Weinreb Amides in Organic Synthesis

Maria del Mar Sanchez

Bibliography March the 07th 2009

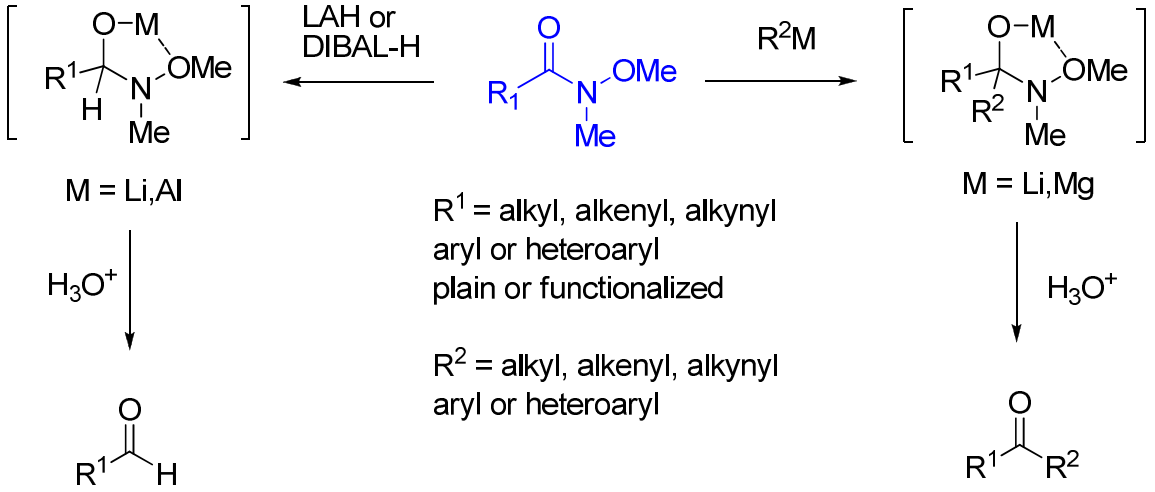
Contents

1. Generalities

N-Methoxy-N-methylamides = Weinreb amides (WAs)

acylating agent

reduction to aldehydes



	R^1	R^2	Yield
a	phenyl	methyl	96
b	phenyl	n-butyl	91
c	phenyl	phenyl	95
d	cyclohexyl	phenyl	100
e	cyclohexyl	n-butyl	97

The four S:

Simplicity: easy preparation by in situ activation of the carboxyl group

Success: effective acylating agent → access to highly functionalized ketones

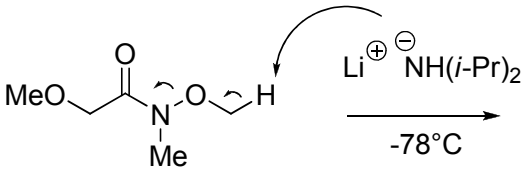
Scale up: use of WA in industry

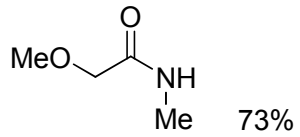
Stability and hence easy storability

Nahm, S.; Weinreb, S. M. *Tetrahedron Lett*. **1981**, 22, 3815

2. Limitations

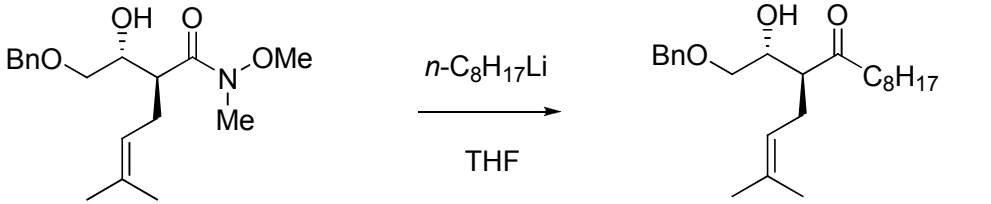
Demethoxylation





73%

E2 elimination

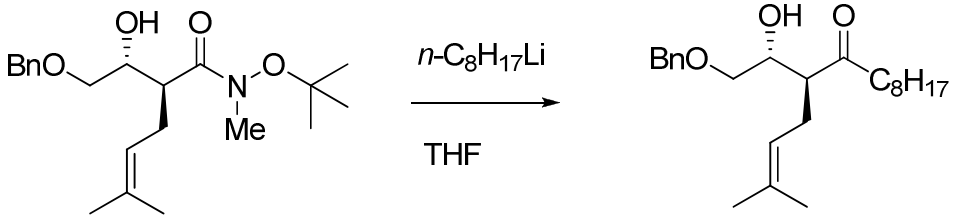


isoavenaciolide

(9 - 24%)

(36 - 63%)

Solution



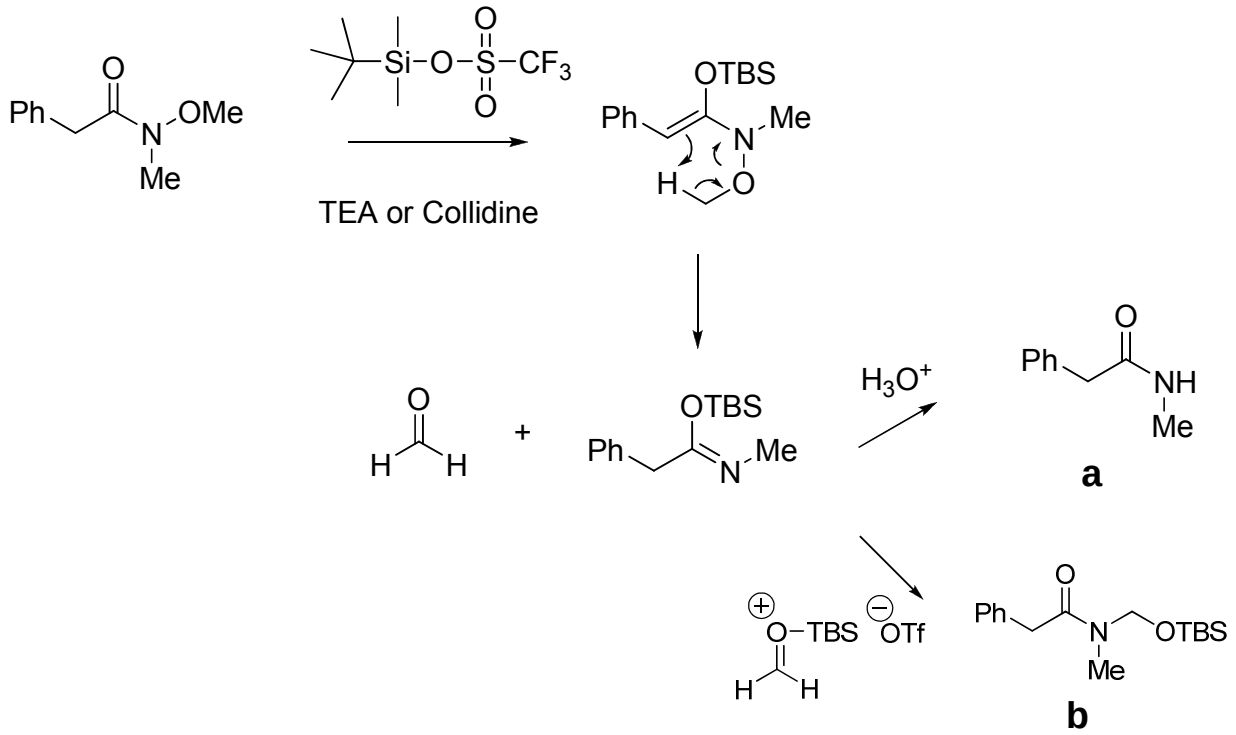
isoavenaciolide 72%

Graham, S. L.; Scholz, T. H. *Tetrahedron Lett*. **1990**, 31, 6269

Labeeuw, O.; Phansavath, P.; Genêt, J-P. *Tetrahedron Lett*. **2004**, 45, 7107

2. Limitations

Demethoxylation and rearrangement



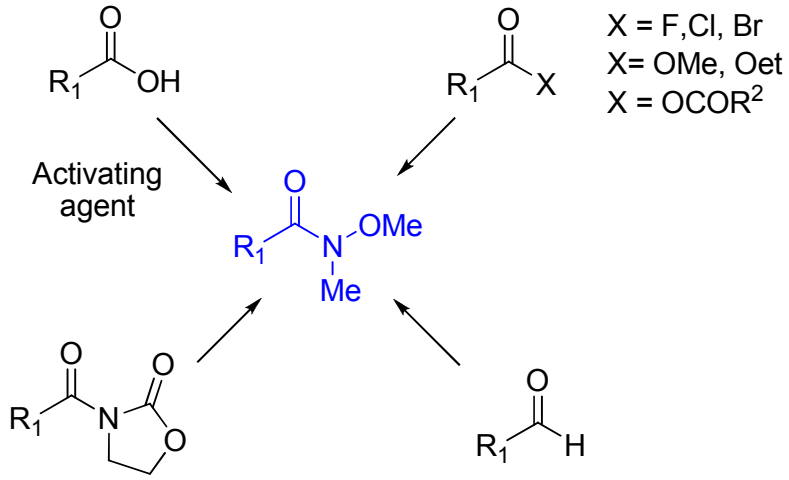
demethoxylation

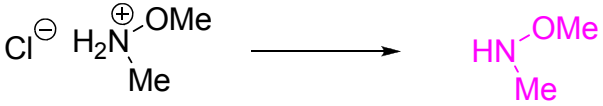
rearrangement

Keck, G. E.; McHardy, S. F.; Murry, J. A. *Tetrahedron Lett*. **1993**, 34, 6215

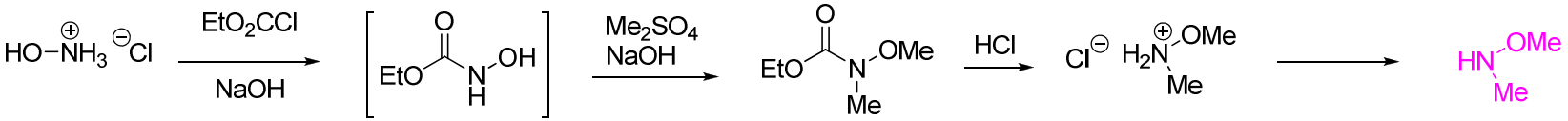
3. Methods for preparation

Preparation of Weinreb amide:



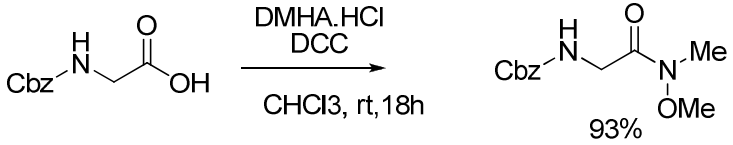


DMHA
N,O-dimethylhydroxylamine
(liquid; bp 47-50 °C)



