Bidirectional Synthesis

and its stereochemical implications

Gaich Literature Seminar

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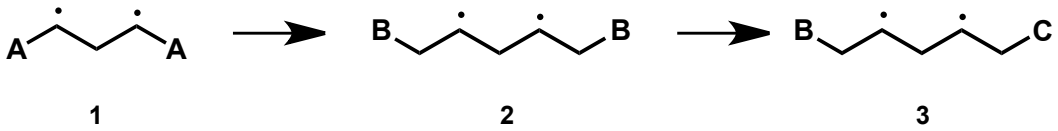
Jan 20, 2014

Introduction

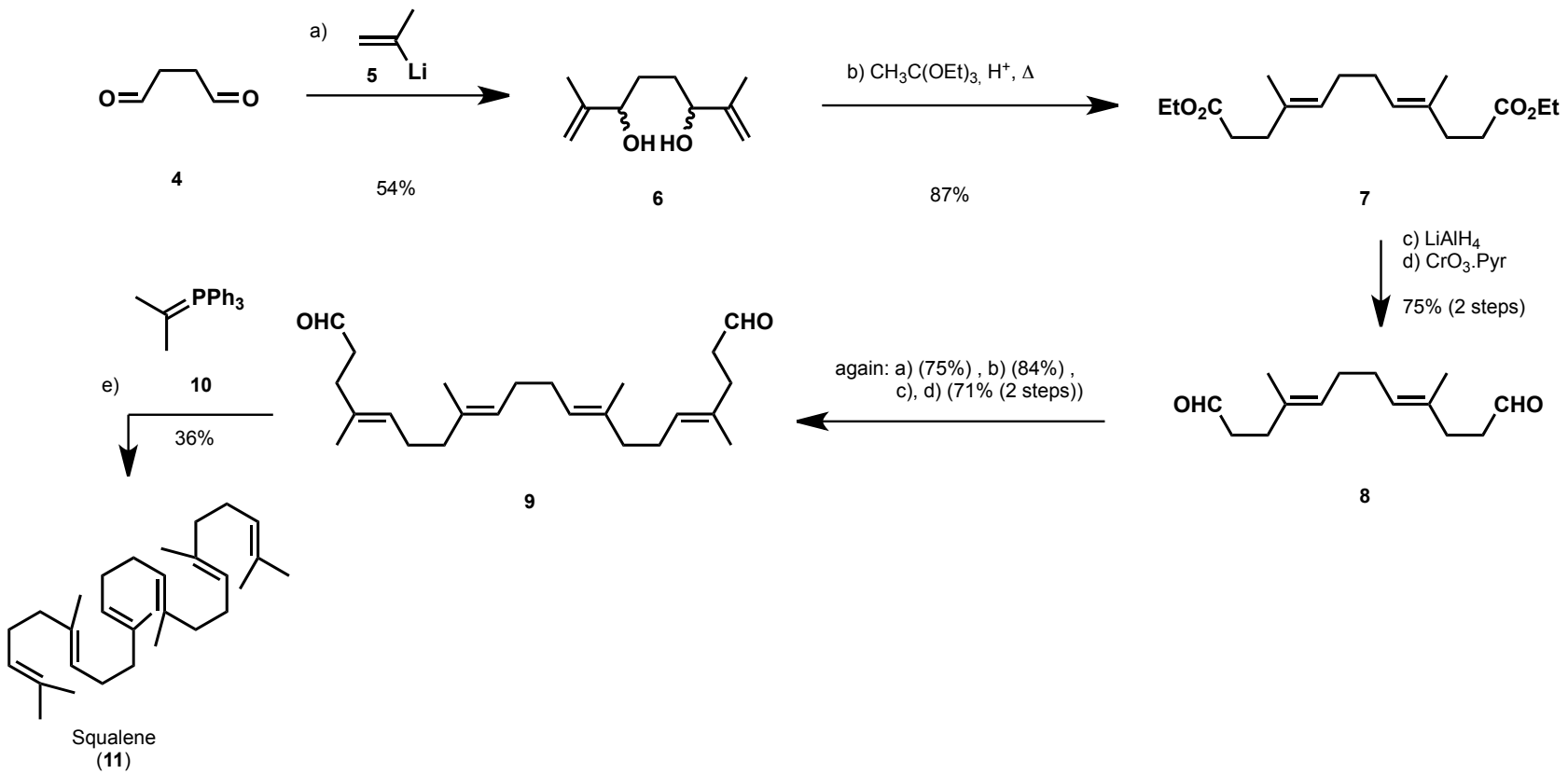
- Two- or Bidirectional Synthesis: simultaneous chain-homogolation or FGI on both chain ends



- Number of steps can be reduced
- Higher selectivities (dr and *ee*)
- Reviews:

  Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27, 9-17*
  Magnuson, S. R. *Tetrahedron* **1995**, *51 (8),* 2167-2213

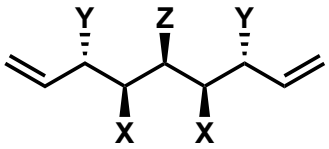
Early example: Synthesis of Squalene



All *E*-double bond configuration (>98% for each transformation)

Johnson, W.S.; Wertheman, L.; Bartlett, W.R.; Brocksom, T.J.; Li, T.; Faulkner, D.J.; Petersen, M.R. *J. Am. Chem. Soc.* **1970**, *92*, 741

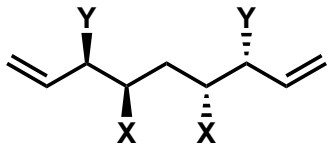
Stereochemical considerations



12

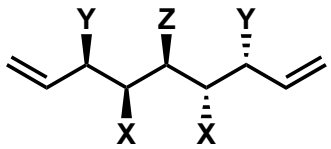
Achiral / *meso* chains

meso compounds: center is pseudo asymmetric
substituents are enantiomorph



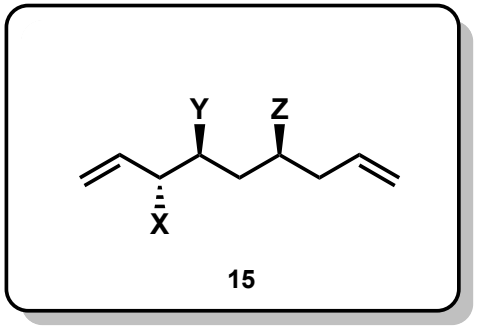
13

C_2 symmetric chains



14

pseudo C_2 symmetric chains
center is not chiral, substituents are identical

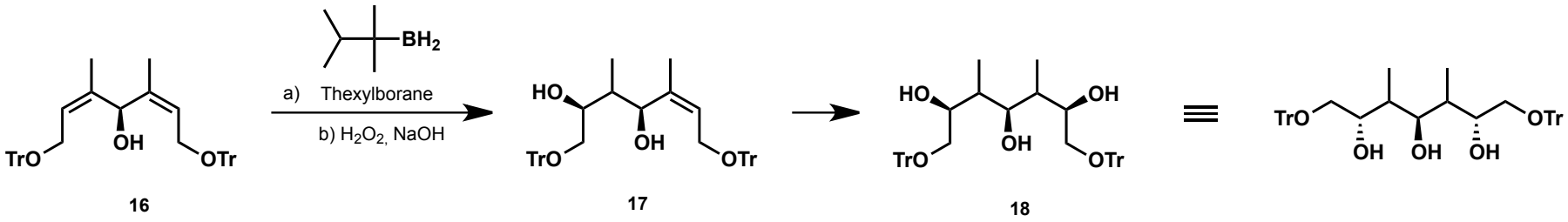


15

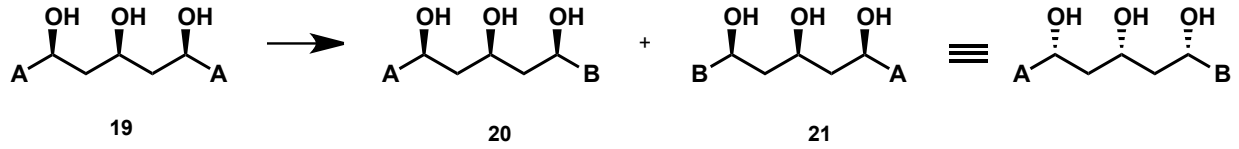
unsymmetric chain

Achiral/meso chains

- Synthesis:
  Generation of new stereogenic centres requires substrate control (chiral reagents lead to chiral products)

