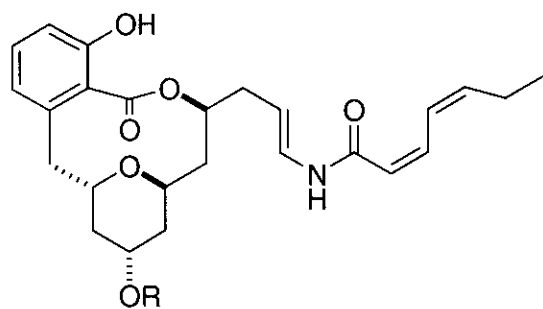


T. Hopkins
8/30/03

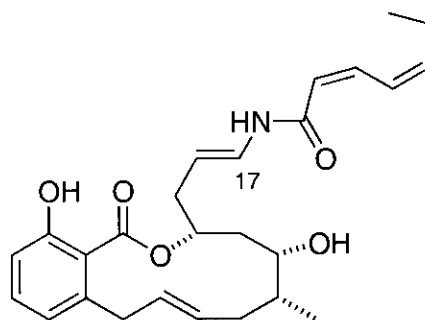
Formal Synthesis of (-)-Apicularen

Graetz, B. R.; Rychnovsky, S. D. *Organic Lett.* **2003**, *5*, 3357.

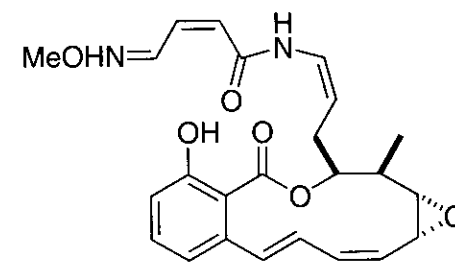
Benzolactone Enamides



R = H, (-)-apicularen A (1)
R = *N*-acetyl- β -glucosamine,
(-)-apicularen B (2)

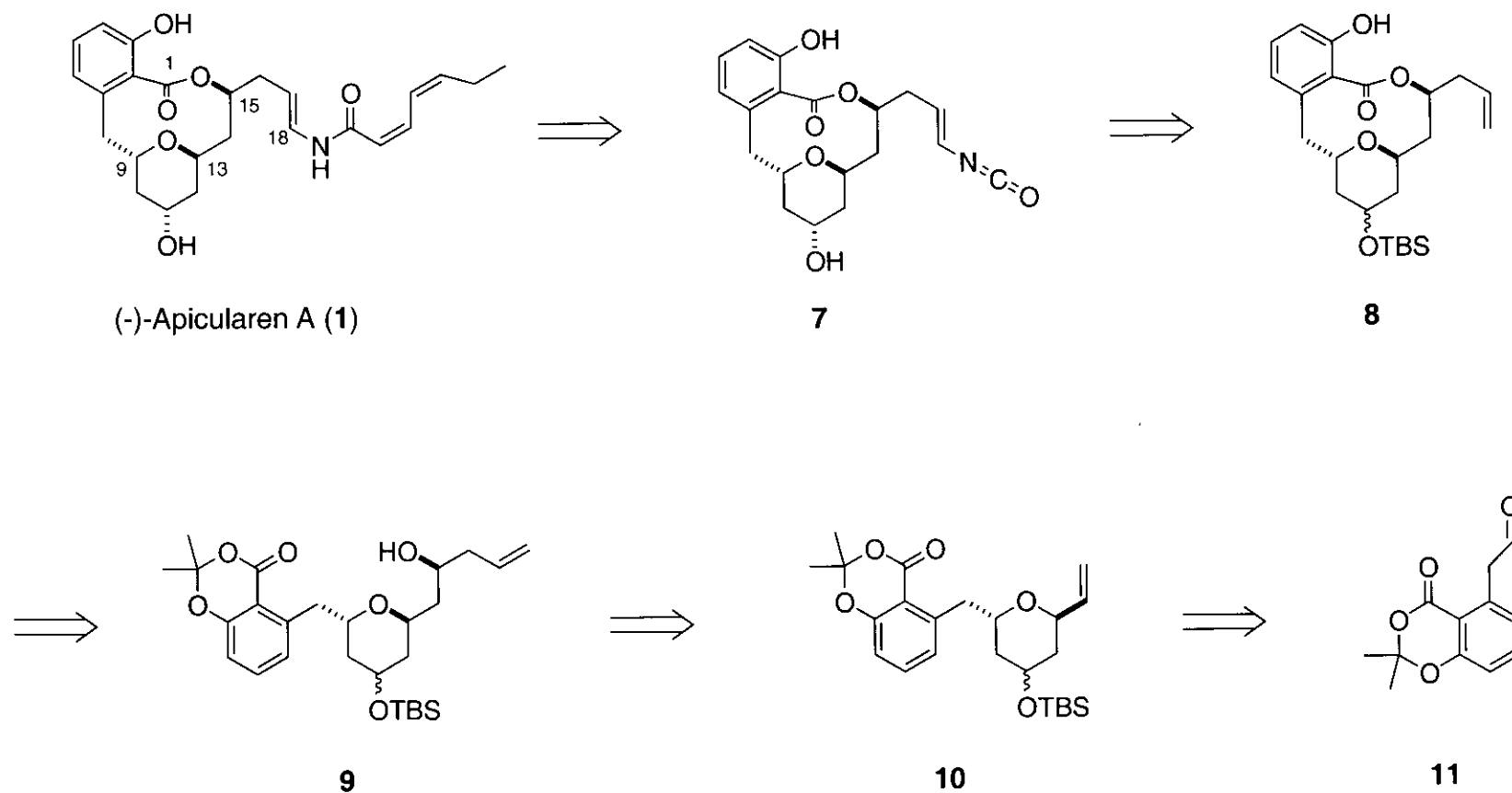


salicylihalamide A (17 E) (3)
salicylihalamide B (17 Z) (4)



oximidine I (5)