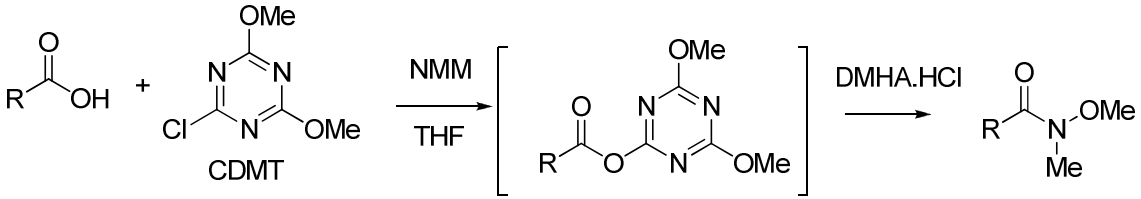
3. Methods for preparation

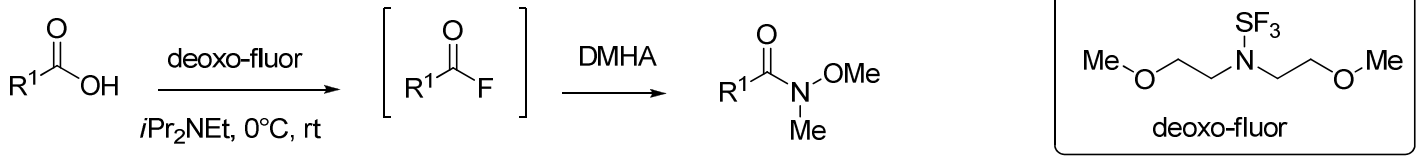
From carboxylic acids



Acid activating agents:

DCC, DEPC, HOBT/DCC, HOBT/EDCI, BOP.PF6, CDI

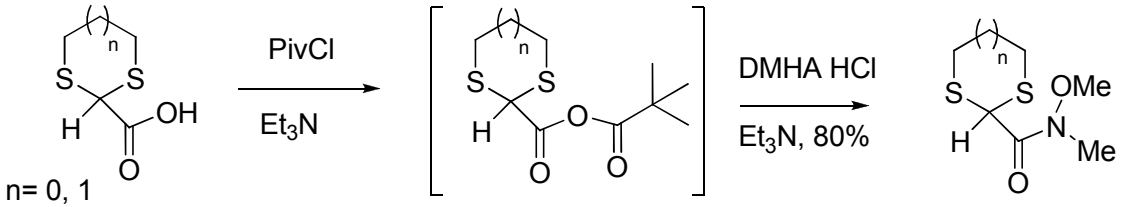




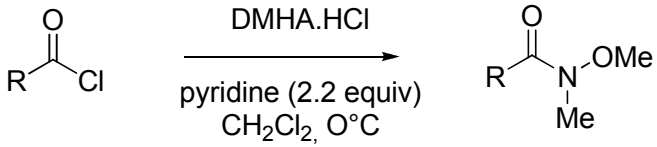
(a) De Luca, L.; Giacomelli, G.; Taddei, M. *J. Org. Chem*. **2001**, 66, 2534 (b) Kangani, C. O.; Kelley, D. E.; Day B. W. *Tetrahedron Lett*. **2006**, 47, 6289

3. Methods for preparation

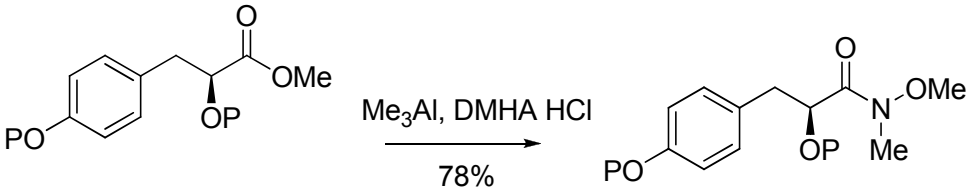
Mixed anhydrides:

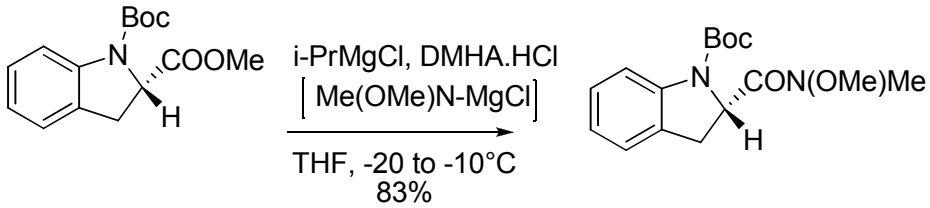


Acid halides:

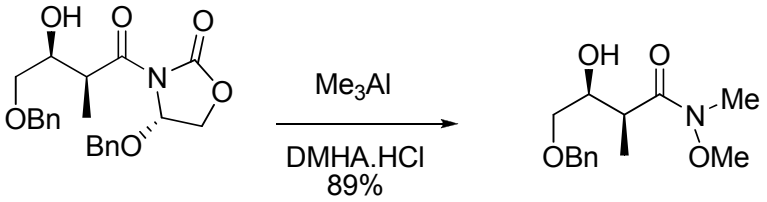


Esters:





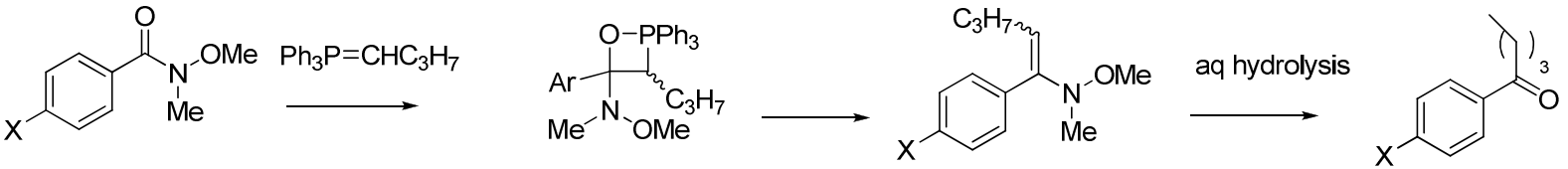
Imides:

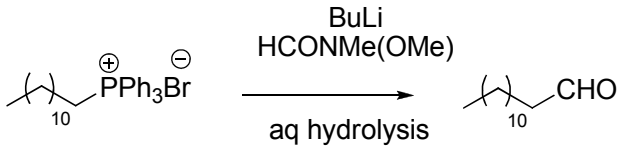


4. Applications

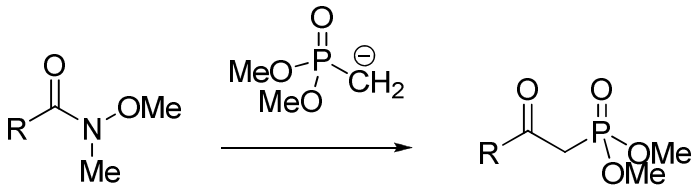
Ketones: Nu = organolithium or organomagnesium reagents
Aldehydes: Hydride = lithium aluminium or diisobutylaluminium hydride

Another nucleophile: alkylidenetriphenylphosphoranes





Formylation of phosphoranes

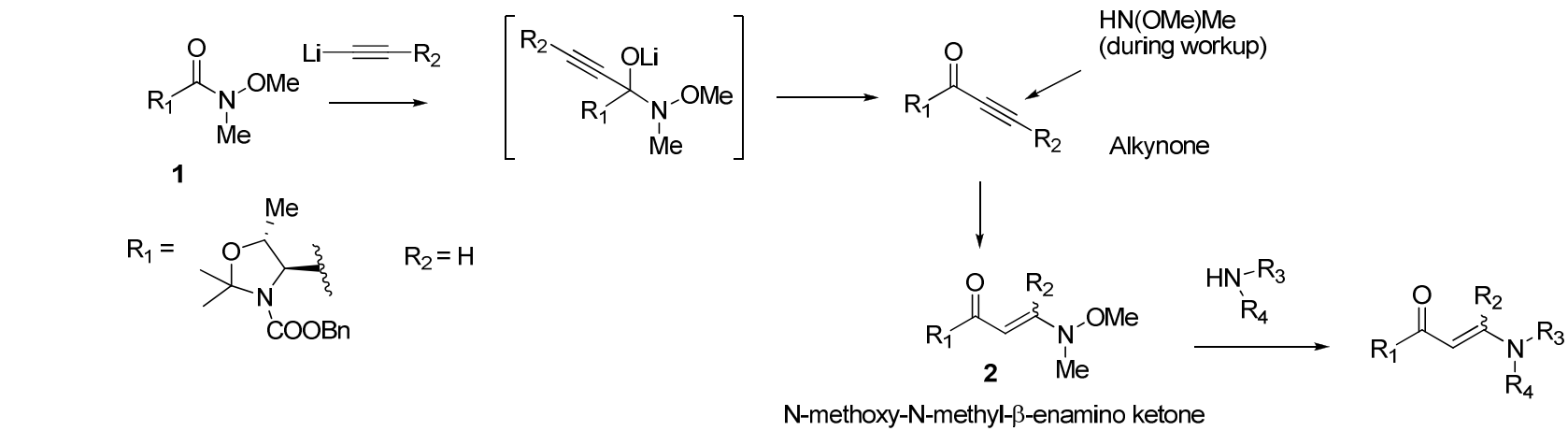


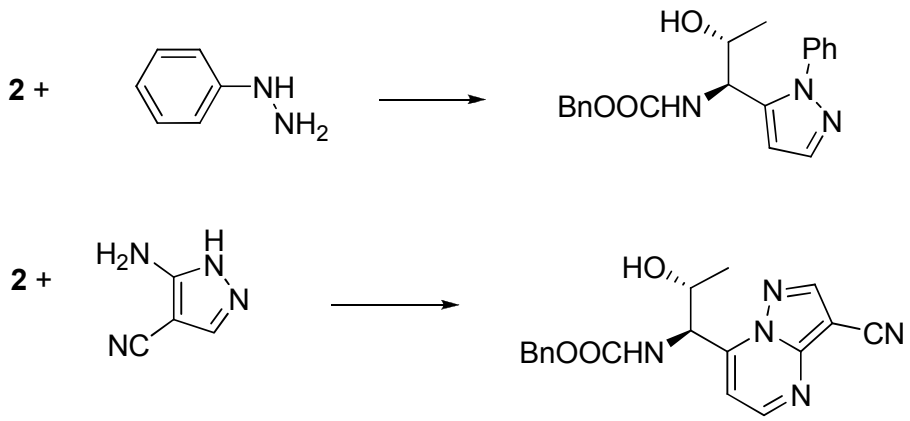
β ketophosphonate

Murphy, J. A.; Commeureuc, A. G. J.; Snaddon, T. N.; McGuire, T. M.; Khan, T. A.; Hisler, K.; Dewis, M. L.; Carling, R. *Org lett.* **2005**, 7, 1427