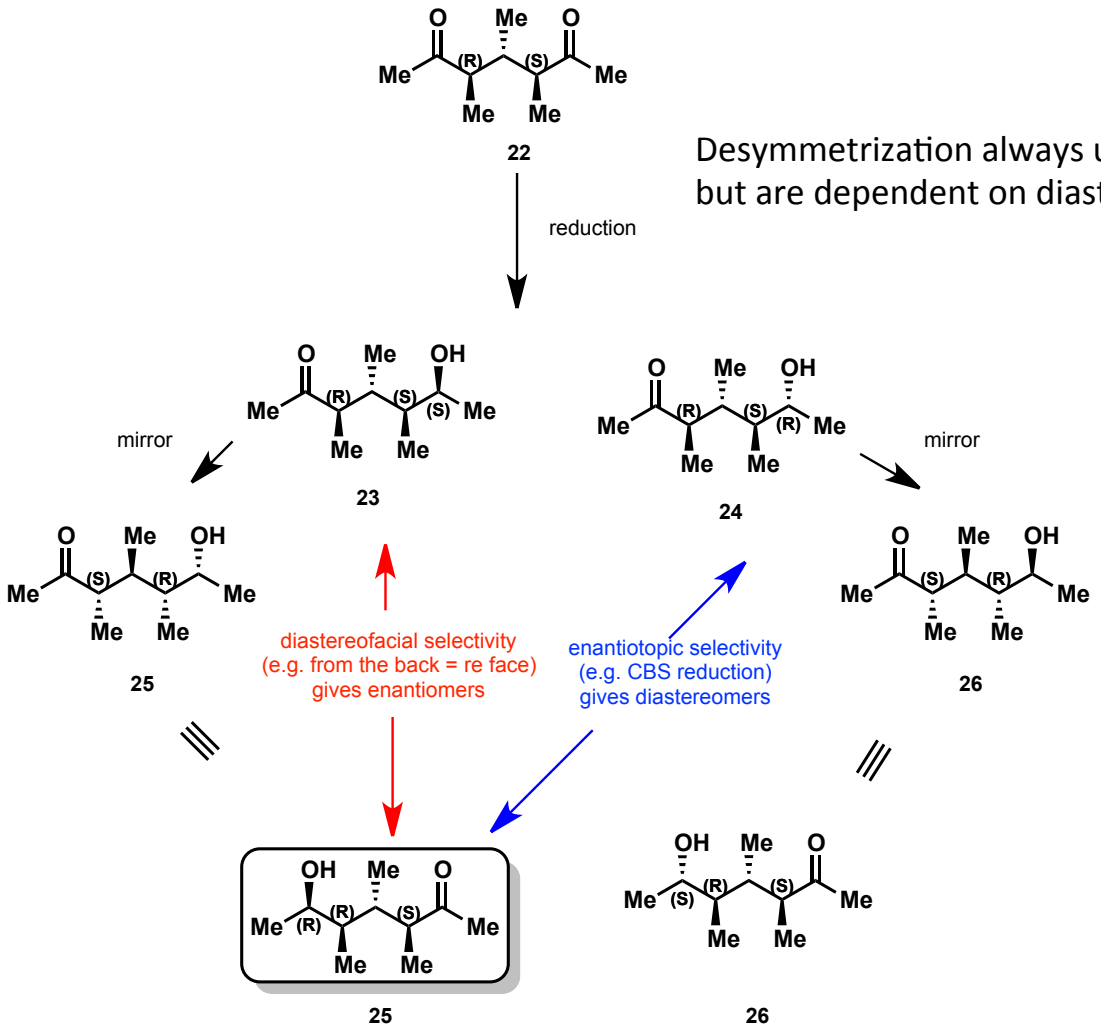


- Desymmetrization:
  Requires enantiotopic group selection & often diastereofacial selectivity: substrate and reagent control



Still, W. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487-2489.

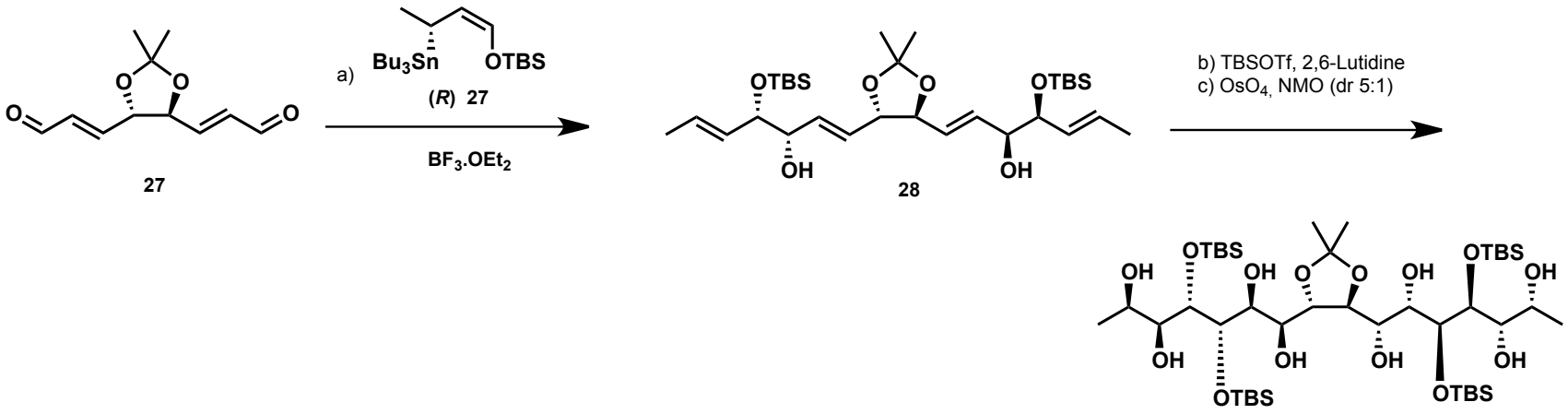
Additional slide: desymmetrization meso compound



Desymmetrization always uses a chiral reagent, but are dependent on diastereofacial selctivity

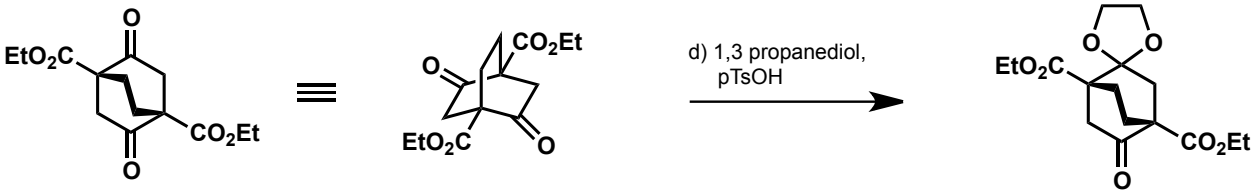
C_2-symmetric chains

- Synthesis:
  Generation of new stereogenic centres require substrate or reagent control



27 28 29

- Desymmetrization: Corresponding groups are homotopic
  Requires monofunctionalisation



