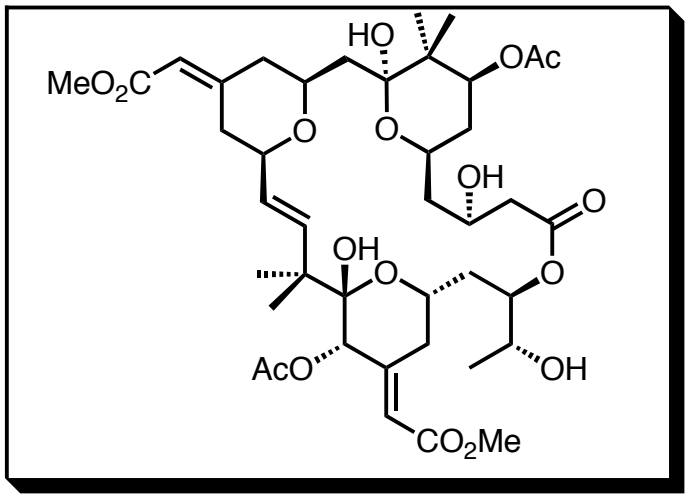
Total Synthesis of Bryostatin 7 *via* C–C Bond-Forming Hydrogenation



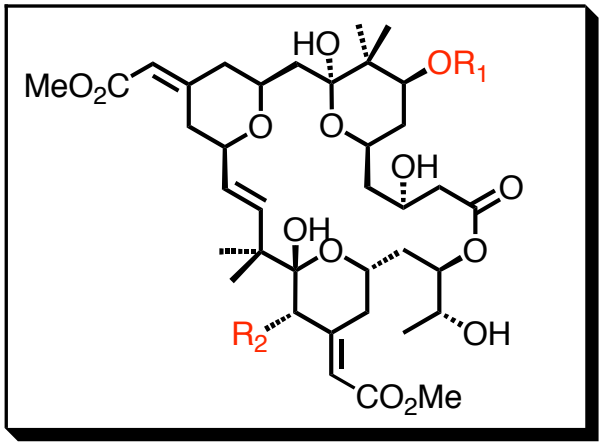
Yu Lu, Sang Kook Wook and Michael J. Krische *J. Am. Chem. Soc.* **2011,** *ASAP,*doi 10.1021/ja205673e.

Melissa Sprachman
Current Literature
September 3, 2011

The Bryostatin Family

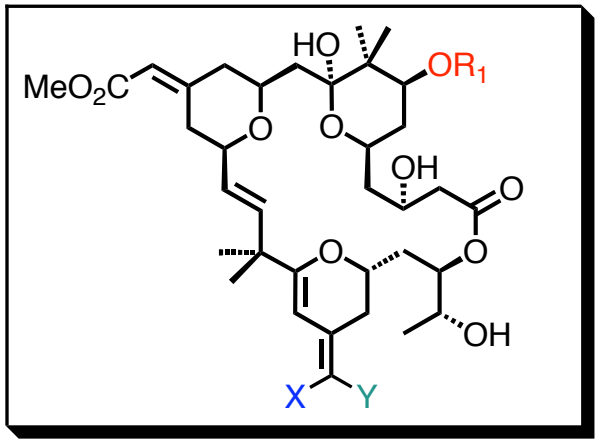
•The Bryostatin family was first isolated by Pettit and coworkers from the bryozoan *Bugula neritina.* (Pettit et al. *J. Am. Chem. Soc.* **1982,** *104,* 6846.)

•Recently, it was reported that the bryostatins are produced by an uncultured bacteria *E. sertula*. The proposed biosynthetic gene cluster and biosynthetic hypothesis are reported in the following reference: Sudek et al. *J. Nat. Prod.* **2007,** *70,* 67.



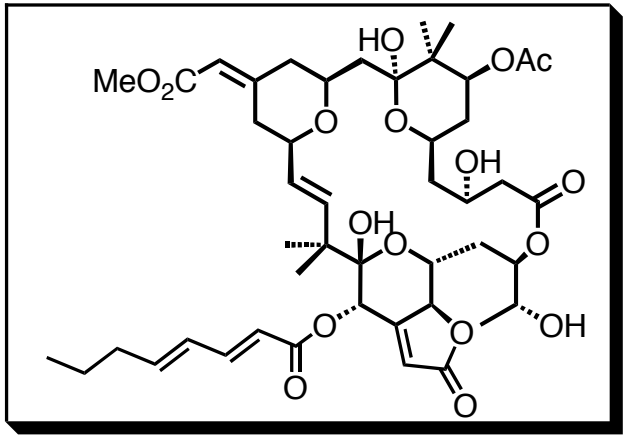
15 members with this core (varying at R_1 and R_2).

Bryostatin 7: R_1 = Ac, R_2 = OAc



Bryostatin 16: R_1 = Piv, X = H, Y = CO_2Me

Bryostatin 17: R_1 = Piv, X = CO_2Me, Y = H



Bryostatin 3

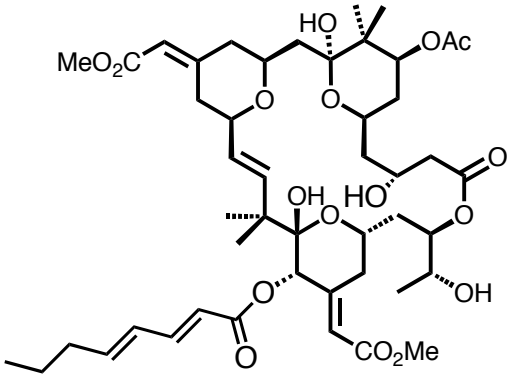
Biological Significance

The bryostatins are being applied to several biological problems including Alzheimer's disease and applications in chemotherapy.

Bryostatin 1 is well studied; 18 g of bryostatin 1 were isolated from 13,000 kg of source organism![1,2]

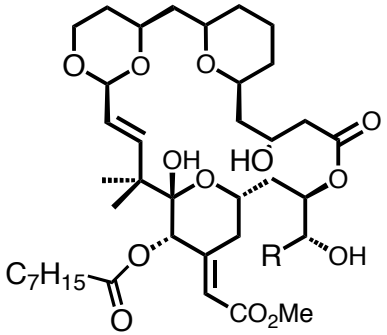
Bryostatin 1 exhibits high affinity binding to the regulatory C1 domains of protein kinase C (PKC). These domains regulate cellular processes including proliferation and apoptosis.[1,3]

Efforts by Keck[3] and Wender[4] have led to the development of bryostatin analogs that maintain efficacy:



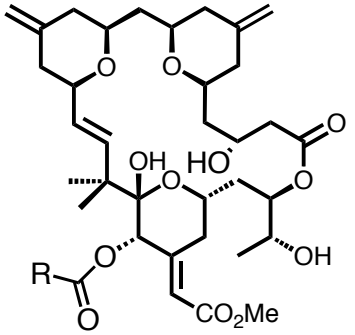
Bryostatin 1

PKC K_i = 1.35 nm



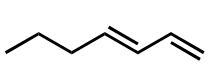
R = Me; PKC K_i = 3.4 nm

R = H; PKC K_i = 0.25 nm



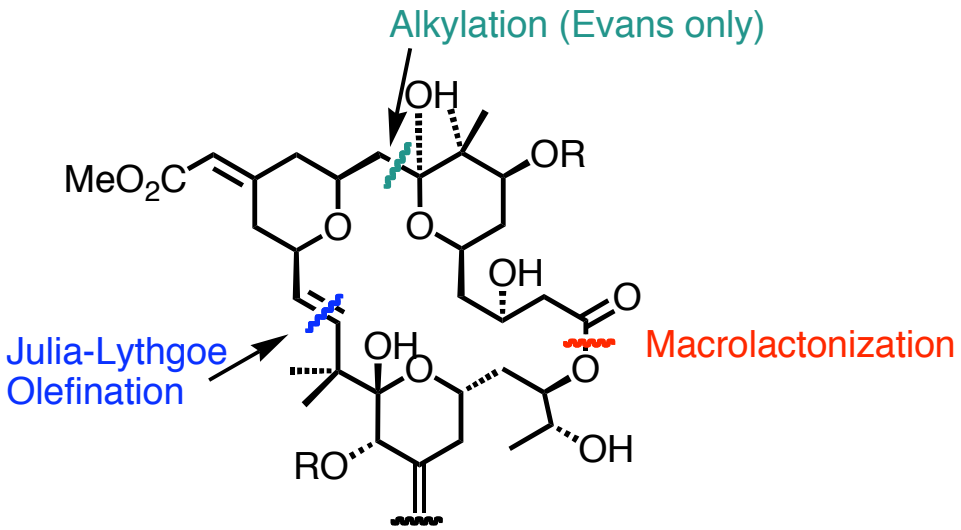
R = Ph; PKC K_i = 0.70 nm

R = C_7H_{15}; PKC K_i = 1.05 nm

R =  PKC K_i = 0.70 nm

[1]Keck et al *Angew. Chem. Int. Ed.***2010,** *49,* 4580.
[2]Schaufelberger et al. *J. Nat. Prod.* **1991,** *54,* 1265.
[3]Keck et al. *J. Am. Chem. Soc.* **2008,** *130,* 6660.
[4]Wender et al. *J. Am. Chem. Soc.* **2002,** *124,* 13648.

Previous Approaches



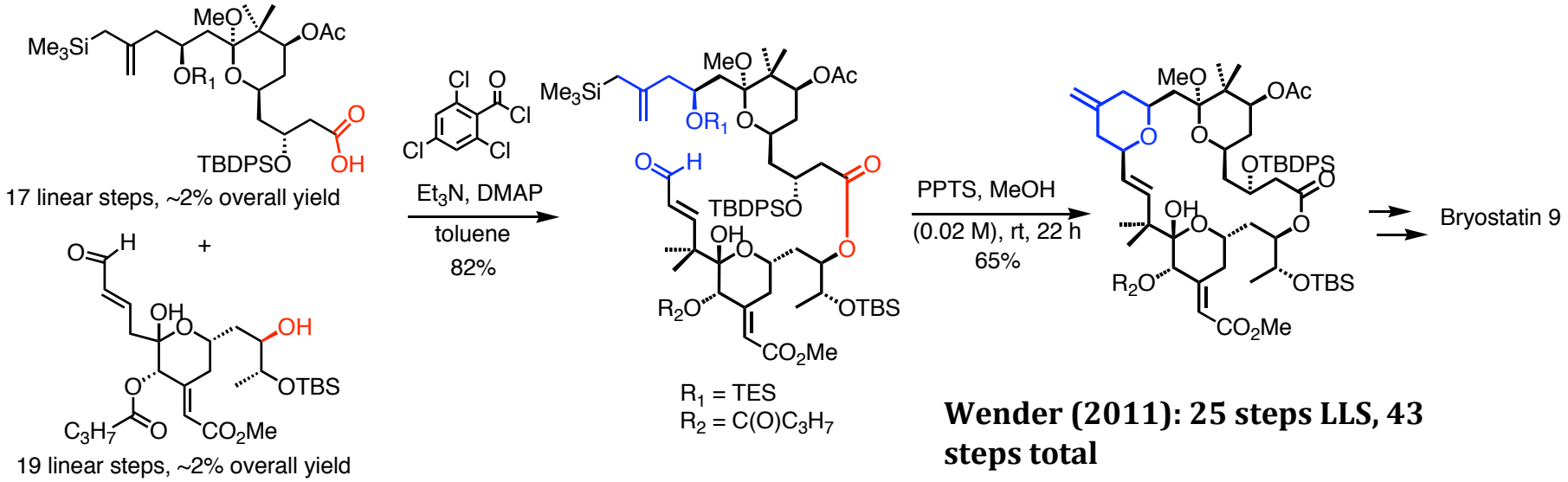
Evans (1998): 42 steps LLS, 72 steps total

Masamune (1990): 41 steps LLS, 79 steps total

Yamamura (2000): 43 steps LLS, 88 steps total

"…the points of convergence of these syntheses necessitate a further 14-21 linear steps to elaborate each target following assembly of their respective pyran-containing backbones, thus limiting step-economical access to diverse analogs." (Wender[1])

Wender, Keck: Convergent Pyran Annulation Strategy (Wender synthesis shown):



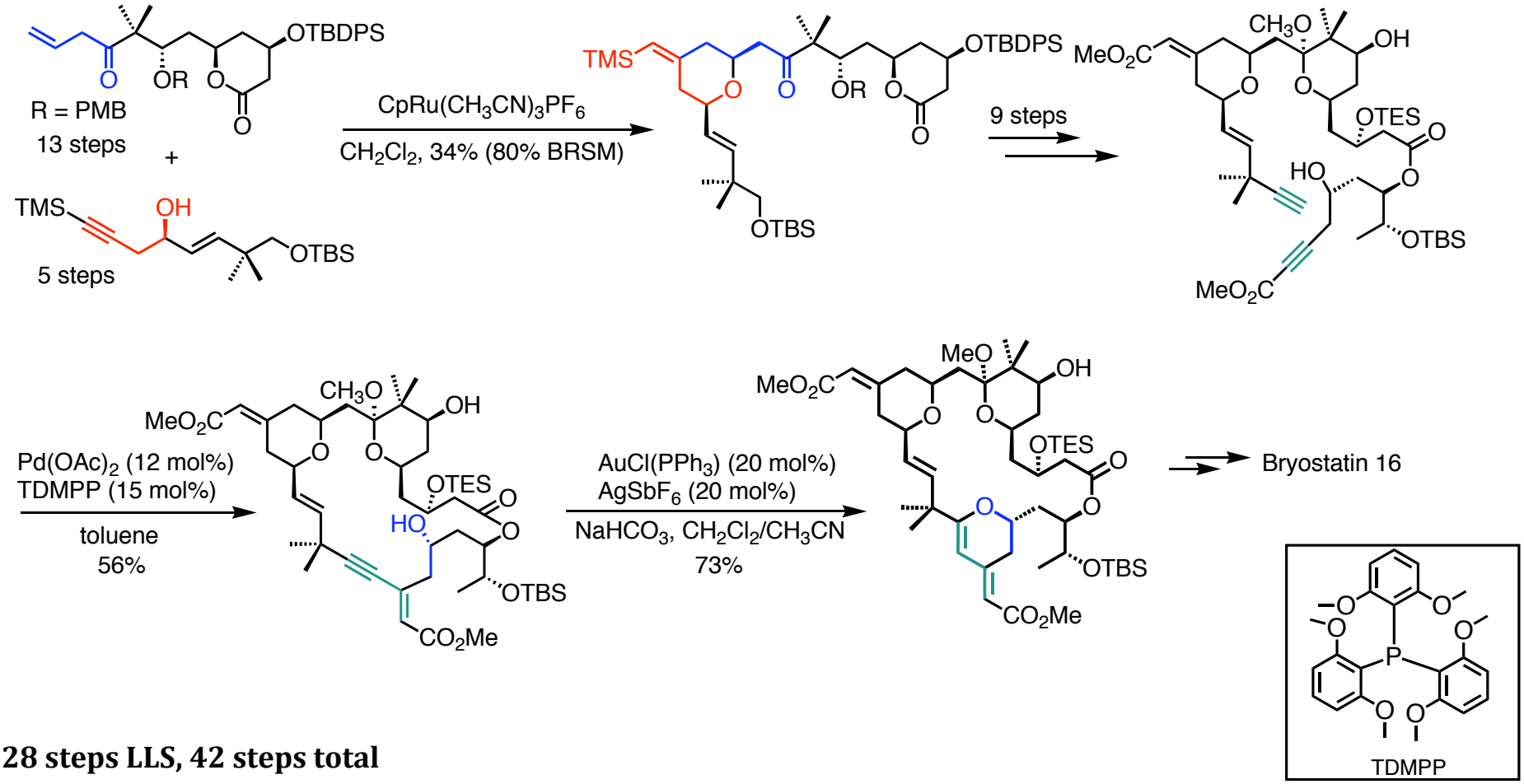
Wender (2011): 25 steps LLS, 43 steps total

