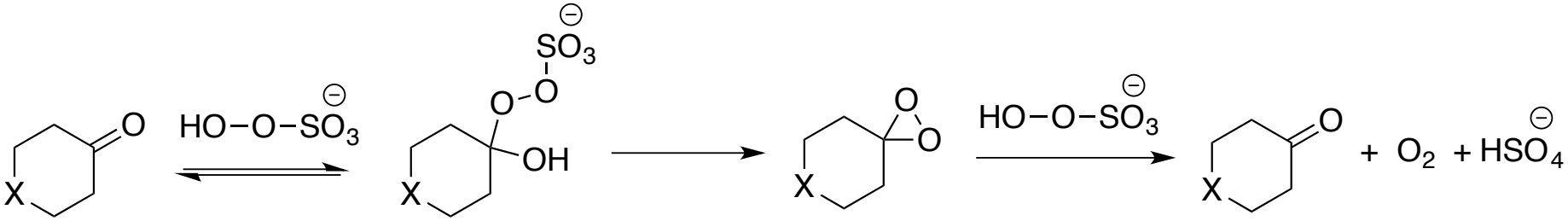
m-CPBA	30%	51%
Oxone +  (cat.)	50%	32%
DMDO	86%	n.d. (0%)

Synthesis of SM: Grainger's precedent



Yang, D.; Yip, Y.-C.; Jiao, G.-S.; Wong, M.-K. *Org. Synth.* **2002**, *78*, 225–233.

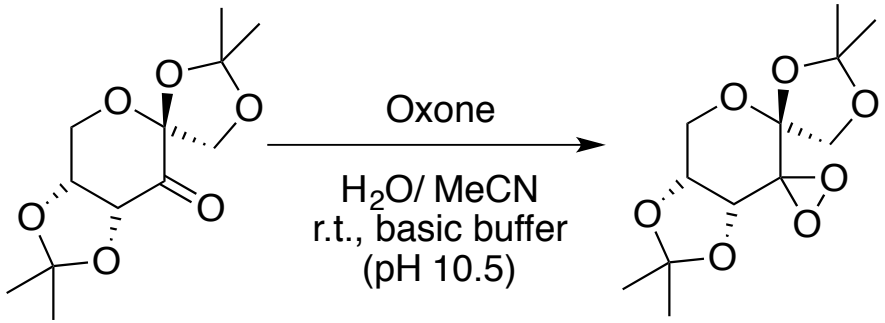
unlike DMDO, doesn't require distillation and titration/ concentration determination



Yang, D.; Yip, Y.-C.; Jiao, G.-S.; Wong, M.-K. *J. Org. Chem.* **1998**, *63*, 8952–8956.

Question: Which other epoxidation (named reaction) works on this same principle?

Shi epoxidation

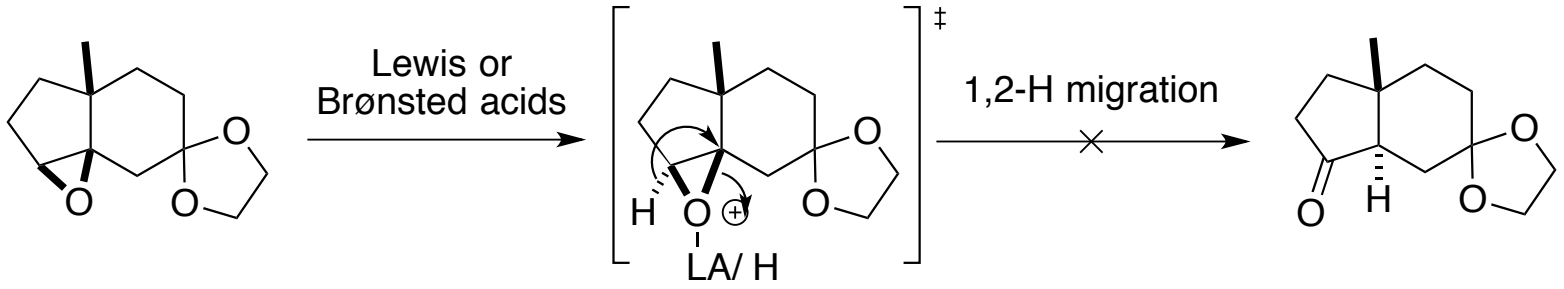


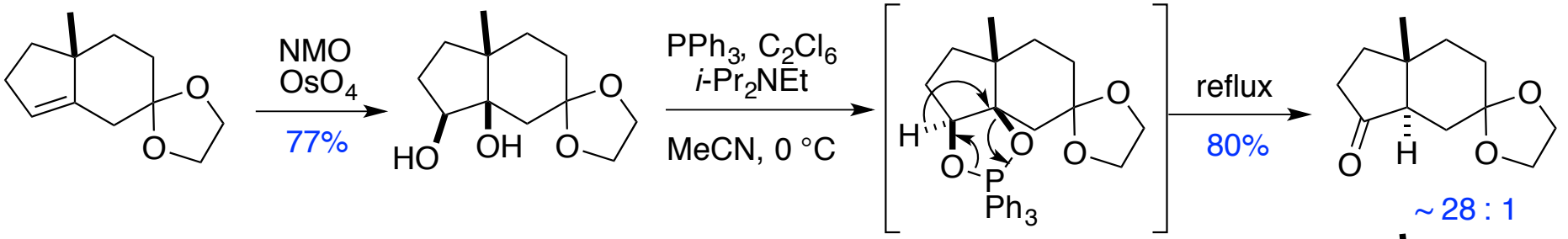
Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806–9807.
Denmark, S. E.; Wu, Z. *Synlett* **1999**, 847–859.

Synthesis of SM: Grainger's precedent

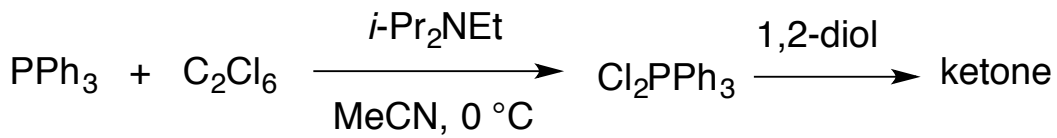
Meinwald rearrangement

Meinwald, J.; Labana, S. S.; Chadha, M. S. *J. Am. Chem. Soc.* **1963**, *85*, 582–585.

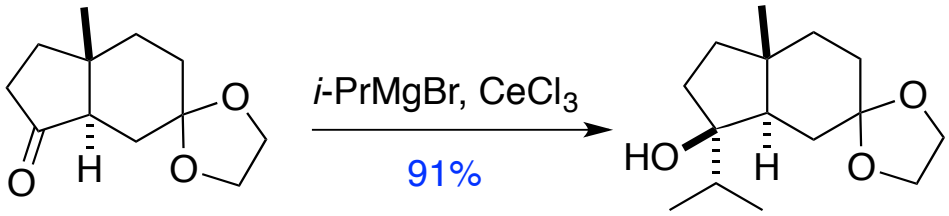




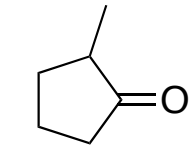
DeCamp, A. E.; Mills, S. G.; Kawaguchi, A. T.; Desmond, R.; Reamer, R. A.; DiMichele, L.; Volante, R. P. *J. Org. Chem.* **1991**, *56*, 3564–3571.