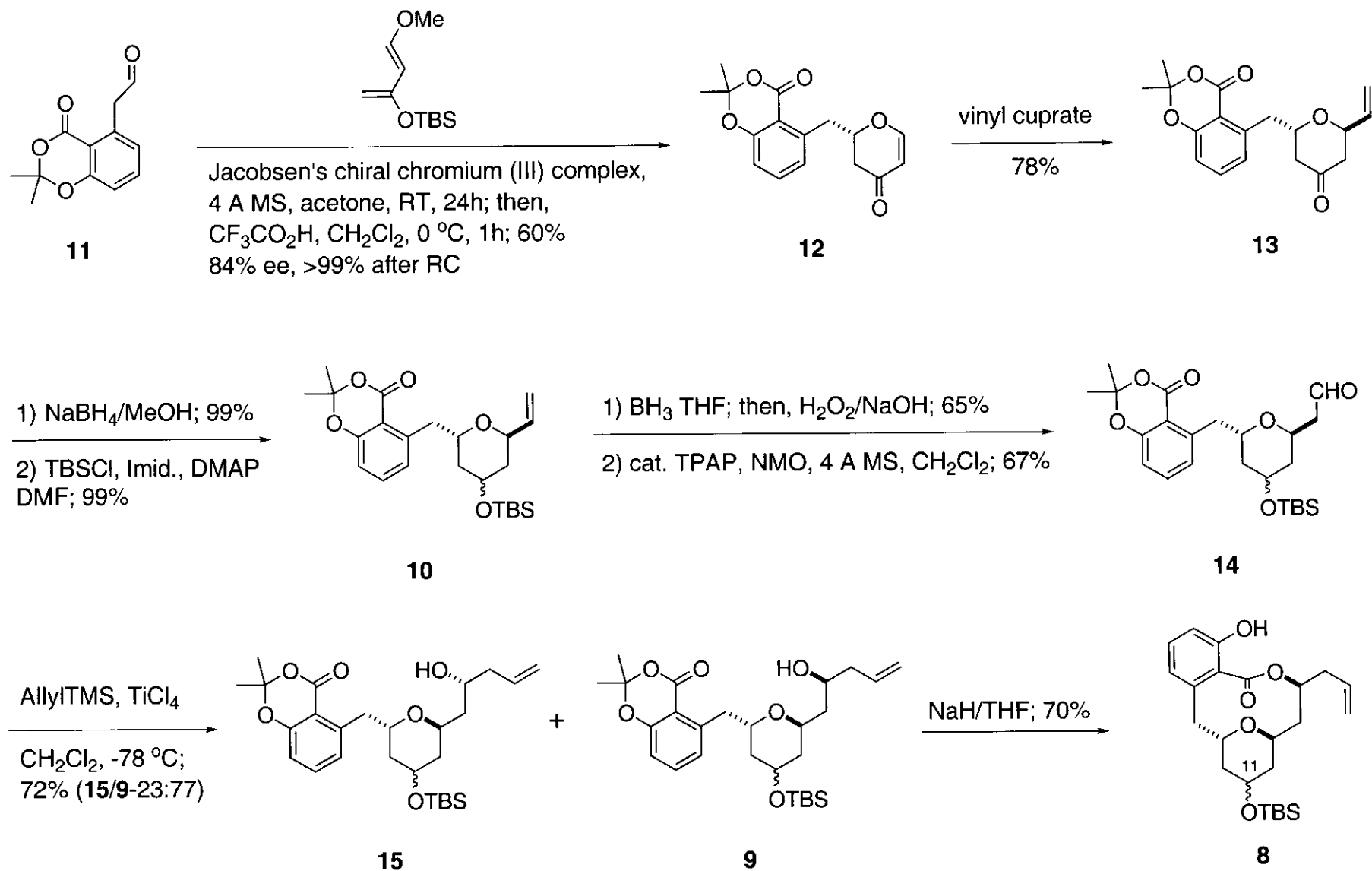
Retrosynthetic Analysis of Apicularen A



De Brabander, J. K.; Bhattacharjee, A. *Tetrahedron Lett.* **2000**, *41*, 8069.

Bhattacharjee, A.; Seguil, O. R.; De Brabander, J. K. *Tetrahedron Lett.* **2001**, *42*, 1217.

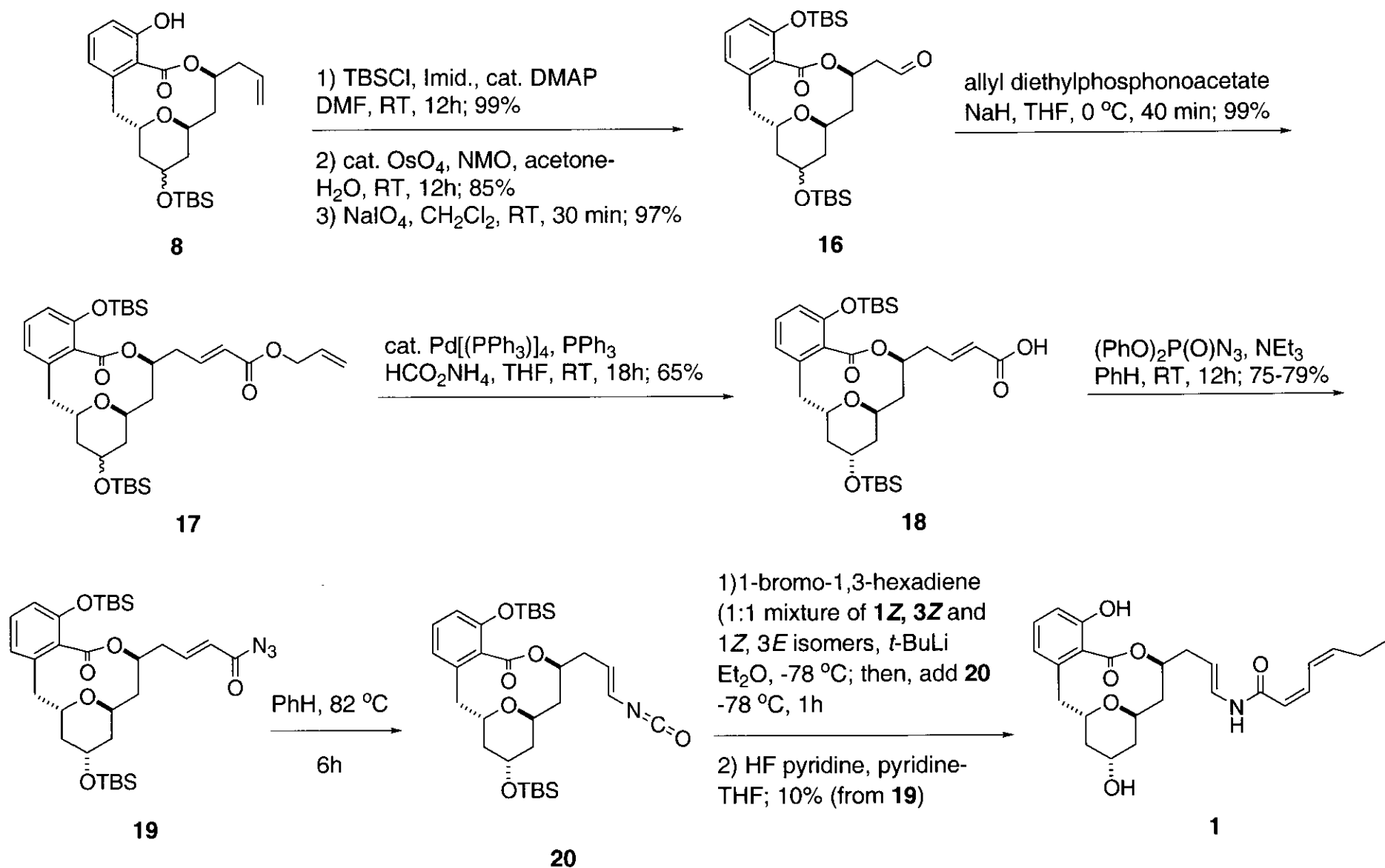
Synthesis of Apicularen A



De Brabander, J. K.; Bhattacharjee, A. *Tetrahedron Lett.* **2000**, *41*, 8069.