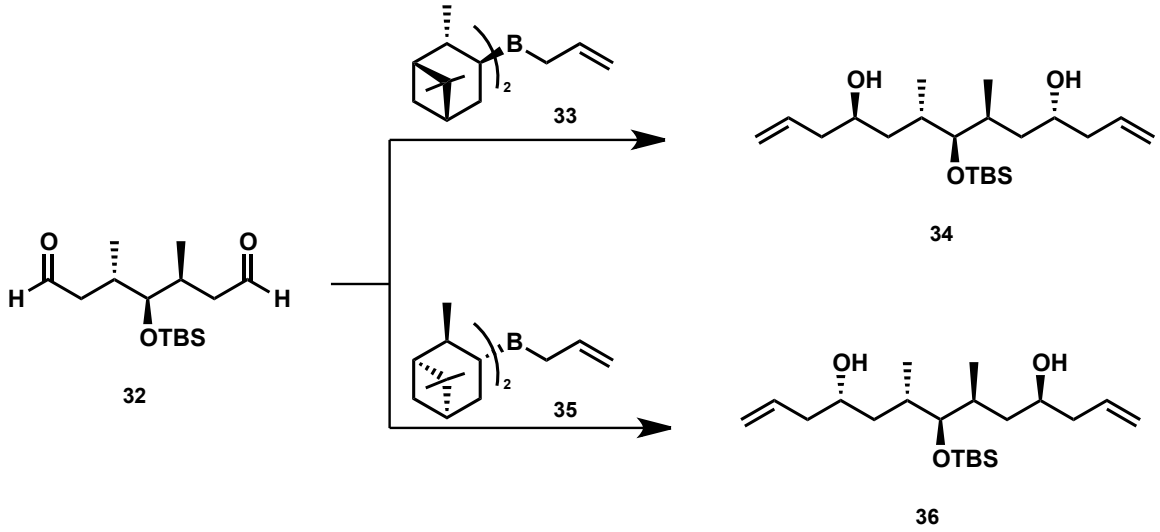
30 31

Saito, S.; Morikawa, T. J. *J. Org. Chem.* **1990**, *55*, 5424

Carreria, E.M. *Angew. Chem. Int. Ed.* **2011**, *50*, 11501

Pseudo C_2-symmetric chains

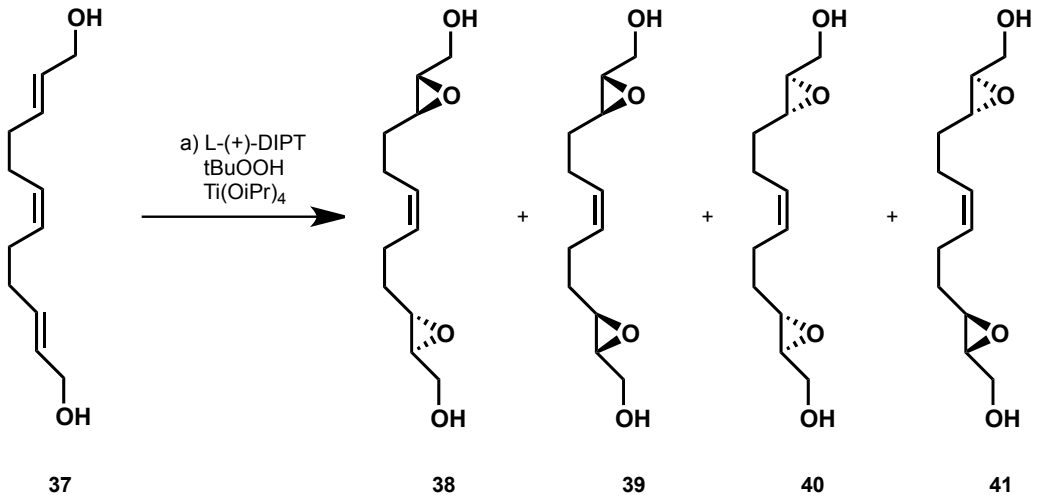
- Synthesis:
  Generation of new stereocenters requires reagent control



- Desymmetrization requires diastereotopic group selection

Magnuson, S. R. *Tetrahedron* 1995, *51 (8),* 2167-2213

Enhanced selectivities with C_2- and Pseudo C_2-symmetric chains



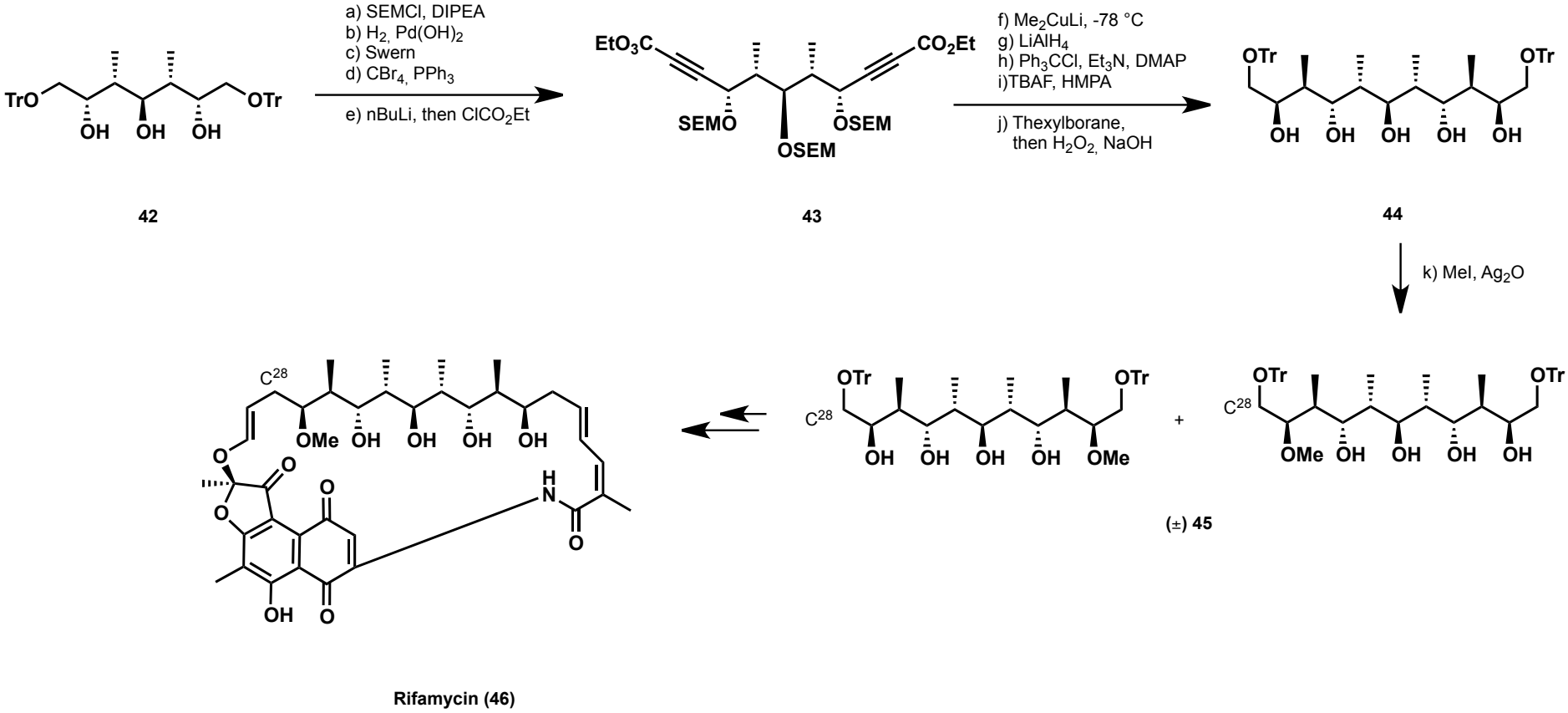
38 : **39** : **40** : **41** = 361 : 19 : 19 : 1

$(a+b)^2 = a^2 + 2ab + b^2$

a : b is the *er*

Hoye, T.R.; Suhaldalnik, J.C. *Tetrahedron* **1986**, *42*, 2855

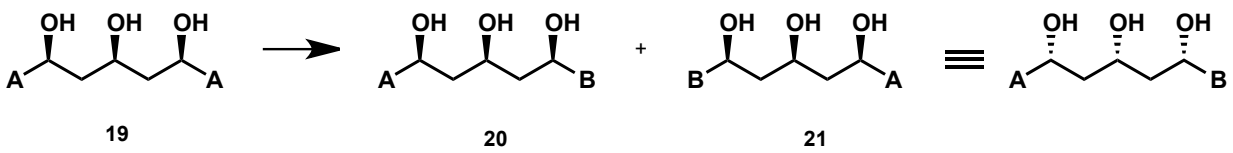
Desymmetrisations: why?