Keck (2010): 31 steps LLS, 58 steps total

[1]Wender, P. A.; Schrier, A. J. *J. Am. Chem. Soc.* **2011,** *133,* 9228.
See also Keck et al. *J. Am. Chem. Soc.* **2010,** *133,* 744.

Previous Approaches

Trost: Transition-metal mediated, atom-economical approach:

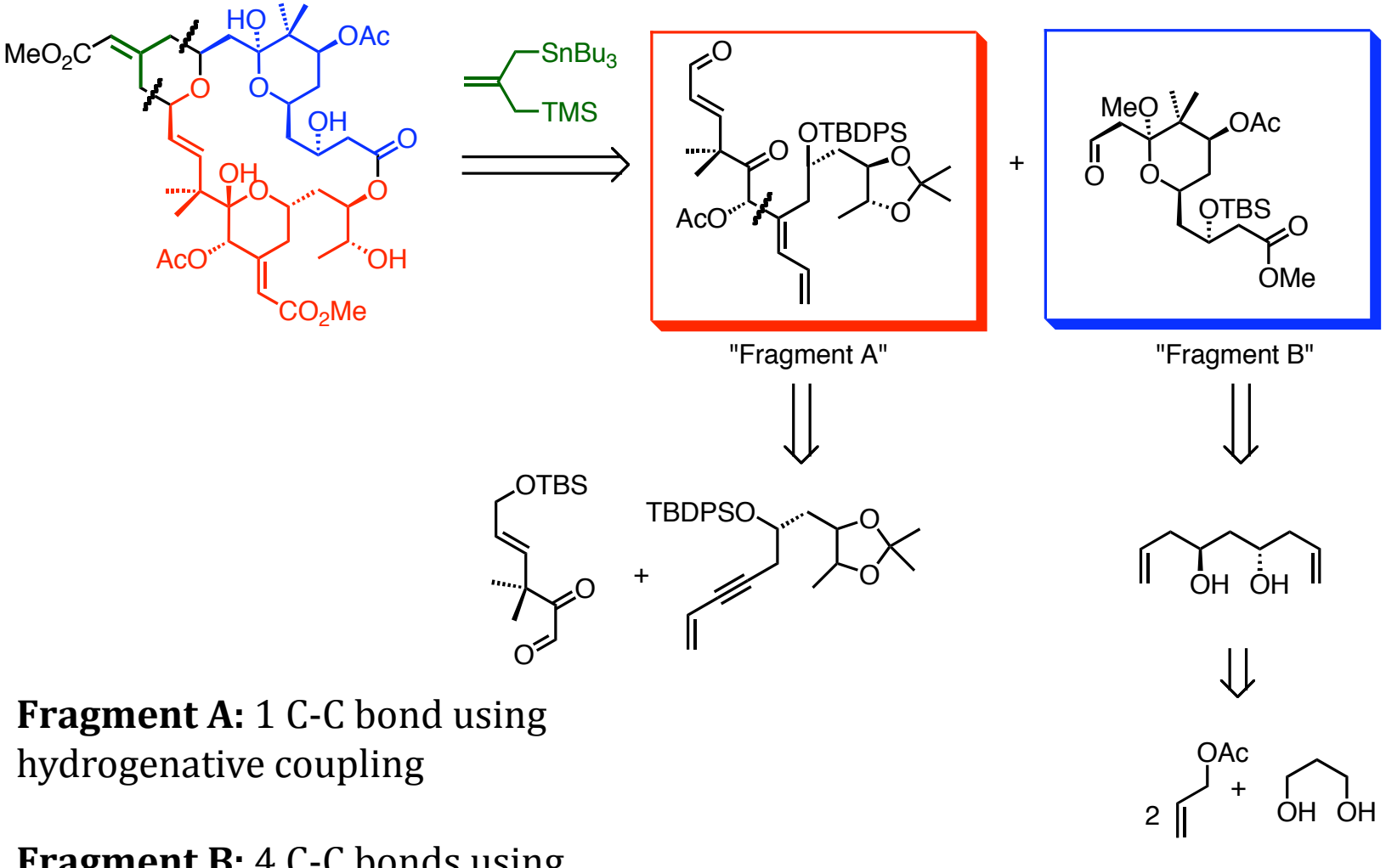


28 steps LLS, 42 steps total

Key Features: 1) Pd-catalyzed reaction of alkynes to form a macrocycle
2) Au-catalyzed dihydropyran formation

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

Retrosynthetic Analysis: Application of Hydrogenative C-C Bond Formation

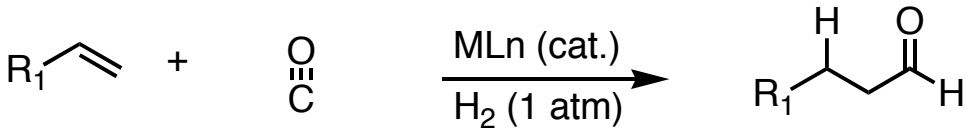


Fragment A: 1 C-C bond using hydrogenative coupling

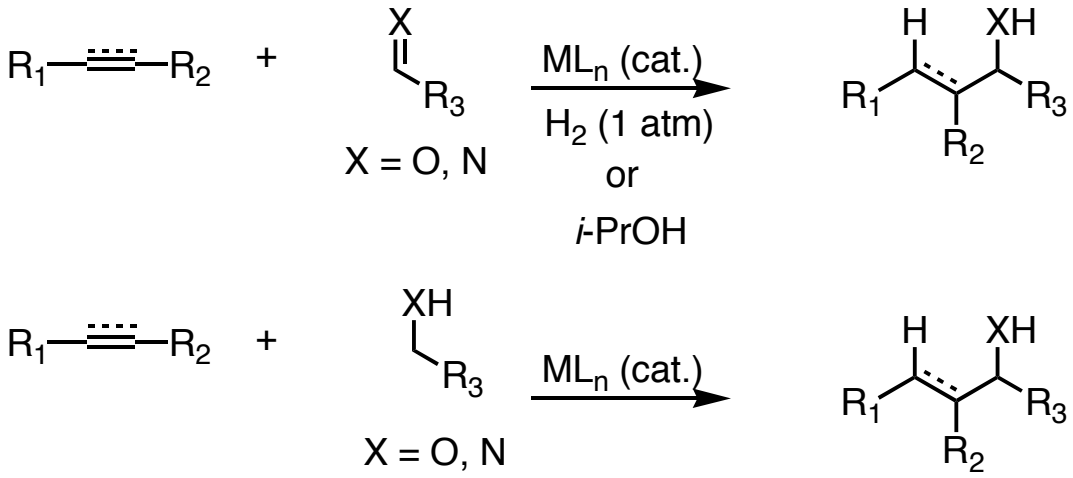
Fragment B: 4 C-C bonds using hydrogenative coupling