4.1 Use in Heterocyclic Chemistry

Addition of alkynyl lithium

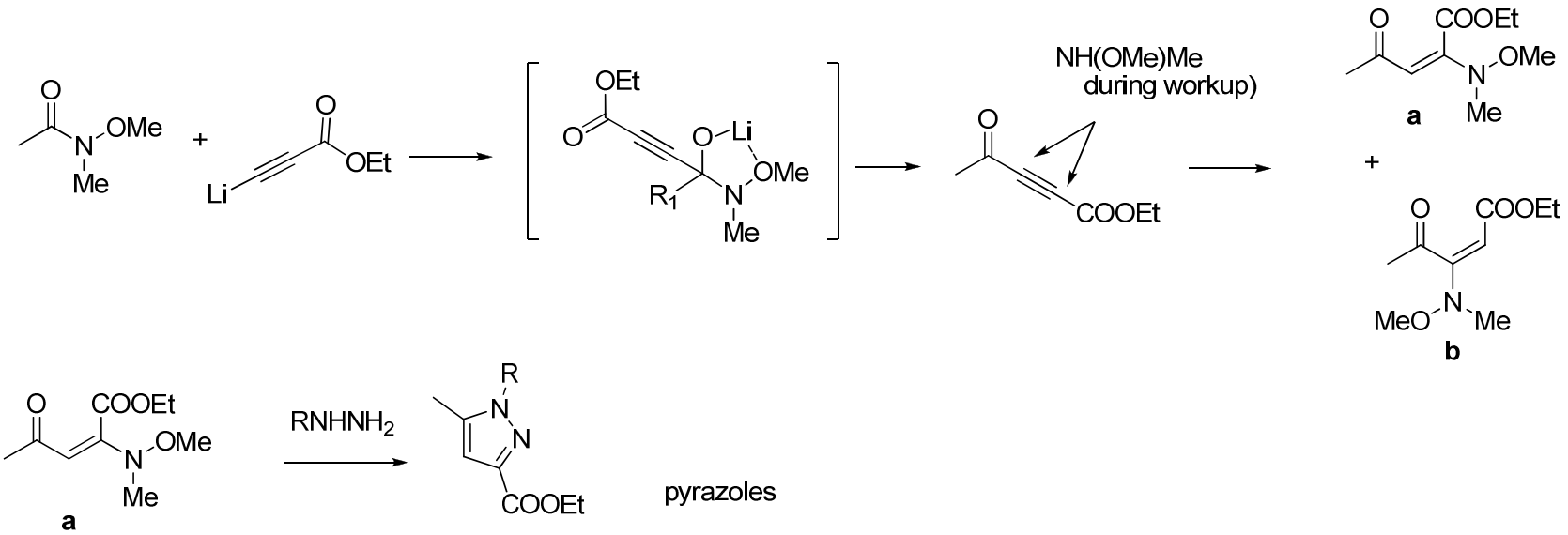




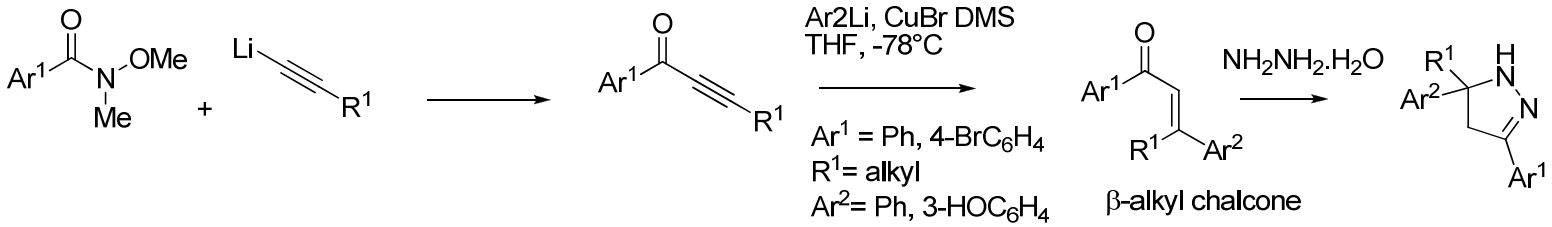
Pirc, S.; Bevk, D.; Golobic, A.; Stanovnik, B.; Svete, J. *Helv. Chim. Acta* **2006**, 89, 30.

4.1 Use in Heterocyclic Chemistry

Pyrrazoles[a]



Dihydropyrrazoles[b]

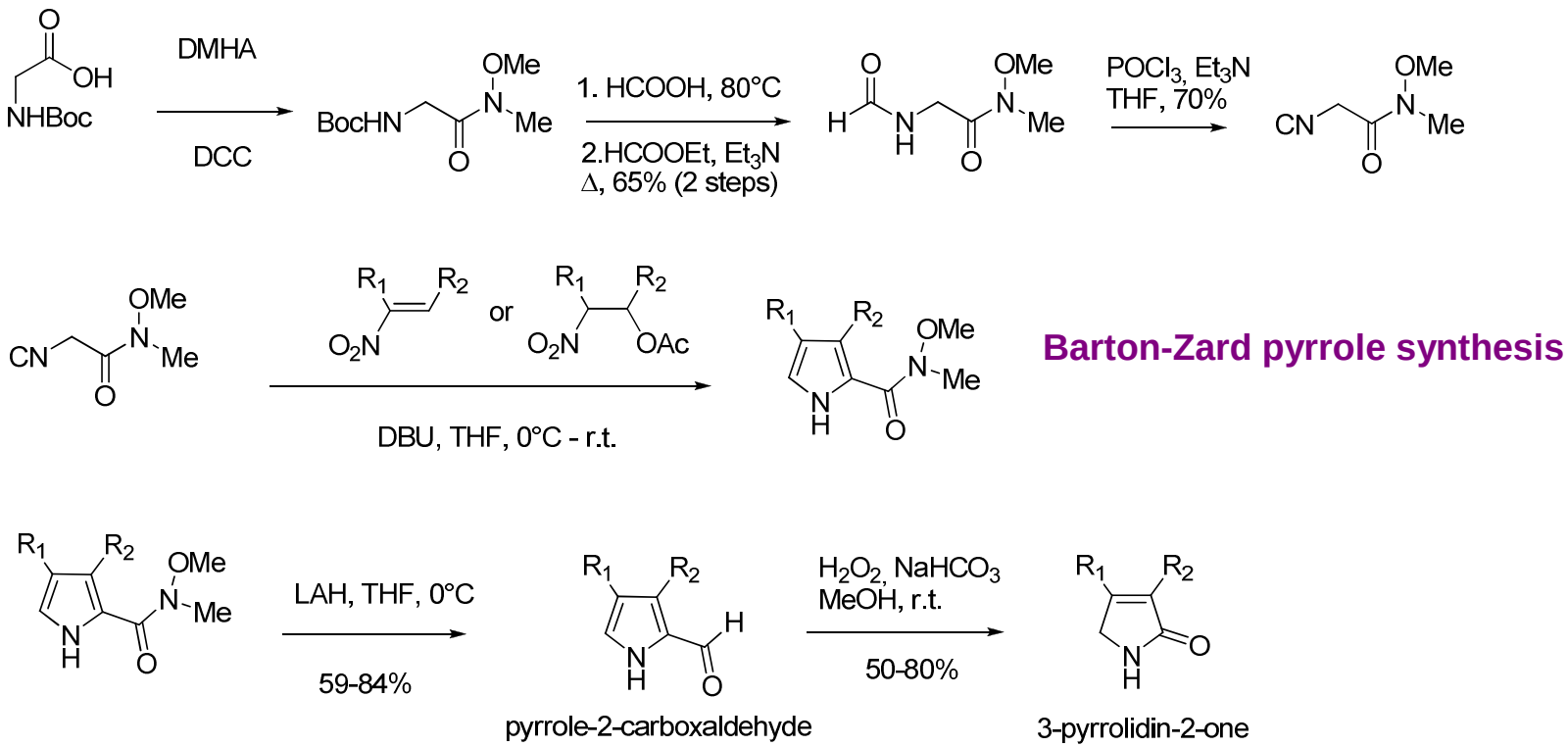


(a)Persson, T.; Nielsen, J. *Org lett*. **2006**, 8, 3219

(b) Cox, C. D.; Breslin, M. J.; Mariano, B. J. *Tetrahedron Lett*. **2004**, 45, 1489

4.1 Use in Heterocyclic Chemistry

Pyrrole-carboxaldehyde and pyrrolidinones

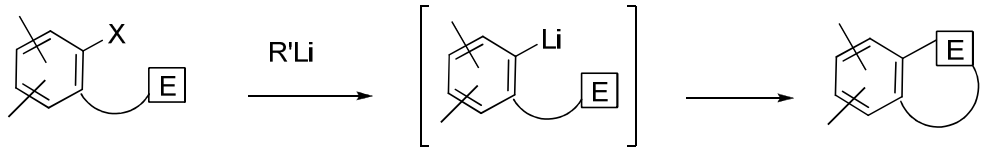


Barton-Zard pyrrole synthesis

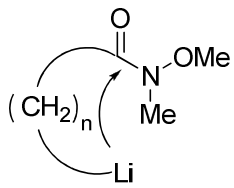
Coffin, A. R.; rousell, M. A. Tserlin, E.; Pelkey, E. T. *J. Org. Chem*. **2006**, 71, 6678

4.1 Use in Heterocyclic Chemistry

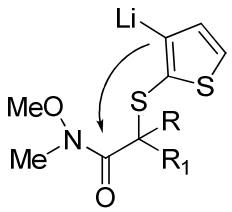
Parham Cyclisation



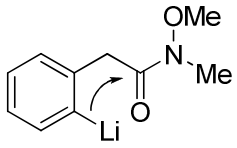
X= Br, I



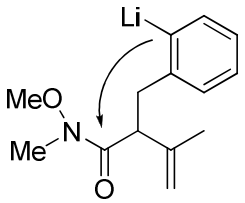
cyclic ketones [a]



thieno[2,3-*b*]thiophenes [b]

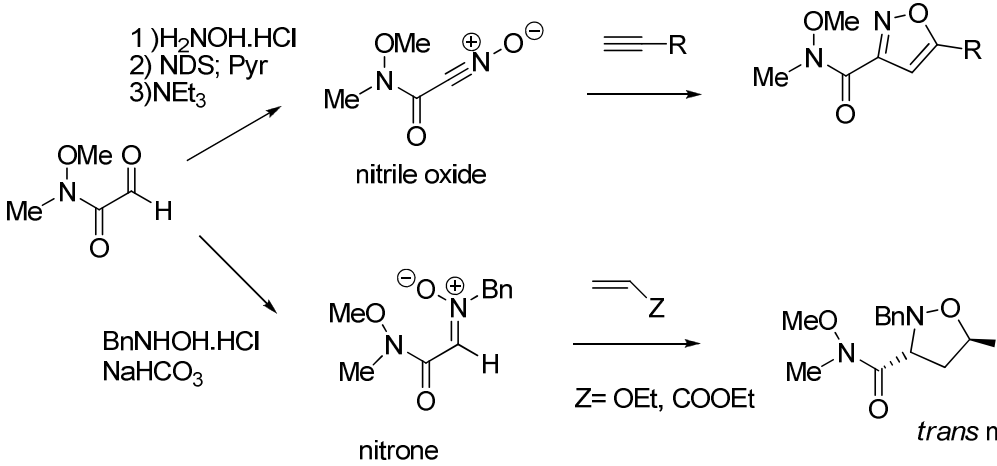


benzocyclobutenones [c]



methylideneindanones [d]