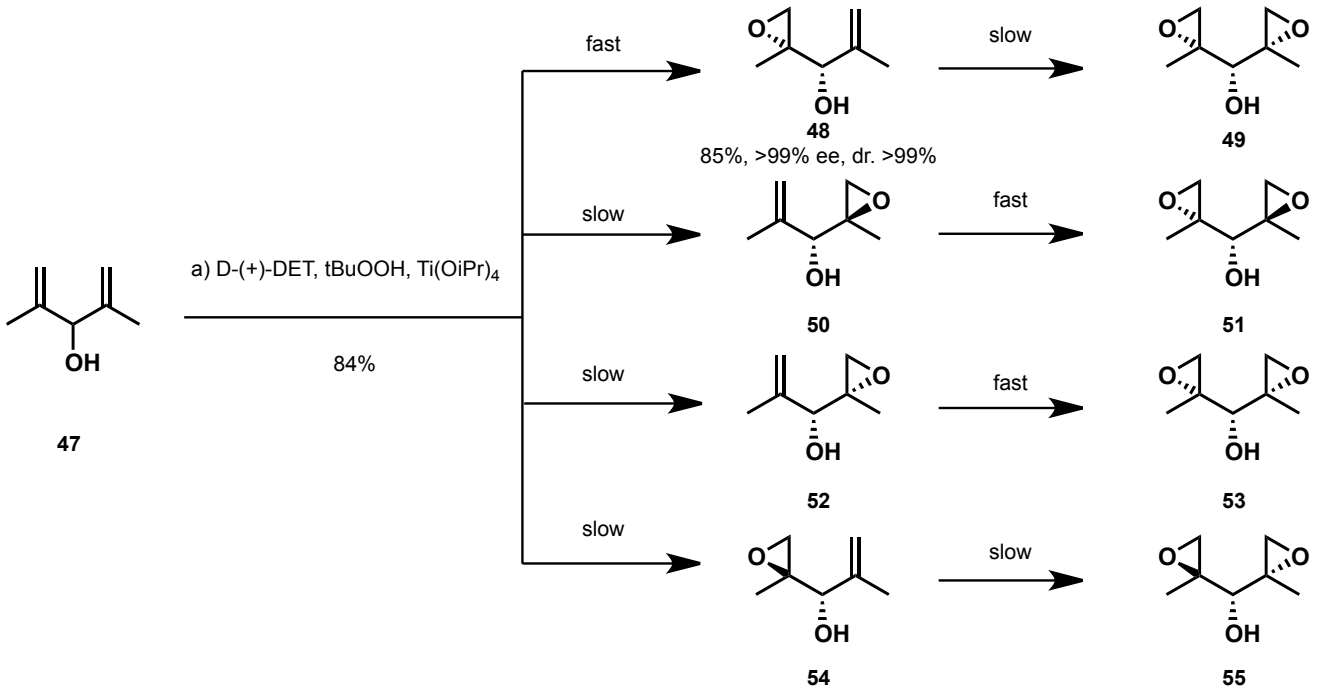


42 43 44

Still, W.C.; Barish, J.C. *J. Am. Chem. Soc.* **1983**, *105*, 2487

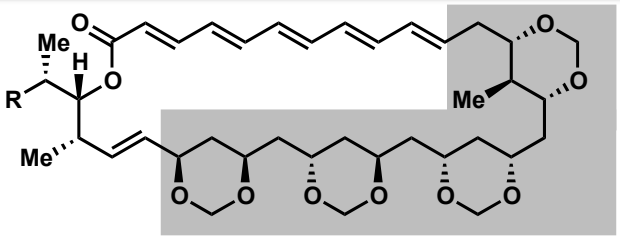
Desymmetrisation of achiral chains: polyols



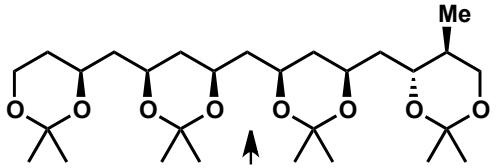


Schreiber, S.L.; Schreiber, T.S.; Smith, D.B. *J. Am. Chem. Soc.* **1987**, *109*, 1525

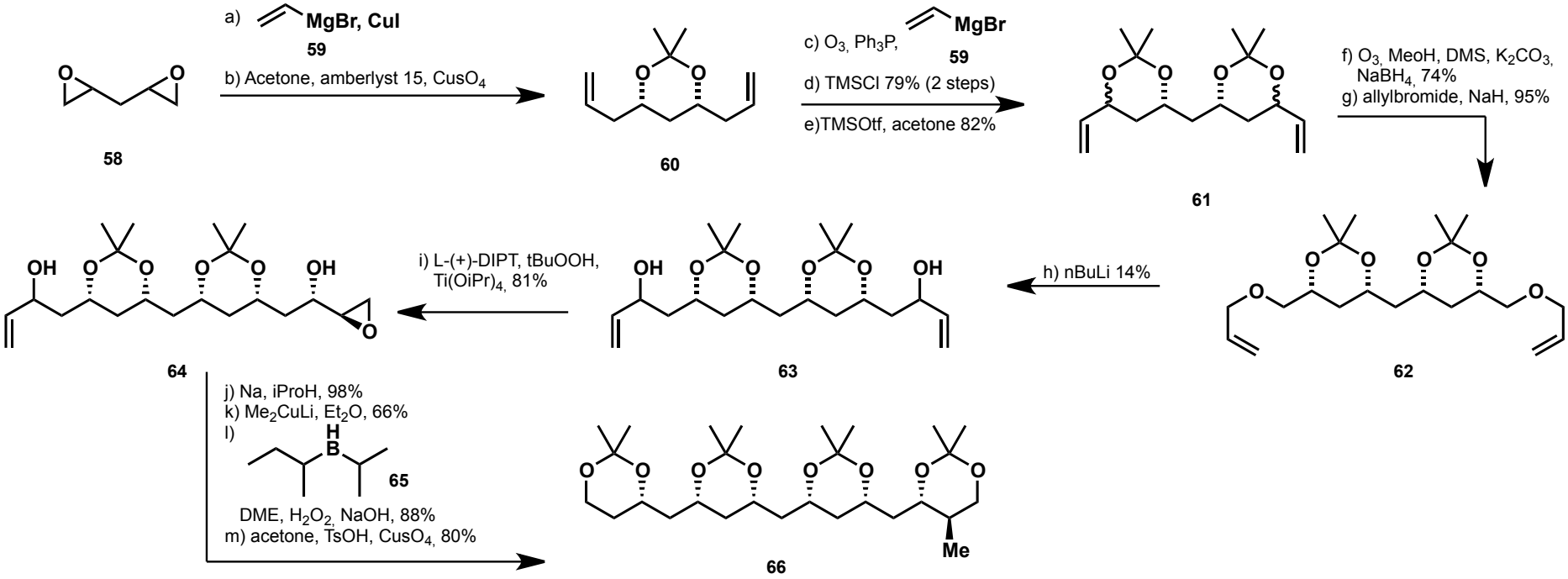
Desymmetrisation of achiral chains: polyols



mycoticin A tetraformylal R = H (**56a**)
mycoticin B tetraformylal R = Me (**56b**)

