Total Synthesis of Bryostatins

Group Meeting Presentation

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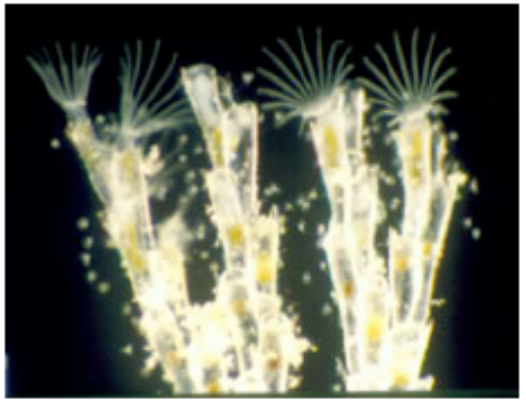
The Wulff Group

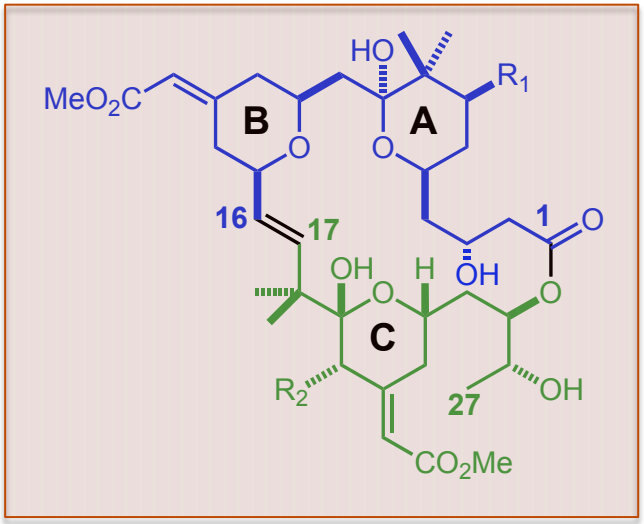
February 20, 2009

Isolation

- In 1968, new macrolides were isolated from the marine bryozoan invertebrates *Bugula neritina Linnaeus* and *Amathia convulata* nearby Jack Rudloe of the Gulf Specimen Company off the west coast of Florida.



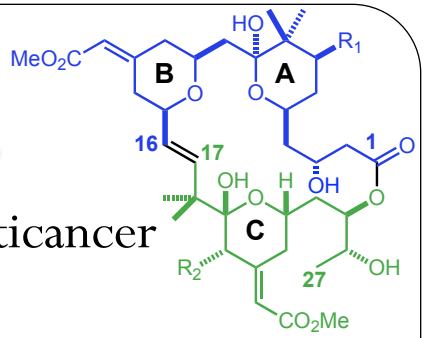
- Bryostatins consist of at least 20 members, which vary at R_1 and R_2.



- Characterised by Pettit *etal* in 1982.

Pettit, G. R. ; Herald, C. L. ; Clardy, J. ; Arnold, E. ;. Doubek, D. L; Herald, D. L. *J. Am. Chem. Soc.*, **1982,** *104*, 6848

Biological Activity



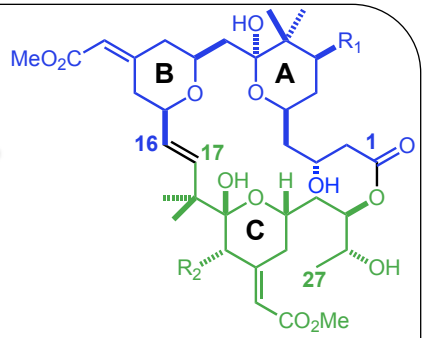
- They exhibit exceptional biological activity, most notable their anticancer activity *in vivo*.

- Bryostatin significantly affects both cognition and memory enhancement in animals, Hence, treatment of Alzheimer's disease, depression and other cognitive impairments.

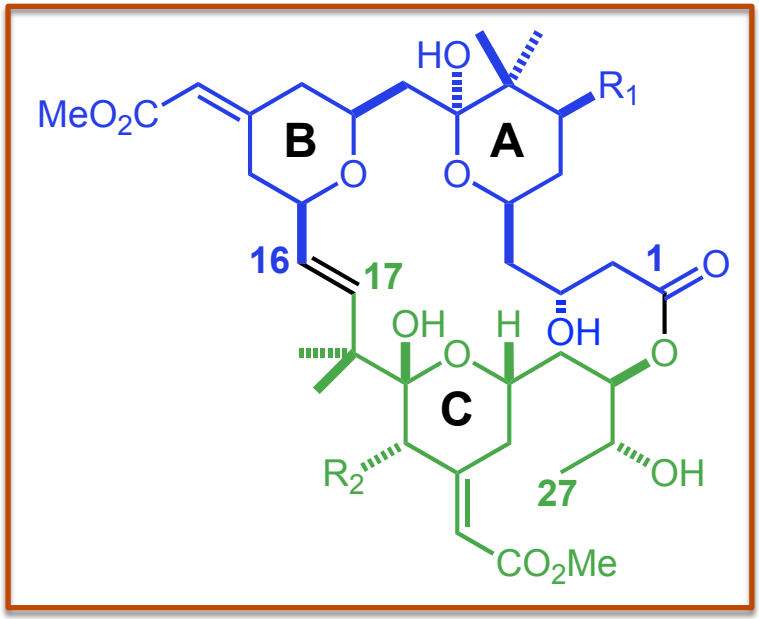
- Their clinical advancement is hampered by the limited availability of bryostatins from isolation, due to low yield (10^{-3} % to 10^{-8} %).

- Currently in phase I and phase II clinical trials for for melanoma, myeloma, chronic lymphocytic leukemia (CLL), AIDS related lymphoma, non-Hodgkin's lymphoma, colorectal, renal, prostate, head and neck, cervix, ovarian, breast, peritoneal, stomach, esophagus, anus, prostate, and nonsmall cell lung cancer.

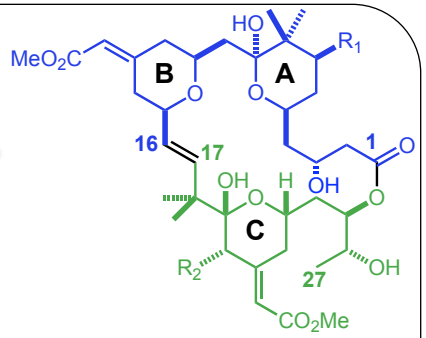
Architectural features



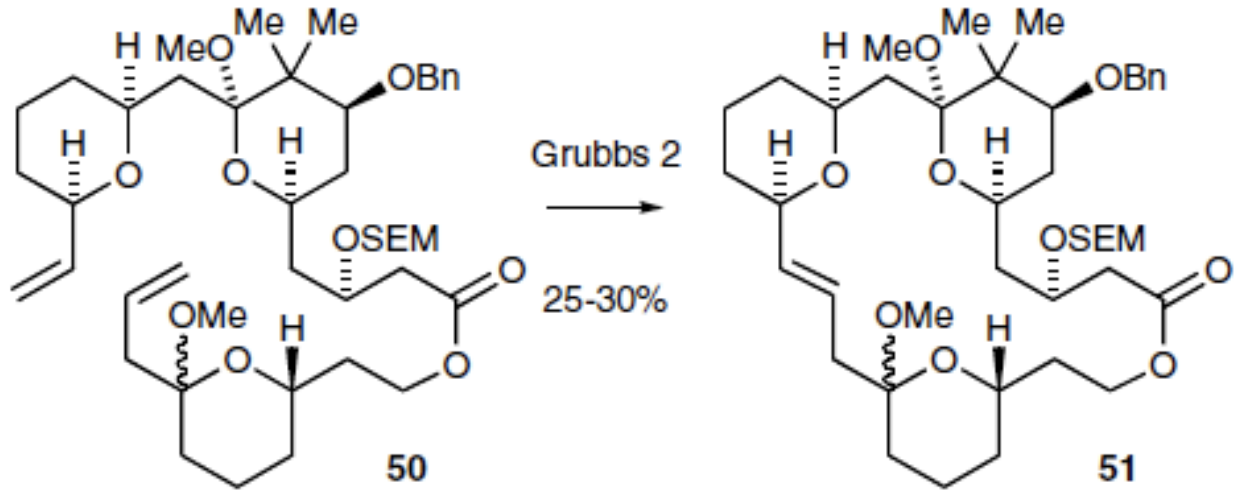
- Two Main Hemispheres:
  - Northern Hemisphere (C1-16)
  - Southern Hemisphere (C17-C22)
- Three heavily substituted tetrahydropyran rings (A, B, C) rings
- Two acid/base-sensitive *exo*-cyclic unsaturated esters
- One congested C16–C17 *trans*-alkene
- Numerous oxygen-containing functionalities on a 26-membered lactone

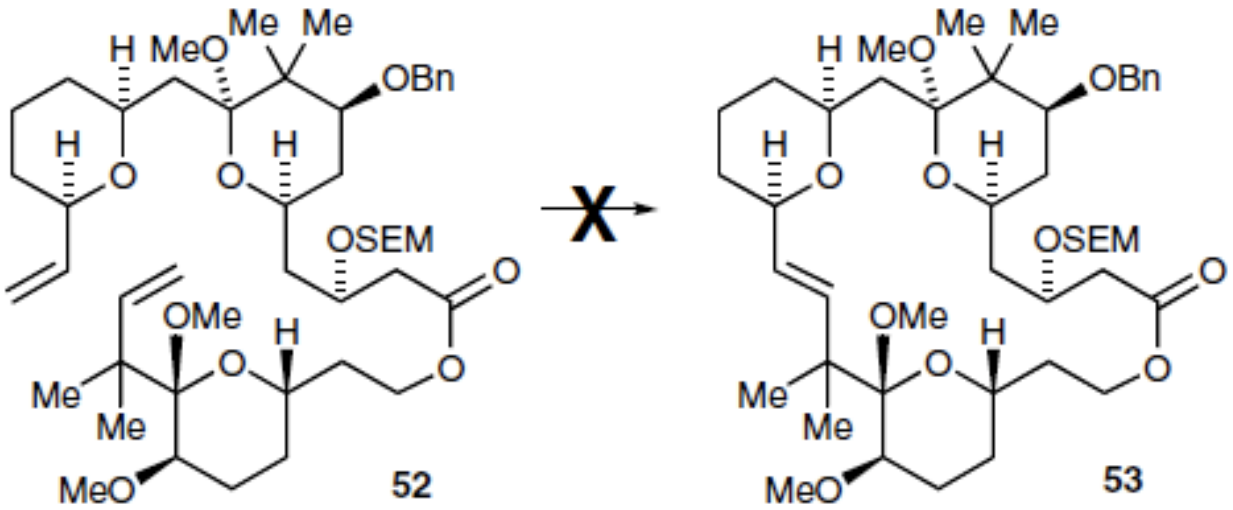


Architectural features



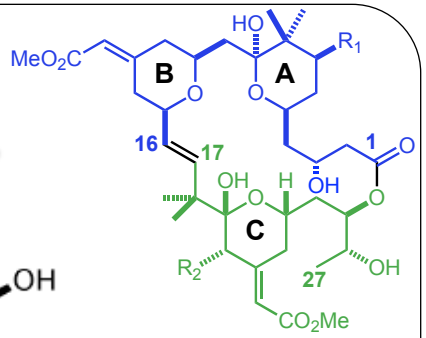
- One congested C16–C17 *trans*-alkene



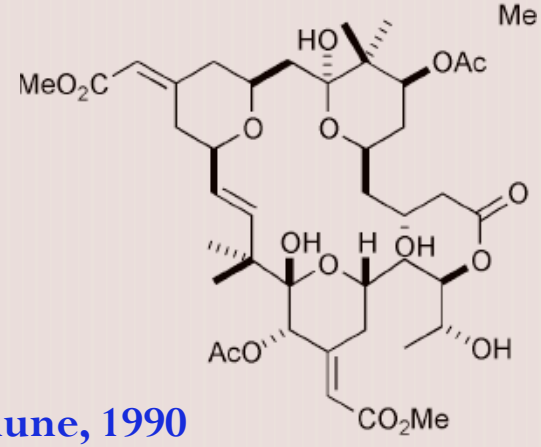


Ball, M. et al. *Tet. Lett.* **2006**, *47*, 2223

Approaches towards Bryostatins



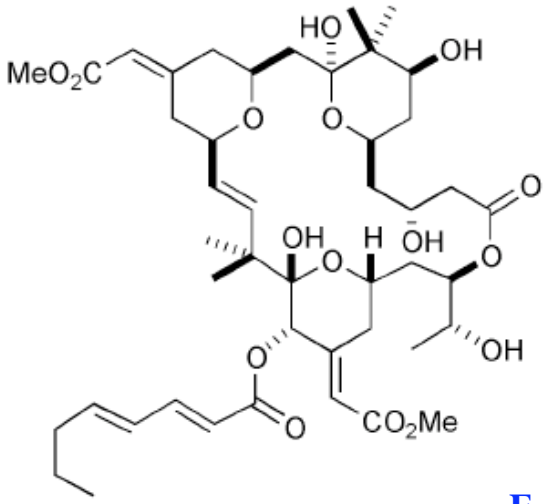
Completed Total Synthesis so far :



Masamune, 1990

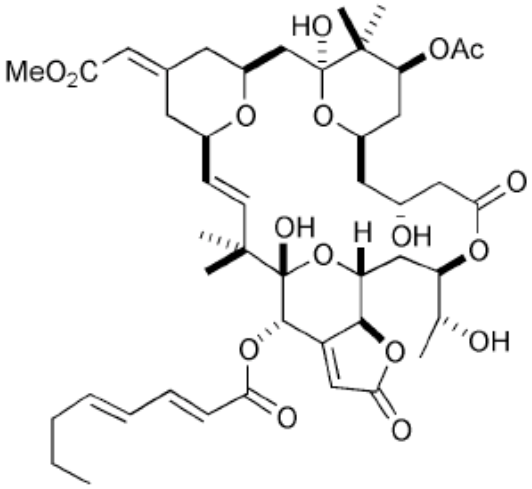
Hale, 2006 (Formal)

Bryostatin 7



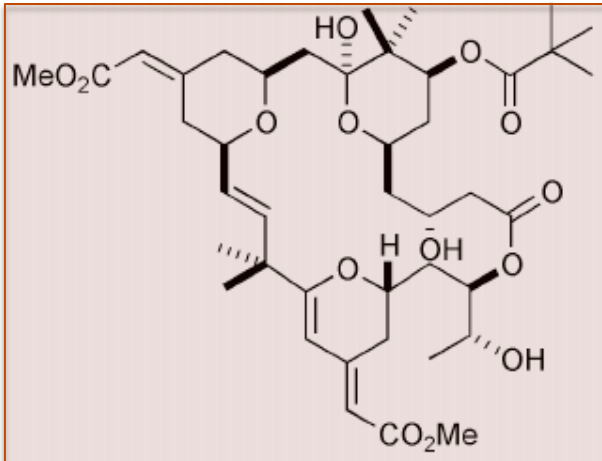
Bryostatin 2

Evans, 1999



Bryostatin 3

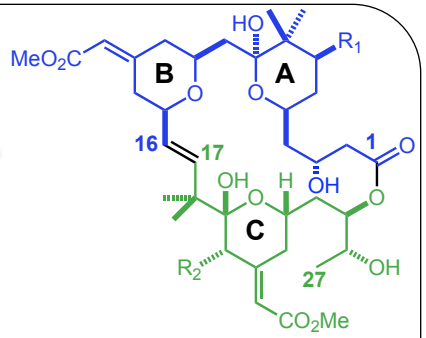
Yamamura, 2000



Bryostatin 16

Trost, 2008

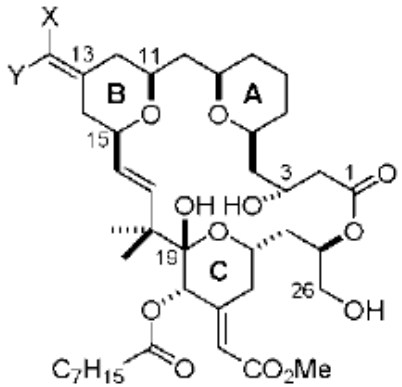
Previous Approaches to Bryostatins



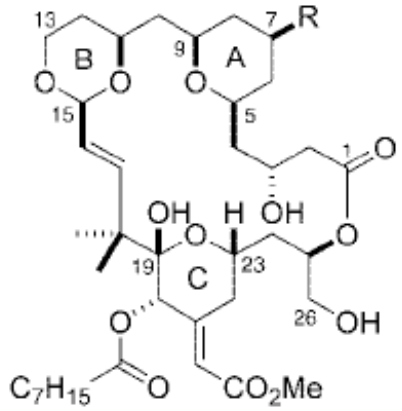
Other Groups Involved:

- E. J. Thomas, Bryostatin 11, C1-C16,C17-C27 **(1989, 1998, 2000, 2004, 2006, 2008)**
- M. Vandewalle, Bryostatin 11,C1-C9, B,C ring **(1991,1994,1997)**
- R. W. Hoffmann, C1-C9 **(1995)**
- M. Kalesse, C1-C9 **(1996)**
- R. Roy, Bryostatin 1, C1-C9, C21-C27 **(1989, 1990)**
- H. M. R. Hoffmann, C1-C16, C1-C9, B ring **(1996,1997,2001)**
- K. D. Janda, Bryostatin 1, C21-C27 **(2000)**
- J. S. Yadav, , Bryostatin 1, C1-C16 **(2001)**
- S. D. Burke, Bryostatin 1, C1-C16, C17-C27 **(2004)**
- G. E. Keck, Bryostatin 1, C1-C16 **(2006)**

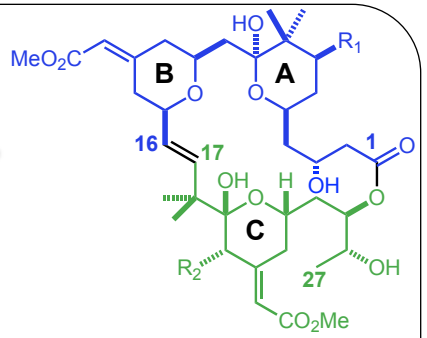
Approaches Towards Bryologs



1 X = Y = H K_i = 1.6 nM
2 X = CO_2Me, Y = H K_i = 2.5 nM
3 X = H , Y = CO_2Me K_i = 0.9 nM

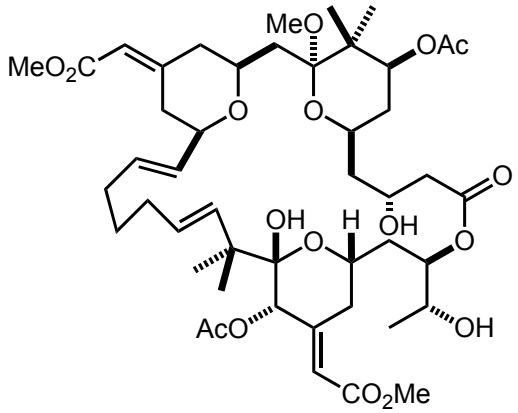


Analog **1**: R = H K_i = 0.25 nM
C7 oxygenated analogs: R = OR'



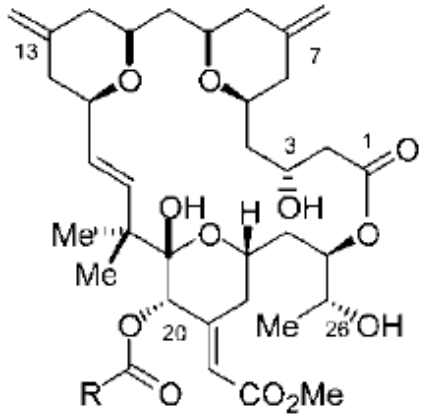
P. A. Wender

(2008)



B. M. Trost

(2007)



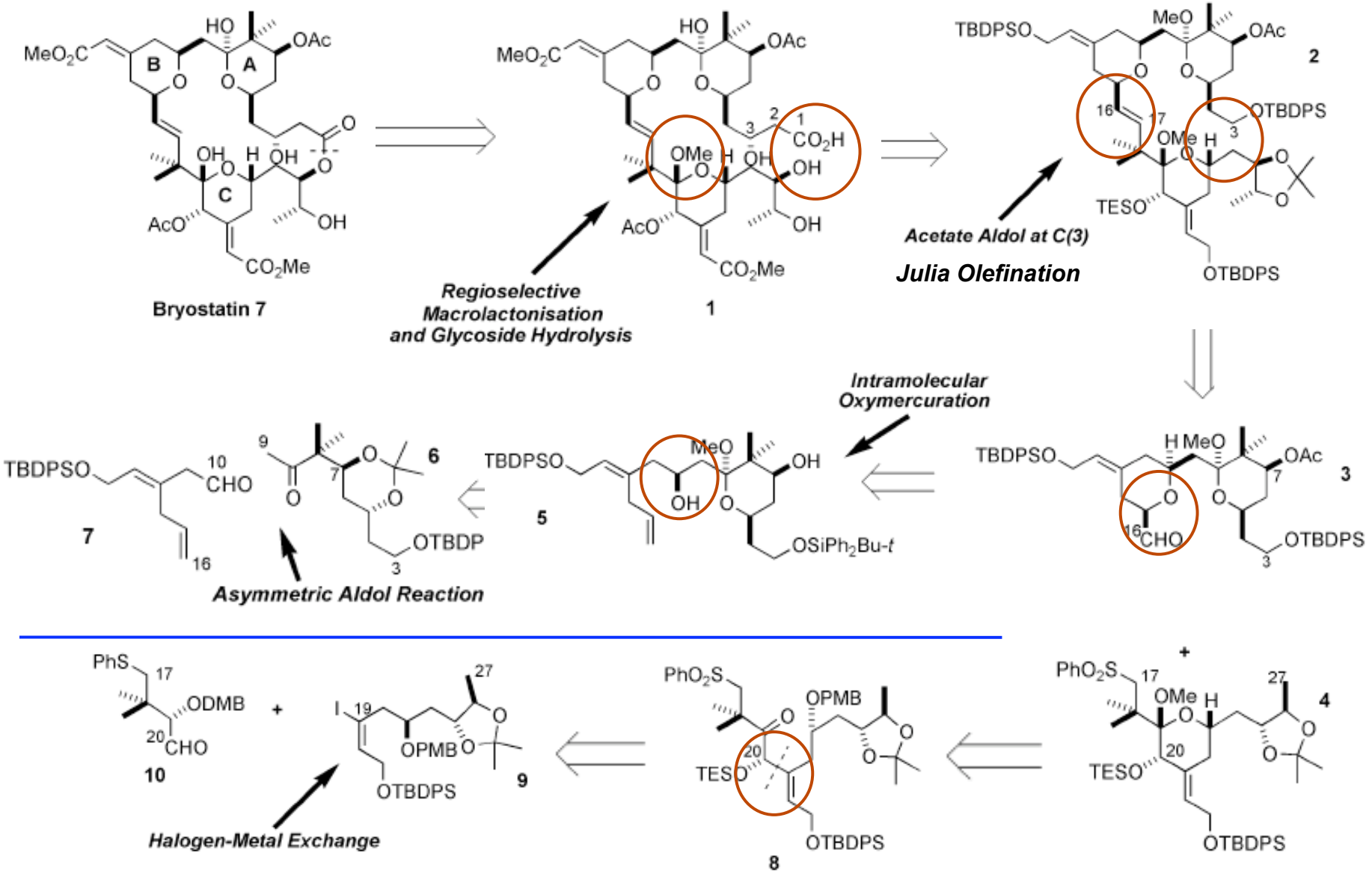
R = Ph Ki = 0.70 ± 0.01nM
R = C_7H_{15} Ki = 1.05 ± 0.04nM
R =  **Ki = 0.70 ± 0.06nM**

G. E. Keck **(2008)**

Bryostatin 1: R = Ac K_i = 1.4 nM
Bryostatin 2: R = H K_i = 5.9 nM

Trost, B. M.;Yang, H.,;Thiel, O. R.; Frontier, A. J.; Brindle, C. S. *J. Am. Chem. Soc.* **2007**,*129*, 2206
Wender, P. A.;DeChristopher, B. A.; Schrier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 6658
Wender, P. A. & Verma, V. A. *Org. Lett.* **2008**, *10*, 3331
Keck, G. E. ; Kraft, M. B.; Truong, A. P.; Li, W.; Sanchez, C. C.; Kedei, N.; Lewin, N. E.; Blumberg, Peter M. *J. Am. Chem. Soc.* **2008**, *130*, 6660

Masamune's Approach to Bryostatin 7



Kageyama, M.; Tamura, T.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S. *J. Am. Chem. Soc.* **1990,** *112*, 7407

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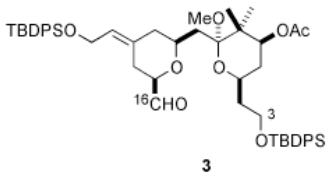

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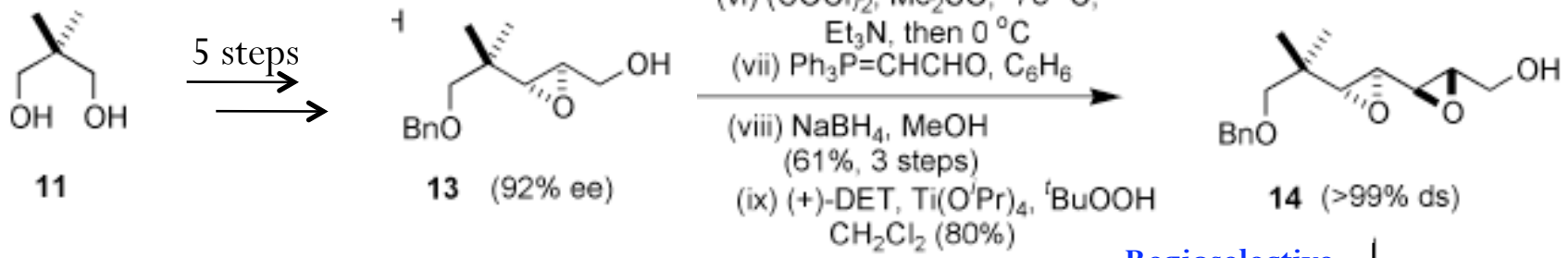
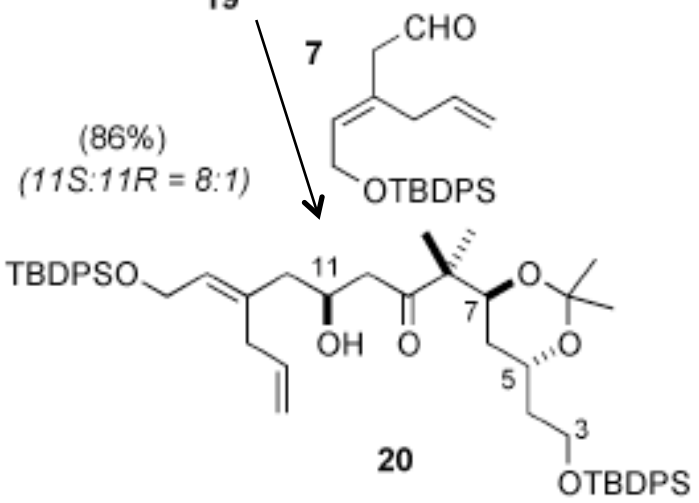
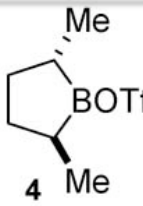
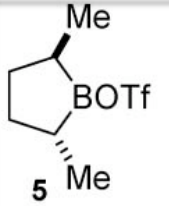




Borane	Et_2BOTf		
		4	5
Diastereoselectivity 1,5-*anti*:1,5-*syn*	66:33	33:66	86:14 (86%)

Kageyama, M.; Tamura, T.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S. *J. Am. Chem. Soc.* **1990,** *112*, 7407

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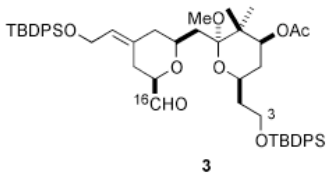

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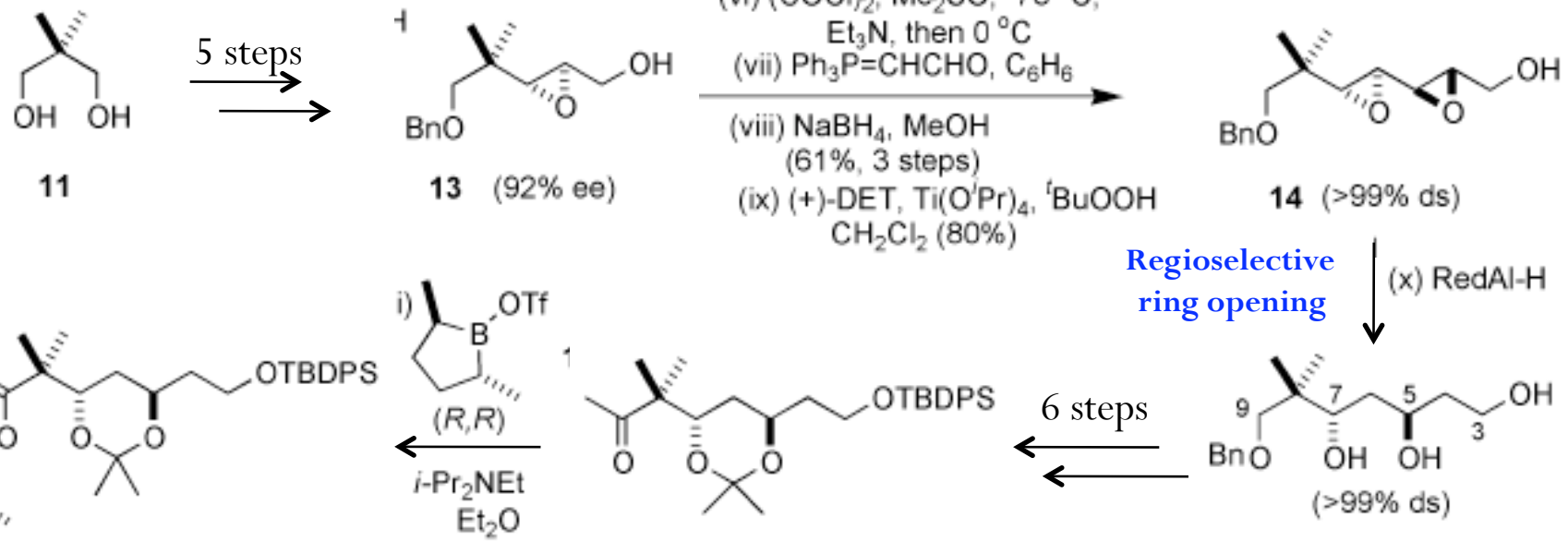
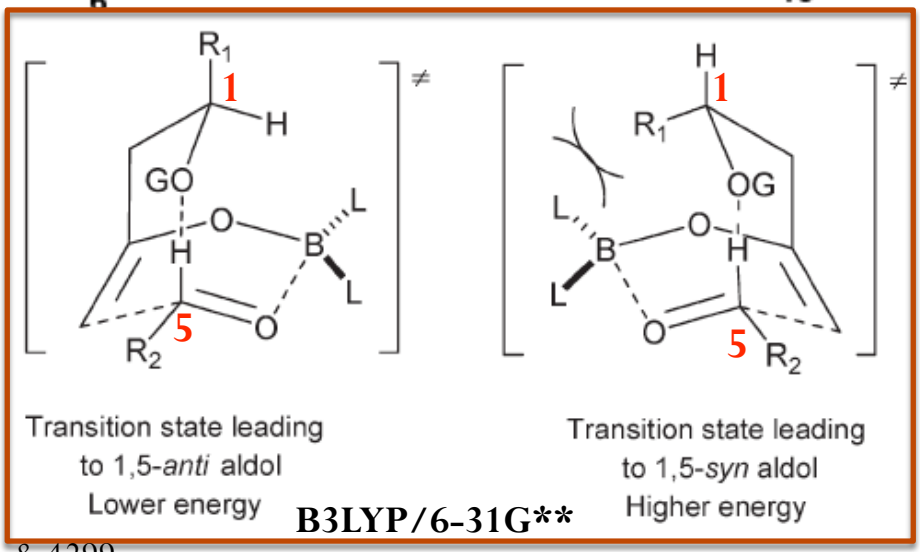