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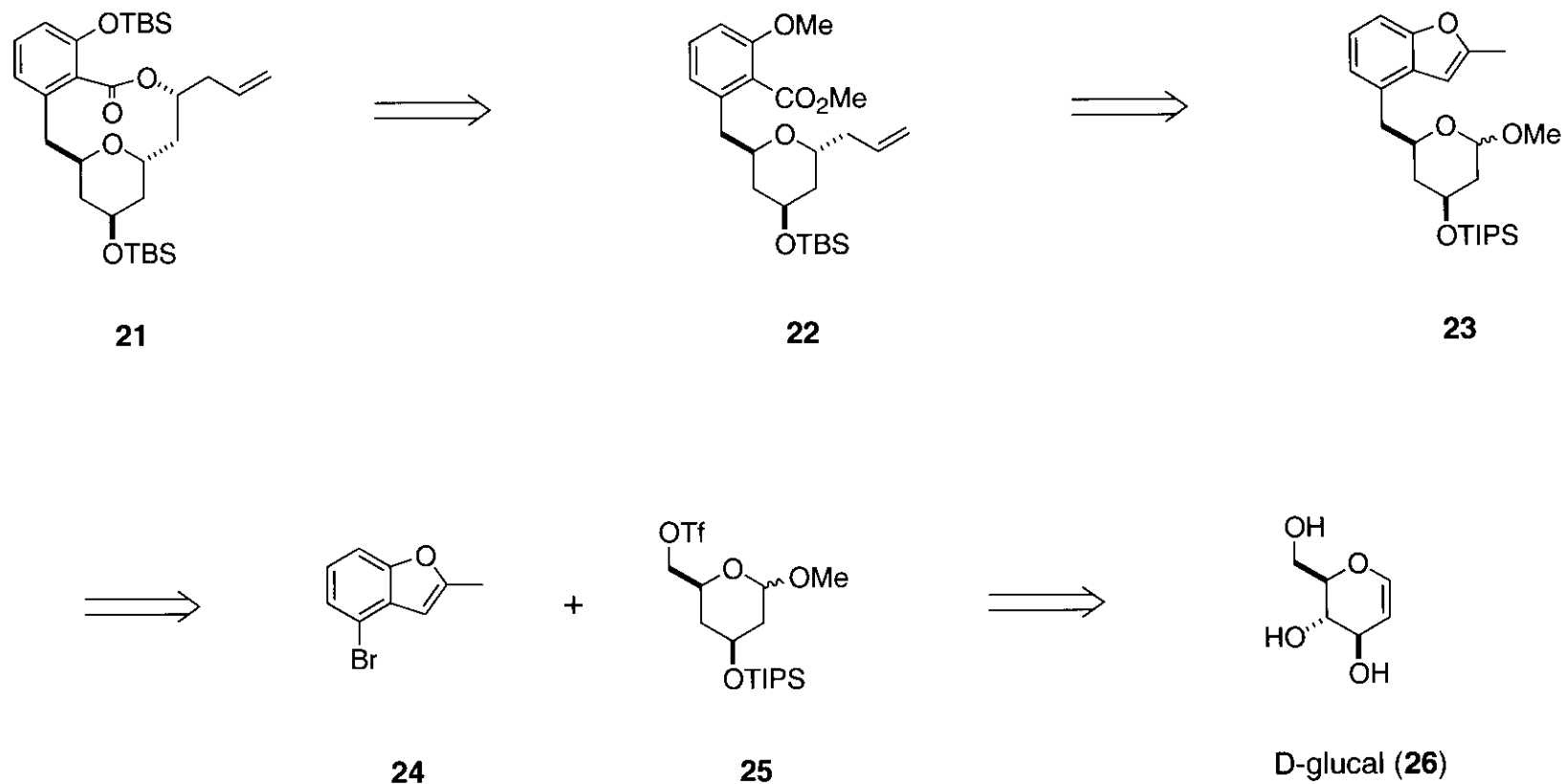
Completion of the Total Synthesis of Apicularen A



Bhattacharjee, A.; Seguil, O. R.; De Brabander, J. K. *Tetrahedron Lett.* **2001**, *42*, 1217.