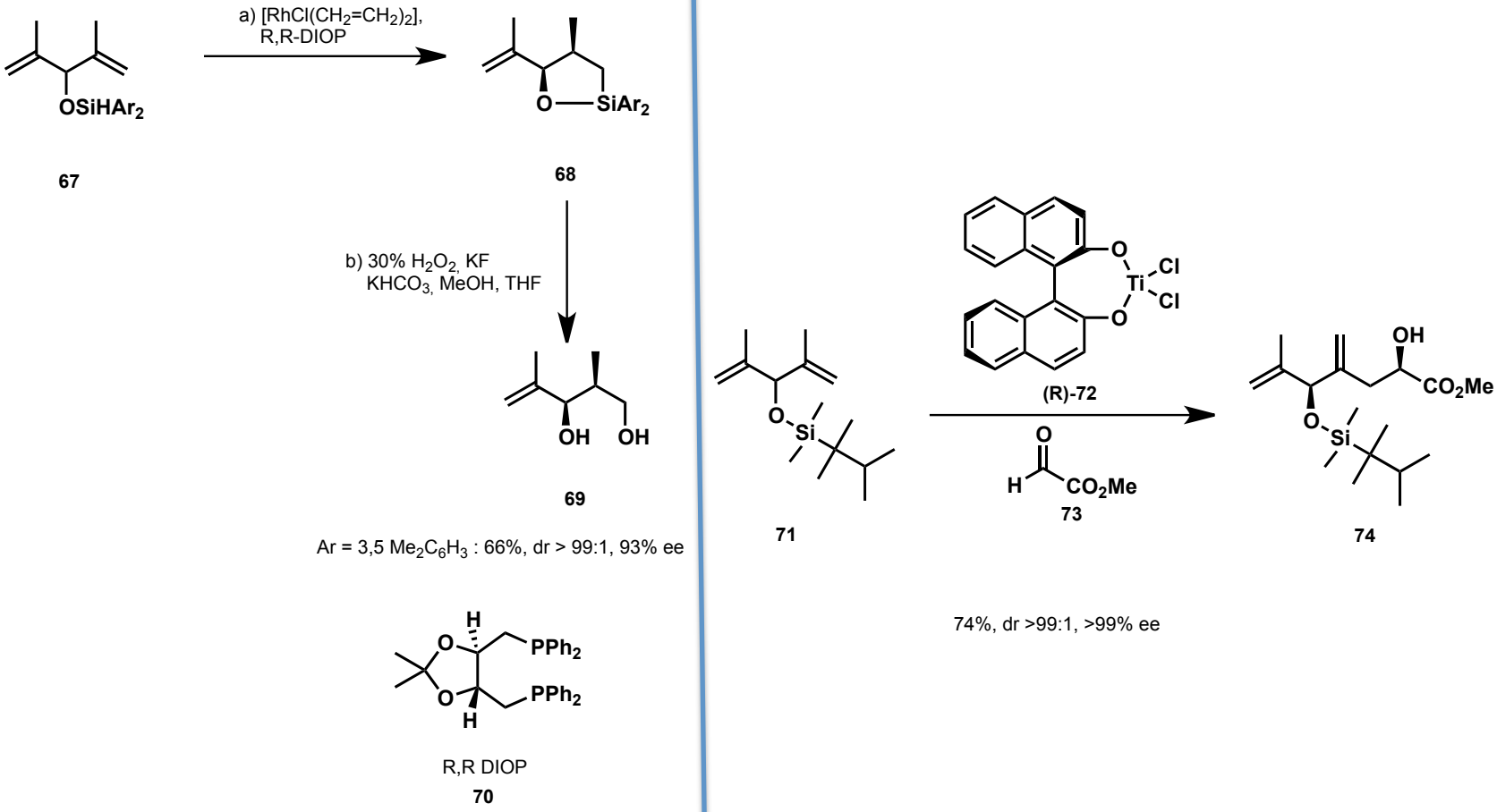


57



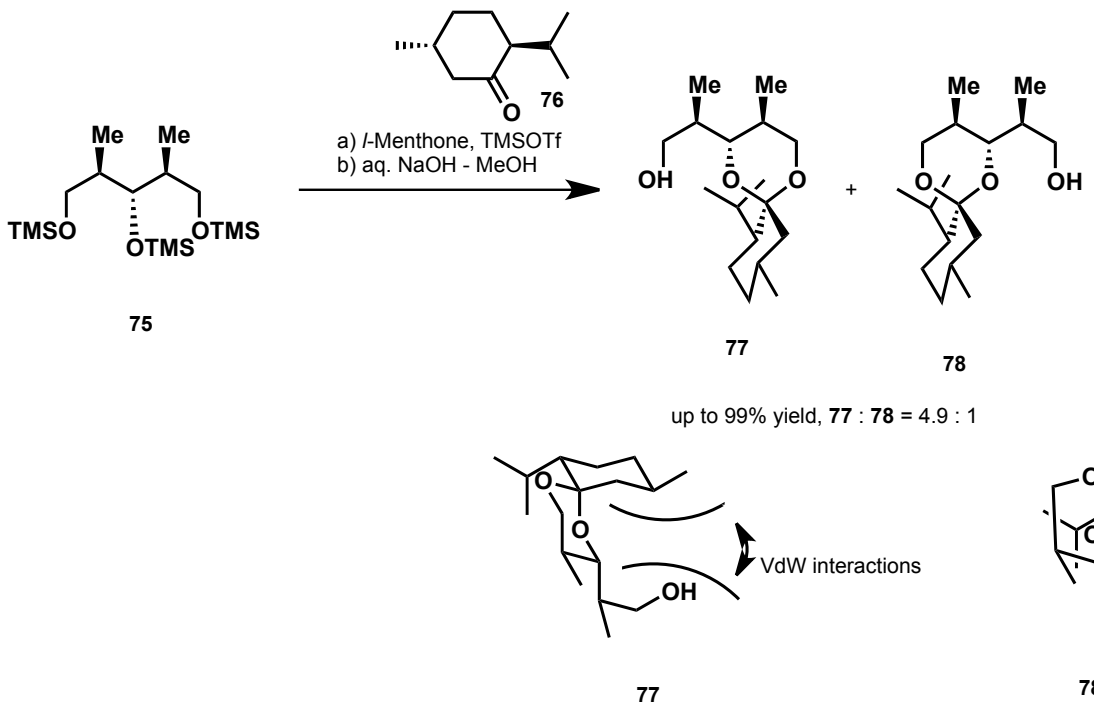
Schreiber, S.L.; Goulet, M.T. *J. Am. Chem. Soc.* **1987**, *109*, 4718

Desymmetrisation of achiral chains: polyols



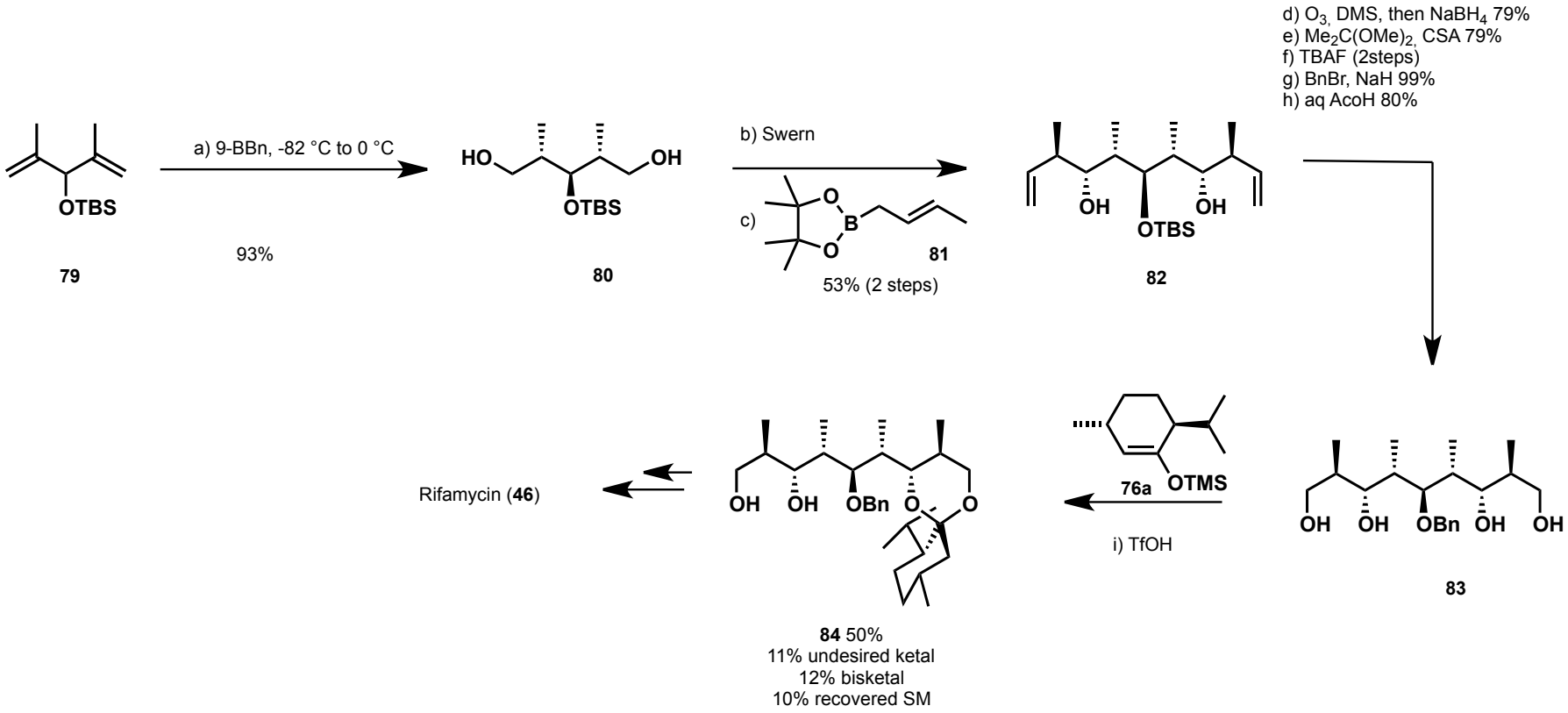
Tamao, K.; Tohma, T.; Iniu, N.; Nakayama, O.; Ito, Y. *Tetrahedron Lett.* **1990**, *31*, 7333
Mikami, K.; Narisawa, S.; Shimizu, M.; Terada, M. *J. Am. Chem. Soc.* **1992**, *114*, 6566