Synthesis of SM: Grainger's precedent



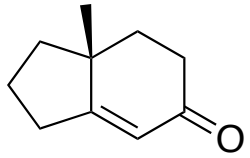
Synthesis of SM: Magauer's asymmetric approach



260 mmol

i) (*S*)-(–)-α-methylbenzylamine
p-TsOH, PhMe, 111 °C, 5 h, D-S
ii) MVK, 40 °C, 4 d

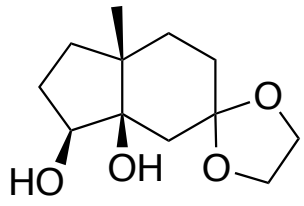
iii) AcOH, H_2O, 23 °C, 2h
iv) KOH, EtOH, 78 °C, 2h

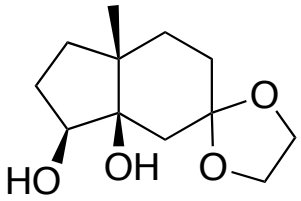


49%
2 extractions, 1 column

i) ethylene glycol, *p*-TsOH,
PhH, Dean-Stark, 5 h, 59%

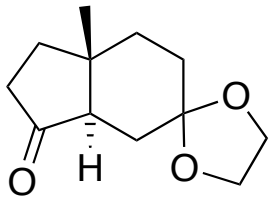
ii) cat. OsO_4, NMO, *t*-BuOH/
H_2O/ THF/ acetone, 3 d, 94%





C_2Cl_6, PPh_3, DIPEA

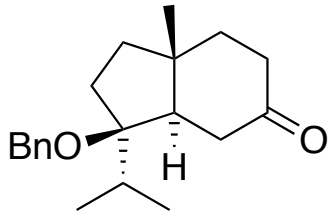
MeCN, 0 to 82 °C, 2.5 h



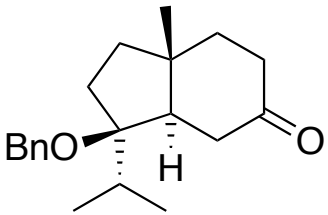
99%

i) *i*-PrMgCl, $CeCl_3$
THF, 0 °C, 1.5 h

ii) BnBr, KHMDS
THF, –78 to 23 °C, 3h
iii) HCl, THF, 23 °C, 3h

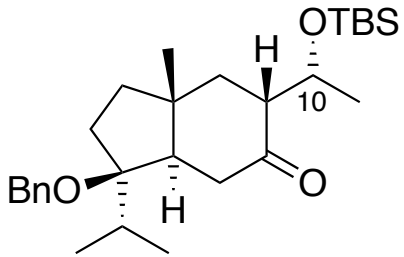


85%
3 extractions, 1 column



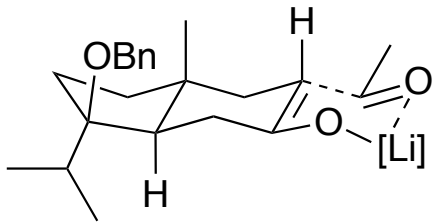
i) LDA; acetaldehyde,
THF, –78 °C, 1.25 h

ii) TBSCl, ImH, DMAP,
DMF, 23 °C, 13 h



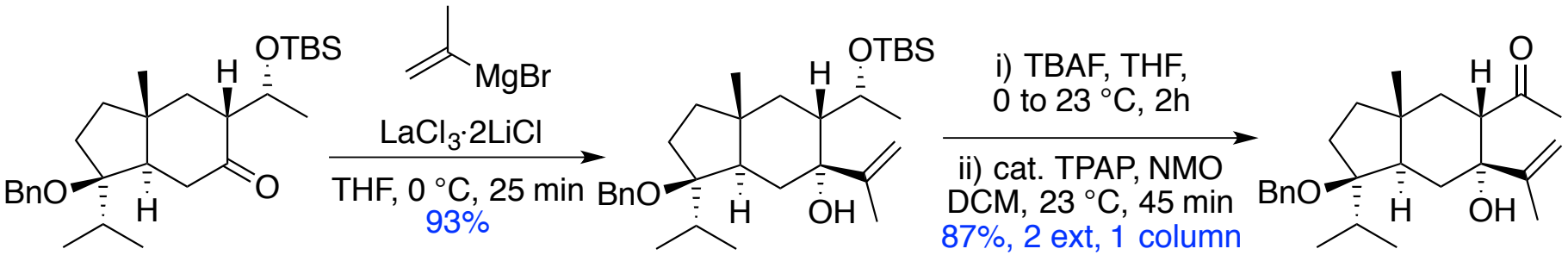
80%, d.r. at C-10 10:1
but inconsequential