Isoxazoles[f]:

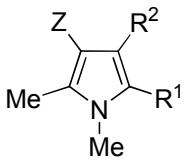


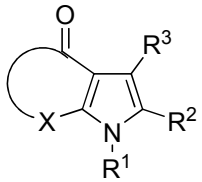
use of heterocycles as peptidomimetics

(a): Souchet, M.; Clark, R. D. *Synlett*. **1990**, 151. (b): Selnick, H. G.; Radzilowski, E. M.; Ponticello, G. S. *Tetrahedron Lett*. **1991**, 32, 721. (c): Aidhen, I. S.; Ahuja, J. R. *Tetrahedron Lett*. **1992**, 33, 5431 (d): Hinkley, S. F. R.; Perry, N. B.; Weavers, R.T. *Tetrahedron Lett*. **1994**, 35, 3775 (f): Parhi, A. K.; Franck, R. W. *Org. Lett*. **2004**, 6, 3063

4.1 Use in Heterocyclic Chemistry

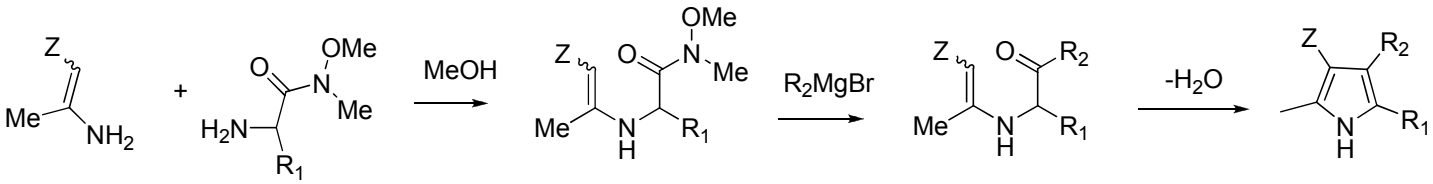
Pyrroles[a]



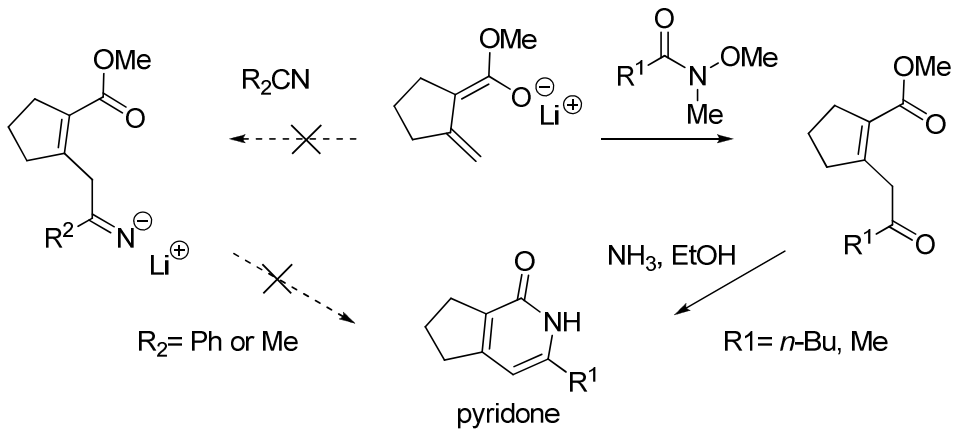


Knorr Approach

Z= CN, COOEt, COMe, COPh
R^1= R^2= H, alkyl



Pyridones[b]

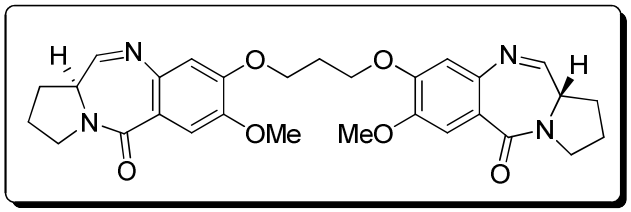


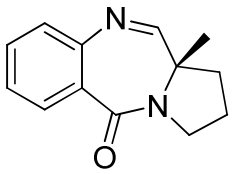
(a)Alberola, A.; Gonzalez-Ortega, A.; Sadaba, M. L.; sanudo, C. *Tetrahedron* **1999**, 55, 6555

(b) Chen, Y.; Li, T.; Sieburth, S; M. *J. Org. Chem*. **2001**, 66, 6826

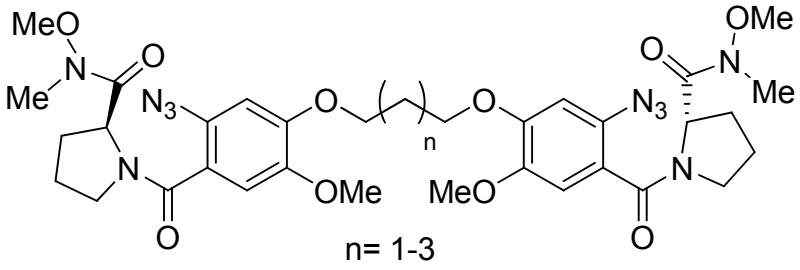
4.2 Use in Total synthesis

Synthesis of DSB-120



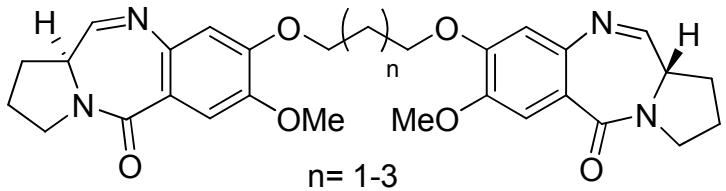


pyrrolo[2,1-c][1,4]benzodiazepine
PBD



n= 1-3

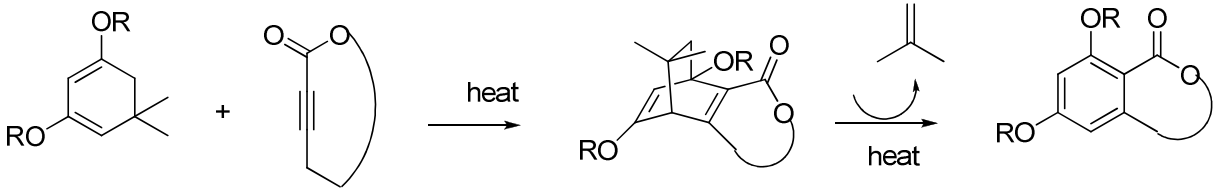
$LiALH_4$ or $LiBH_4$
in THF
50-68%

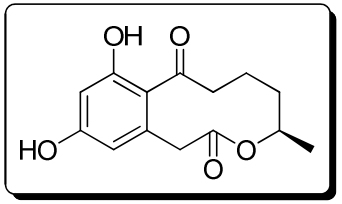


n= 1-3
when n= 1 DSB-120

Kamal, A.; Shankaraiah, N.; Markandaya, N.; Reddy, L. K.; Reddy, S. *Tetrahedron Lett*. **2008**, 49, 1465