Substrate Controlled Aldol Reaction

Matched Case



Transition state leading to 1,5-*anti* aldol
Lower energy

Transition state leading to 1,5-*syn* aldol
Higher energy

B3LYP/6-31G**

Paton, R. S. ; Goodman, J. M. *Org. Lett.*, **2006**, *8*, 4299

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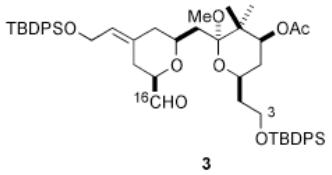

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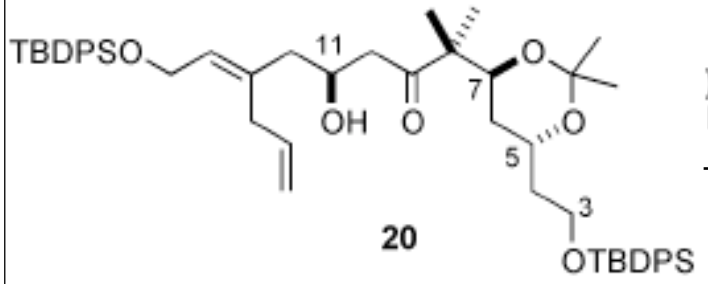
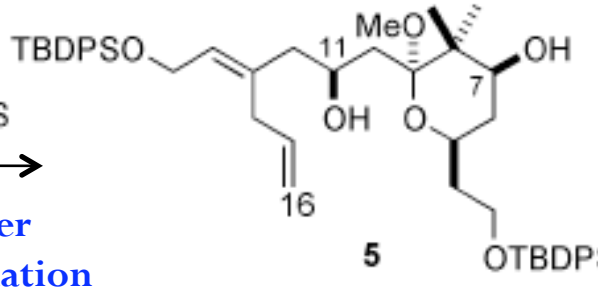


20

) $(MeO)_3CH$, MeOH, PPTS (84%)

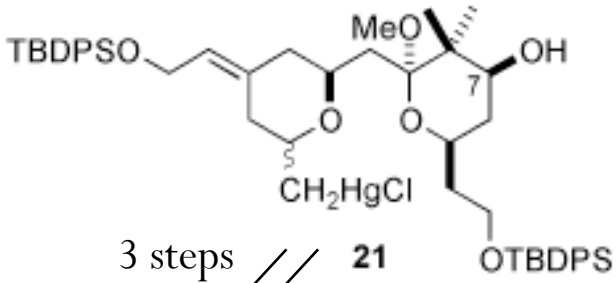
Fischer Glycosidation



5

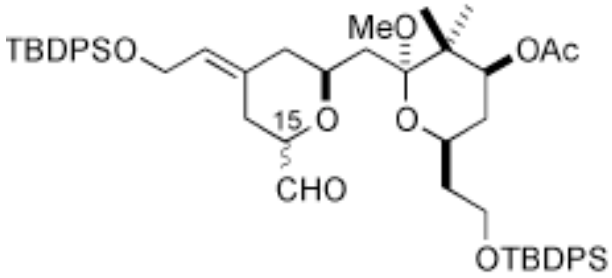
Intramolecular alkoxy mercuration

$Hg(OAc)_2$, THF, MeOH, then KCl



21

3 steps

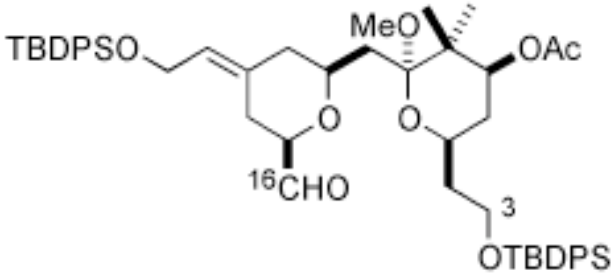


24

1:1

Al_2O_3 (3% H_2O), CH_2Cl_2

(60%, 2 steps)



9:1

3

Kageyama, M.; Tamura, T.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S. *J. Am. Chem. Soc.* **1990,** *112*, 7407

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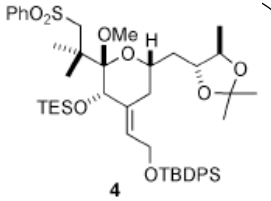

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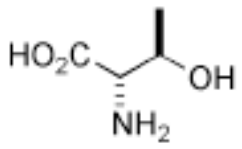
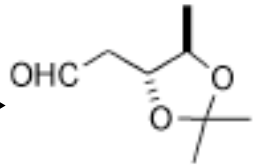


29

7 steps

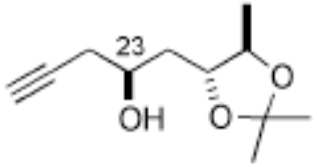


34

Allenyl-ZnBr
(53%)

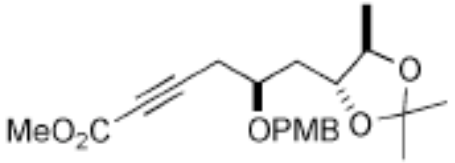
8:1

Chelation –Controlled
Nucleophilic addition



35

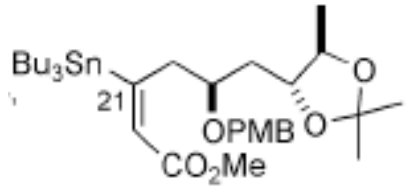
2 steps



37

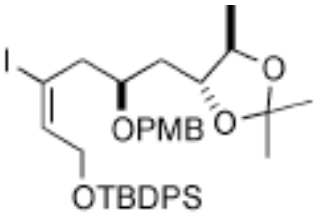
n-Bu$_3$SnCu·LiBr·Me$_2$S (64%, 3 steps)

Piers
stannylcupration



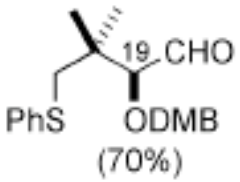
38

3 steps



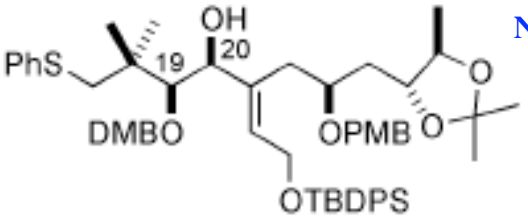
9

Chelation –Controlled
Nucleophilic addition
n-BuLi, then



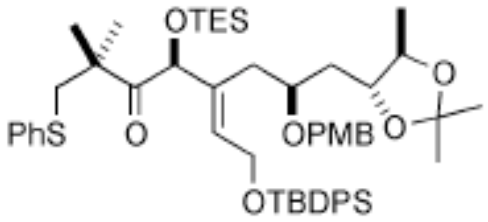
10

(70%)



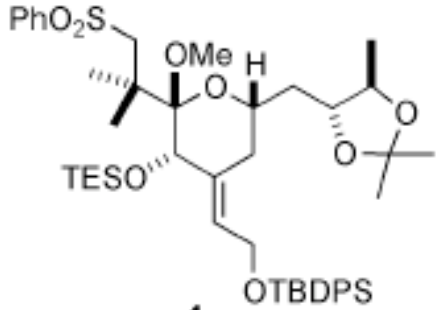
40

TESOTf, 2,6-Lutidine
DDQ (1 eq)
Me_2SO, Ac_2O, Et_3N
(70%, 3 steps)



41

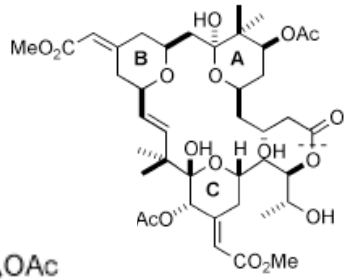
(xix) MoO_5·HMPA·H_2O
(xx) DDQ, SiO_2
(xxi) TMSOTf, TMSOMe
or BF_3·OEt_2, MeOH
(40%, 3 steps)

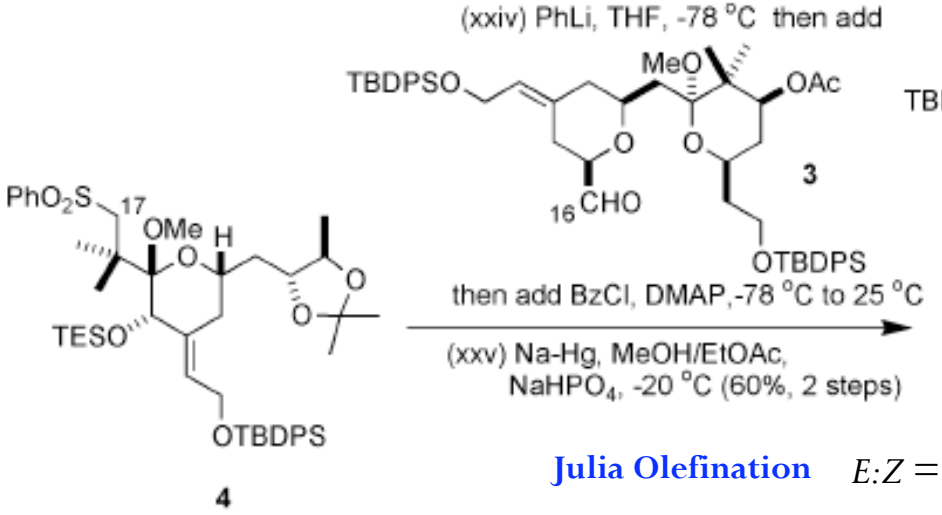


4

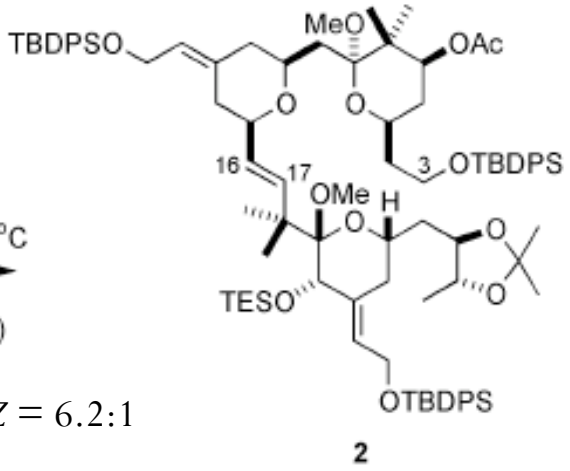
Kageyama, M.; Tamura, T.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S. *J. Am. Chem. Soc.* **1990,** *112*, 7407

Masamune's Approach to Bryostatin 7

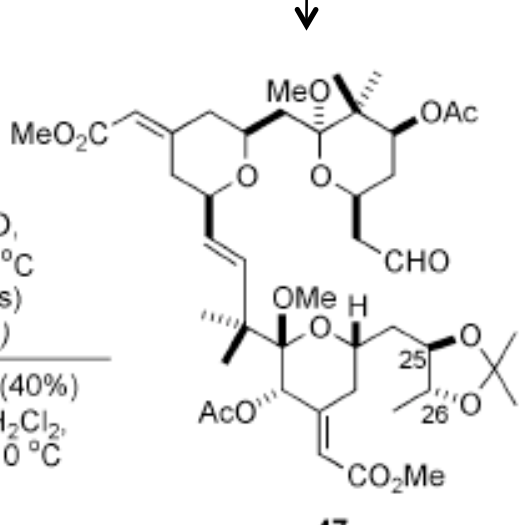


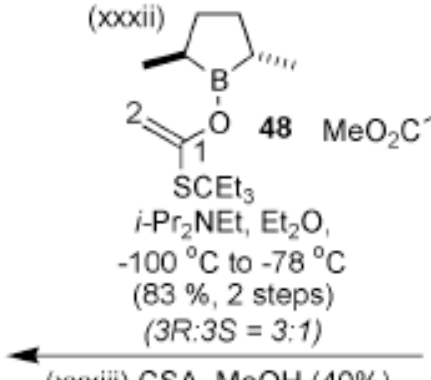


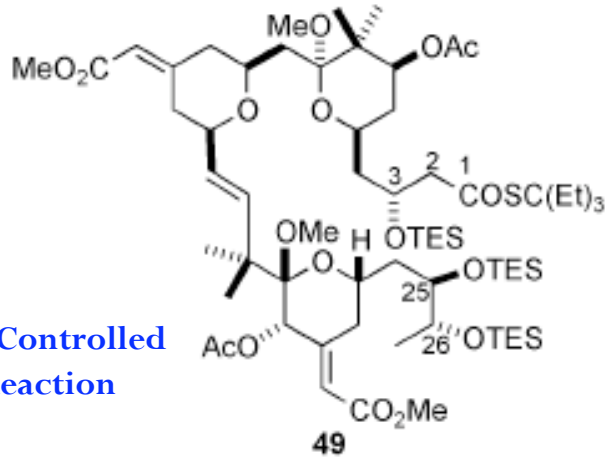
Julia Olefination $E:Z = 6.2:1$



6 steps



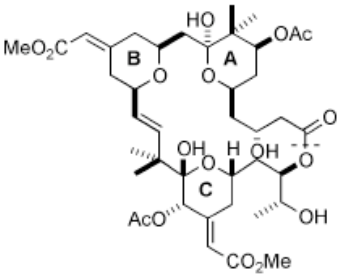


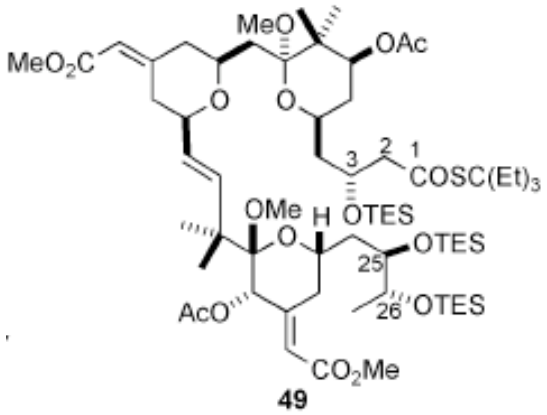


Substrate Controlled Adol Reaction

Kageyama, M.; Tamura, T.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S. *J. Am. Chem. Soc.* **1990,** *112*, 7407

Masamune's Approach to Bryostatin 7

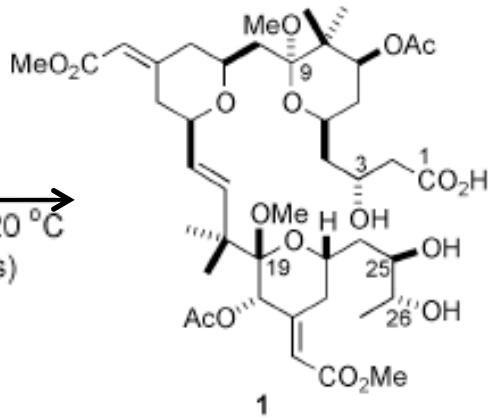




(xxxv) $Hg(O_2CCF_3)_2$, $NaHPO_4$, THF

(xxxvi) HF·py, THF, -20 °C

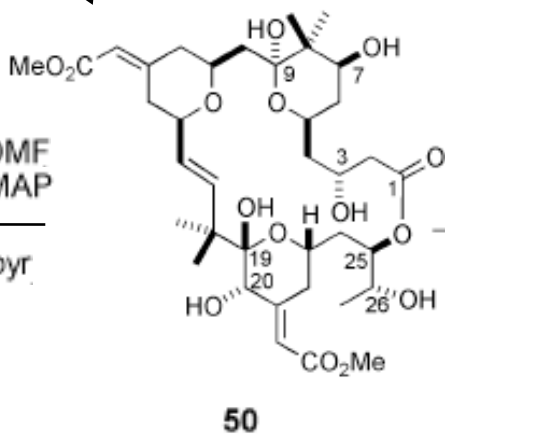
(64%, 3 steps)