due to ring, stereospecifically via
trans-enolate giving anti-aldol

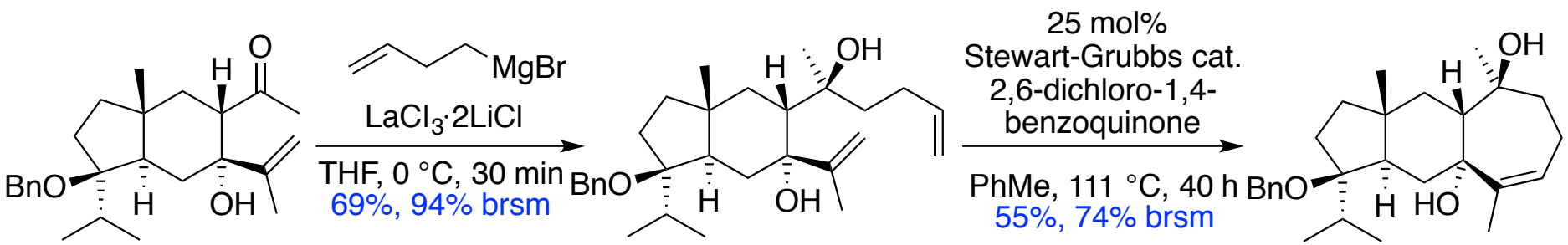


methyl group not so differentiating

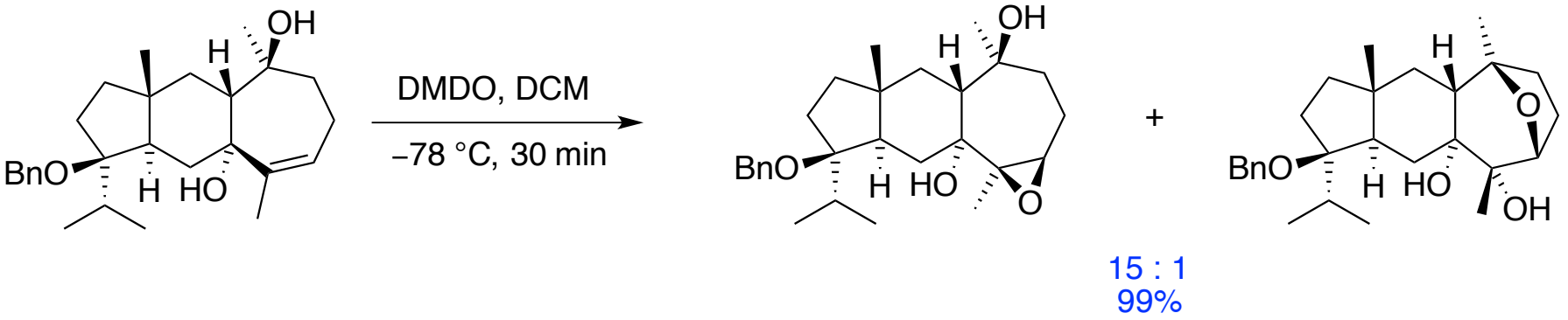
Middle-game

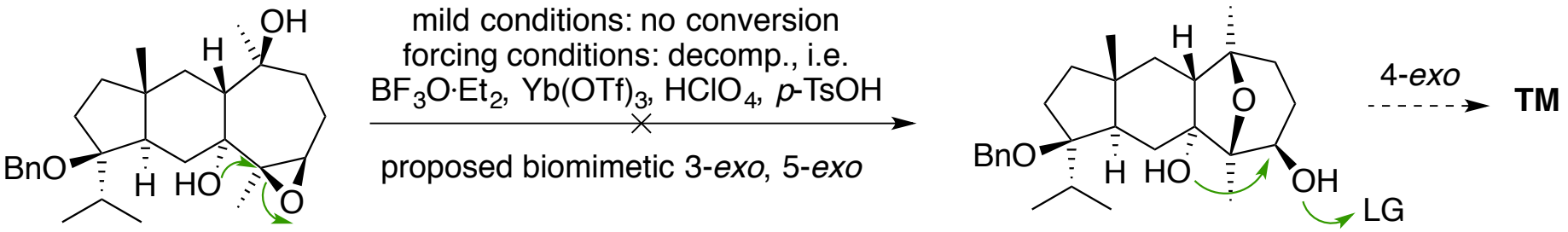


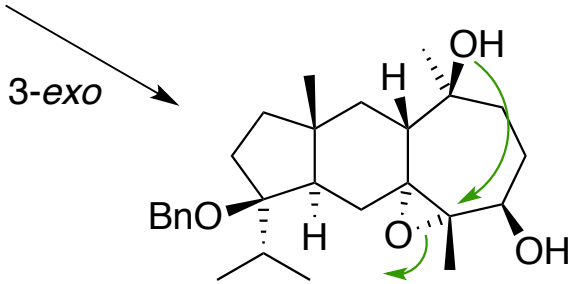
Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 497–500.

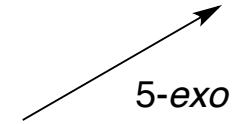


Middle-game


OH
H
BnO
H HO
DMDO, DCM
–78 °C, 30 min
O
+
15 : 1
99%


mild conditions: no conversion
forcing conditions: decomp., i.e.
$BF_3O{\cdot}Et_2$, $Yb(OTf)_3$, $HClO_4$, *p*-TsOH
proposed biomimetic 3-*exo*, 5-*exo*
4-*exo*
TM
LG

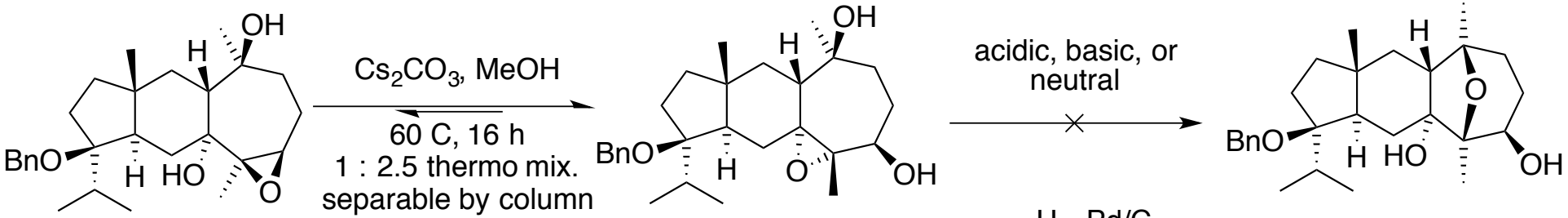

3-*exo*

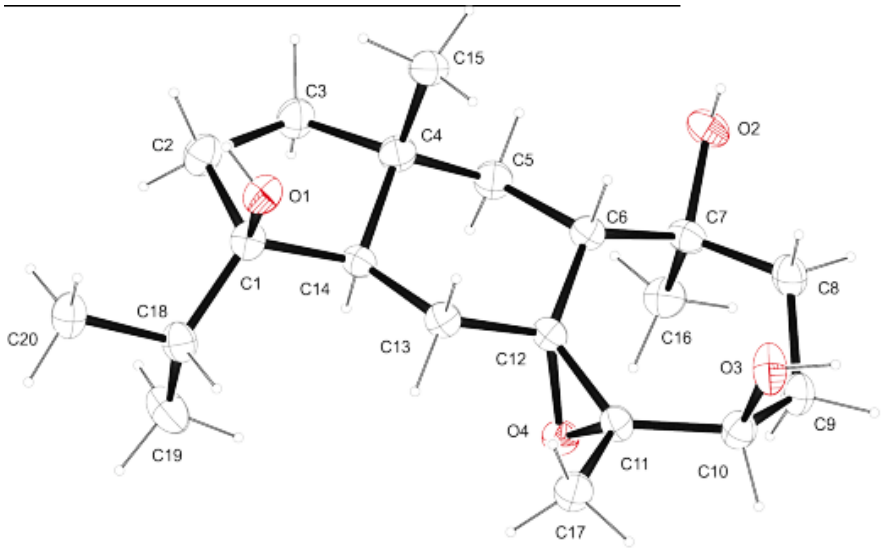

5-*exo*


Brick wall 1.0!