Reductive C-C Bond Formation

"Old" chemistry: hydroformylation (carbonylative hydrogenation):



Krische group methodology: C-C coupling via hydrogenation or transfer hydrogenation:



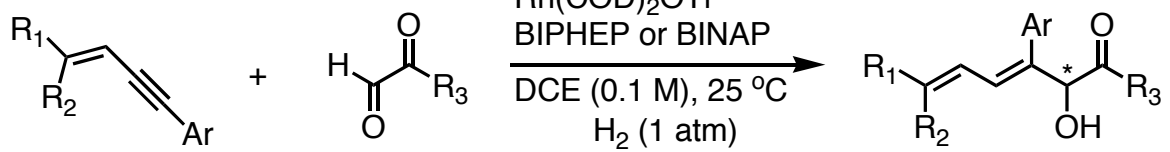
Reviews: Patman, R. L.; Bower, J. F.; Kim, I. S.; Krische, M. J. *Aldrichimica Acta* **2008,** *41,* 95.
Bower, J. F.; Krische, M. J. *Top. Organomet. Chem.* **2011,** *43,* 107.

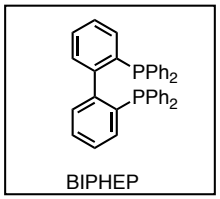
Condensation of Aldehydes and Alkynes

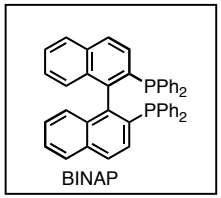
Main concept: heterolytic activation of elemental hydrogen by cationic Rh catalysts:

$$H_2 + Rh^+X^- \longrightarrow Rh\text{-}H + HX$$

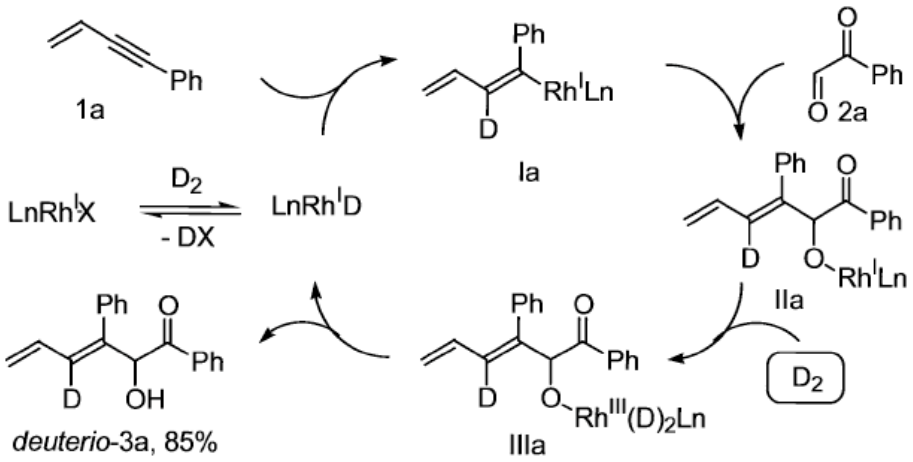
General Scheme:



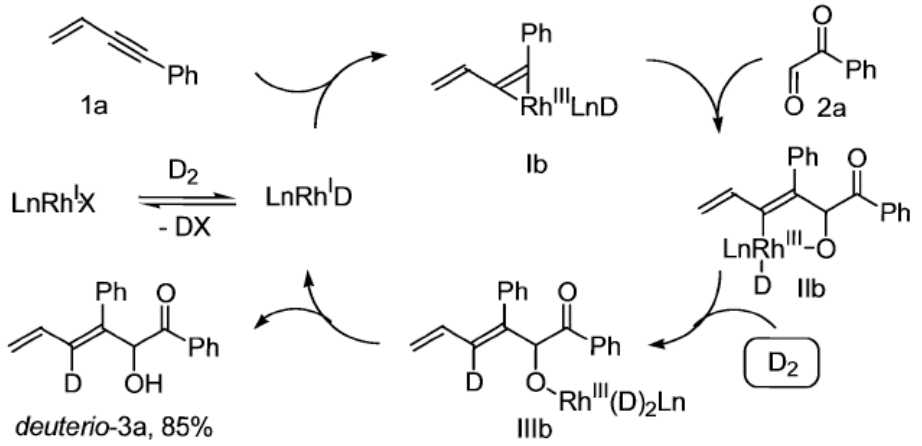




Hydrometallative Mechanism



Carbonyl Insertion Mechanism

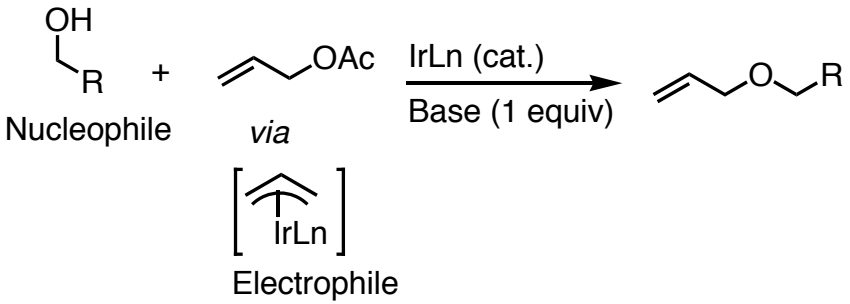


Jang, H-Y.; Huddleston, R. R.; Krische, M. J. *J. Am. Chem. Soc.* **2004,** *126,* 4664. See also Cho, C.-W.; Krische, M. J. *Org. Lett.* **2006,** *8,* 891.