Regeoselective Steglich Macrolactonisation & Glycoside hydrolysis (C9 vs C19)

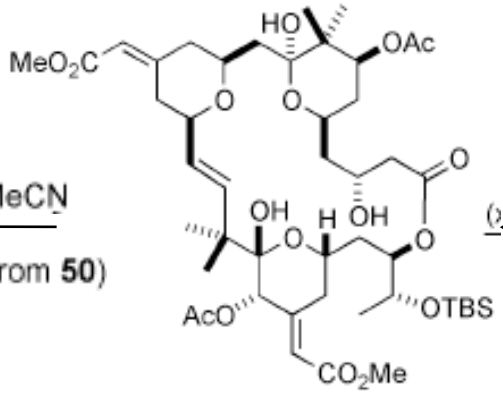
(i) DCC, PPTS, py, $ClCH_2CH_2Cl$, reflux (51%)

(ii) K_2CO_3, MeOH, then 5% aqueous HCl workup (54%)



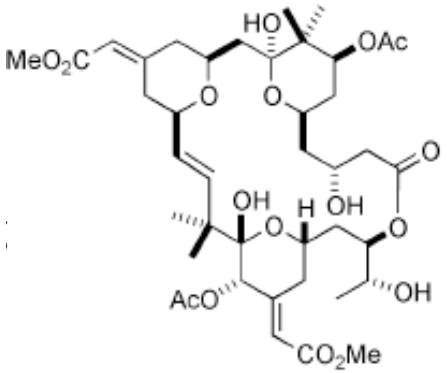
(i) TBSCl, DMF, Et_3N, DMAP

(ii) Ac_2O, pyr



HF-MeCN

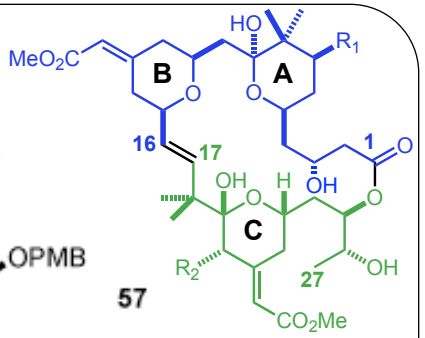
(40% from **50**)

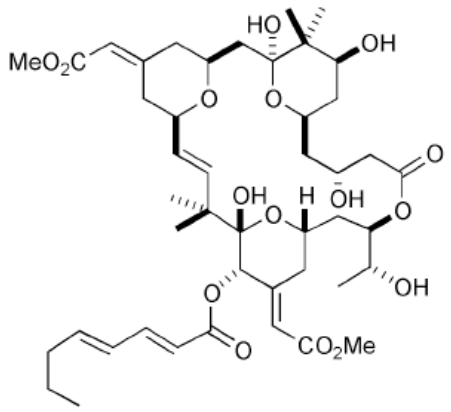


Bryostatin 7

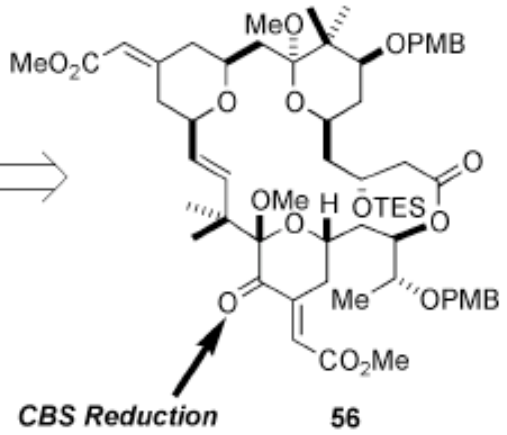
Kageyama, M.; Tamura, T.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S. *J. Am. Chem. Soc.* **1990,** *112*, 7407

Evans Approach to Bryostatin 2



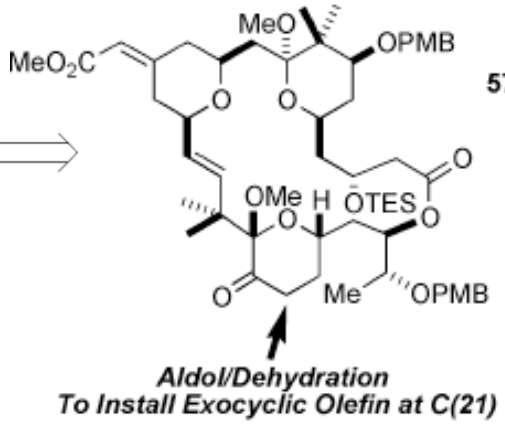


Bryostatin 2



CBS Reduction

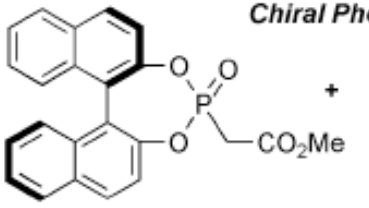
56



57

Aldol/Dehydration
To Install Exocyclic Olefin at C(21)

Olefination via Fuji's
Chiral Phosphonoacetate



59

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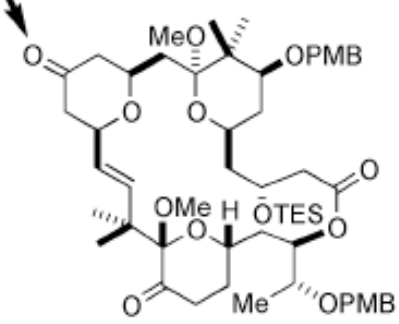

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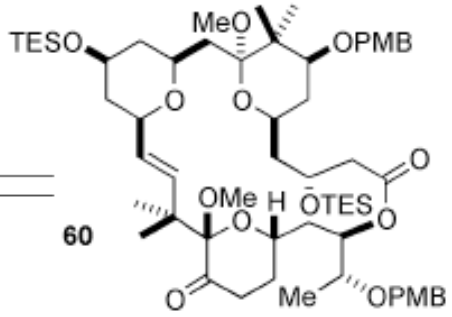

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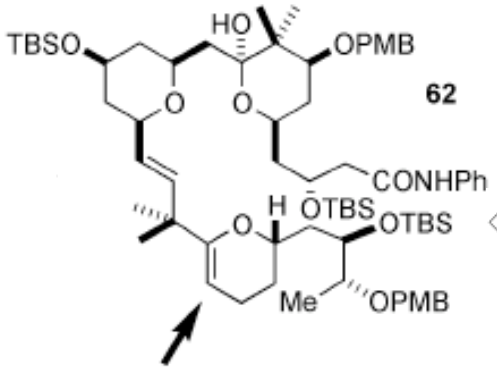


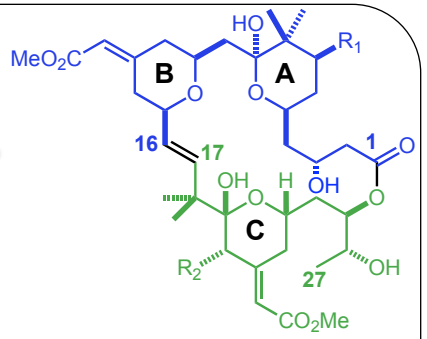
62

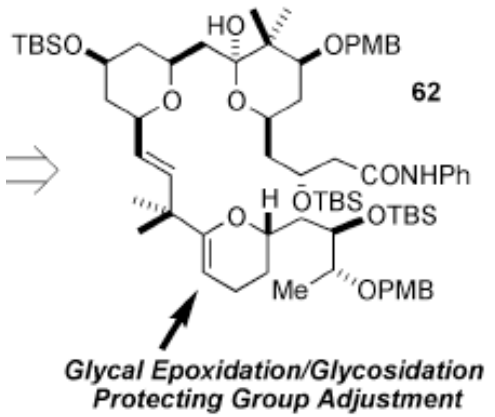
Glycal Epoxidation/Glycosidation
Protecting Group Adjustment

Macrolactonisation

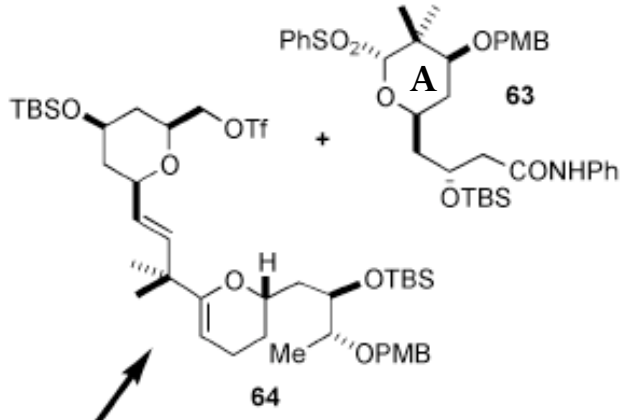
Evans, D. A.; Carter, P. H.; Carreira, E. M.; Charette, A. B.; Prunet, J. A.; Lautens, M. *J. Am. Chem. Soc.* **1999,** *121,* 7540.

Evans Approach to Bryostatin 2

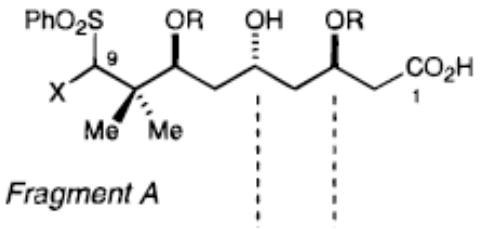




Glycal Epoxidation/Glycosidation
Protecting Group Adjustment

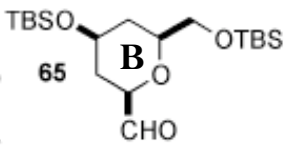


Sulfone Anion Displacement

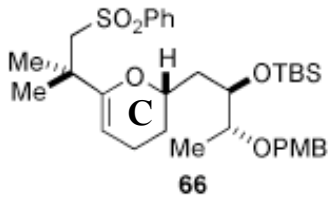


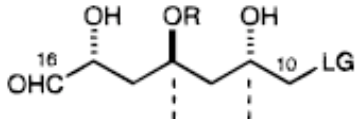
Fragment A

Julia Olefination

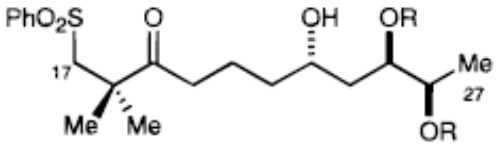


\+

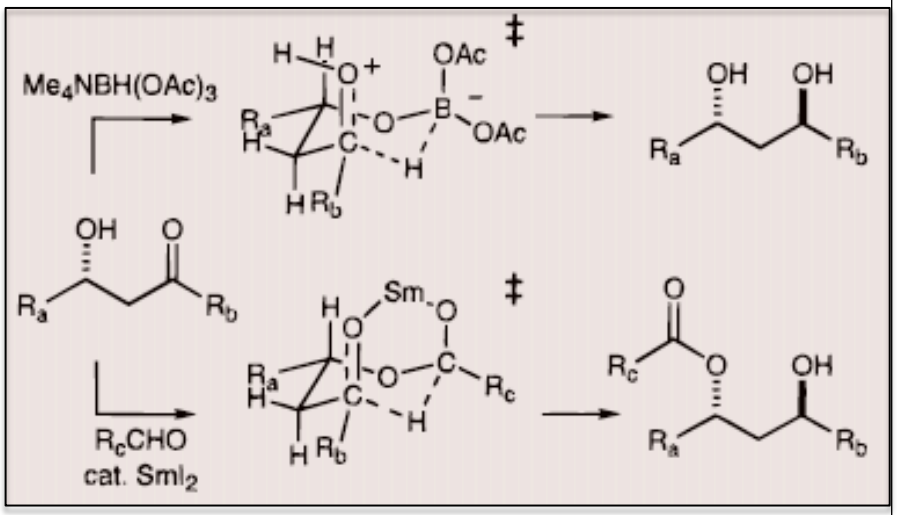




Fragment B

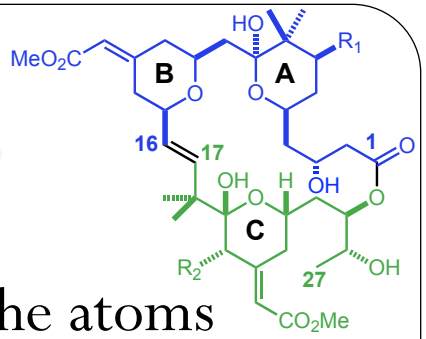


Fragment C



Evans, D. A.; Carter, P. H.; Carreira, E. M.; Charette, A. B.; Prunet, J. A.; Lautens, M. *J. Am. Chem. Soc.* **1999,** *121,* 7540.

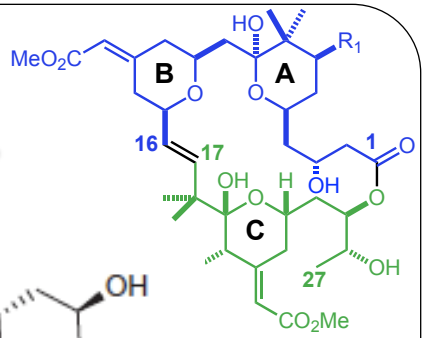
Trost's Approach to Bryostatin 16



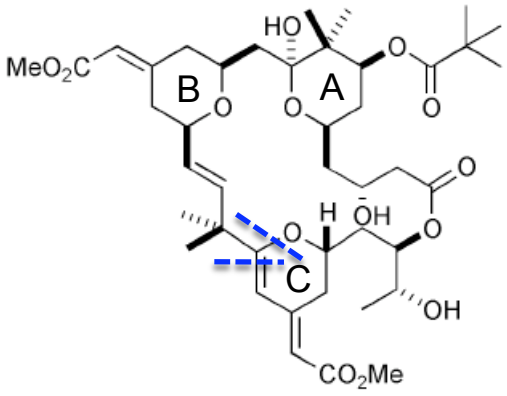
- **Atom economy** (the use of routes in which most of the atoms present in the reactants also end up in the product)
- **Chemoselectivity** (the use of reactions that take place only at desired positions in a molecule).
- A pivotal parent structure allowing access to all other bryostatins
- New analogues, might be readily obtained simply by variations in this natural product's synthesis.
- Palladium catalysed alkyne–alkyne coupling as a macrocyclization method for complex natural product synthesis.
- Gold catalysed conversion of the product of above step into a dihydropyran (the 'C ring' of bryostatins)

Trost, B. M.; Dong, G. *Nature*, **2008**, *456*,485

Trost's Retrosynthesis

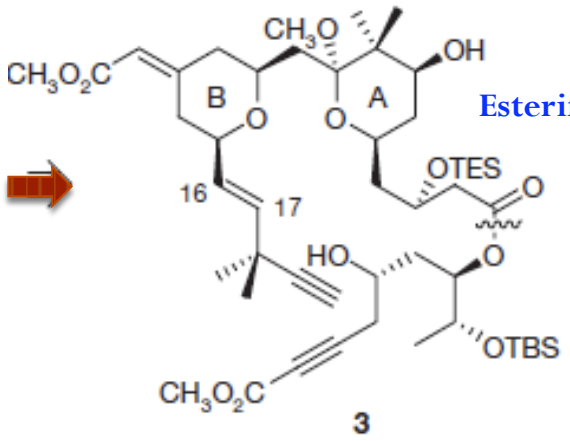


Previous Approaches: a difficult Julia olefination followed by a lactonization



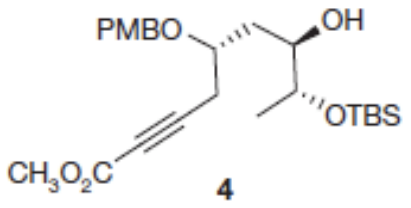
Bryostatin 16

Pd-catalysed chemoselective alkyne–alkyne coupling and a metal-catalysed 6-endo-dig cyclization



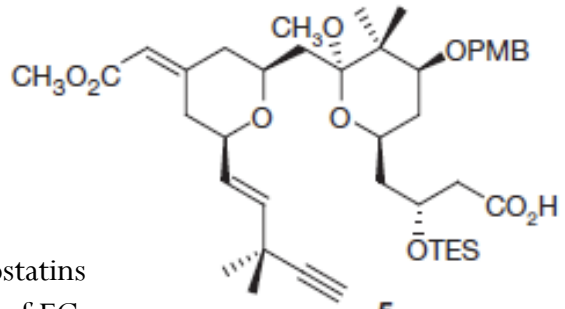
3

Esterification

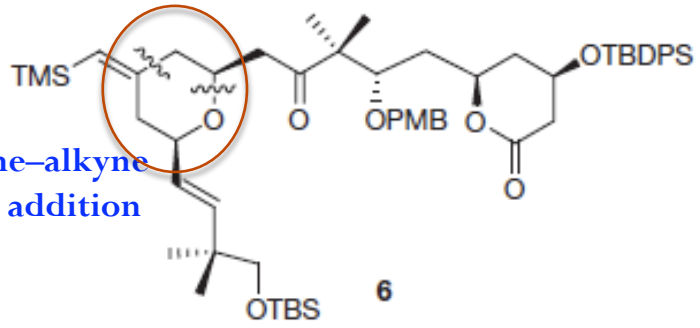


4

late variations for access to other bryostatins or analogues, as well as minimization of FG transformation and protecting group usage.