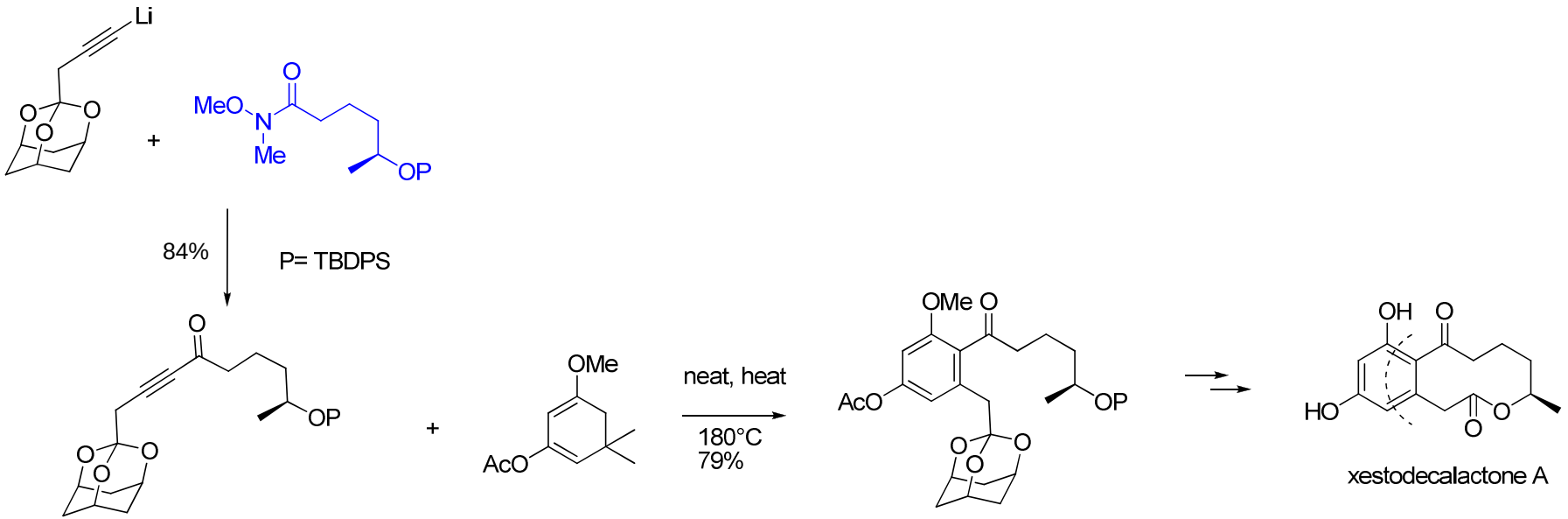
4.2 Use in Total synthesis





Resorcinylic scaffold

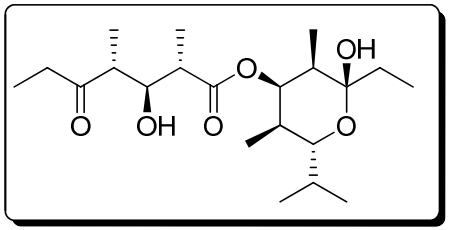
Synthesis of Xestodecalactone A

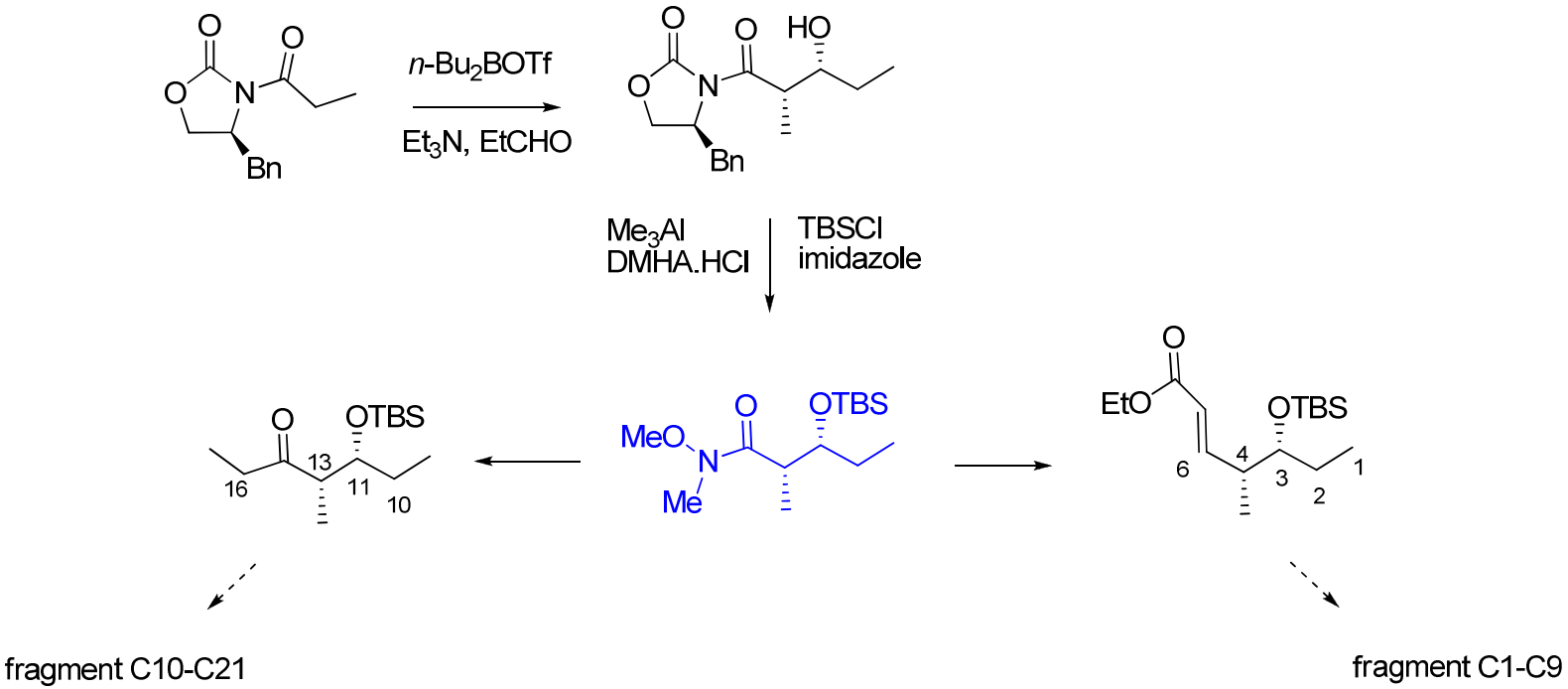


Yoshino, T.; Ng, F.; Danishefsky, S. J. *J. Am. Chem. Soc*. **2006**, 128, 14185

4.2 Use in Total synthesis

Synthesis of dolabriferol

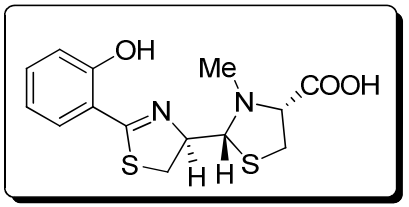


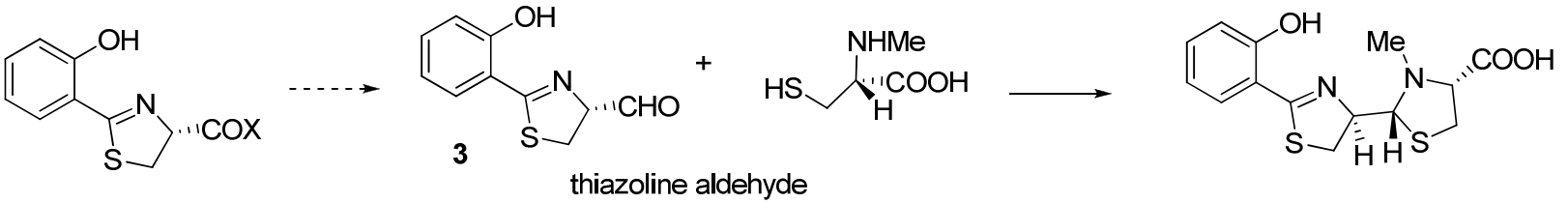


Dias, L. Z.; De Sousa, M. A. *Tetrahedron Lett*. **2003**, 44, 5625

4.2 Use in Total synthesis

Synthesis of pyochelin





thiazoline aldehyde

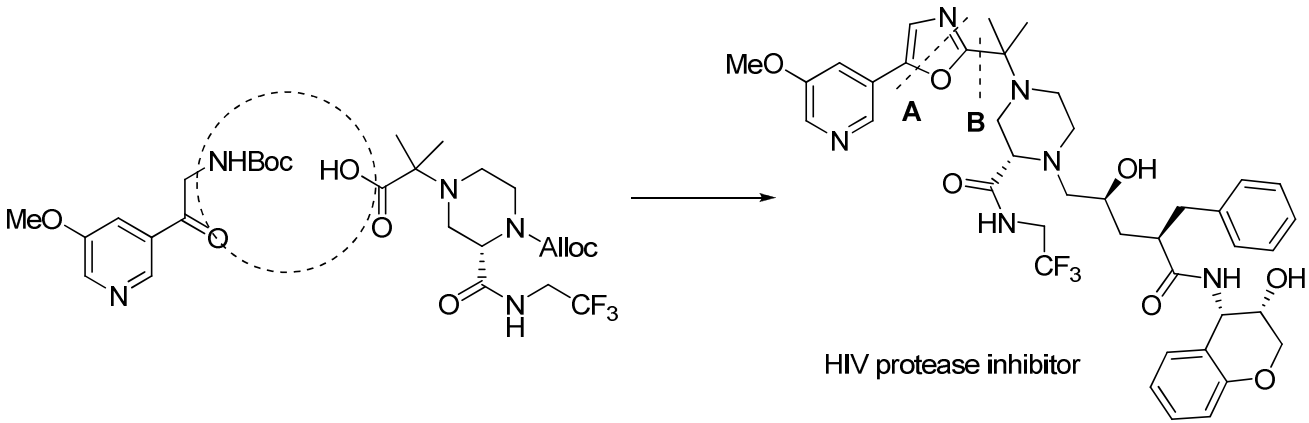
4a X= OH
4b X= OMe
4c X= N(OMe)Me

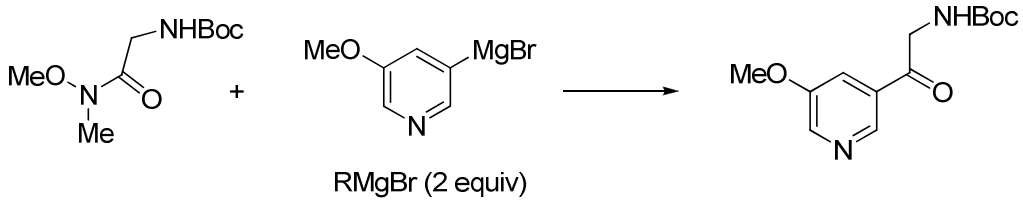
compound	conditions	results	
4a	thexylborane	**3** (15%)	
4b	-78°C, DIBAL(2eq) -50°C, DIBAL (3eq)	**3** (61%) + SM over-reduction	
4c	-20°C; LAH (3eq)	**3** (94%)	no epimerization no trace of starting material no over-reduced product