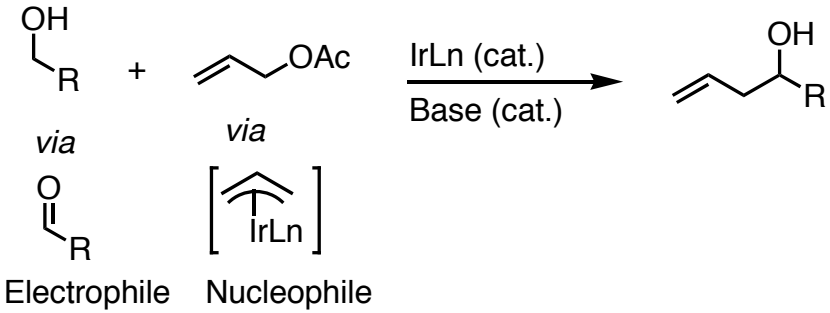
Iridium-Catalyzed Transfer Hydrogenative Coupling

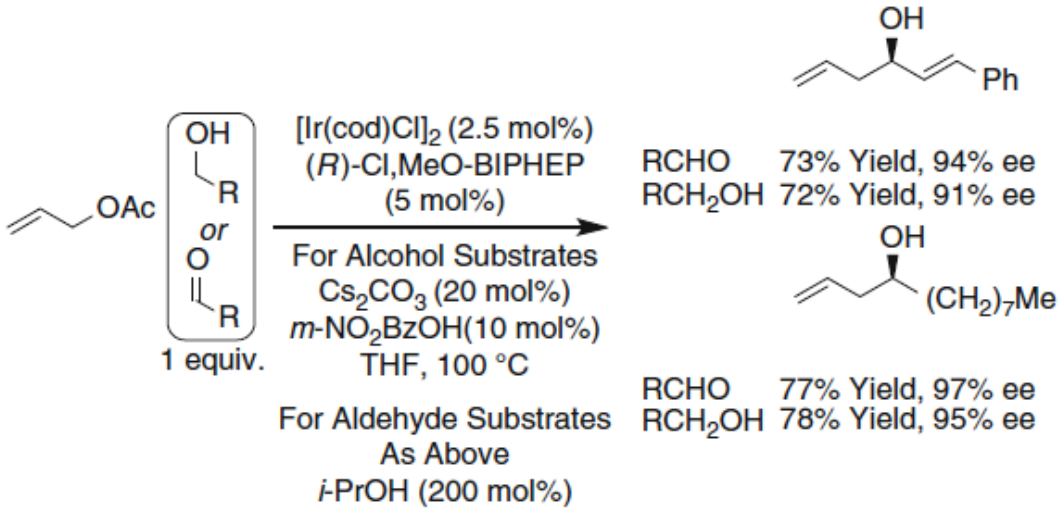
I. Allylation Reactions: polarity reversal of π-allyl iridium species:

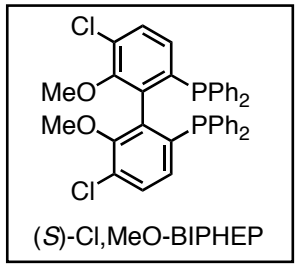
***O*-Allylation (conventional substitution):**



***C*-Allylation (Transfer Hydrogenative Coupling):**



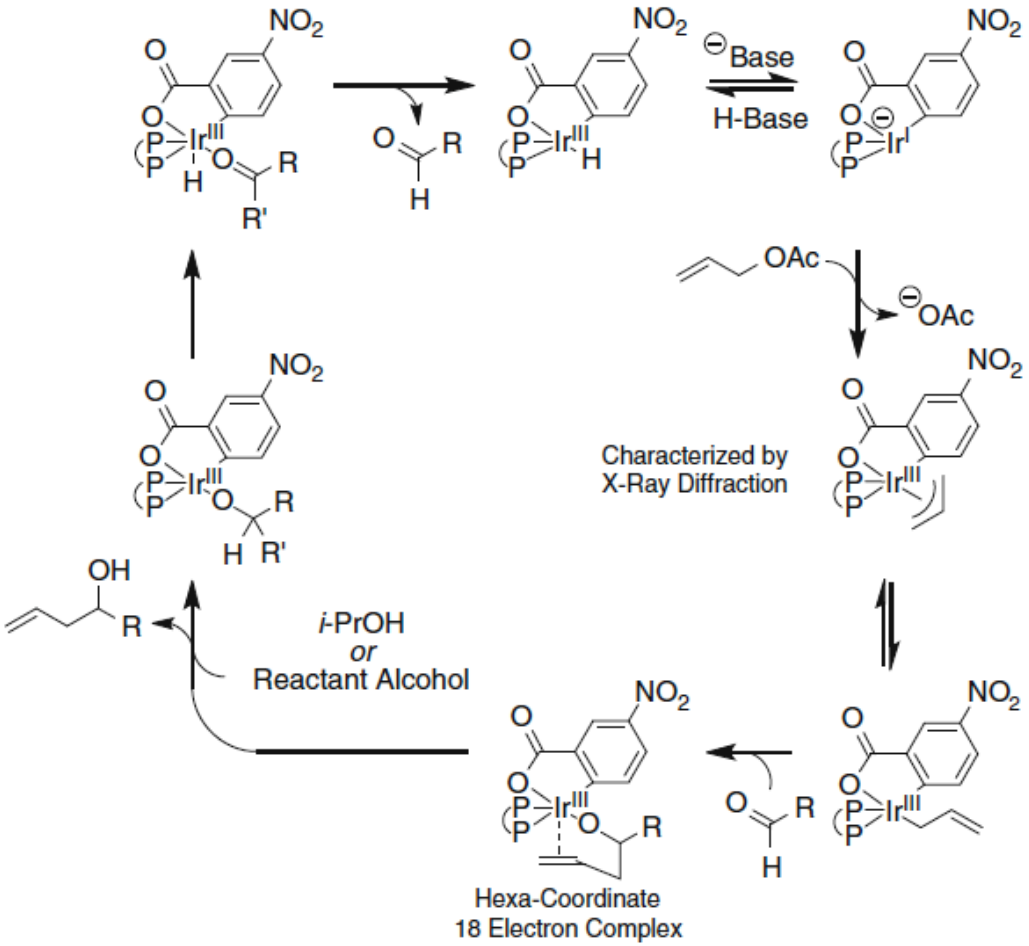




Kim, I. S.; N, N-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008,** *130,* 6340.
Kim, I. S.; N, N-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008,** *130,* 14891.

Proposed Mechanism for Iridium-Catalyzed Carbonyl Allylation

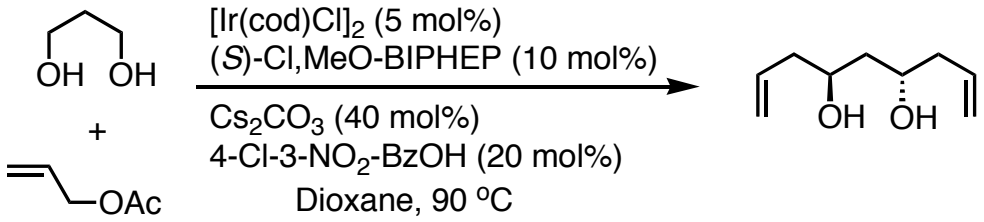
"Organic molecules, by definition, are composed of carbon and hydrogen. Hence, the ability to direct C-C coupling through the use of catalytic hydrogenation and transfer hydrogenation evokes numerous possibilities for the construction of diverse molecular architectures, circumventing use of preformed organometallic reagents." (Kim, I. S.; N, N-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008,** *130,* 14891.)



Copied from: Bower, J. F.; Krische, M. J. *Top. Organomet. Chem.* **2011,** *43,* 107.