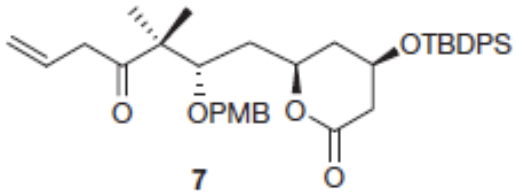


5



6

Ru-catalysed alkene–alkyne coupling/Michael addition



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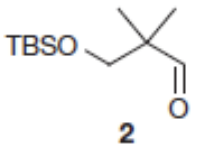

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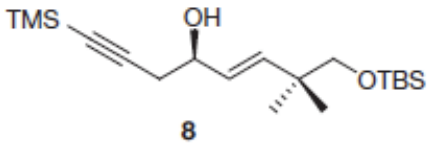
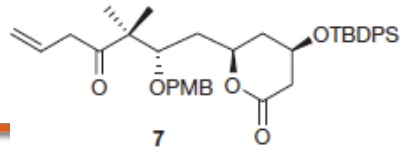
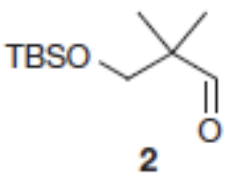


8

Installation of congested C16-C17 *trans*-alkene in an early stage.

Synthesis of fragment 7

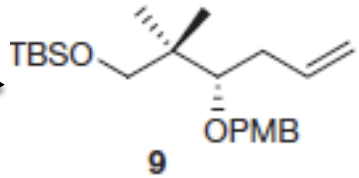




(-)$(Ipc)_2B(allyl)$, Et_2O, –90 °C
67%, 94% *ee*

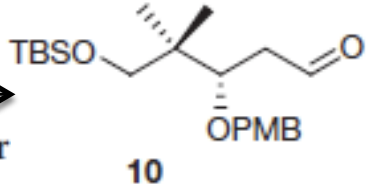
PMB-Br, NaH, DMF
90%

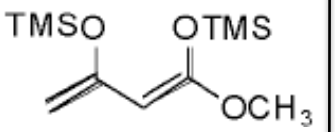
Asymmetric Brown Allylation



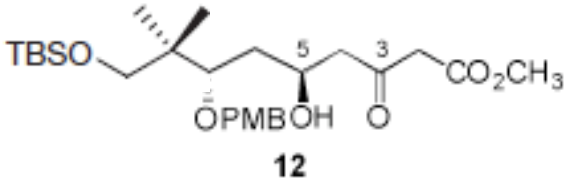
OsO_4 (2 mol%)
2,6-lutidine,

$NaIO_4$, dioxane/water
(3:1), 87%





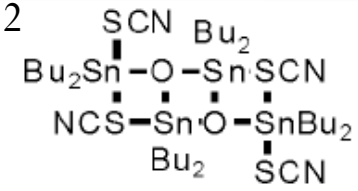
$Ti(O\,i\text{-}Pr)_2Cl_2$,
toluene, −78 °C



Lewis Acid mediated Acetoacetate aldol Condensation

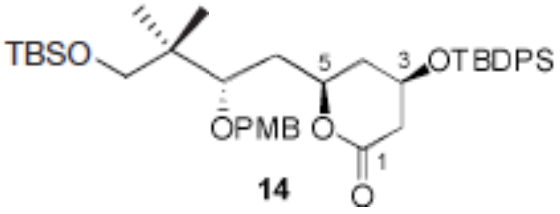
1 $Me_4NBH(OAc)_3$
AcOH/CH_3CN, −35 °C
96%, 15:1 dr at C(3)

2

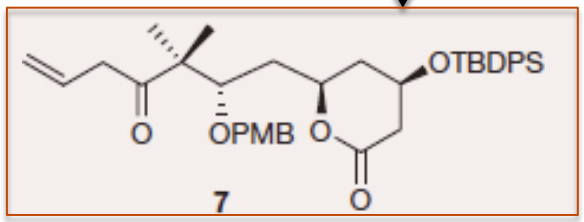


Otera's catalyst
hexane, reflux;

3 TBDPSCl, imidazole, DMF
50 °C, quantitative

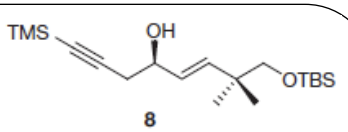


1 AcOH/H_2O (4:1), 69%
2 Dess–Martin oxidation
3 allyl iodide, In, DMF, rt,
66% over two steps;
4 Dess–Martin oxidation
85%

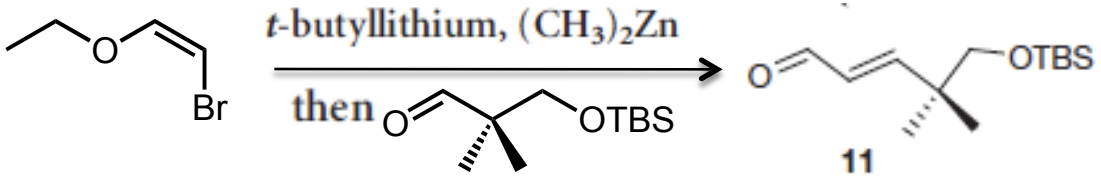


Trost, B. M.; Yang, H.; Thiel, O. R.; Frontier, A. J.; Brindle, C. S.
J. Am. Chem. Soc. **2007,** *129*, 2206

Synthesis of fragment **8**

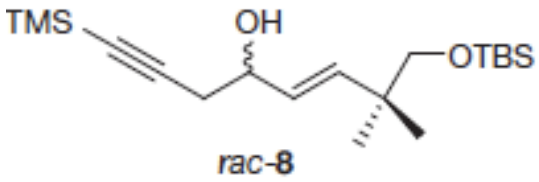


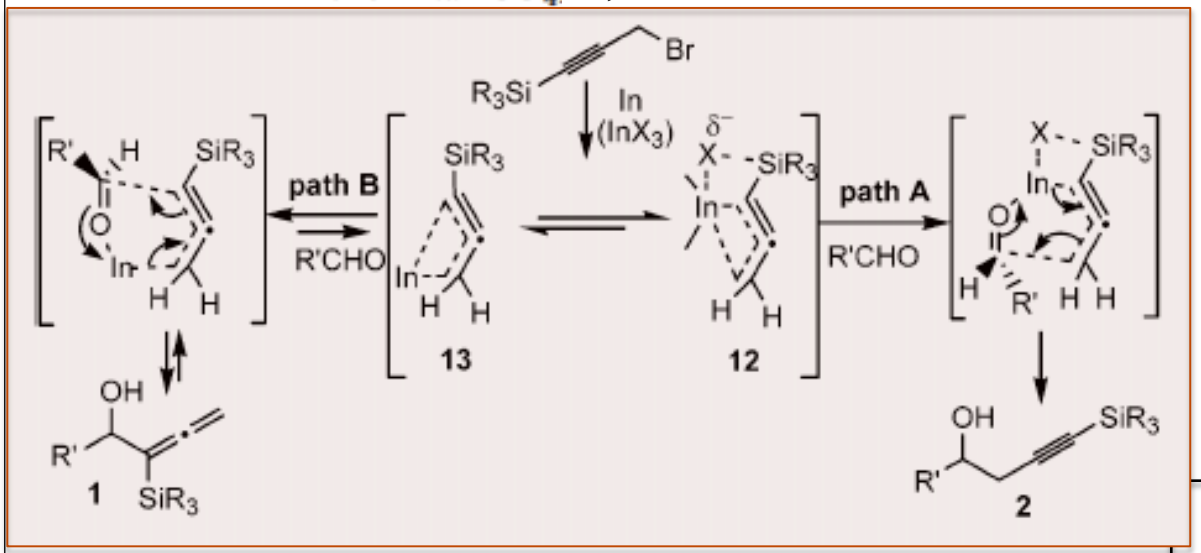
Indium –mediated propargylation



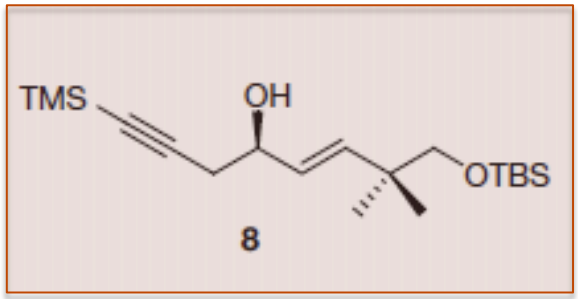
indium powder, InF_3 (10 mol%),

THF, 65 °C, 68%



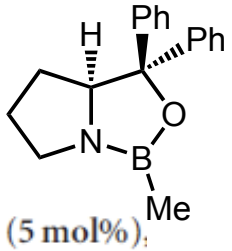


Lin, M. & Loh, T. *J. Am. Chem. Soc.* **2003**, *125*, 13042



90%, 90% e.e. over two steps.

Dess–Martin periodinane, $NaHCO_3$,



(5 mol%)

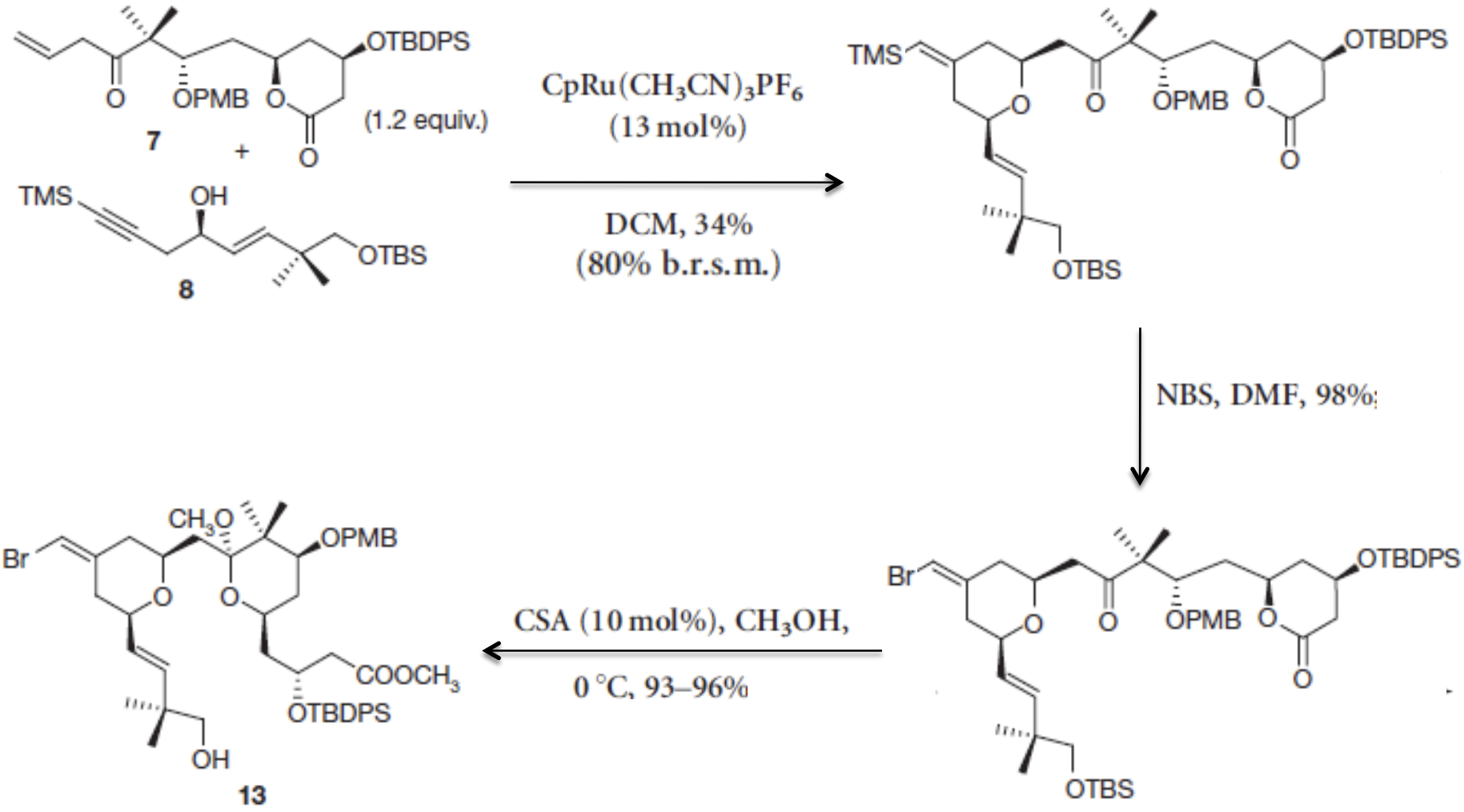
catecholborane, DCM, –78 °C

CBS Reduction

Lin, M.; Loh, T. *J. Am. Chem. Soc.* **2003,** *125,* 13042

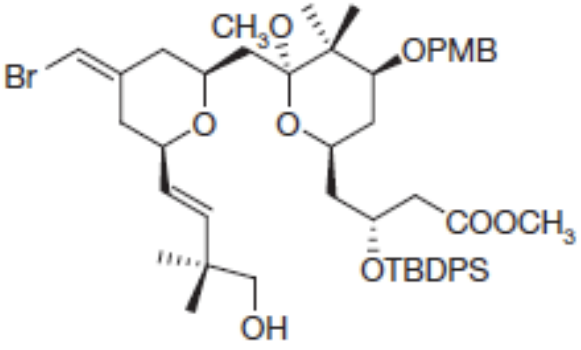
Synthesis of Acid Funtionality

Ru-catalysed tandem alkene–alkyne coupling/Michael addition



Trost, B. M.; Yang, H.; Wuitschik, G. A. *Org. Lett.* **2005**, 7, 4761–4764

Synthesis of Acid Funtionality

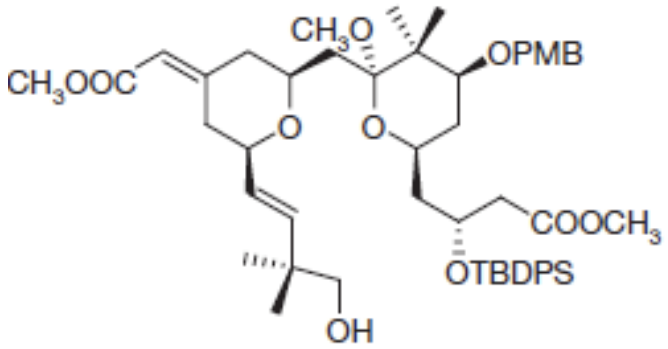


13

$PdCl_2(CH_3CN)_2$ (10 mol%)

dppf (30 mol%)CO (1 atm)
CH_3OH, $(C_2H_5)_3N$, DMF,
80 °C, 83% (90% b.r.s.m.)