Middle-game

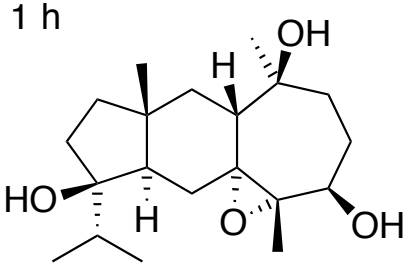
3-*exo* or Payne rearrangement under basic conditions

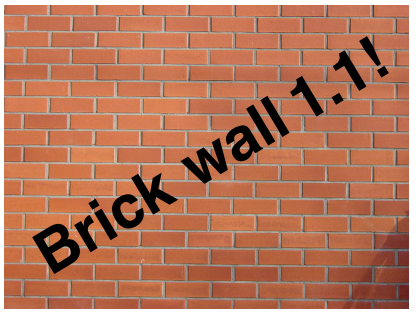




7-membered ring chair like;
C-10-OH in equatorial position

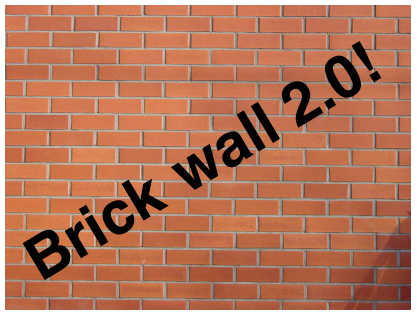
H_2, Pd/C
THF, 23 °C, 1 h
80%

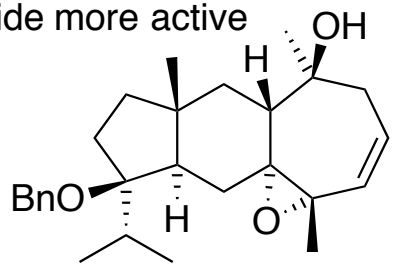




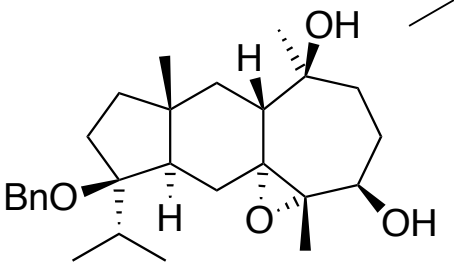
Middle-game

change ring geometry and make epoxide more active



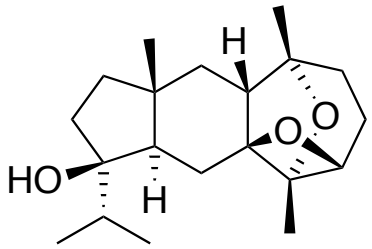


desired elimination/ dehydration

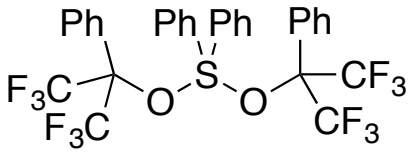


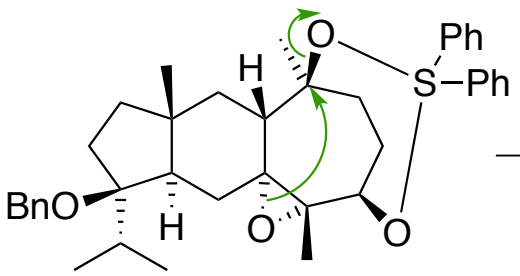
i) Martin sulfurane
DCM, 0 °C, 15 min

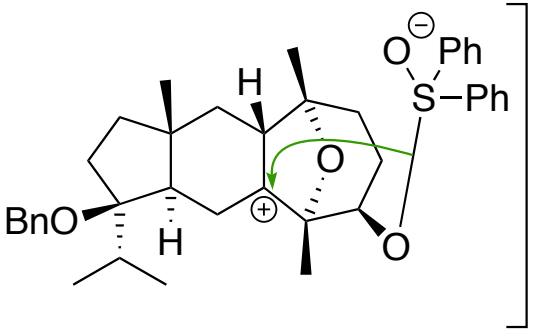
ii) H_2, Pd/C
THF, 23 °C, 1 h
60% 2 steps



tetra-epi-**TM** [x-ray of triol]



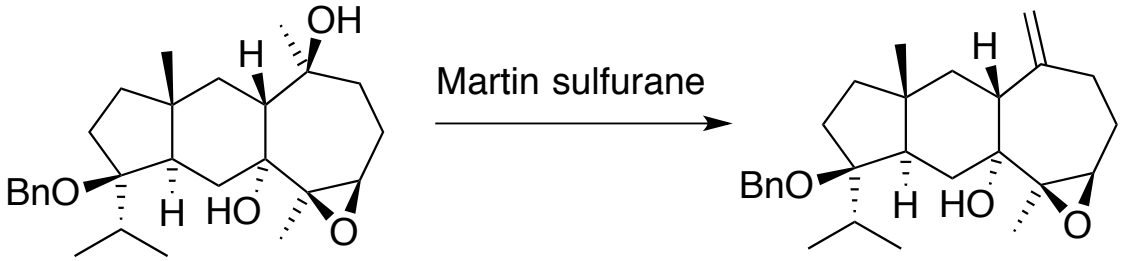




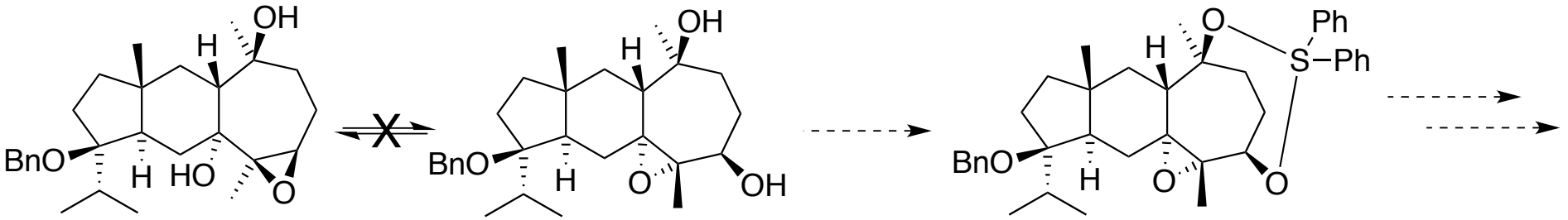
deprotect Bn

Middle-game

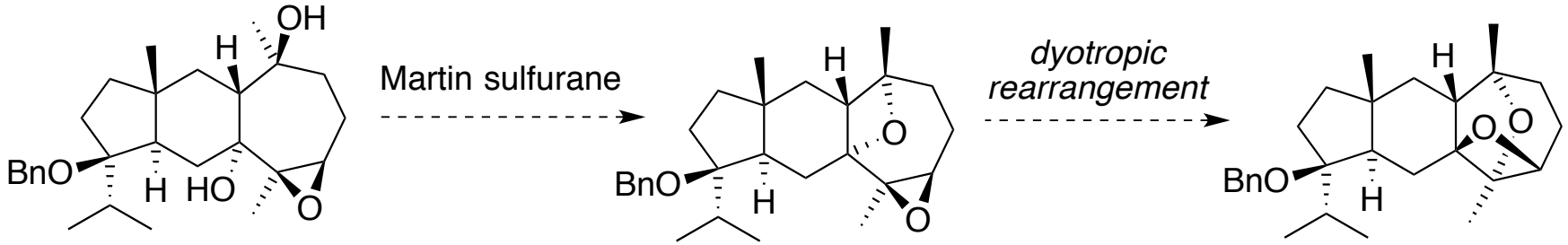
Martin sulfurane treatment of isomeric epoxide gave directly dehydration



therefore not possible to go via Payne rearrangement



but it was postulated that the following could have been possible (as an alternative mechanism to one described)



Could this idea be developed into a workable strategy?

But first, what is a dyotropic rearrangement?