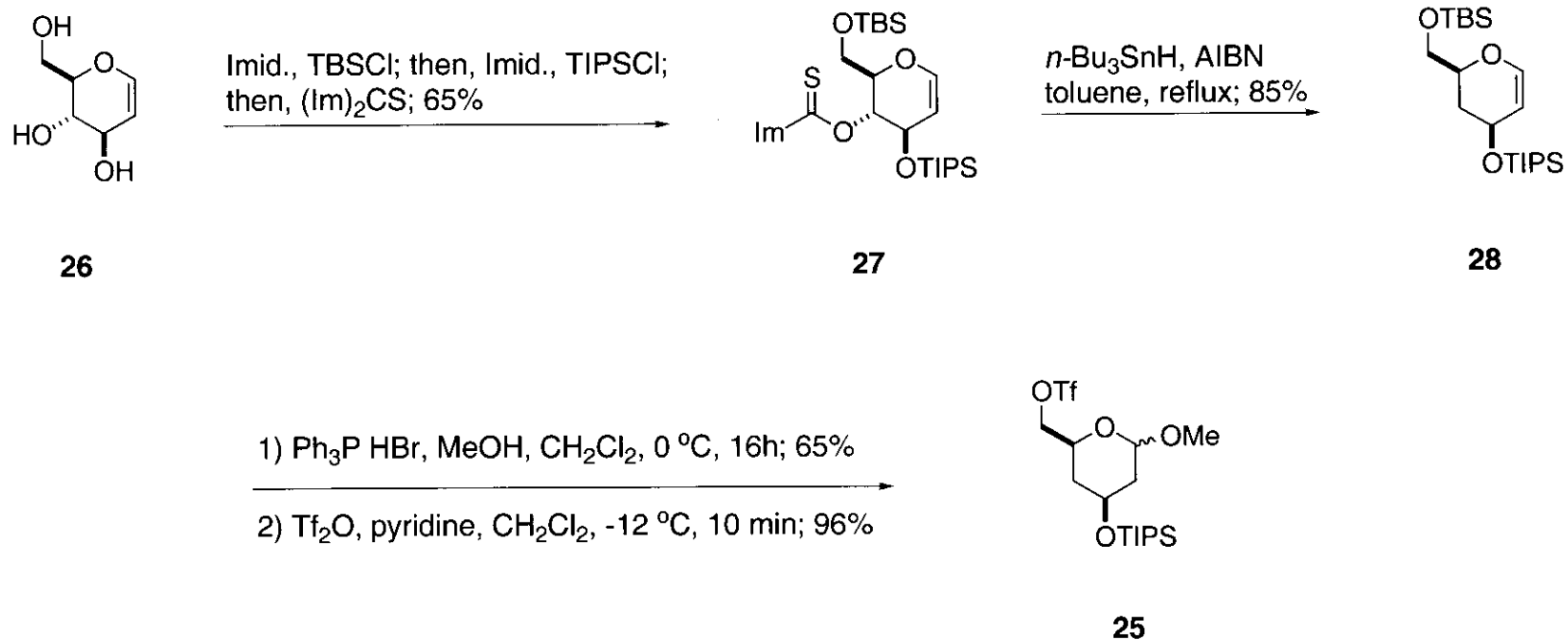
Tamara Hopkins @ Wipf Group

Retrosynthetic Analysis of (+)-Apicularen



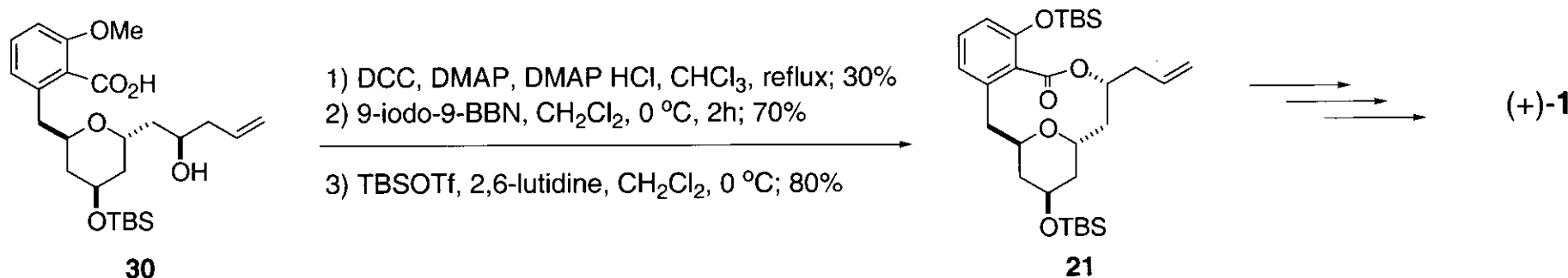
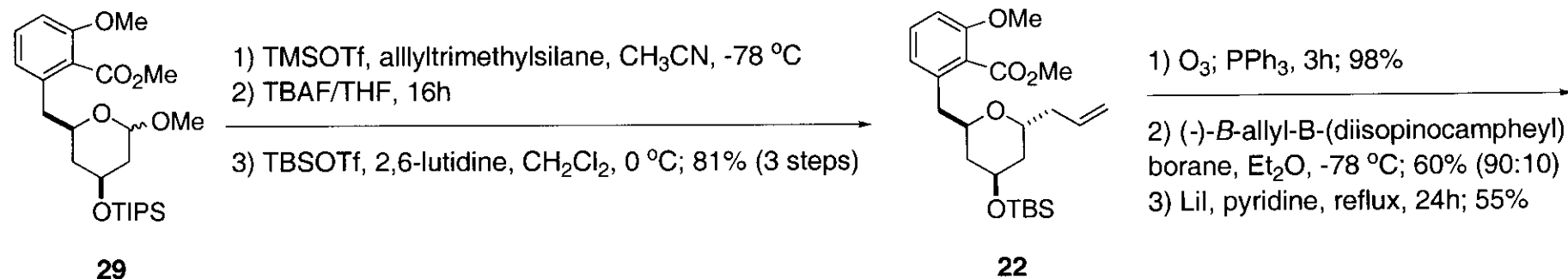
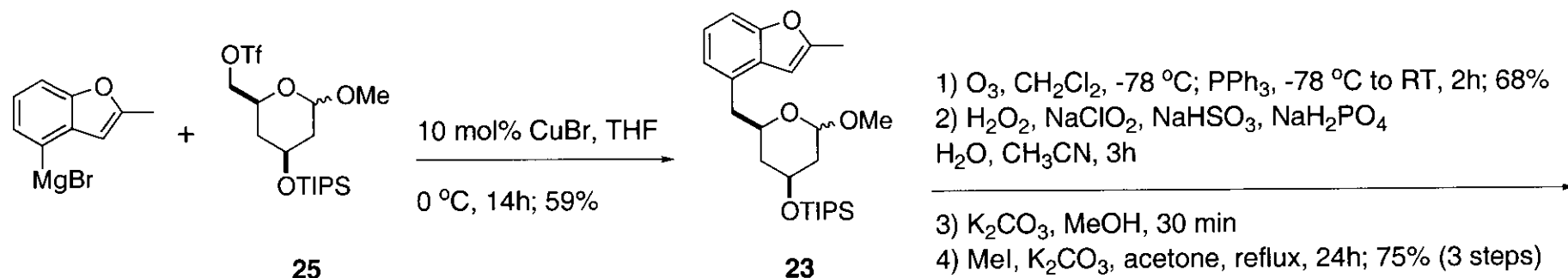
Lewis, A.; Stefanuti, I.; Swain, S. A.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2001**, 42, 5549.

Construction of Pyran 25



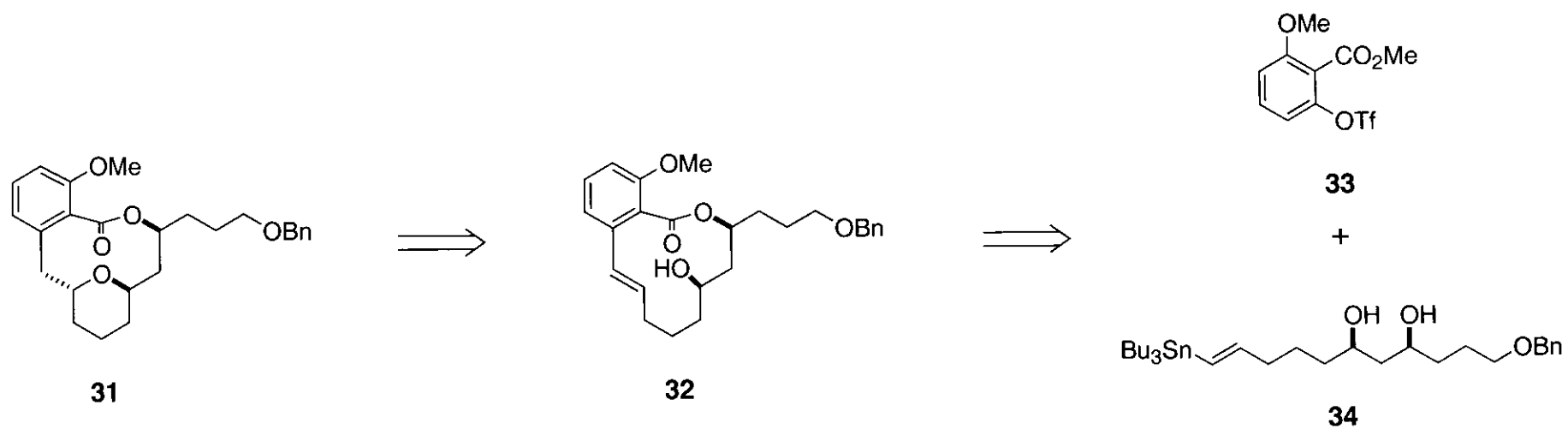
Lewis, A.; Stefanuti, I.; Swain, S. A.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2001**, *42*, 5549.

Formal Total Synthesis of (+)-Apicularen A



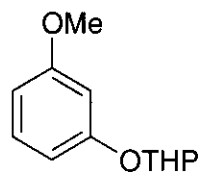
Lewis, A.; Stefanuti, I.; Swain, S. A.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2001**, 42, 5549.

Retrosynthetic Analysis of a Core Structure of Apicularen A



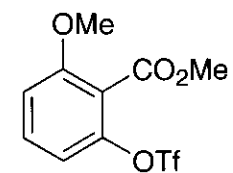
Kuhnert, S. M.; Maier, M. E. *Org. Lett.* **2002**, *4*, 643.