Desymmetrisation of achiral chains: polyols



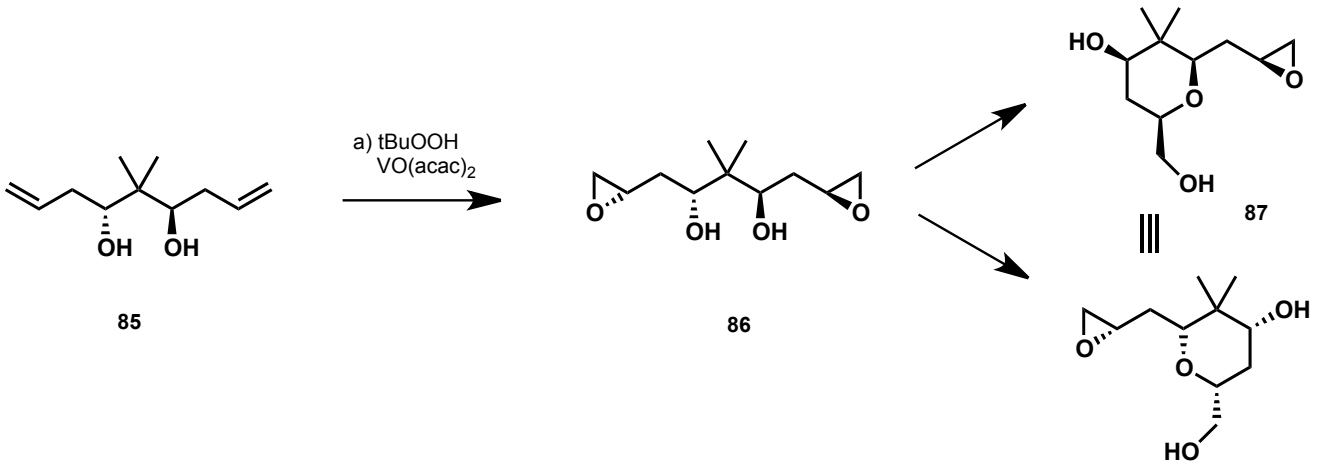
Harada, T.; Tanaka, S.; Oku, A. *Tetrahedron* **1992**, *48*, 8621

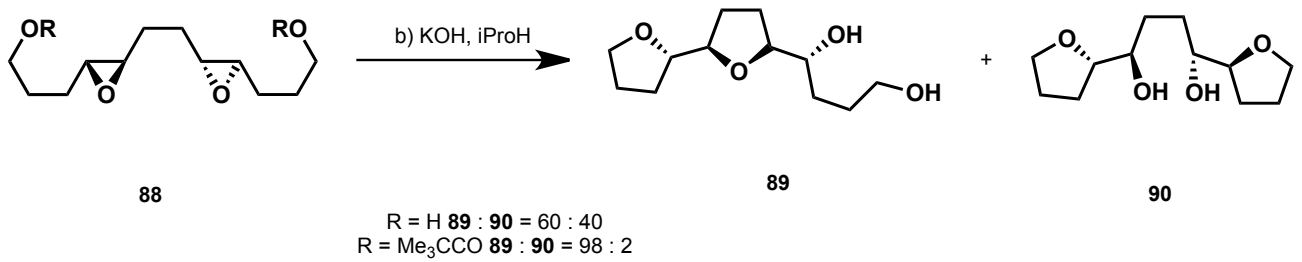
Desymmetrisation of achiral chains: polyols



Harada, T.; Kagamihara, Y.; Tamaka. S.; Sakamoto, K.; Oku, A. *J. Org. Chem., Chem. Commun.* **1990**, 21

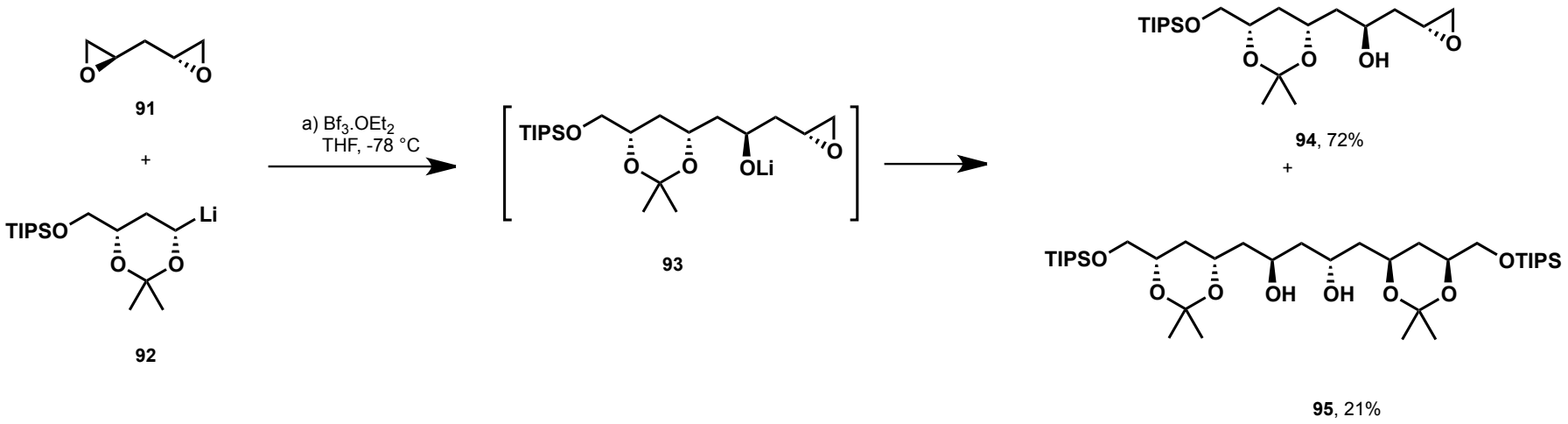
Desymmetrisation of C_2 symmetric chains: intramolecular functionalisation





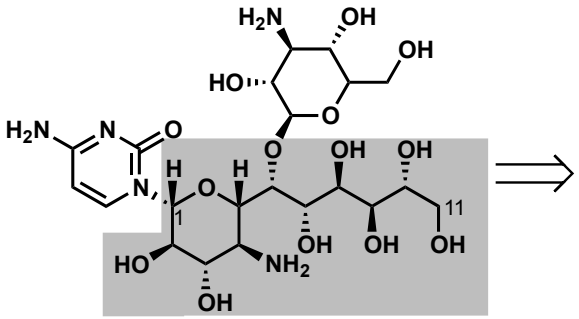
Tsuzuki, K.; Nakajima, Y.; Watanabe, T.; Yanagiya, M.; Matsumoto, T. *Tetrahedron Lett.* **1978**, 989
Hoye, T.R.; Witowsky, N.E. *J. Am. Chem. Soc.***1992**, *114*, 7291

Desymmetrisation of C_2 symmetric chains: steric proximity effects

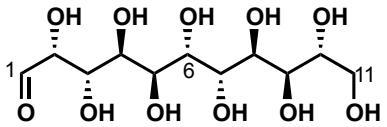


Rychnovsky, S.D.; Witowski, N.E. *J. Am. Chem. Soc.* **1991**, *56*, 5161

Desymmetrisation of C_2 symmetric chains: reactivity difference



(-) hikizimycin (**96**)



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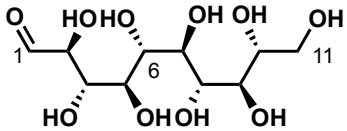

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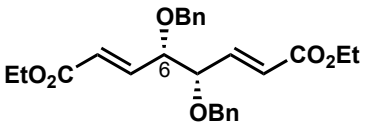
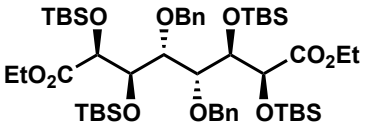