Dyotropic rearrangement

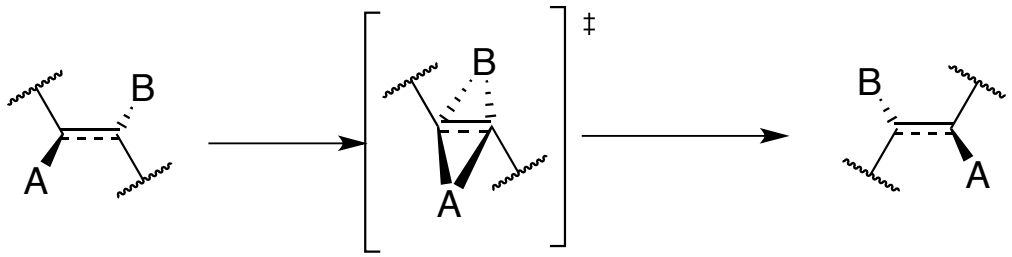
Dyotropic rearrangement

Dyo from Greek meaning two.

Pericyclic valence isomerization where two σ-bonds migrate simultaneously and intramolecularly.

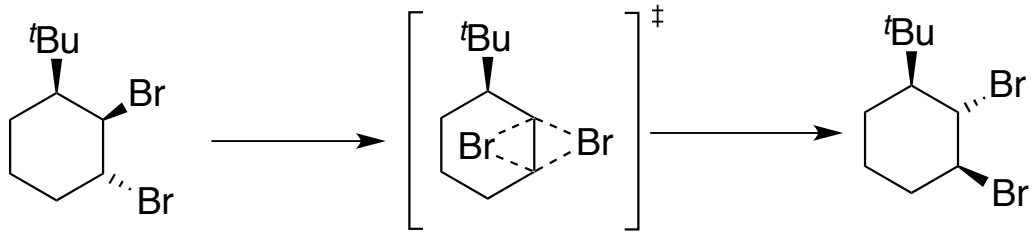
For a comprehensive, but poor review: Fernández, I.; Cossío, F. P.; Sierra, M. A. *Chem. Rev.* **2009**, *109*, 6687–6711.
Reasearch article gives a better review: Leverett, C. A.; Purohit, V. C.; Johnson, A. G.; Davis, R. L.; Tantillo, D. J.; Romo, D. *J. Am. Chem. Soc.* **2012**, *134*, 1334–13356.

Type I
Two groups intercahnge their relative position

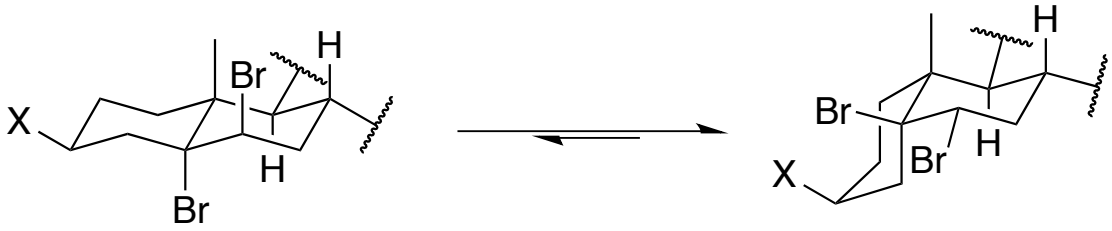


- two groups migrate on a stationary scaffold
- *anti* conformation forces suprafacial migration
- inversion of stereochemistry

Dyotropic rearrangement: Type I



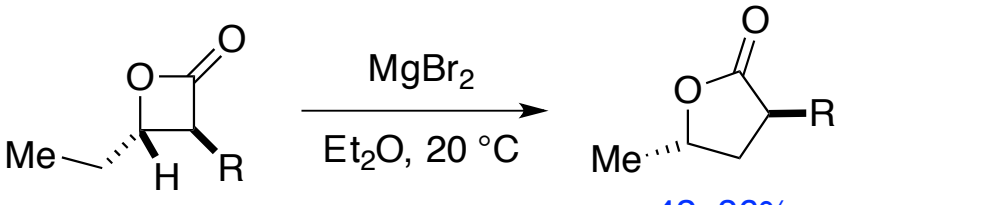
Barili, P. L.; Bellucci, G.; Berti, G.; Marioni, F.; Marsili, A.; Morelli, I. *J. Chem. Soc. D* **1970**, 1437–1438.



switch configuration of cholesterol skeleton

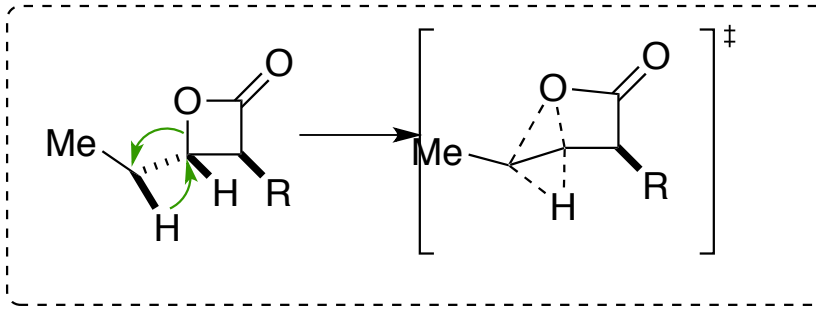
Grob, C. A.; Winstein, S. *Helv. Chim. Acta* **1952**, *35*, 782–802.

gives access to γ-subs butyrolactones



42–86%

R = Me, Et, Ph, OMe, OPh, SPh



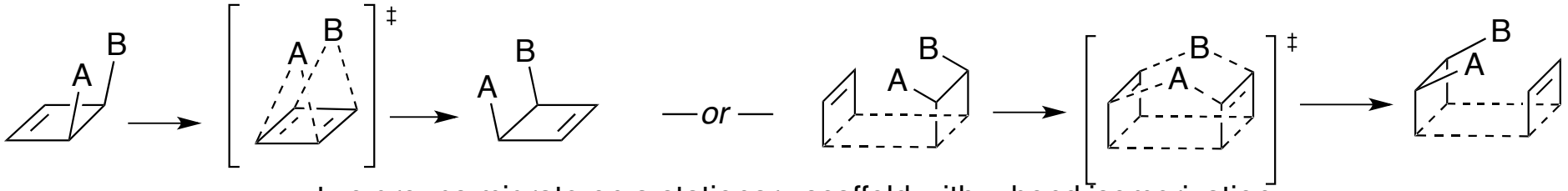
Hydride migration

Wagner-Meerwein type dyotropic rearrangement

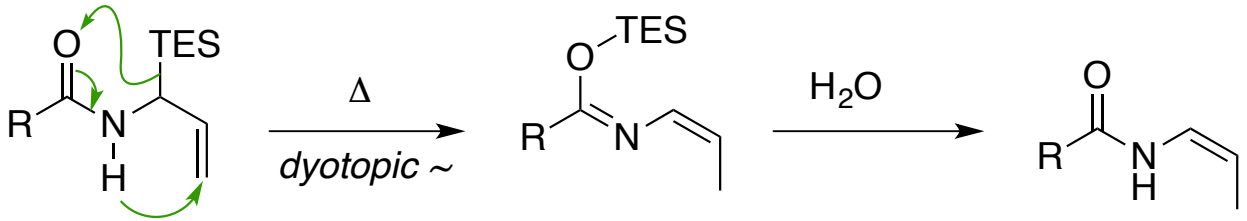
Mulzer, J.; Brütrup, G. *Angew. Chem. Int. Ed.* **1979**, *18*, 793–794.