Synthesis of Building Blocks

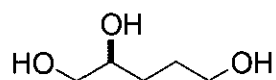


35

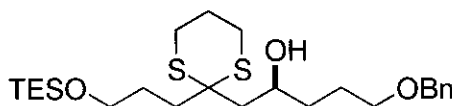
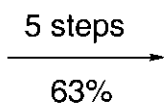
- 1) *n*-BuLi, Et₂O, 0 °C; then, CO₂; then, H₃O⁺; 77%
2) MeI, DBU; 85%
3) Tf₂O, pyridine, CH₂Cl₂; 93%



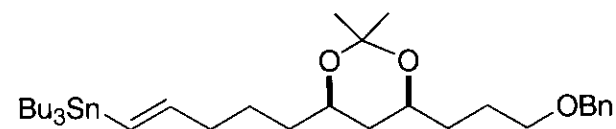
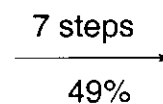
33



36



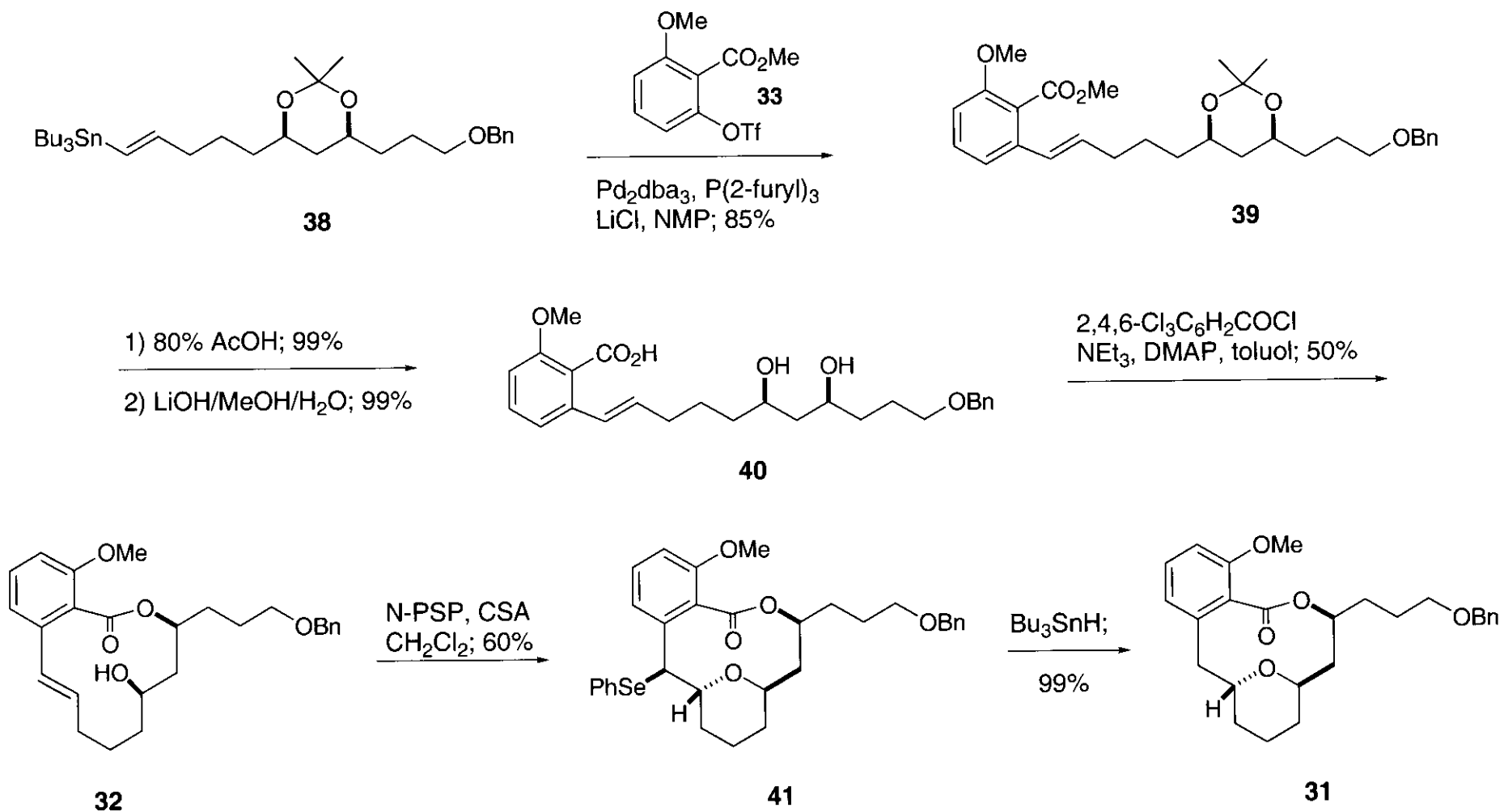
37



38

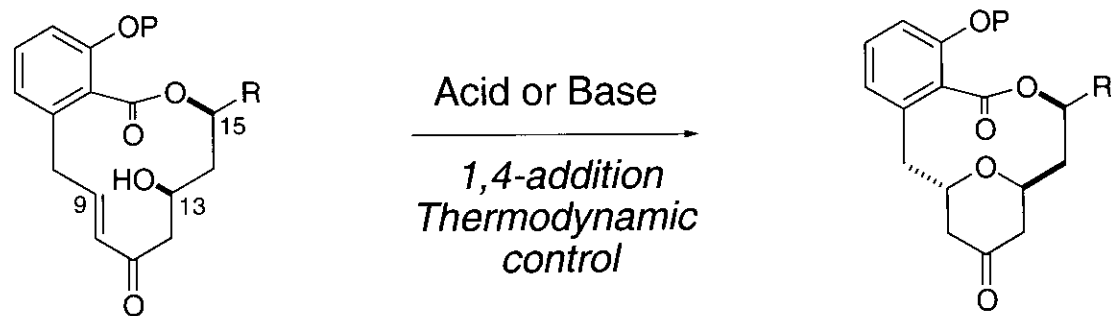
Kuhnert, S. M.; Maier, M. E. *Org. Lett.* 2002, 4, 643.