Zamri, A.; Abdallah, M. A. *Tetrahedron* **2000**, 56, 249

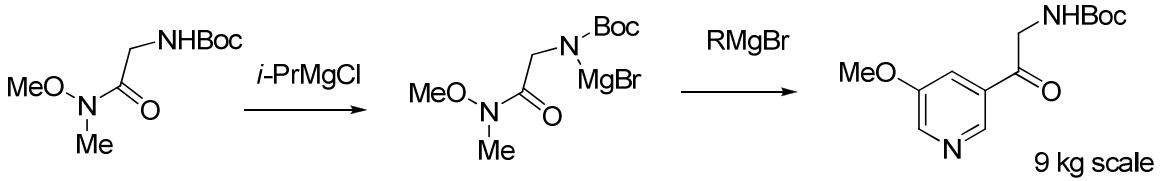
4.3 Use in Industry on Kilogram Scale

Merck





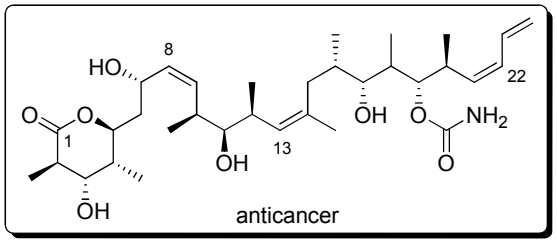
Too expensive

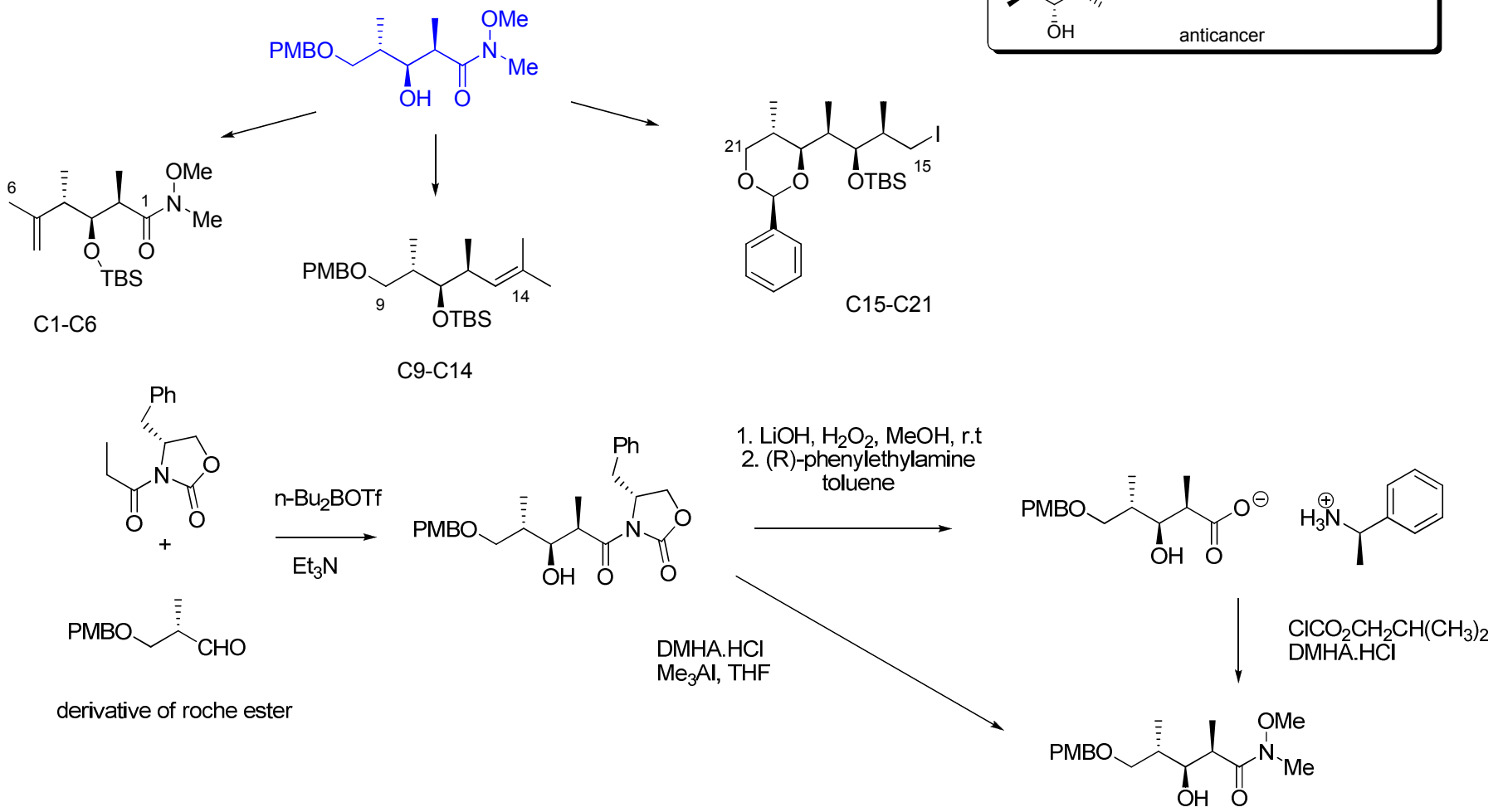


Liu, J.; Ikemoto, N.; Petrillo, D.; Armstrong, J. D. III *Tetrahedron Lett*. **2002**, 43, 8223

4.3 Use in Industry on Kilogram Scale

Synthesis of Discodermolide (Novartis)

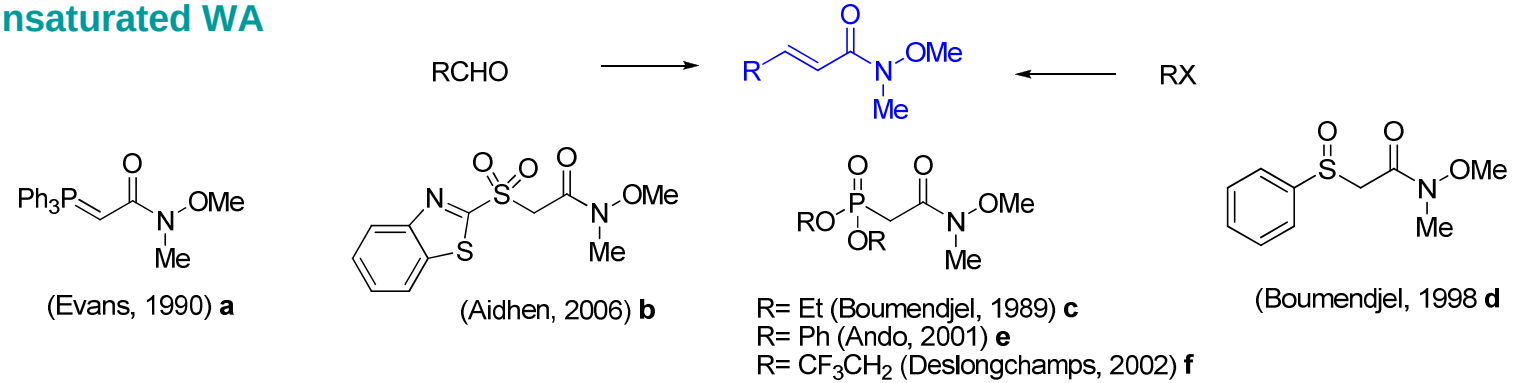




Mickel et al. *Org process Res. Dev*. **2004**, 8, 92

4.4 Synthetic Equivalents and Building Blocks

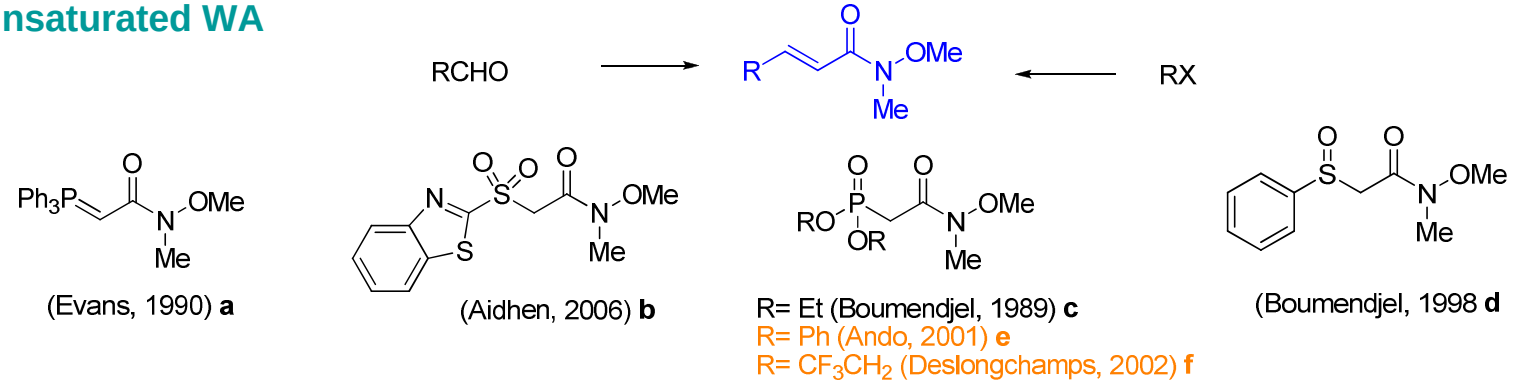
α,β Unsaturated WA



(a) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, 112, 7001. (b) Manjunath, B. N.; Sane, N. P.; Aidhen, I. S. *Eur. J. Org. Chem* **2006**, 2851. (c) Nuzillard, J-M.; Boumendjel, A.; Massiot, G. *Tetrahedron Lett*. **1989** 30, 3779. (d) Beney, C.; Boumendjel, A.; Mariotte, A-M. *Tetrahedron Lett*. **1998**, 39, 5779. (e) Ando, K. *Synlett* **2001**, 1272. (f) Fortin, S.; Dupont, F.; Deslongchamps, P. *J. Org. Chem*. **2002**, 67, 5437

4.4 Synthetic Equivalents and Building Blocks

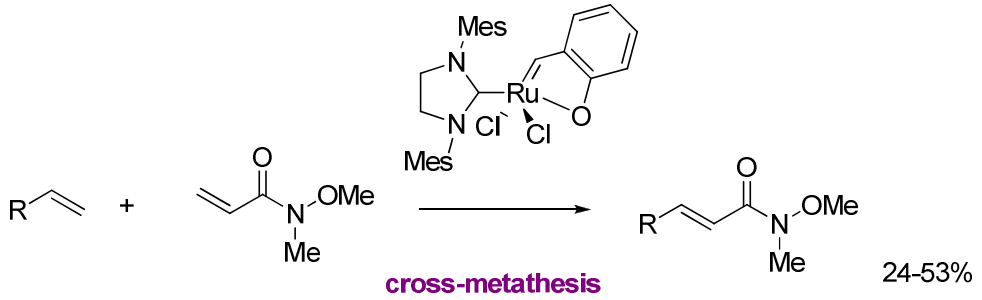
α,β Unsaturated WA



(a) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, 112, 7001. (b) Manjunath, B. N.; Sane, N. P.; Aidhen, I. S. *Eur. J. Org. Chem* **2006**, 2851. (c) Nuzillard, J-M.; Boumendjel, A.; Massiot, G. *Tetrahedron Lett*. **1989** 30, 3779. (d) Beney, C.; Boumendjel, A.; Mariotte, A-M. *Tetrahedron Lett*. **1998**, 39, 5779. (e) Ando, K. *Synlett* **2001**, 1272. (f) Fortin, S.; Dupont, F.; Deslongchamps, P. *J. Org. Chem*. **2002**, 67, 5437

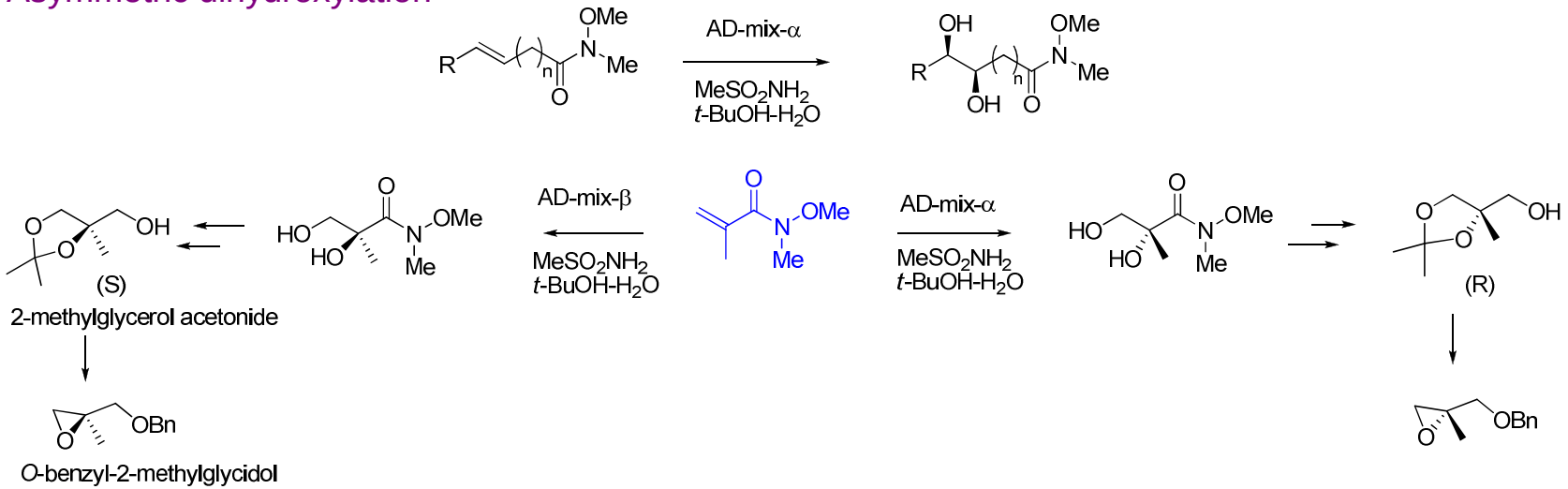
4.4 Synthetic Equivalents and Building Blocks