Pd-catalysed carbonylation

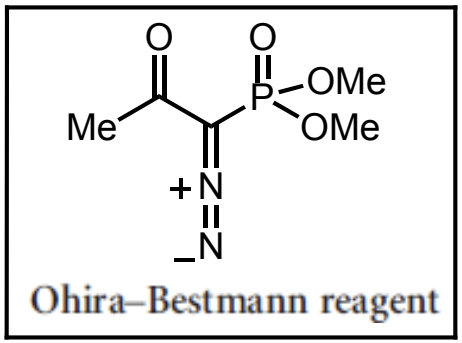


14

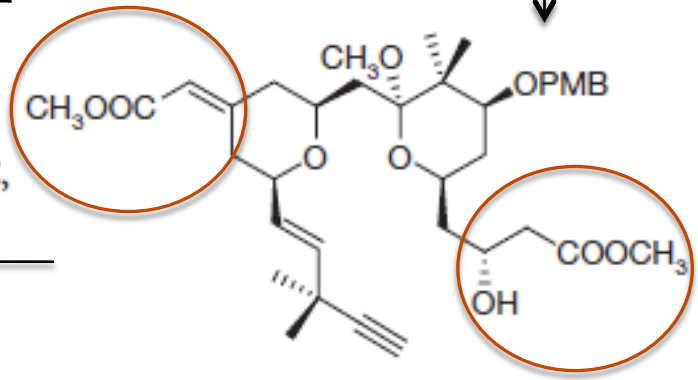
Dess–Martin periodinane
$NaHCO_3$, DCM, 88%

Ohira–Bestmann reagent
K_2CO_3, CH_3OH, 97%

TBAF, HOAc, THF
90% (96% b.r.s.m.)



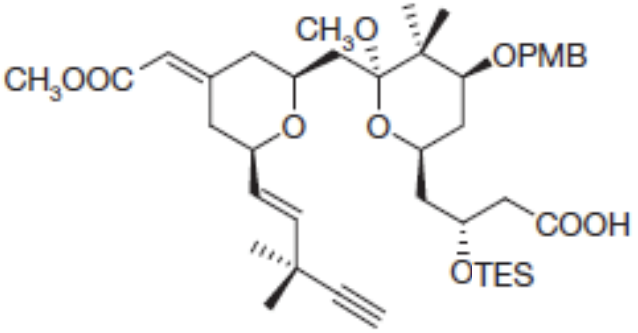
Ohira–Bestmann reagent



15

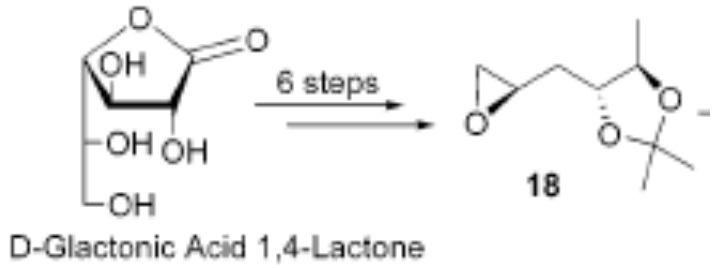
1 $(CH_3)_3SnOH$, DCE, 80 °C,
84%

2 TESOTf, 2,6-lutidine,
DCM, −10 °C to 0 °C
76–79%



Nicolaou, K. C.; Estrada, A.A.; Zak, M.; Lee, S. H.; Safina, B. S. *Angew. Chem. Int. Ed.* **2005,** *44,* 1378

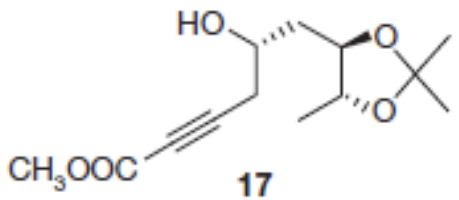
Synthesis of Alcohol Funtionality



18

n-BuLi, methyl propynate

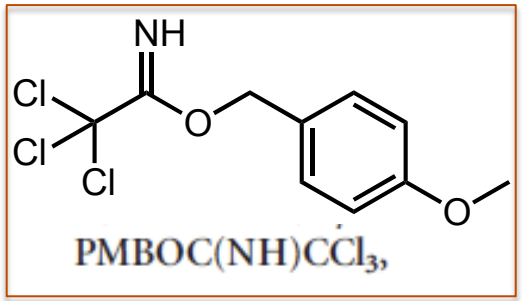
$BF_3{\cdot}OEt_2$,
THF, −78 °C, 92%

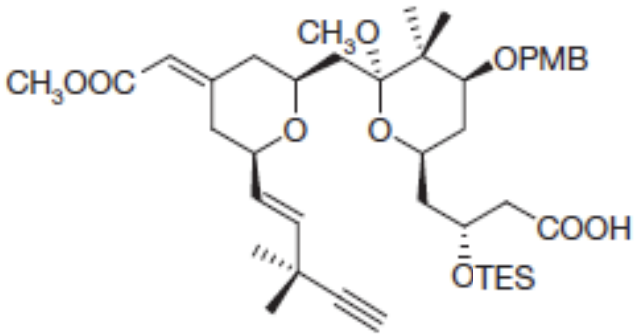


17

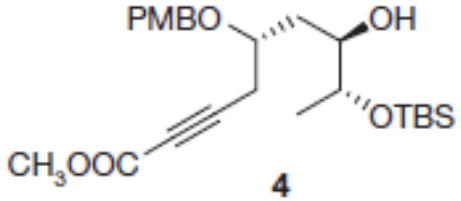
$Cu(OTf)_2$ (3 mol%),
$PMBOC(NH)CCl_3$,
toluene, –10 °C;

PPTS, CH_3OH,
93% over two steps

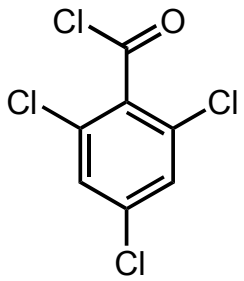




TBSOTf., 2,6-lutidine,
DCM, –78 °C, 71%

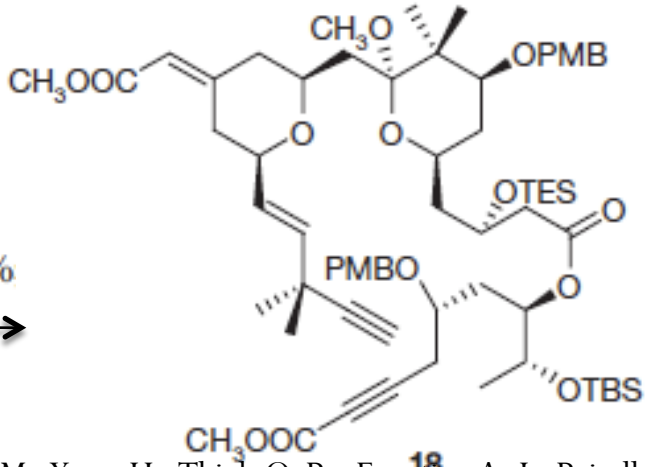


4



Yamaguchi
esterification
then **4**, DMAP, 92%

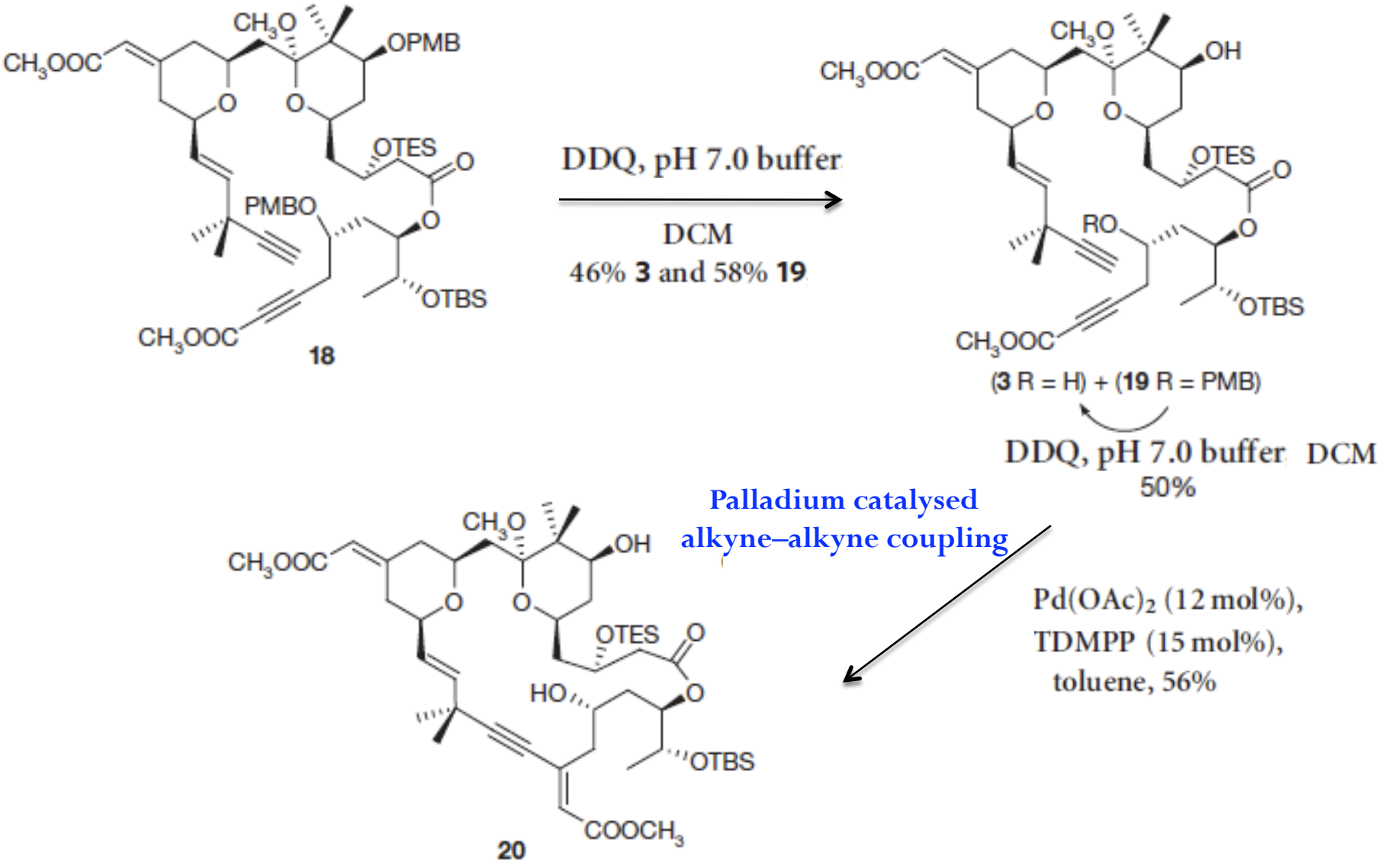
$(C_2H_5)_3N$, toluene,



18

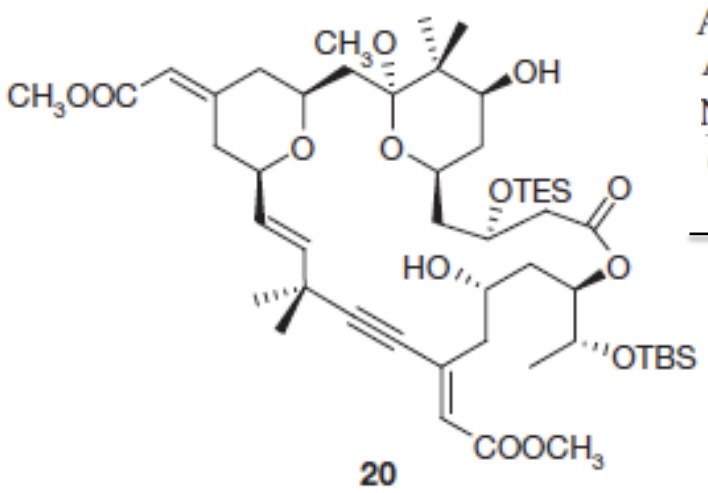
Trost, B. M.; Yang, H.; Thiel, O. R.; Frontier, A. J.; Brindle, C. S. *J. Am. Chem. Soc.* **2007,** *129*, 2206

Trost's Approach to Bryostatin 16



Trost, B. M.; Matsubara, S.; Caringi, J. J. *J. Am. Chem. Soc.* **1989,** *111,* 8745

Trost's End Game to Bryostatin 16

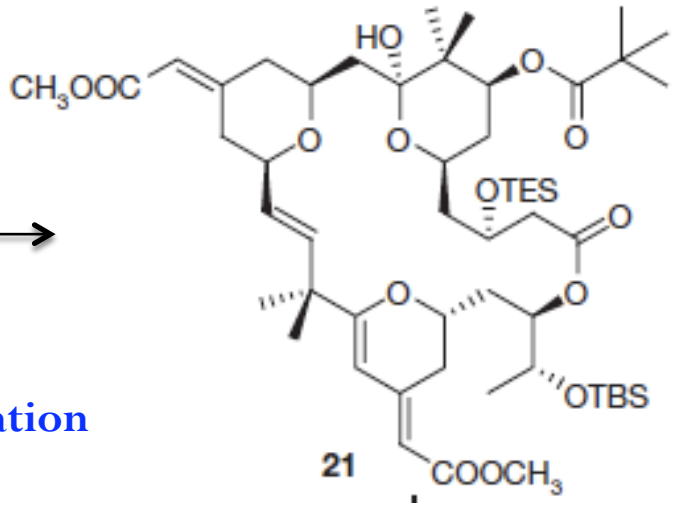


20

$AuCl(PPh_3)$ (20 mol%),
$AgSbF_6$ (20 mol%)
$NaHCO_3$, DCM/CH_3CN,
0 °C to room temperature,
73%

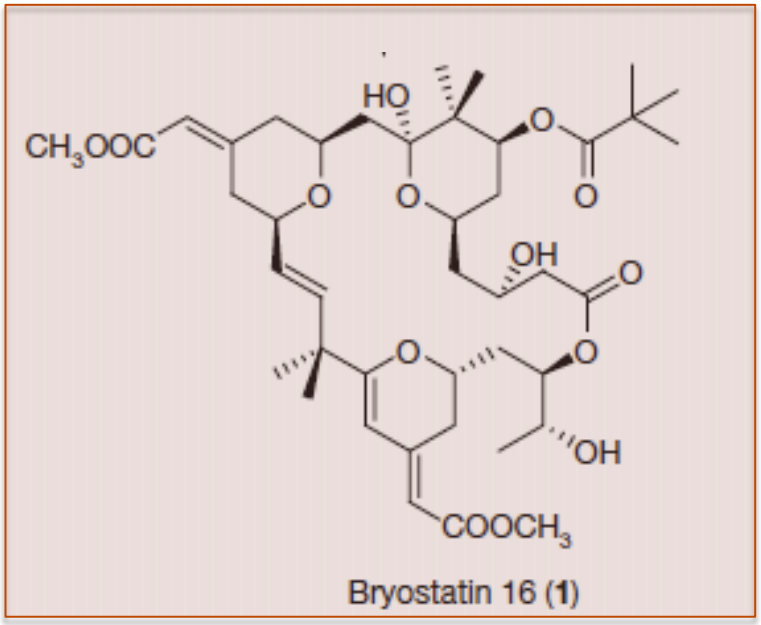
Piv_2O, DMAP,
DCM, 50 °C, 62%

6-endo-dig cyclization



21

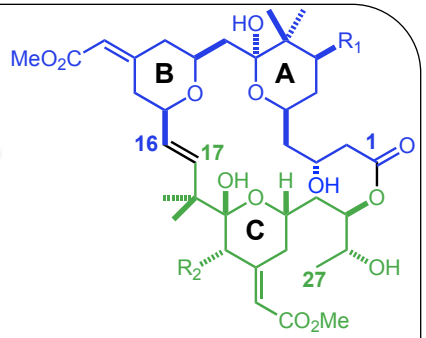
TBAF, THF, ~52%.