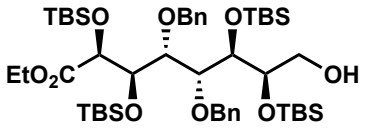
98

a) OsO_4, NMO, d.r.: 8:1, 71%
b) TBSOTf, 2,6 Lutidine, 100%



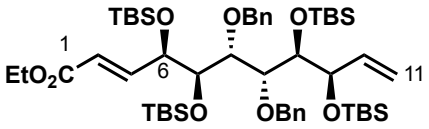
99

c) DIBAL, DCM, -78 °C, 82%



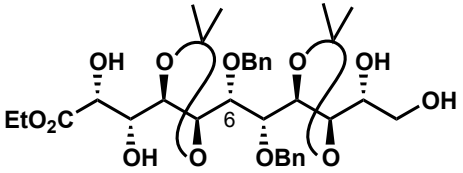
100

d) Swern, 97%
e) Tebbe, 82%
f) DIBAL, 95%
g) Swern, 98%
h) HWE, 97%



101

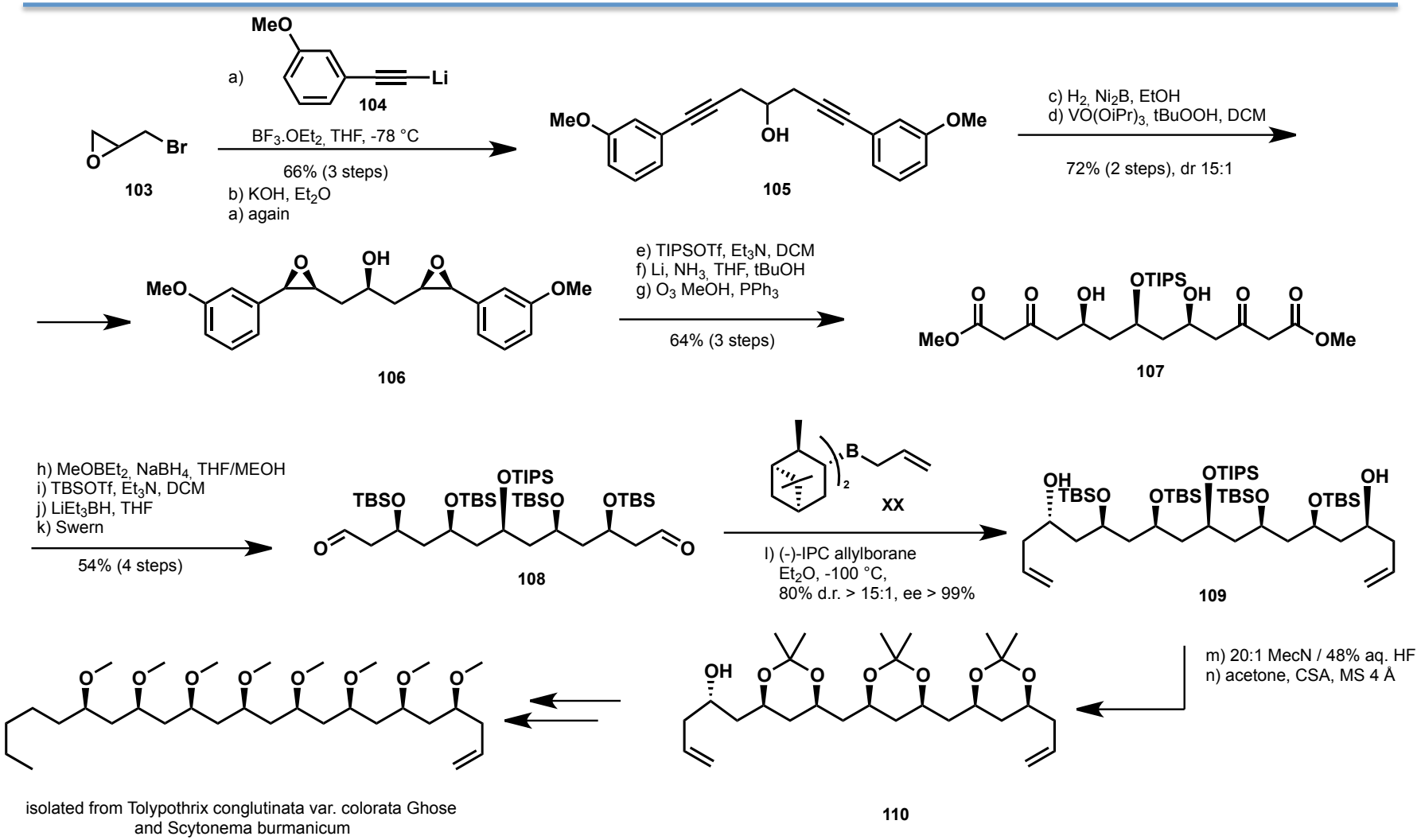
i) TBAF, 86%
j) acetone, H_2SO_4, 89%
k) OsO_4, NMO, 88% d.r.: 3:1



102

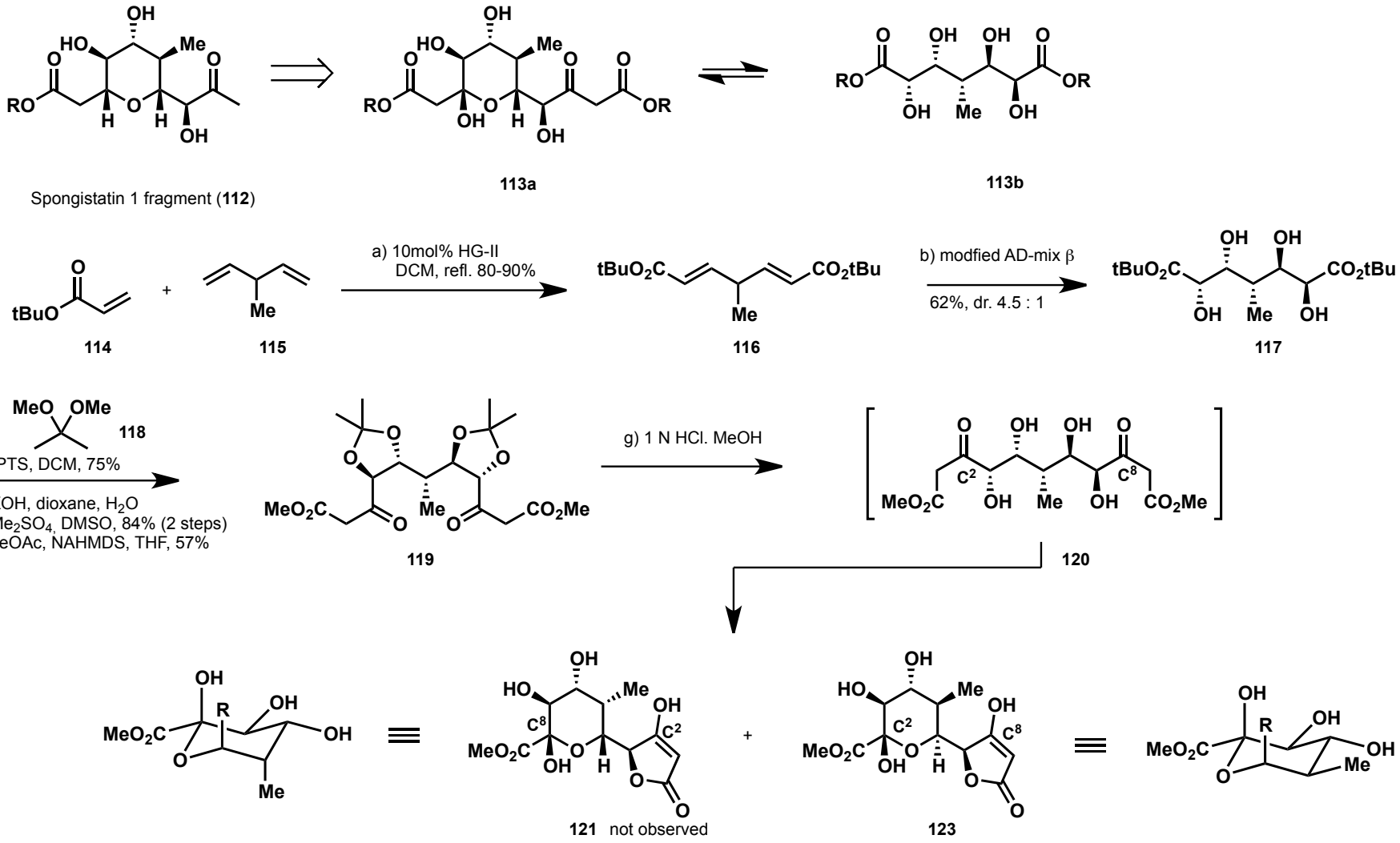
Ikemoto, N.; Schreiber, S.L. *J. Am. Chem. Soc.* **1990**, *112*, 9657