α,β Unsaturated WA



Application of α,β Unsaturated WA

Asymmetric dihydroxylation

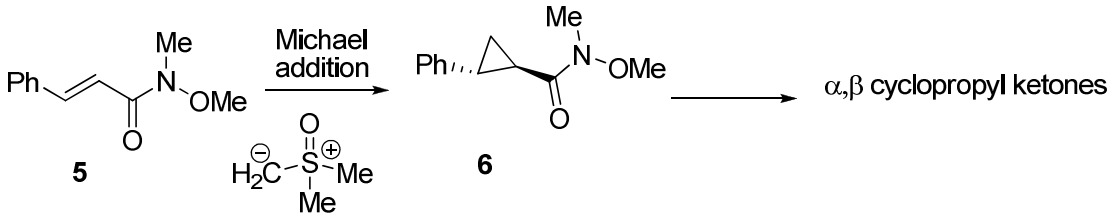


Vedrenne, E.; Dupont, H.; Oualef, S.; Elkaim, L.; Grimaud, L. *Synlett* **2005**, 670

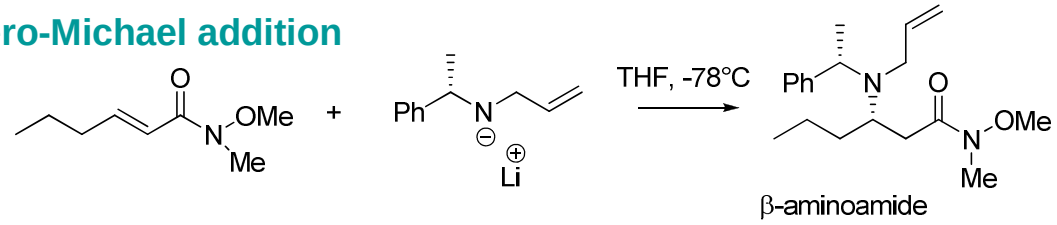
Avenoza, A.; Cativiela, C.. Peregrina, J. M. Sucunza, D.; Zurbano, M. M. *Tetrahedron: asymmetry* **2001**, 12, 1383

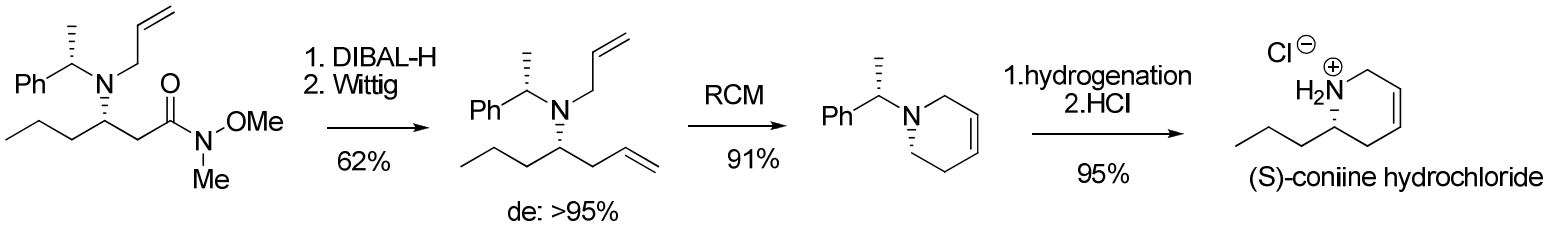
4.4 Synthetic Equivalents and Building Blocks

Cyclopropanation



Hetero-Michael addition



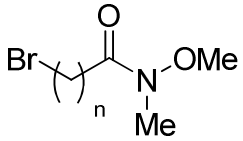


Rodriques, K. E.; *Tetrahedron Lett*. **1991**, 32, 1275

Davies, S. G.; Iwamoto, K.; Smethurst, C. A. P.; Smith, A.D.; Rodriguez-Solla, H. *Synlett* **2002**, 1146

4.4 Synthetic Equivalents and Building Blocks

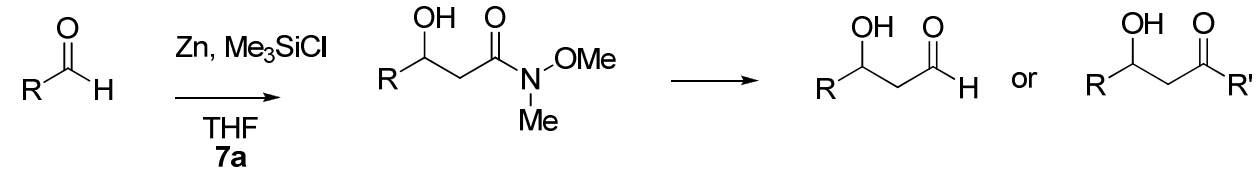
Bromoalkanoic acid derived WAs



7

a: n = 1, **b**: n = 2
c: n = 4, **d**: n = 5

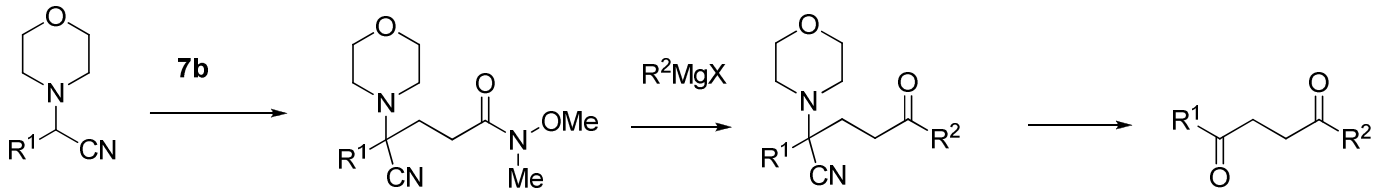
Use of 7 as nucleophilic synthon: **Reformatsky reaction**



R= phenyl

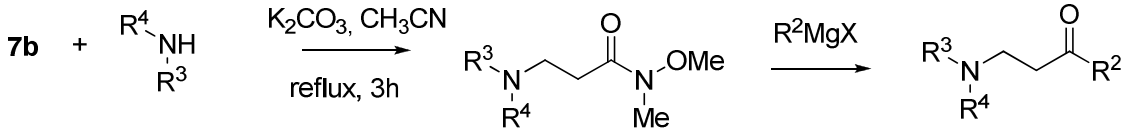
β-hydroxy WA:
Masked aldol products

Use of 7 as electrophilic synthon: synthesis of unsymmetrical 1,4-diketones and β-(N,N-disubstituted)amino ketones



R^1= aryl or heteroaryl

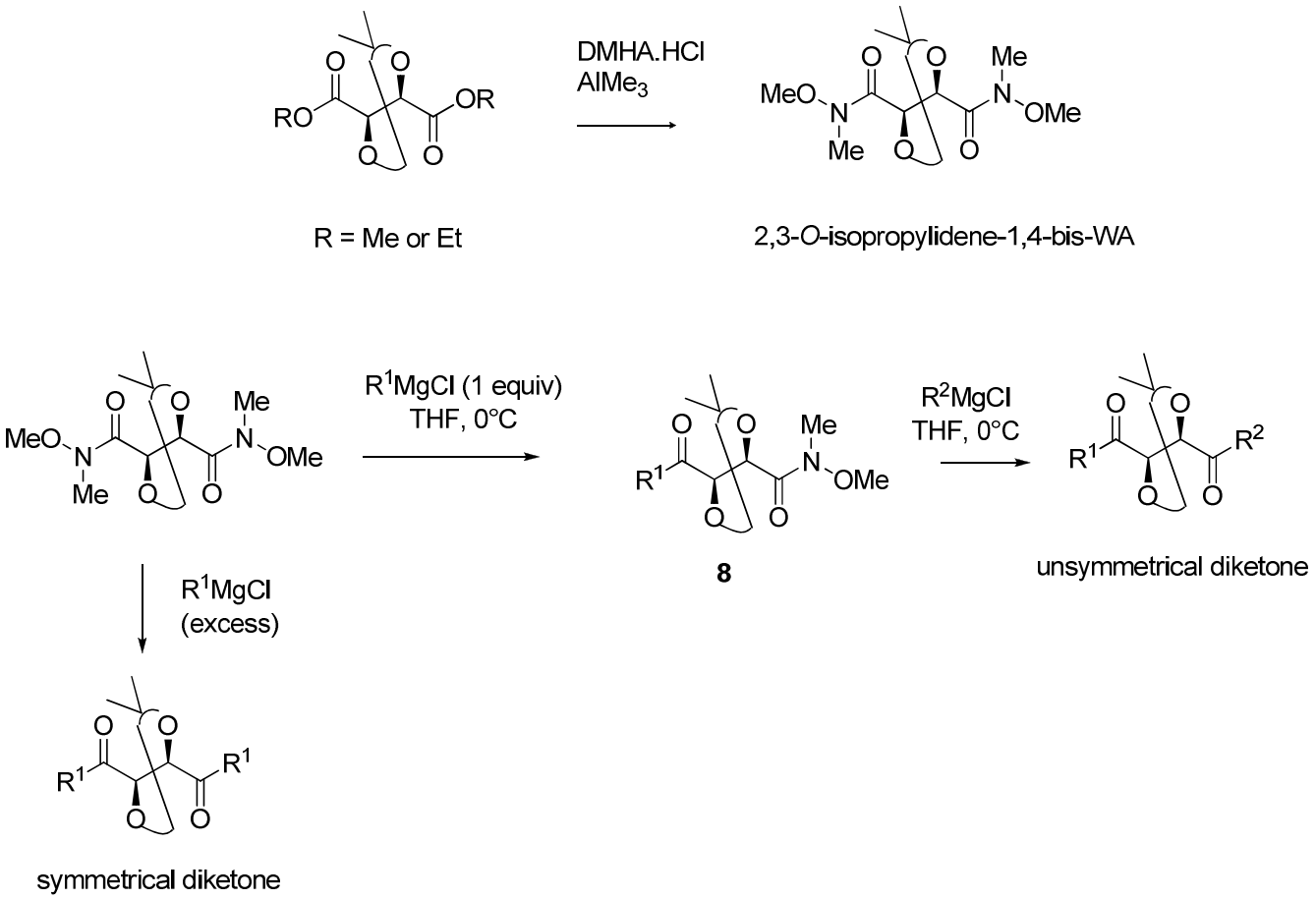
R^2= aryl or alkyl



Selvamurugan, V.; Aidhen, I. S. *Tetrahedron*, **2001**, 57, 6065
Selvamurugan, V.; Aidhen, I. S. *Synthesis*, **2001**, 2239

4.4 Synthetic Equivalents and Building Blocks

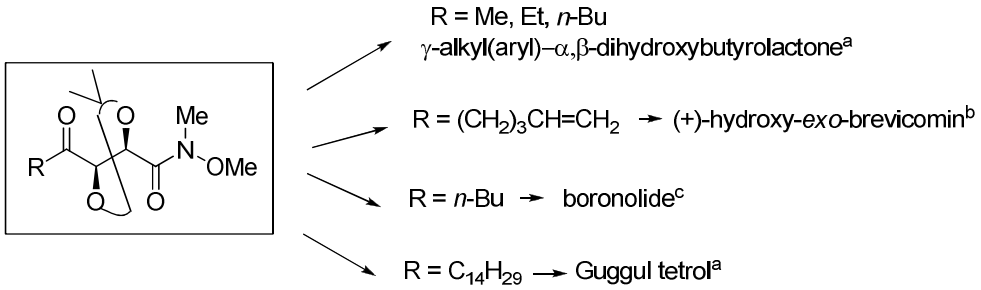
Tartaric acid WA



Nugiel, D. A et al. *J. Med. Chem*. **1996**, 39, 2156
McNulty, J.; Grunner, V.; Mao, J. *Tetrahedron Lett*. **2001**, 42, 5609