Coupling, Macrolactonization and Transannular Etherification



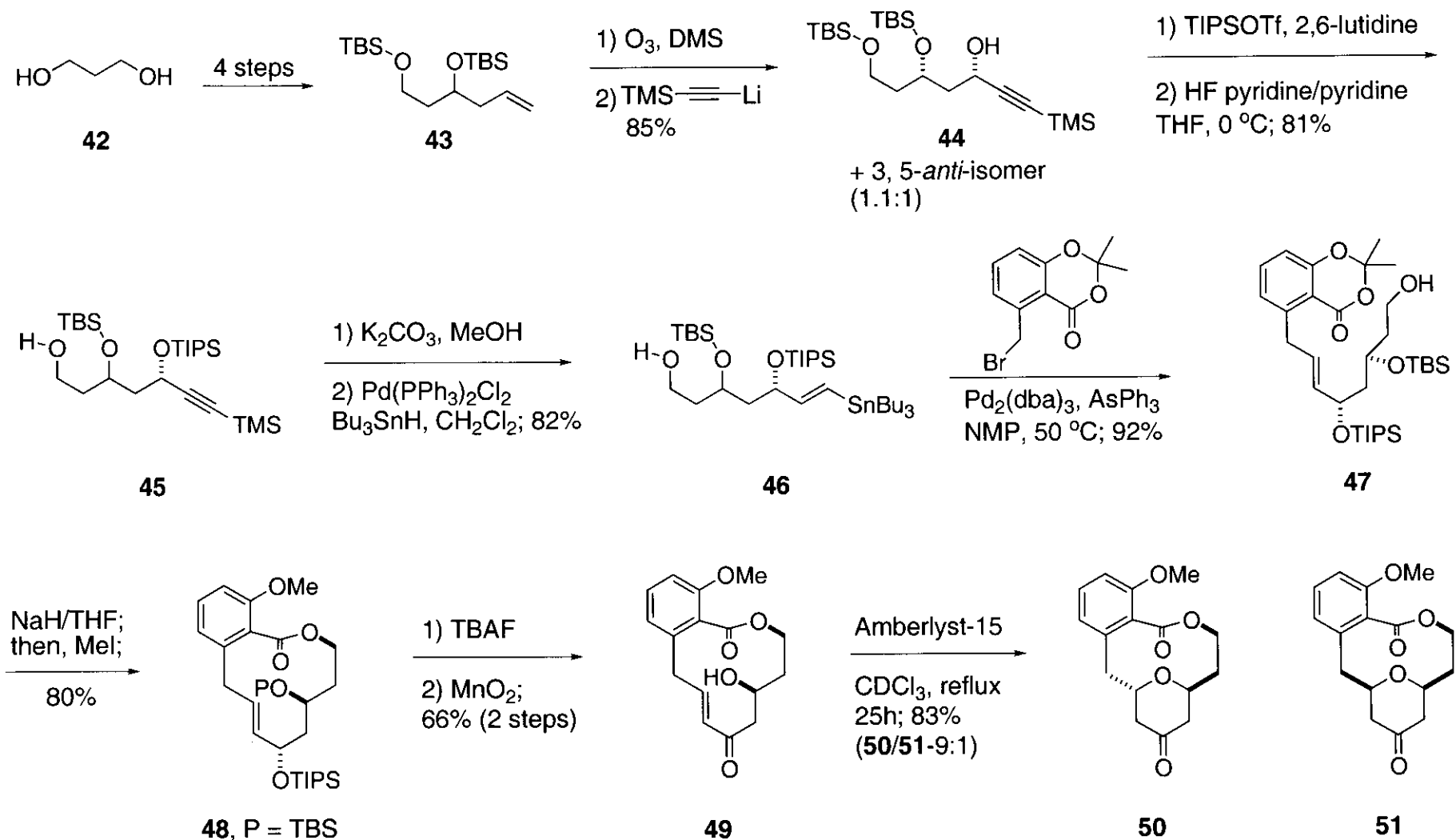
Kuhnert, S. M.; Maier, M. E. *Org. Lett.* **2002**, *4*, 643.

Proposed Transannular Conjugate Addition Pathway



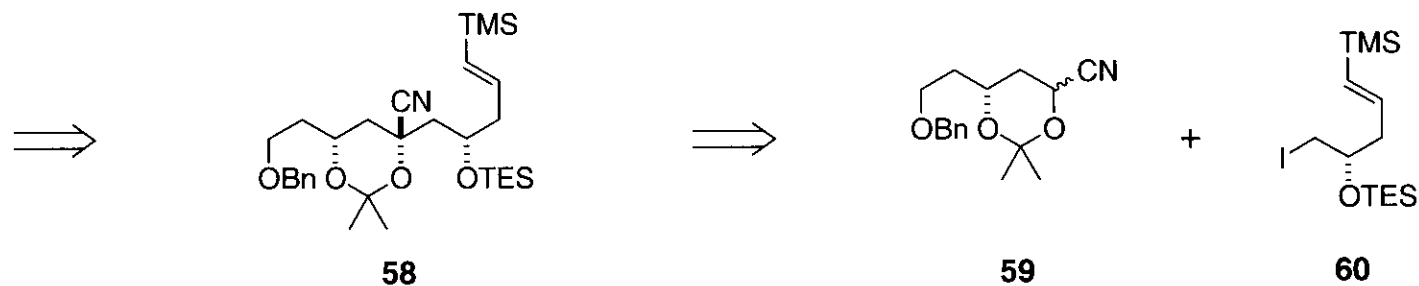
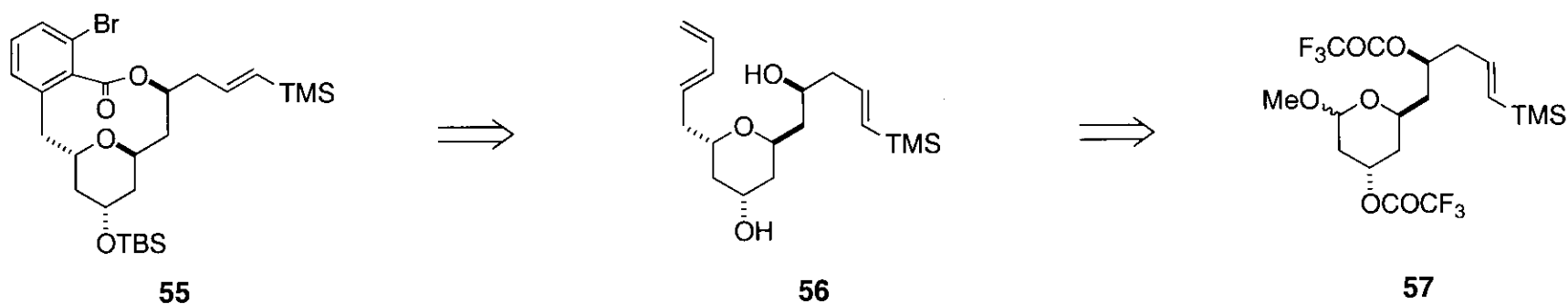
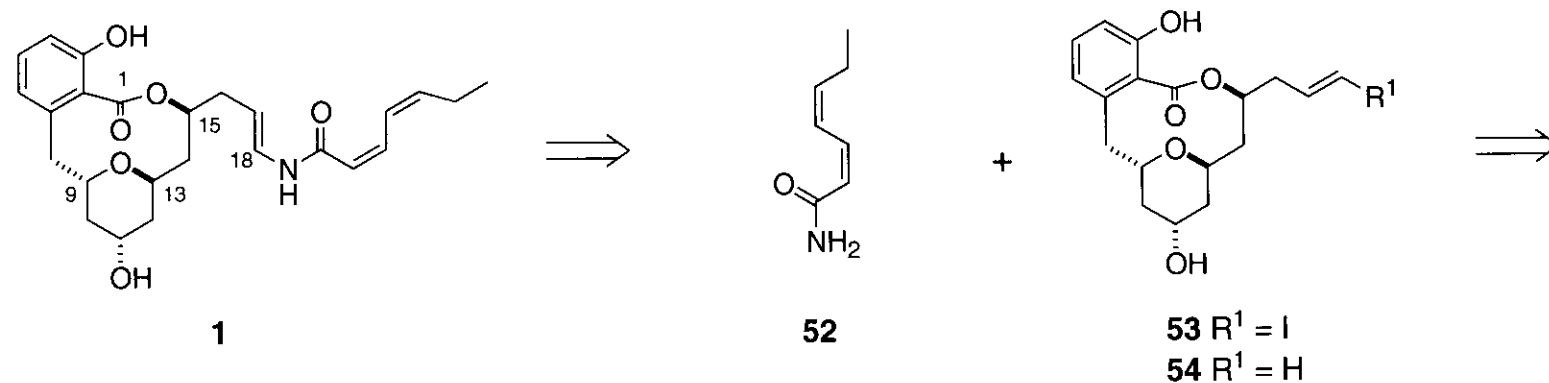
Hilli, F.; White, J. M.; Rizzacasa, M. A. *Tetrahedron Lett.* **2002**, 43, 8507.