Dyotropic rearrangement: Type II

Type II
Two groups migrate to new bonding sites but maintain their relative position



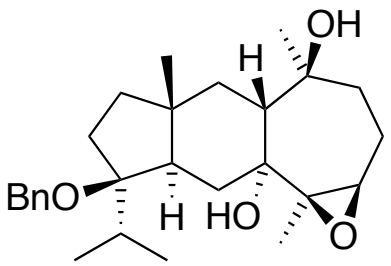
- two groups migrate on a stationary scaffold with π-bond isomerization
- either over an adjacent π-bond
- or a π-bond held in close proximity



unusal access to *cis*-enamide

Lin, S.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 512–515.

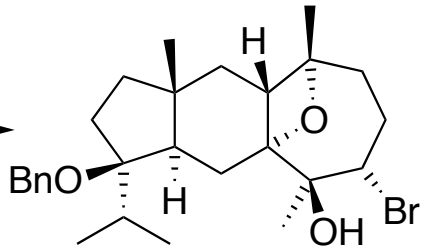
End-game

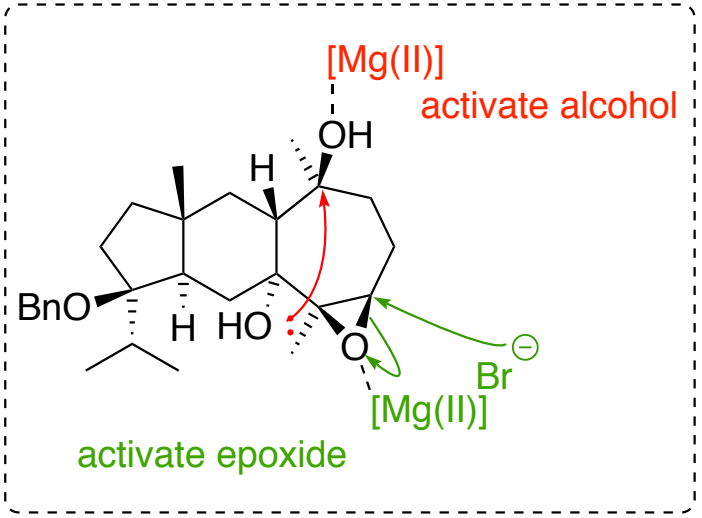


$MgBr_2 \cdot Et_2O$, TBAB

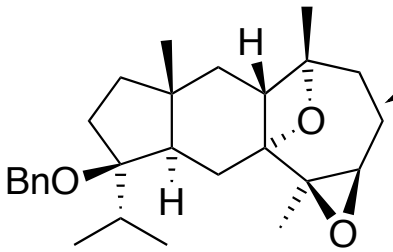
DCM, 23 °C, 2.5 h

51%





Clever use of TBAB and LA to make bromohydrin in situ as a protected/ masked epoxide, which is easily deprotected/ revealed with a mild basic treatment

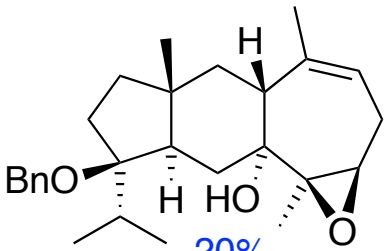


K_2CO_3, MeOH,
0 °C, 1.5 h
94%

Martin sulfurane

No reaction: supports mechanistic suggestion that this oxetane-epoxide intermediate is not an intermediate in the formation of tetra-epi-Bn-TM

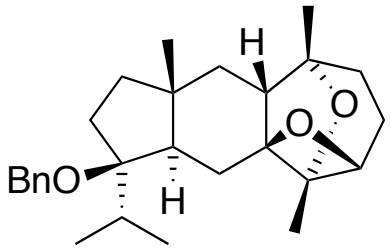
$Cu(BF_4)_2 \cdot xH_2O$
DCM,
23 °C, 2 h