Desymmetrization of pseudo C2 symmetric chains: Diastereotopic group selection



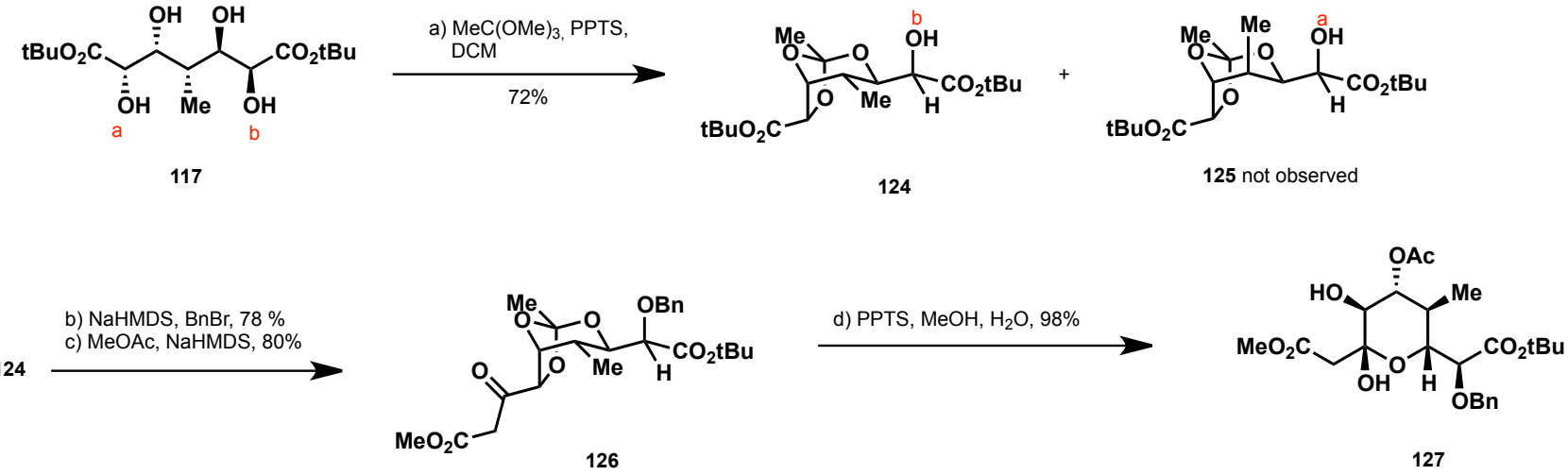
Wang, Z.; Deschênes, D. *J. Am. Chem. Soc.* **1992**, *114*, 1090-1091

Desymmetrization of pseudo C2 symmetric chains: Diastereotopic group selection

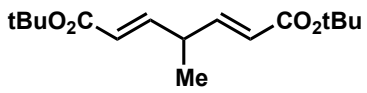


Tanis, P.S.; Infantine, J.R.; Leighton, J. L. *Org. Lett.* **2013**, *15*, 5464

Desymmetrization of pseudo C2 symmetric chains: Diastereotopic group selection

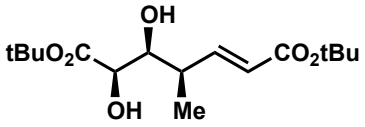


The „Eliel“ Effect



116

first dehydroxylation



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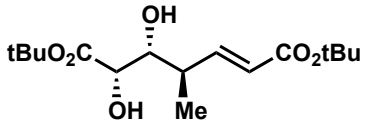

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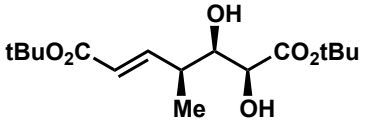

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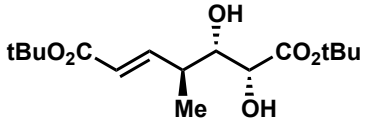

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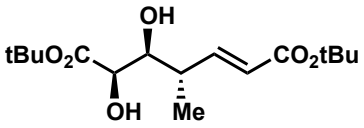

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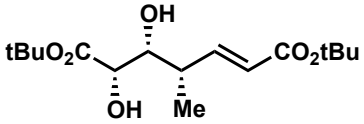

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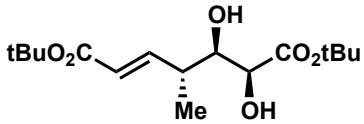

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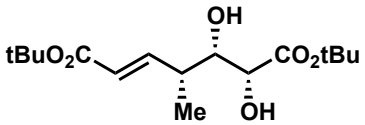
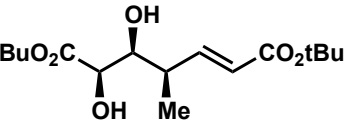


135

After removal of duplicates



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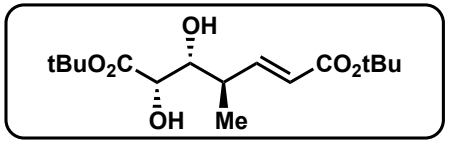

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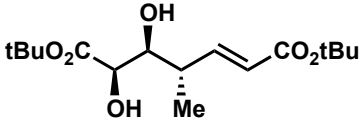

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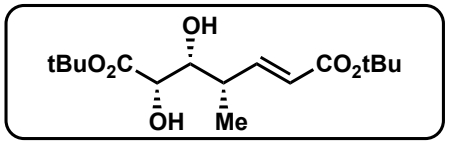

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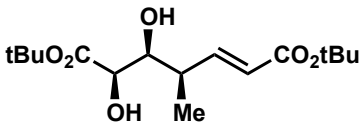
Kogure, T.; Eliel, E. L. *J. Org. Chem.* **1984**, *49*, 576

The „Eliel“ Effect



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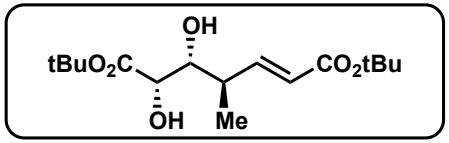

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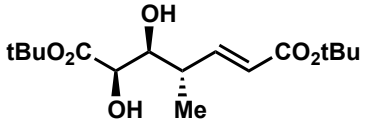

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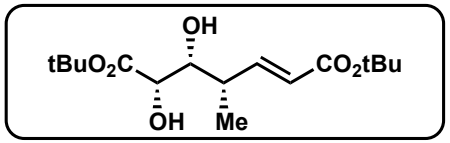

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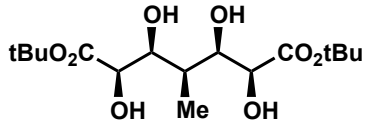
second dehydroxylation



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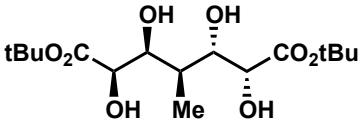

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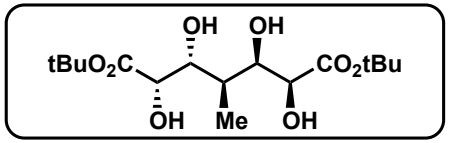

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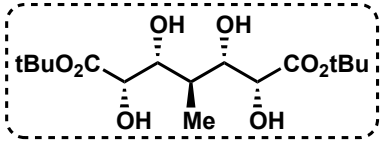

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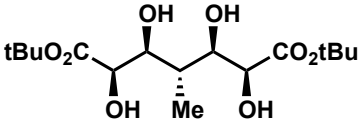

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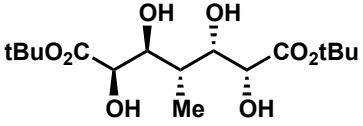

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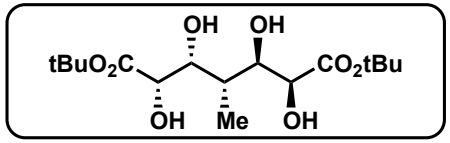

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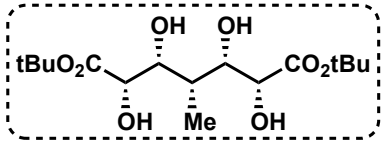

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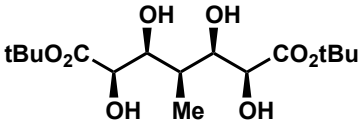
Removal of duplicates



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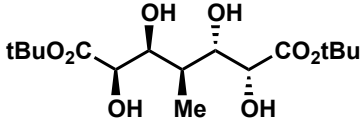

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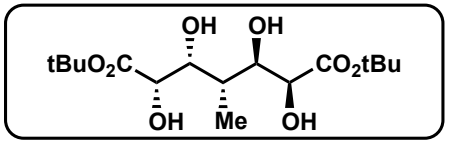

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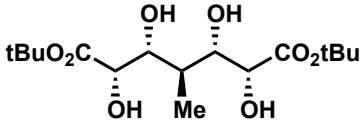

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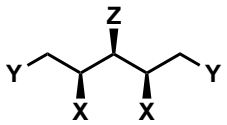
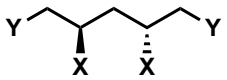
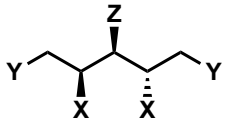
Summary

Chain Type	Synthesis	Desymmetrization
 Achiral (including meso)	Generation of new stereocenters requires substrate control	Requires enantiotopic group selection & often diastereofacial selection Requires substrate and reagent control
 C_2 symmetric	Generation of new stereocenters requires substrate or reagent control	Corresponding groups are homotopic Requires monofunctionalization
 Pseudo C_2 symmetric	Generation of new stereocenters requires reagent control	Requires diastereotopic group selection