Synthesis of the Core of Apicularen A by Transannular Conjugate Addition



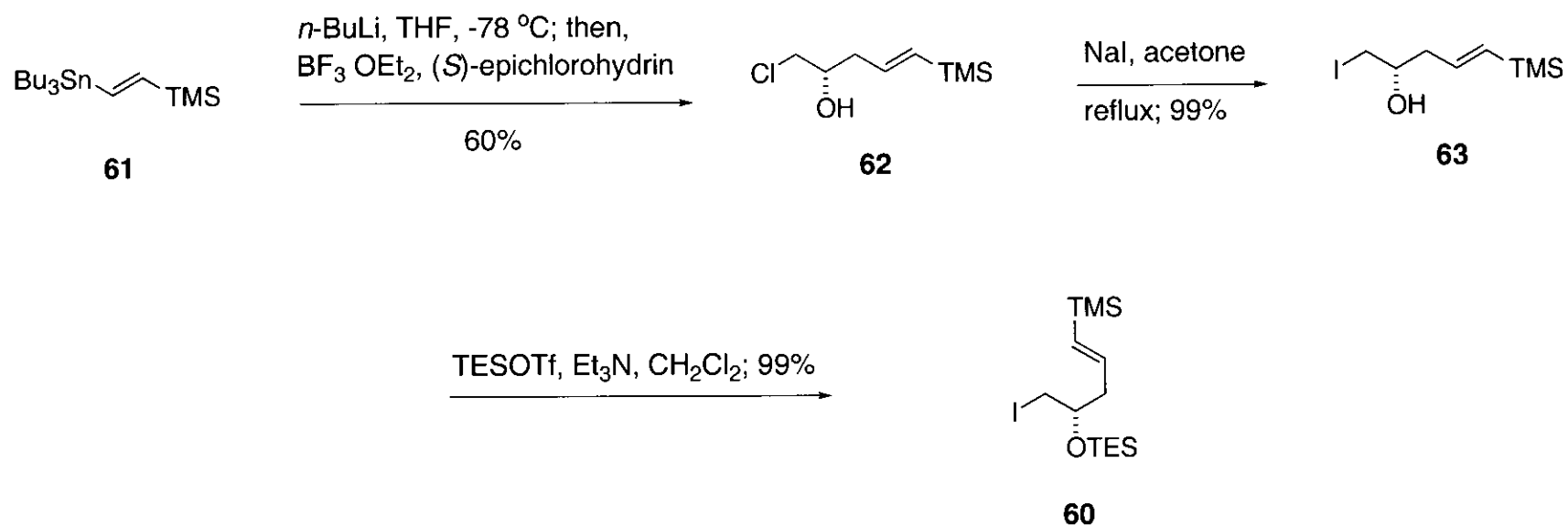
Hilli, F.; White, J. M.; Rizzacasa, M. A. *Tetrahedron Lett.* **2002**, *43*, 8507.

Retrosynthetic Analysis of (-)-Apicularen A



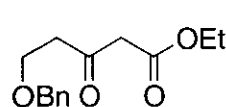
Graetz, B. R.; Rychnovsky, S. D. *Organic Lett.* **2003**, *5*, 3357.

Synthesis of Fragment 60

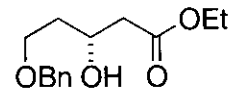
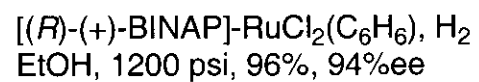


Graetz, B. R.; Rychnovsky, S. D. *Organic Lett.* **2003**, *5*, 3357.

Synthesis of Cyanohydrin Acetonide 59



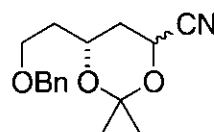
64



65

1) TMSCl, Et₃N, CH₂Cl₂
2) DIBAL-H, Et₂O, -78 °C
3) TMSCN, 18-C-6/KCN (cat.)
CH₂Cl₂

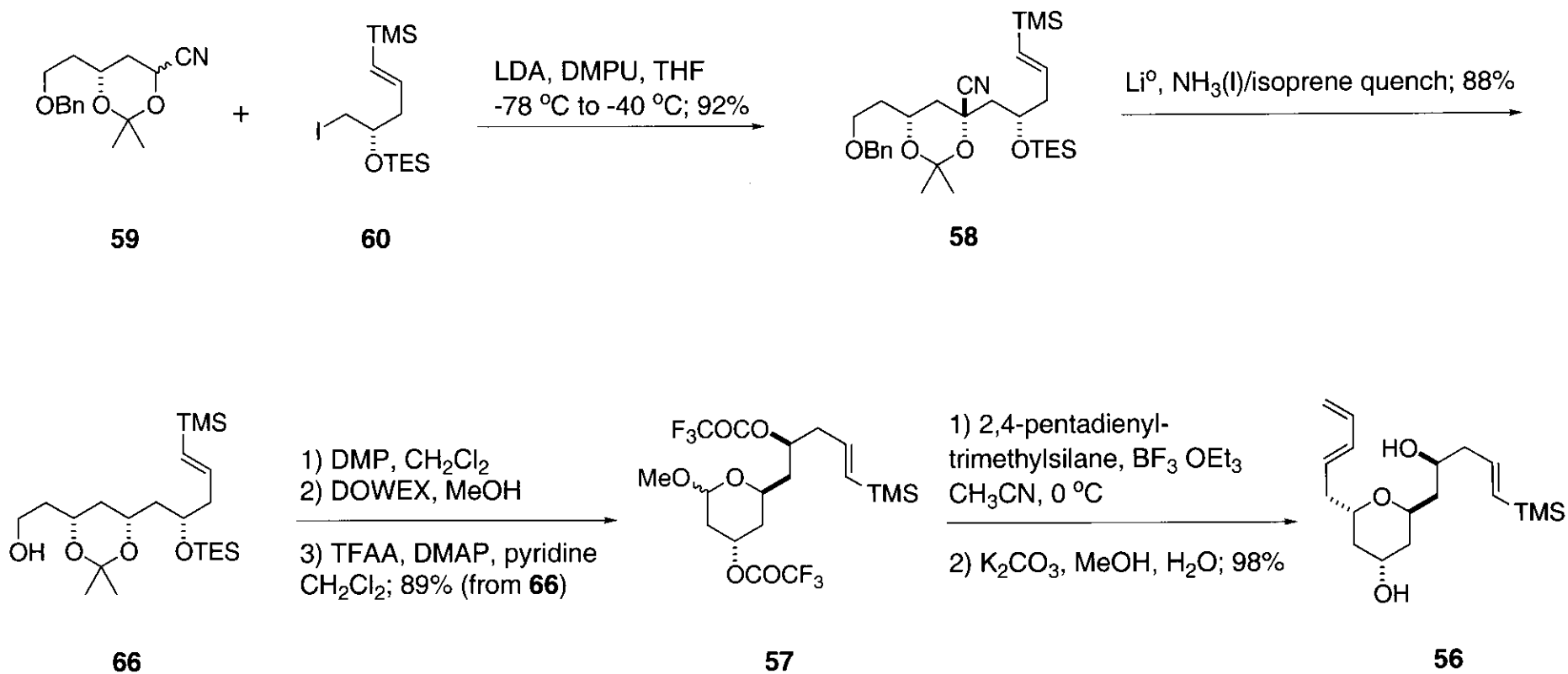
4) 2,2-dimethoxypropane,
acetone, CSA (cat.);
80% (from 65)