20%

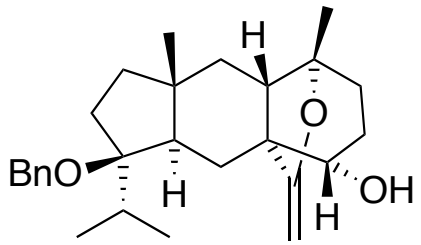
+

Type I
dyotopic rearrangement



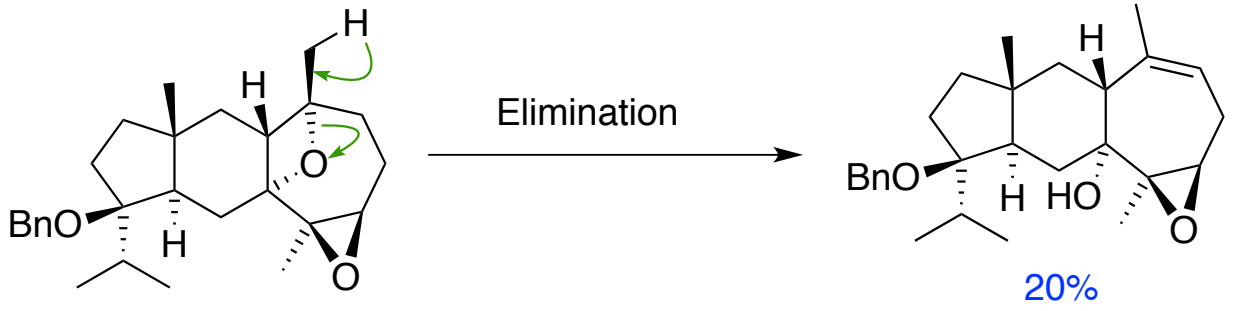
36%

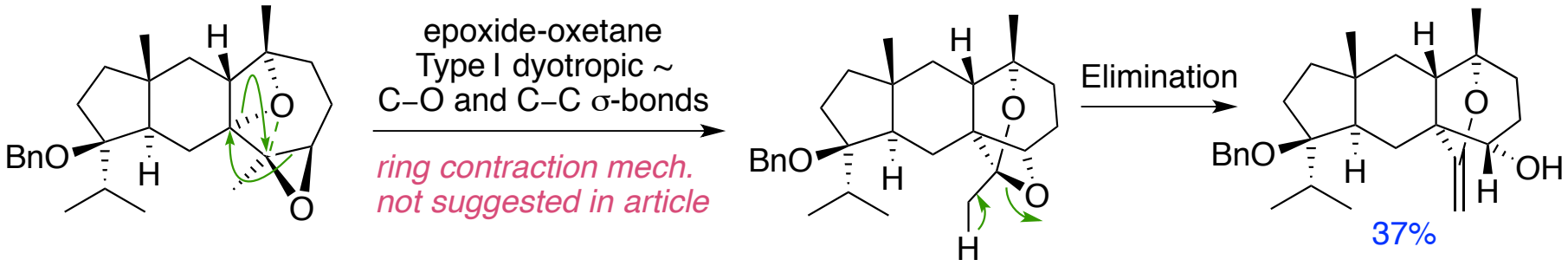
+

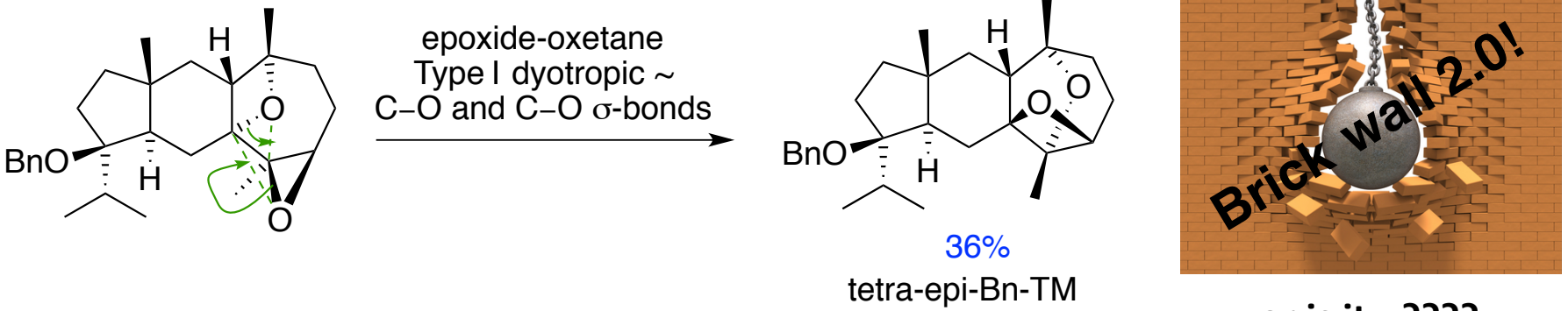


37%

End-game

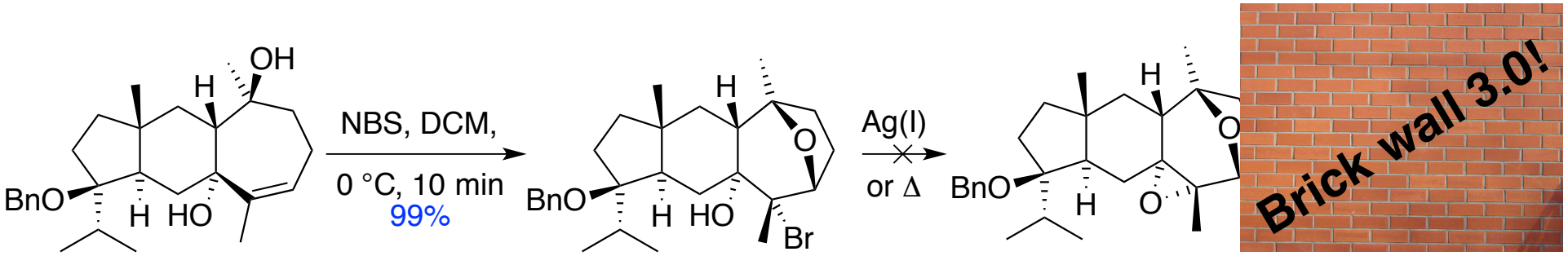


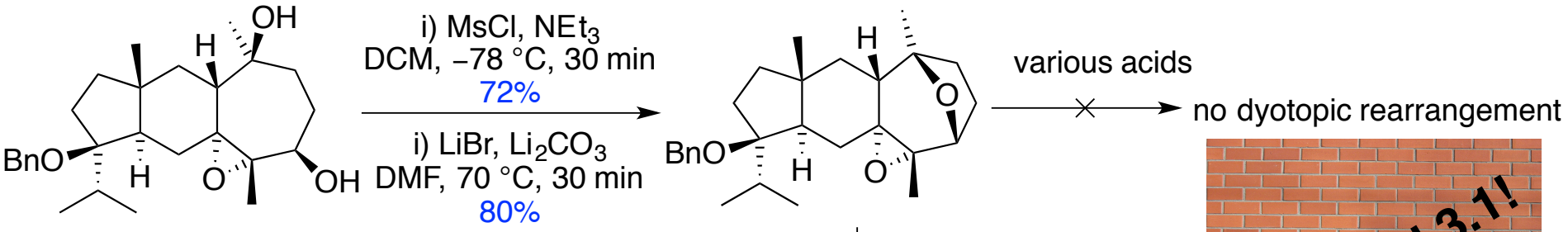


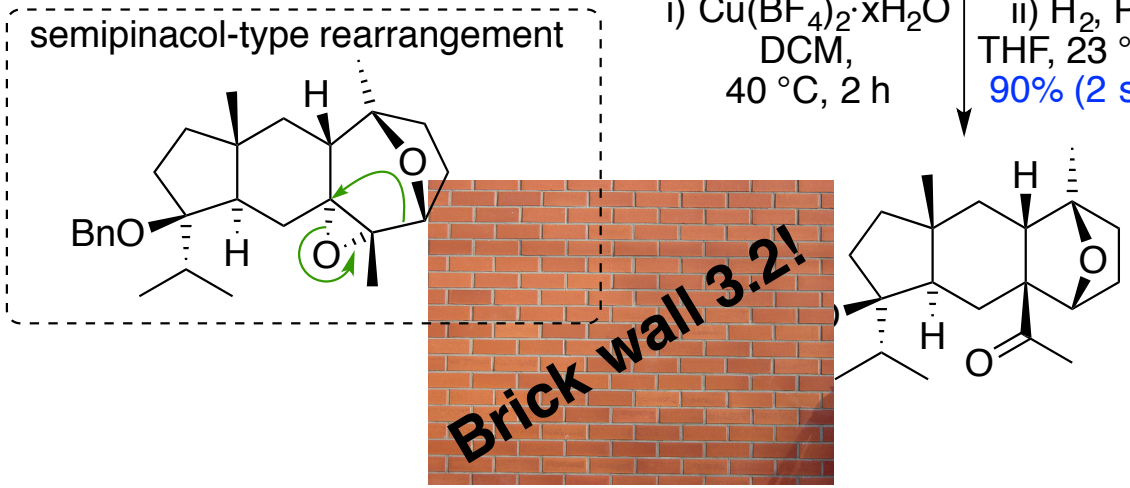


or is it...????