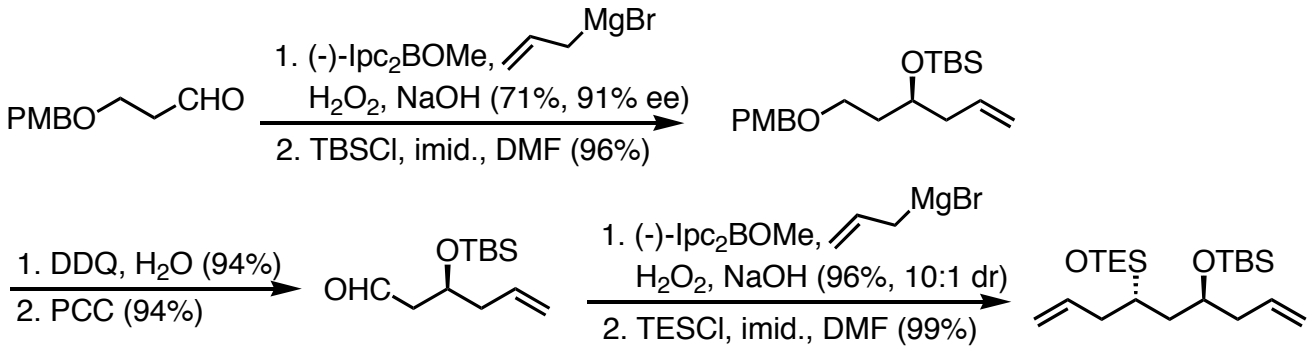
Utility of the Methodology

Synthesis of C_2-Symmetric Diol (use as a dialdehyde equivalent):



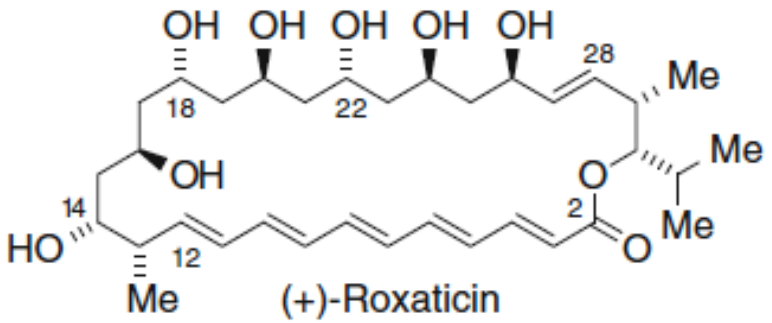
(title paper; see also Lu, Y.; Kim, I. S.; Hassan, A.; Del Valle, D. J.; Krische, M. J. *Angew. Chem. Int. Ed.* **2009,** *48,* 5018.

Alternative synthesis (classical route):



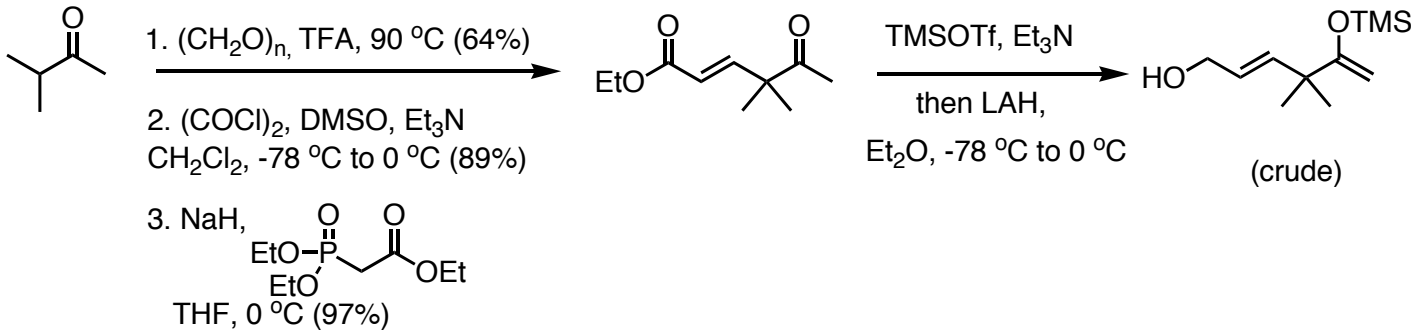
Smith, A. B.; Minbiole, K. P.; Verhoest, P. R.; Schelhass, M. *J. Am. Chem. Soc.* **2001,** *123,* 10942.

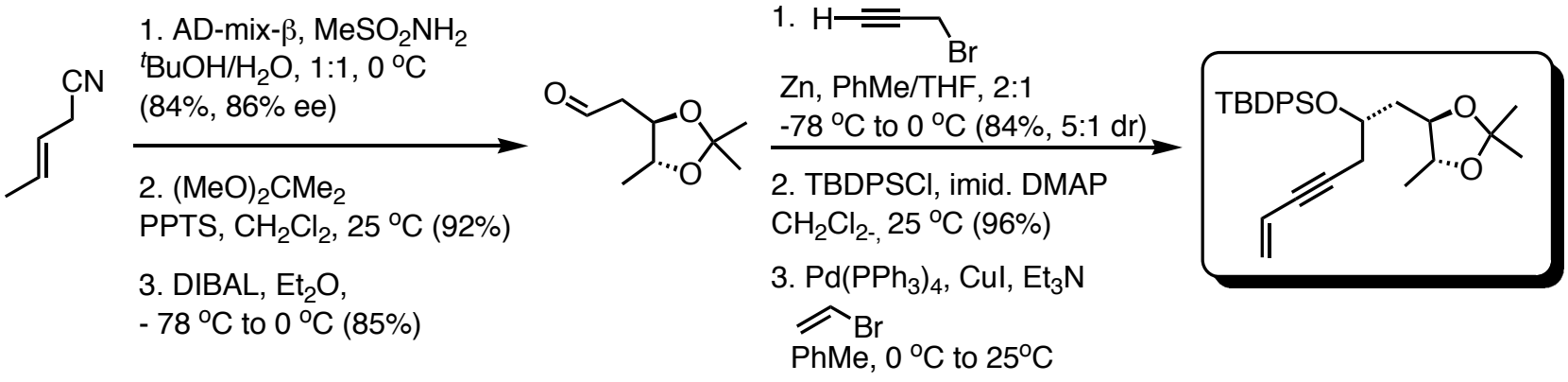
The methodology led to a concise synthesis of the polyketide natural product (+)-Roxaticin using iterative transfer hydrogenation reactions:



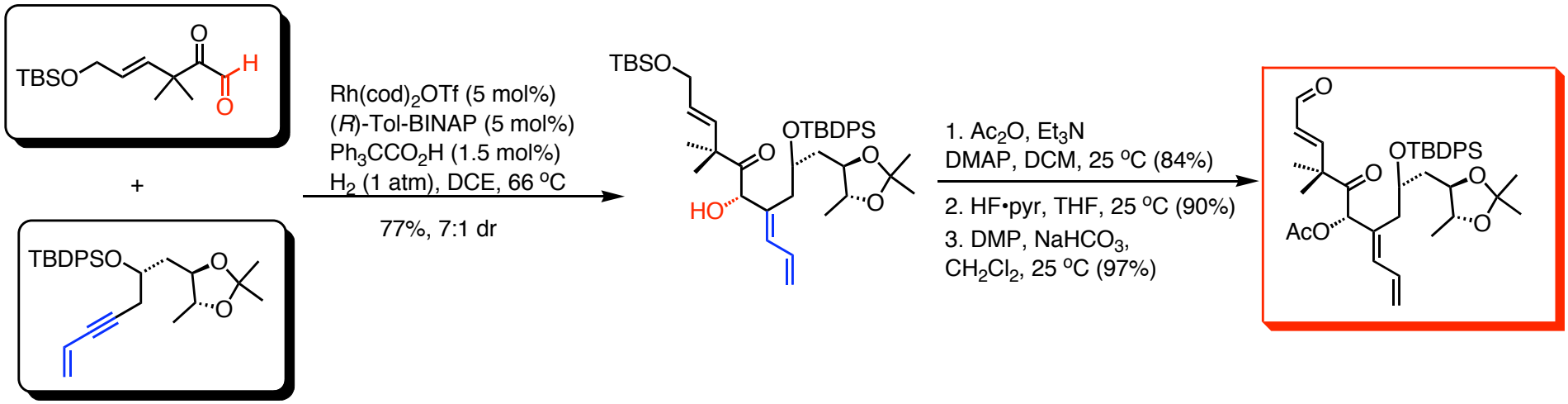
Han, S. B.; Hassan, A.; Kim, I. S.; Krische, M. J. *J. Am. Chem. Soc.* **2010,** *132,* 15559.