59

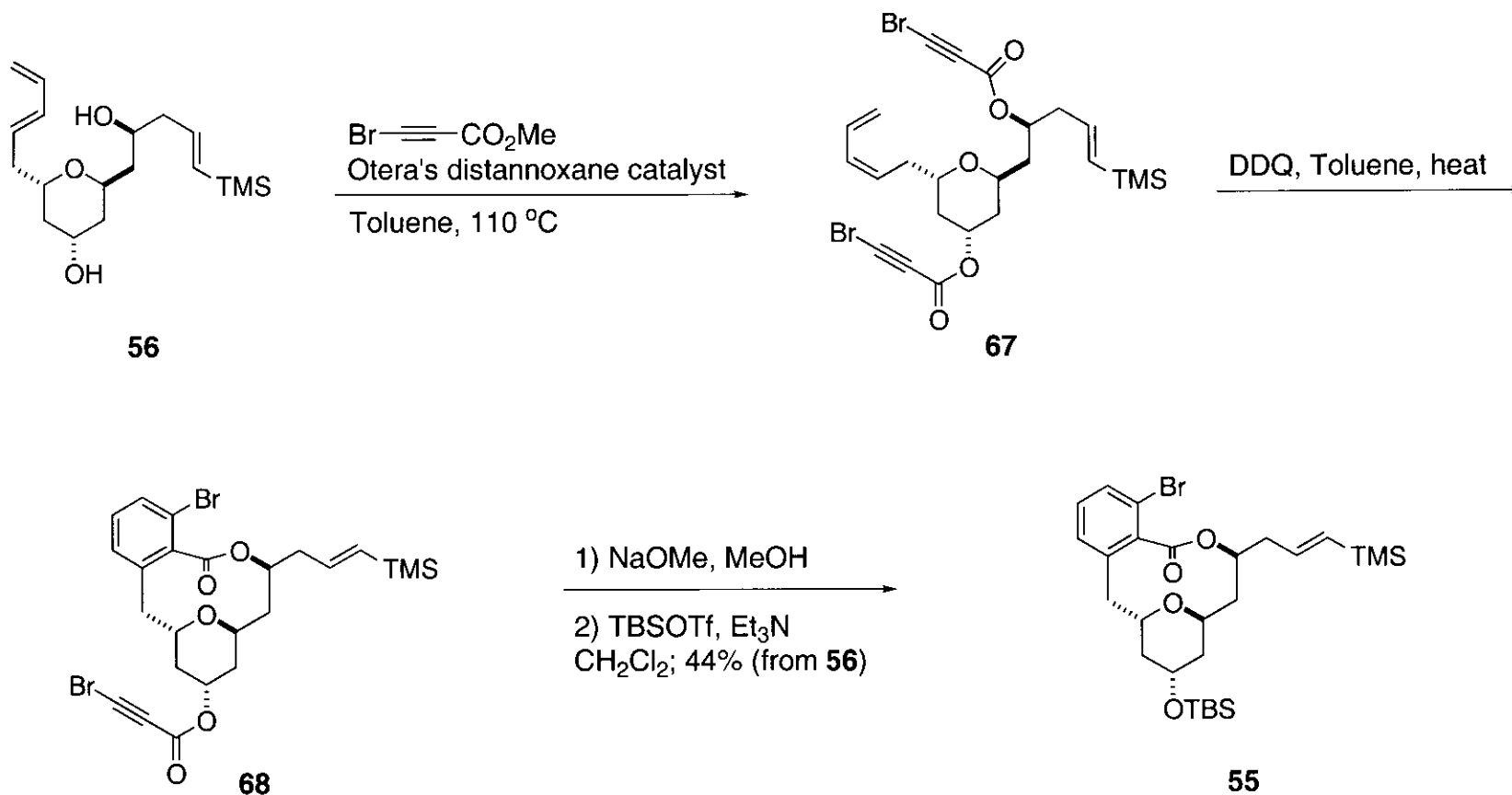
Graetz, B. R.; Rychnovsky, S. D. *Organic Lett.* **2003**, *5*, 3357.

Synthesis of Macrocycle Precursor



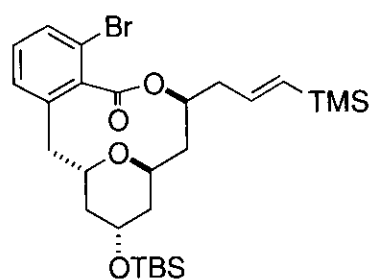
Graetz, B. R.; Rychnovsky, S. D. *Organic Lett.* **2003**, *5*, 3357.

Construction of the Macrocycle via an Intramolecular Diels-Alder Reaction



Graetz, B. R.; Rychnovsky, S. D. *Organic Lett.* **2003**, *5*, 3357.

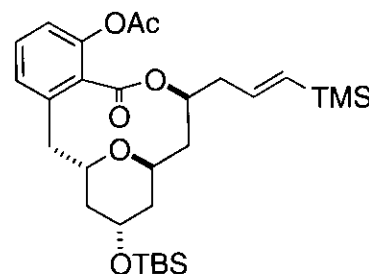
Completion of the Formal Synthesis of Apicularen A



55

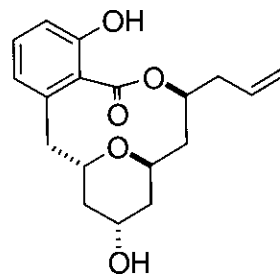
1) *n*-BuLi, THF, -78 °C;
then, (TMSO)₂; 50%

2) Ac₂O, DMAP
pyr., CH₂Cl₂; 94%



1) NIS, CH₃CN
2) K₂CO₃, MeOH

3) DOWEX, MeOH; 78%
4) Bu₃SnH, AIBN, PhH; 80%



54

Graetz, B. R.; Rychnovsky, S. D. *Organic Lett.* **2003**, *5*, 3357.