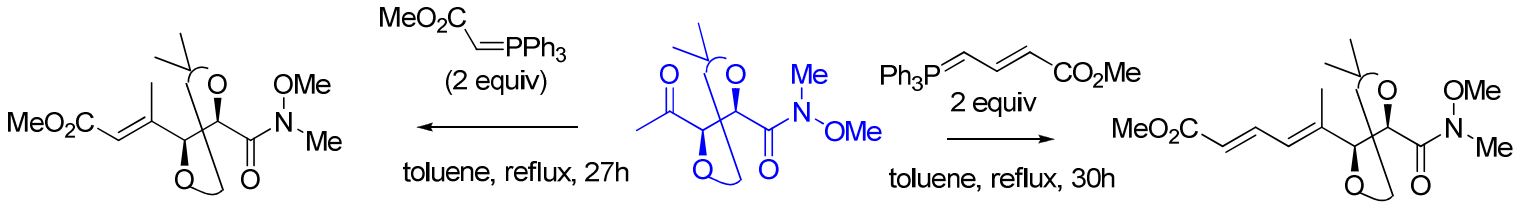
4.4 Synthetic Equivalents and Building Blocks

Use of ketoamide **8** in the synthesis of various natural products



Wittig olefination[d]

Use of ketoamide **9** for the synthesis of butenolide moiety of peridinin

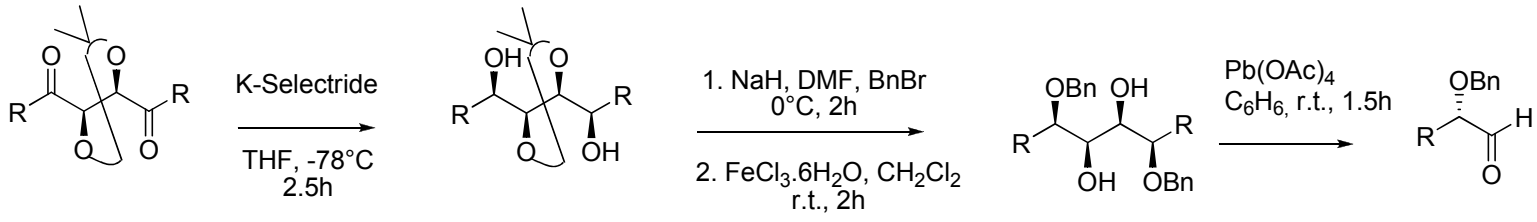


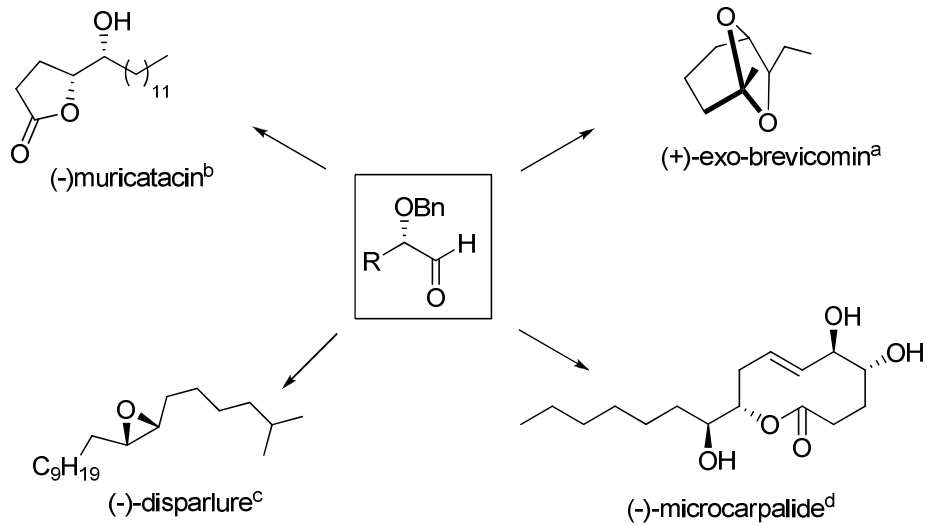
9

(a): Prasad, K. R.; Chandrakumar, A. *Tetrahedron* **2007**, 63, 1798. (b): Prasad, K. R.; Anbarasan, P. *Tetrahedron Lett*. **2006**, 47, 1433. (c): Prasad, K. R.; Anbarasan, P. *Tetrahedron asymmetry* **2006**, 17,1146. (d): Olpp, T.; Bruckner, R. *Angew. Chem. Int. Ed*. **2005**, 44, 1533

4.4 Synthetic Equivalents and Building Blocks

C2-symmetric 1,4-diketones for enantioselective synthesis of α-O-benzylated aldehydes

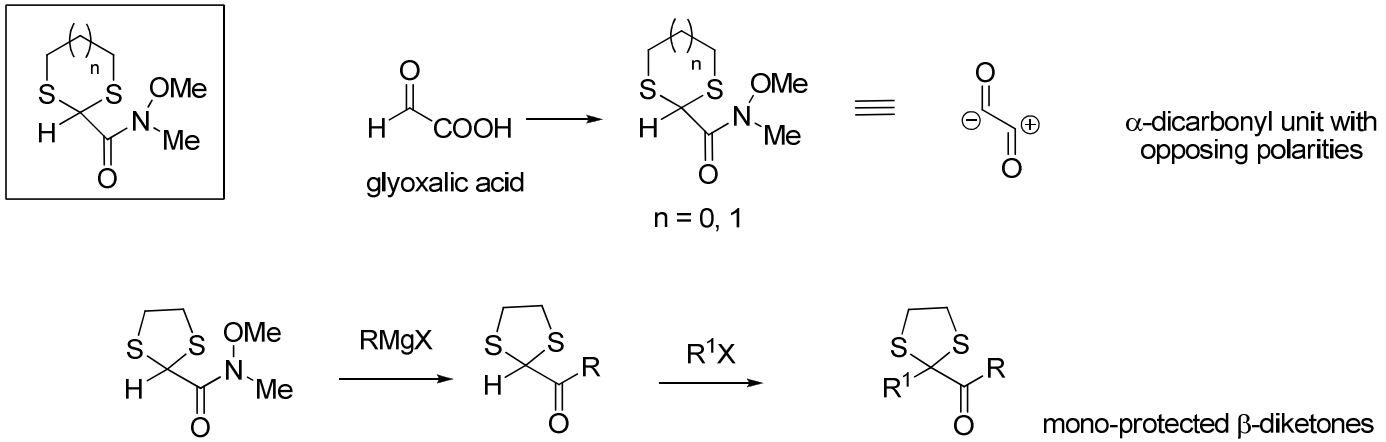




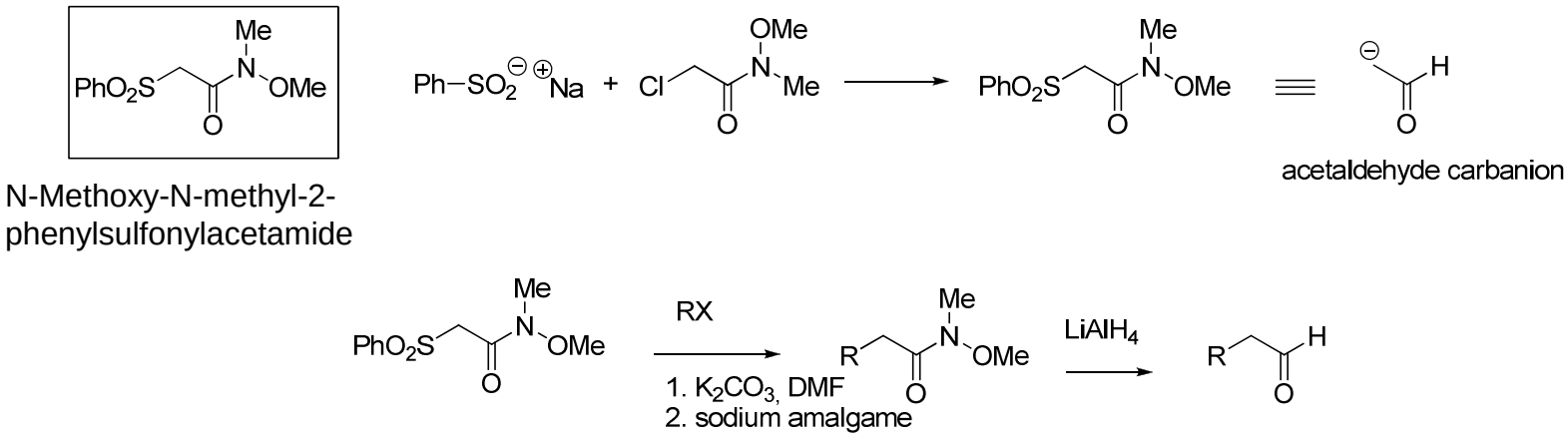
(a) Prasad, K. R.; Anbarasan, P. *Tetrahedron asymmetry* **2005,** 16, 3951. (b): Prasad, K. R.; Anbarasan, P. *Tetrahedron asymmetry* **2006,** 17, 2465. (c): Prasad, K. R.; Anbarasan, P. *J. Org. Chem*. **2007**, 72, 3155. (d): Prasad, K. R.; Penchalaiah, K.; Choudhary, A.; Anbarasan, P. *Tetrahedron Lett.* **2007**, 48, 3155

4.4 Synthetic Equivalents and Building Blocks

Synthesis of mono-protected β-diketones[a]



two-carbon homologation of alkyl halides[b]



(a) Sivaraman, B.; Aidhen, I. S. Synlett, 2007, 959
(b) Satyamurthi, N.; Singh, J.; Aidhen, I. S. *Synthesis* **2000**, 375

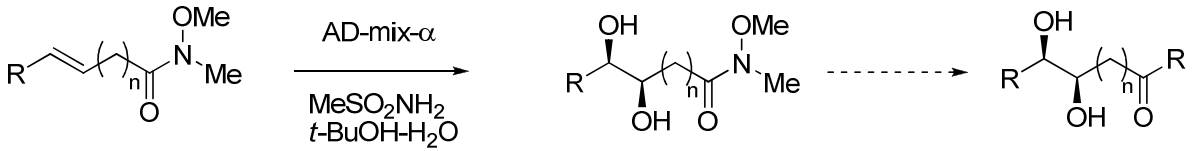
5. Conclusion

- Good stability

- Easy preparation with excellent to good yields

- Effective acylating agent

- Synthetic equivalents of ketones or aldehydes which have more reactivity in specific reactions



⇨ Growing interest in WA