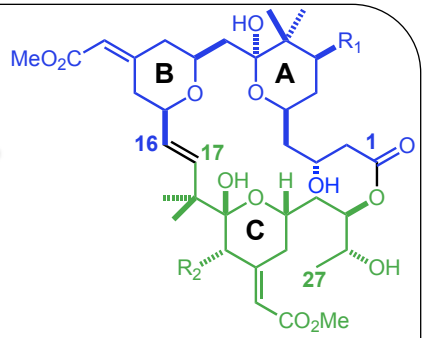
Bryostatin 16 (**1**)

Trost, B. M.; Dong, G. *Nature*, **2008**, *456*,485

Conclusion

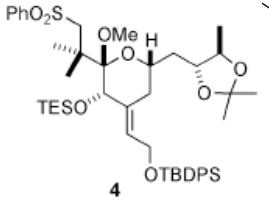


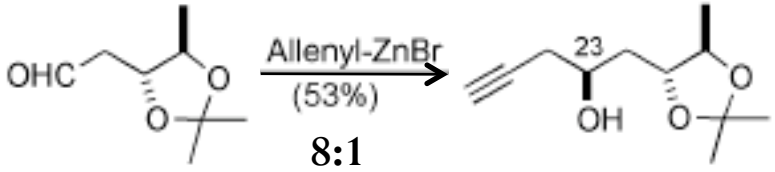
- Previous Syntheses have used more than 60 steps.
- Trost's synthesis is a highly concise strategy (26-step longest linear sequence, 39 total steps from aldehyde **2**)
- A pivotal parent structure allowing access to all other bryostatins
- New analogues, might be readily obtained simply by variations in this natural product's synthesis.
- Palladium catalysed alkyne–alkyne coupling as a macrocyclization method for complex natural product synthesis.
- Gold catalysed conversion of the product of above step into a dihydropyran (the 'C ring' of bryostatins)

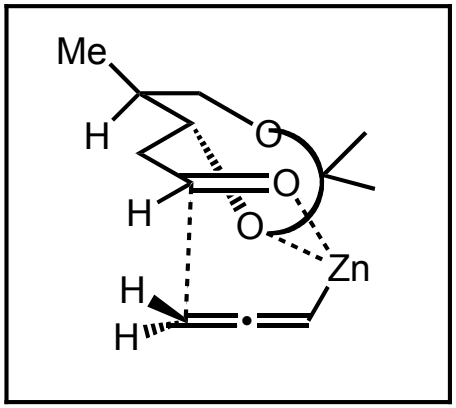


Thanks

Chelation Controlled Nu Attack



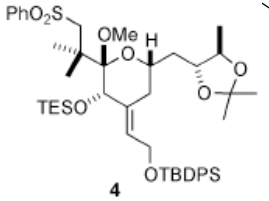




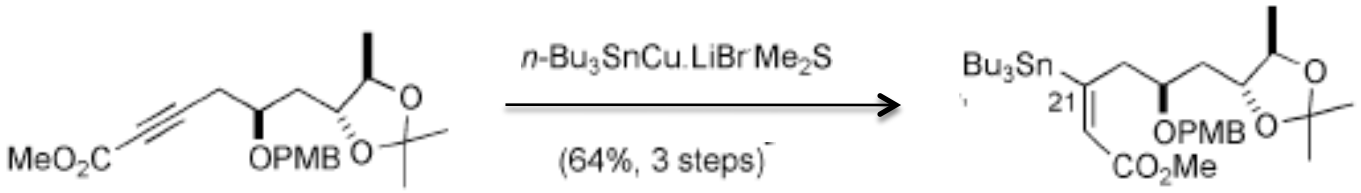
Chelation –Controlled Nucleophilic addition

Kageyama, M.; Tamura, T.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S. *J. Am. Chem. Soc.* **1990,** *112*, 7407

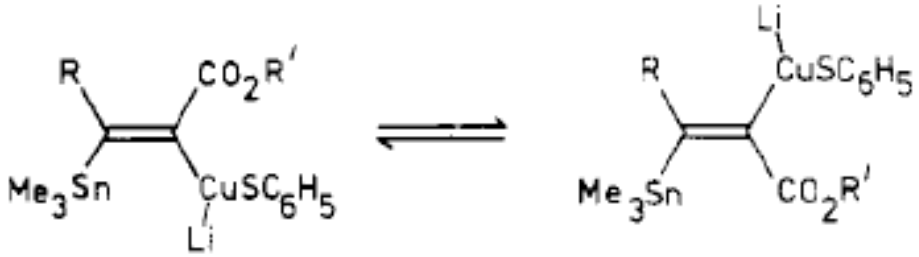
Piers stannylcupration



4



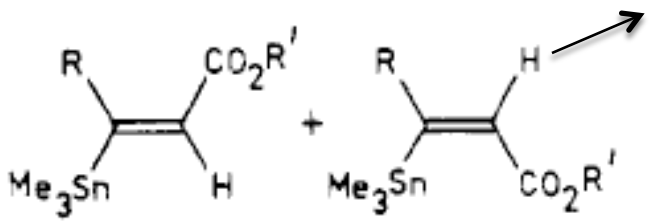
37 38



11 12

Kinetic Control

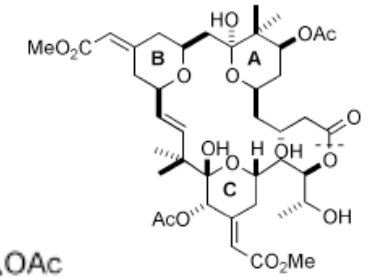
Thermodynamic Control

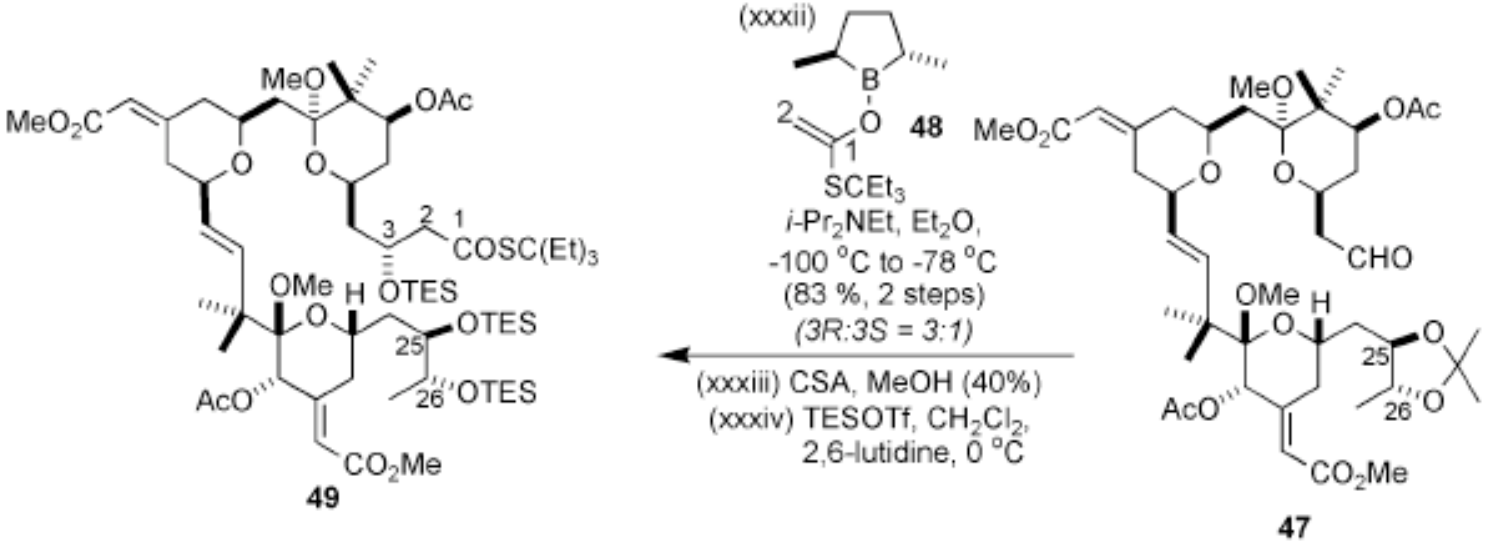


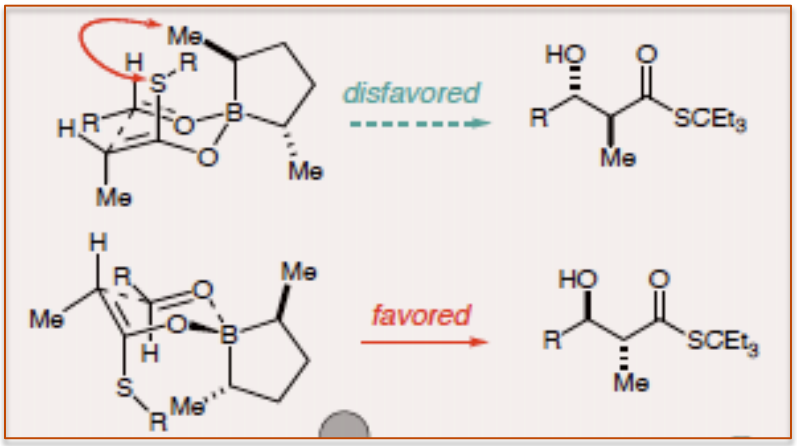
From methanol

Edward Piers,* Howard E. Morton *J. Org. Chem.* **1980**, *45*, 4263

Substrate Controlled Aldol Reaction

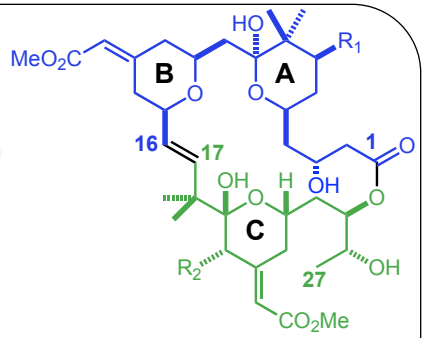




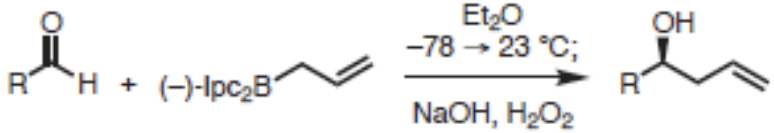


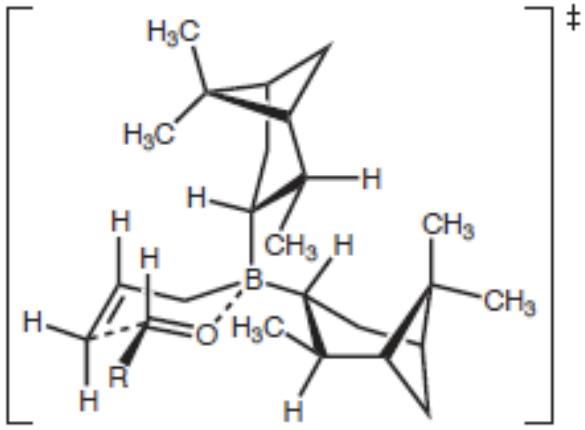
Kageyama, M.; Tamura, T.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S. *J. Am. Chem. Soc.* **1990,** *112*, 7407

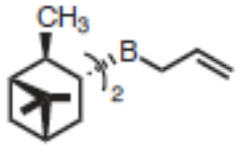
Brown's Asymmetric Allylation



Enantioselective Allylboration



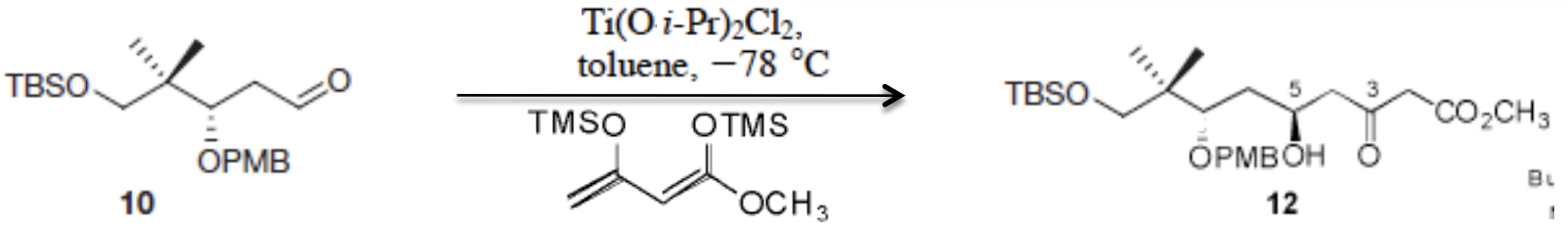


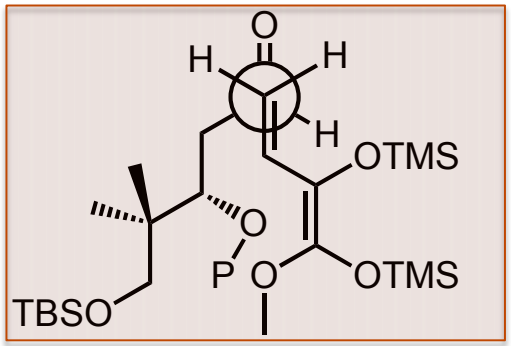


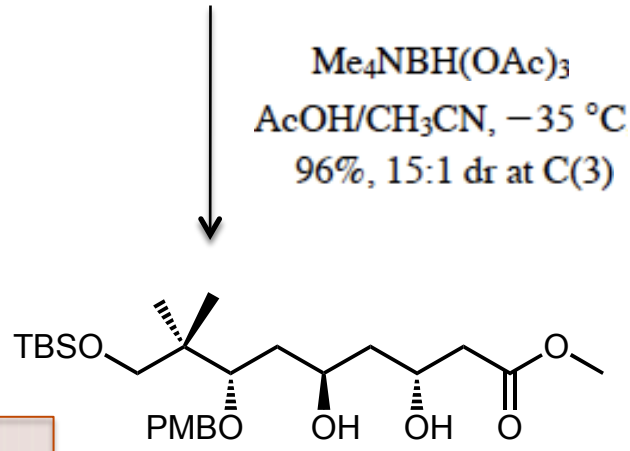
Allylation of aldehydes proceeds through a chair-like TS where R occupies an equatorial position and the aldehyde facial selectivity derives from minimization of steric interactions between the axial Ipc ligand and the allyl group.