Synthesis of Fragment A

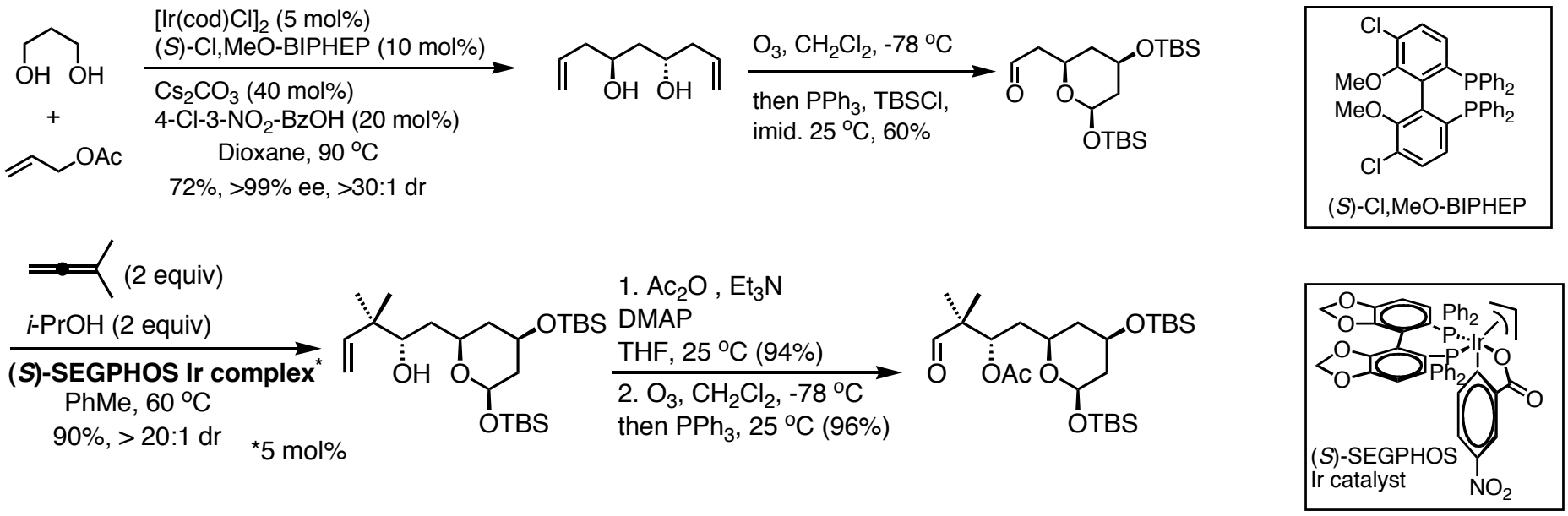




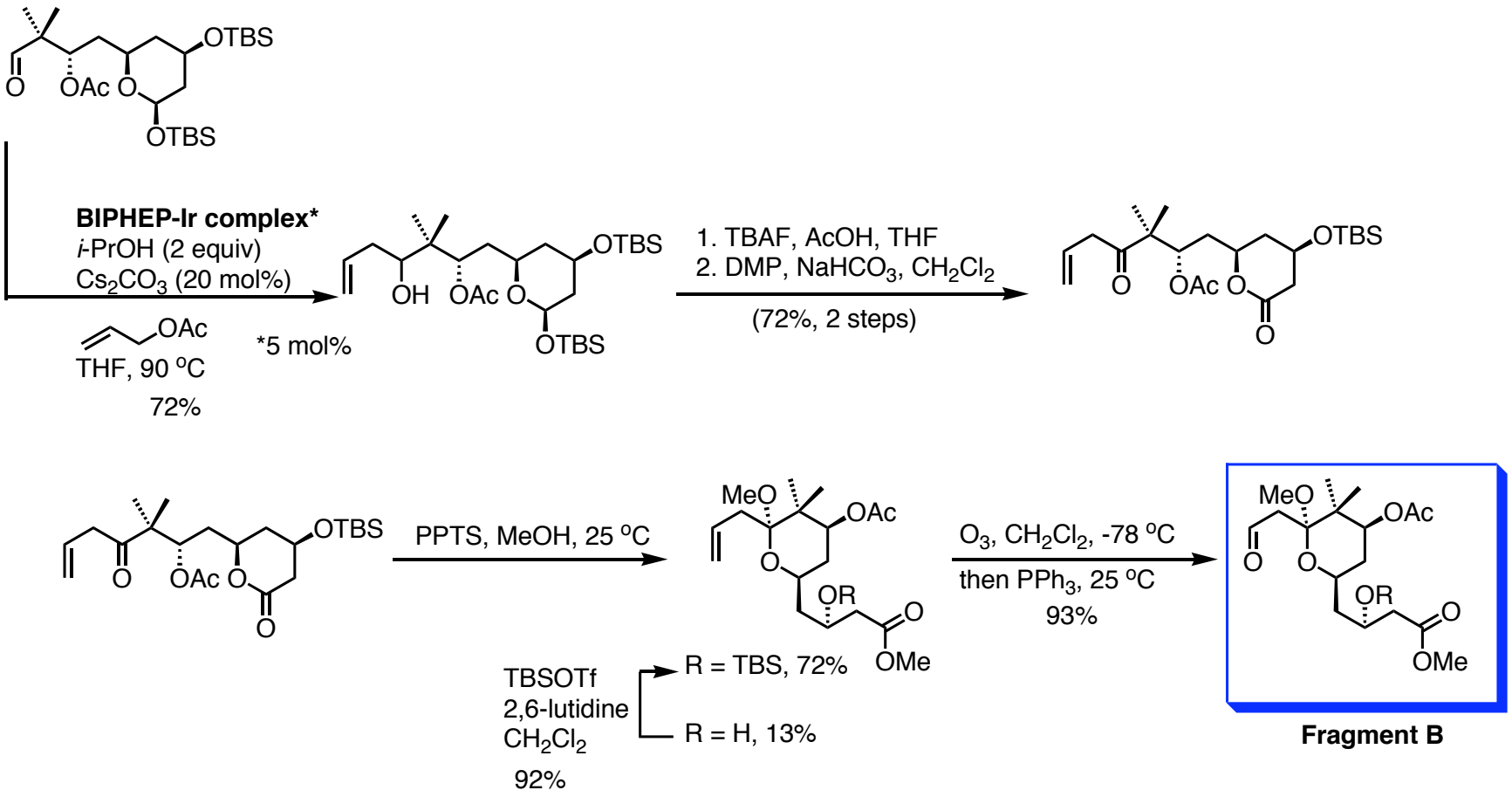
Synthesis of Fragment A



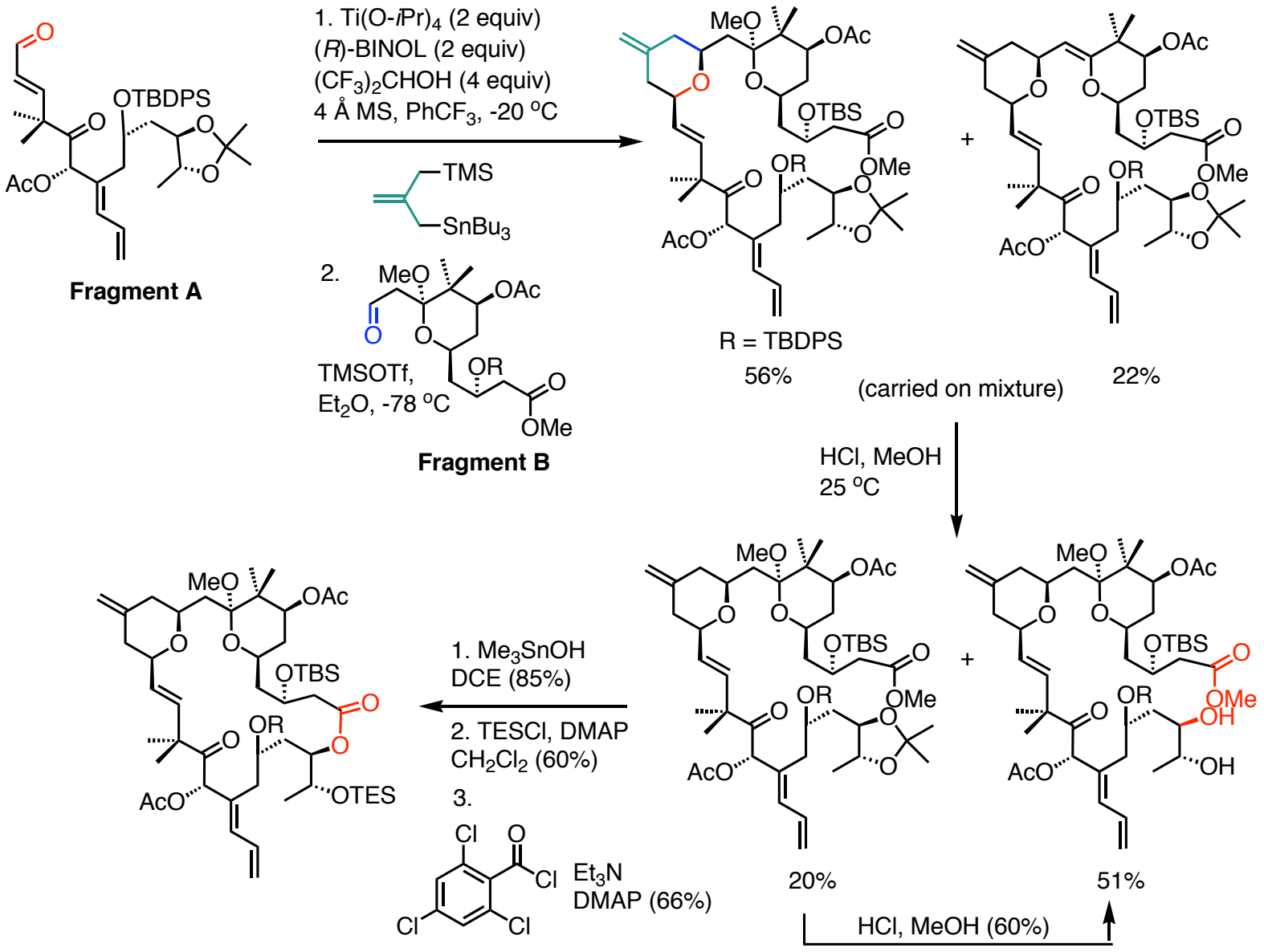
Fragment B Synthesis:



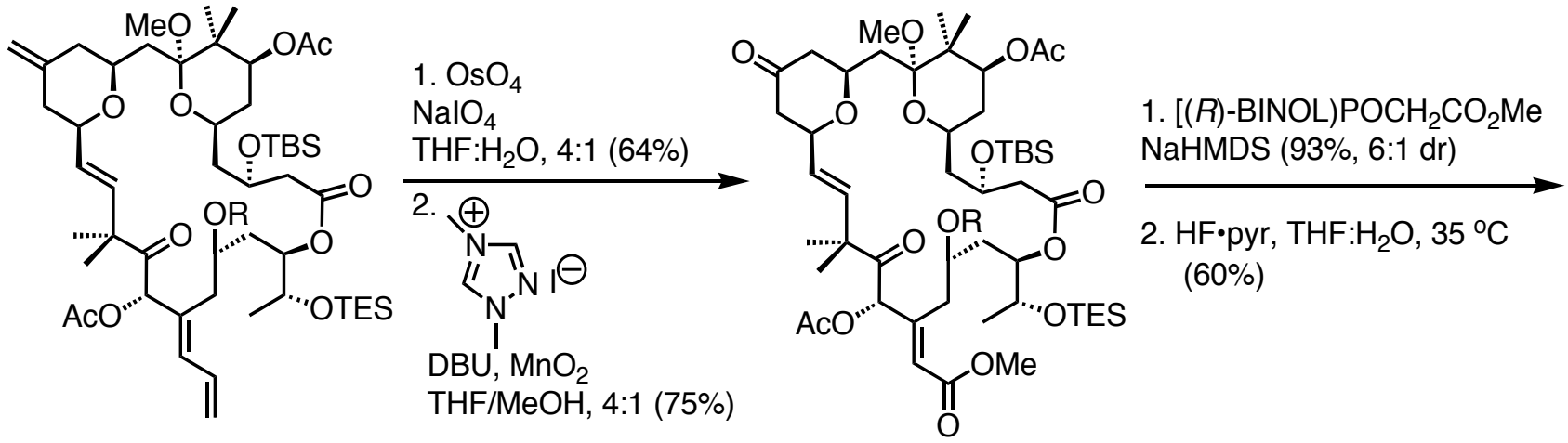
Synthesis of Fragment B

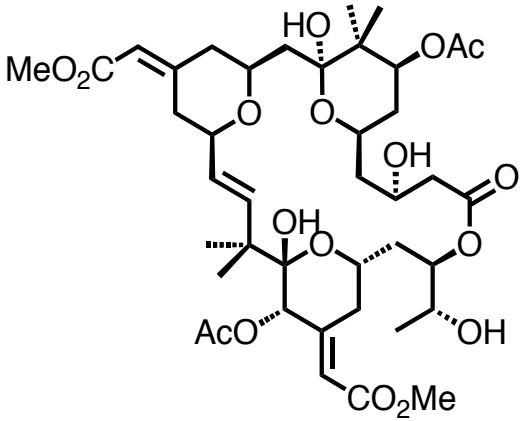


Uniting the Fragments and End Game



End Game (Continued)





Bryostatin 7

20 Linear steps
36 Total steps

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Summary

- The Krische group has published the shortest synthesis of a bryostatin to date.
- The point of convergence is earlier in the Krische synthesis than in the Wender synthesis
- The use of C-C bond forming hydrogenation in complex molecule synthesis showcases the utility of the methodology.