End-game

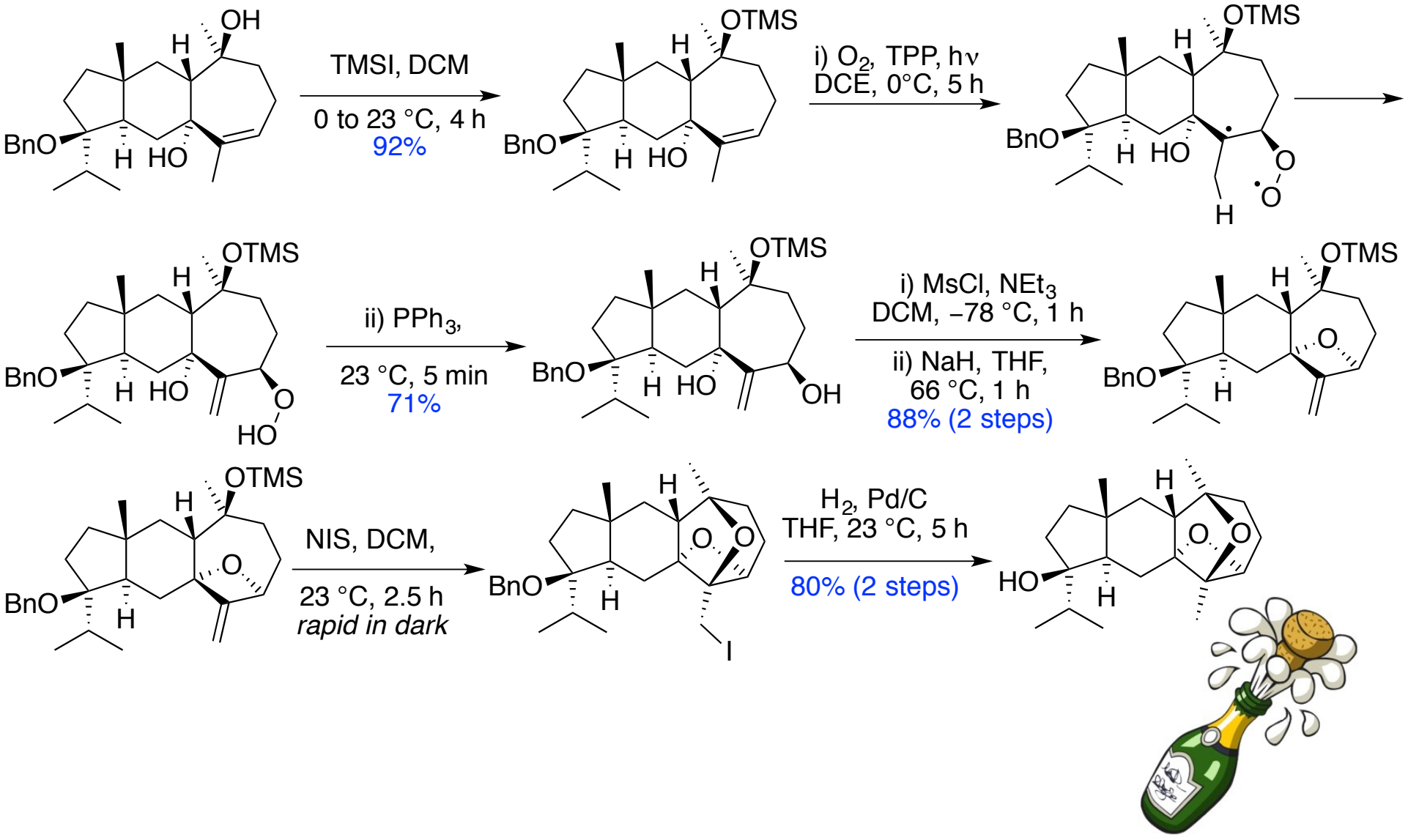

NBS, DCM,
0 °C, 10 min
99%
Ag(I)
or Δ
Brick wall 3.0!


i) MsCl, NEt3
DCM, –78 °C, 30 min
72%
i) LiBr, Li2CO3
DMF, 70 °C, 30 min
80%
various acids
no dyotopic rearrangement
Brick wall 3.1!


semipinacol-type rearrangement
i) Cu(BF4)2·xH2O
DCM,
40 °C, 2 h
ii) H2, Pd/C
THF, 23 °C, 2 h
90% (2 steps)
Brick wall 3.2!

End-game

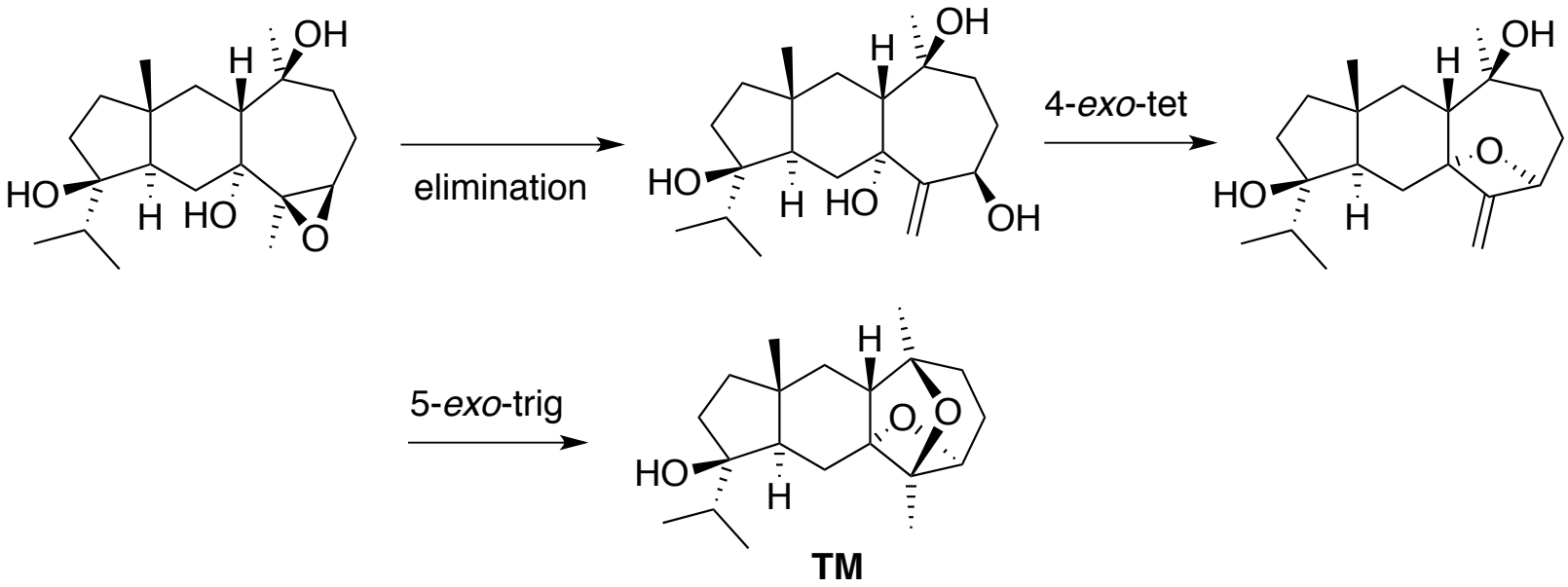
TPP = tetraphenylporphyrin



Conclusions

- Built on preceding work
- Completed first total synthesis of dictyoxetane
- Asymmetric synthesis
- Now in collaboration with chemical biologists to determine activity
- Access to synthetic sample confirmed absolute configuration

Magauer's non-biomimetic/ non-enzymetic alternative path



TM

Thanks for attention!

And

any questions?