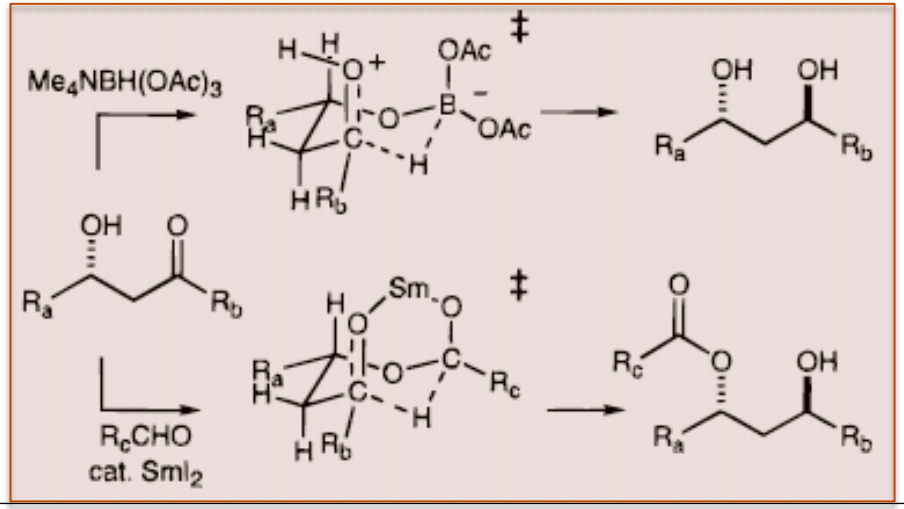
Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* 1983, *105*, 2092-2093.
Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* 1986, *108*, 5919-5923.
Racherla, U. S.; Brown, H. C. *J. Org. Chem.* 1991, *56*, 401-404.

Evans Diastereoselective Vinylogous Aldol Reaction and Hydroxyl Directed Reduction

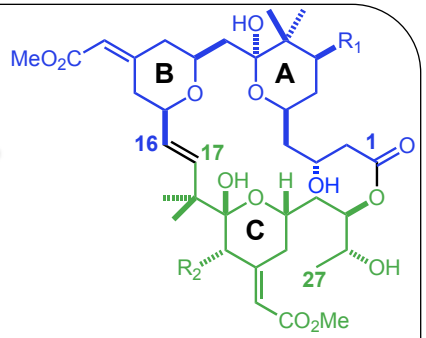


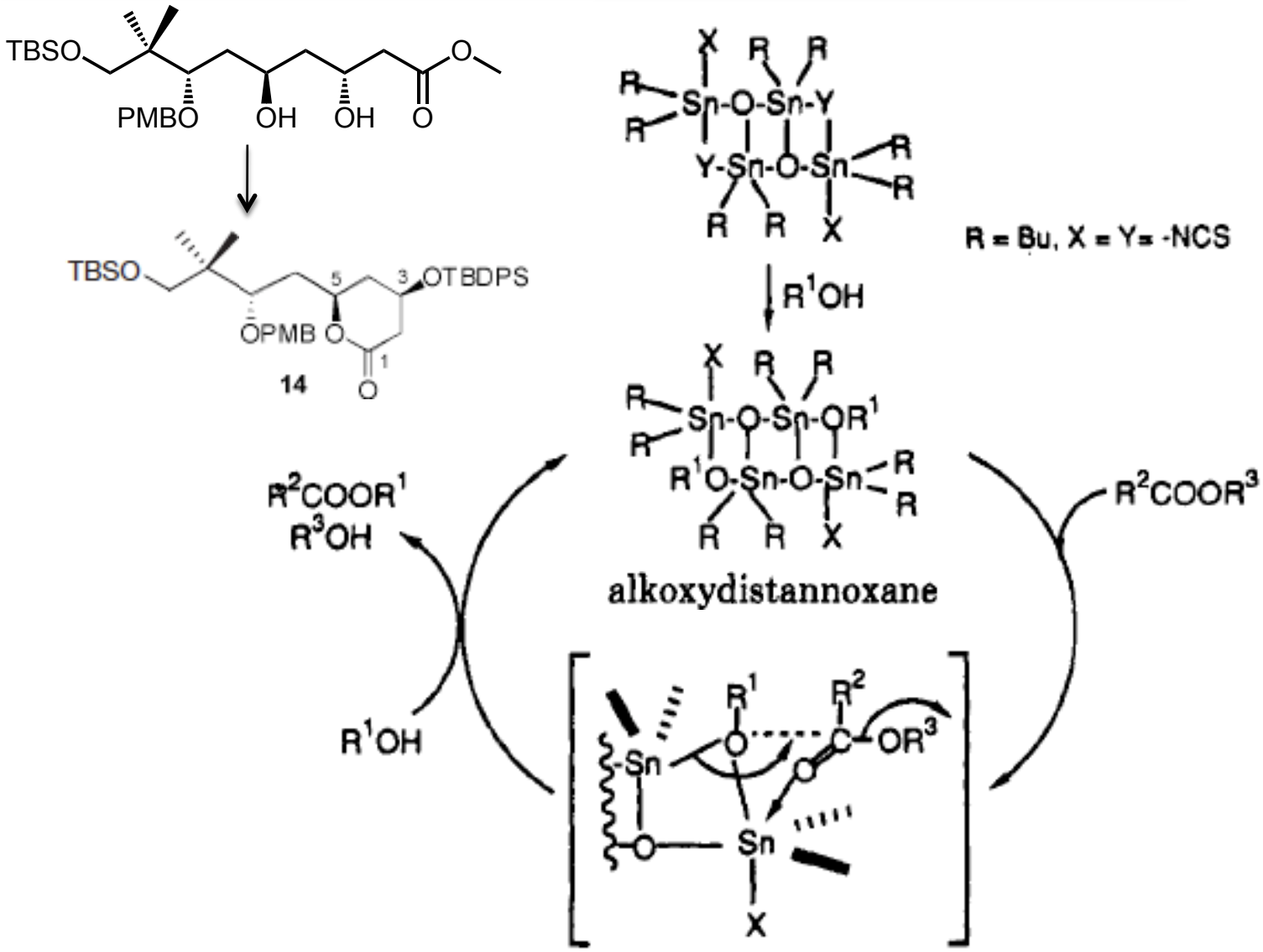






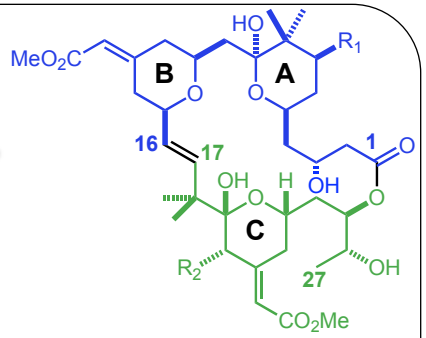
Otera's Catalyst for Transesterification





Otera, J et al (1991). "Novel template effects of distannoxane catalysts in highly efficient transesterification and esterification". J. Org. Chem. 56 (18): 5307–5311

Otera's Catalyst for Transesterification



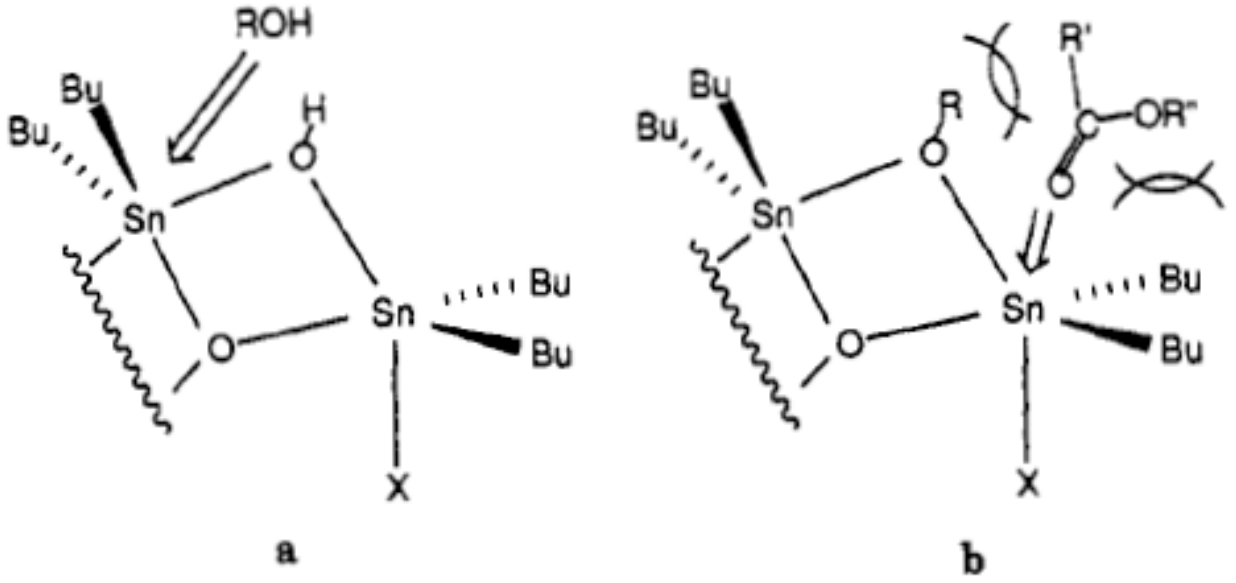
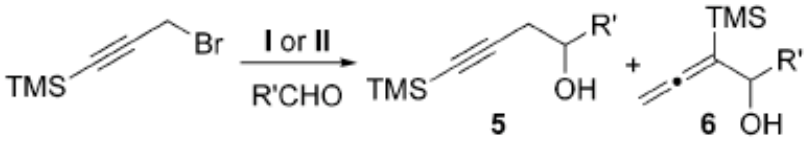


Figure 1. (a) Approach of the alcohol reactant to the distannoxane template. (b) Approach of the ester reactant to the distannoxane template.

Otera, J et al (1991). "Novel template effects of distannoxane catalysts in highly efficient transesterification and esterification". J. Org. Chem. 56 (18): 5307–5311

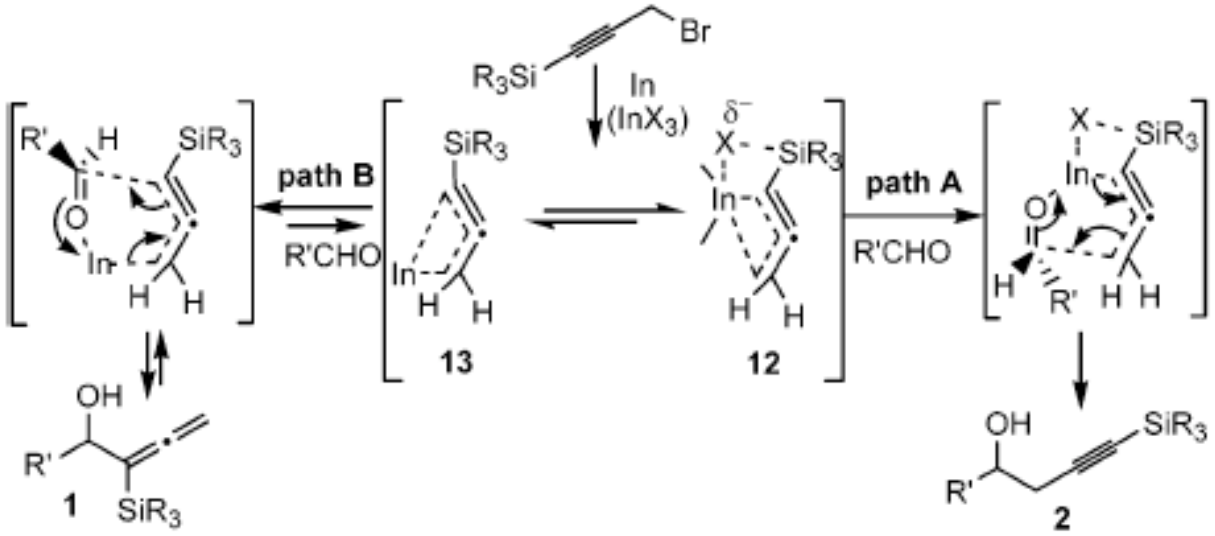
Indium –mediated Propargylation



I: In/10mol% $InBr_3$, THF, reflux, 20h

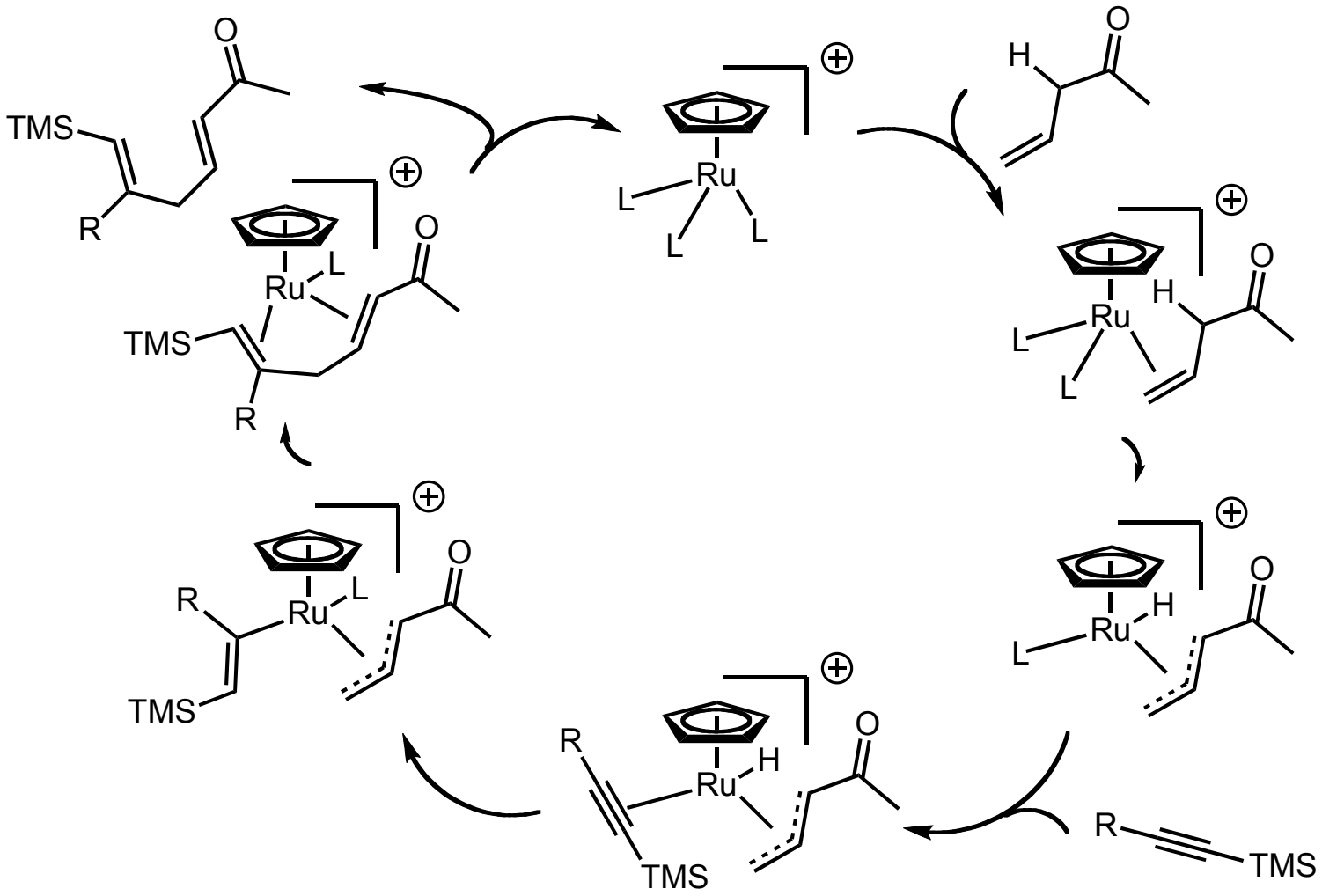
II: In/10mol% InF_3, THF, reflux, 9h

entry	aldehyde	5	I (5:6) yield[b] %	II (5:6) yield[b] %
1	hydrocinnamaldehyde	**a**	85 (99:1)	89 (99:1)
2	cinnamaldehyde	**b**	89 (99:1)	92 (99:1)
3	cyclohexanecarbaldehyde	**c**	90 (99:1)	94 (99:1)
4	benzaldehyde	**d**	92 (99:1)	92 (99:1)
5	nonyl aldehyde	**e**	95 (99:1)	93 (99:1)



Lin, M.; Loh, T. *J. Am. Chem. Soc.* **2003,** *125,* 13042

Ru-catalysed alkene-alkyne coupling



Palladium catalysed alkyne–alkyne coupling