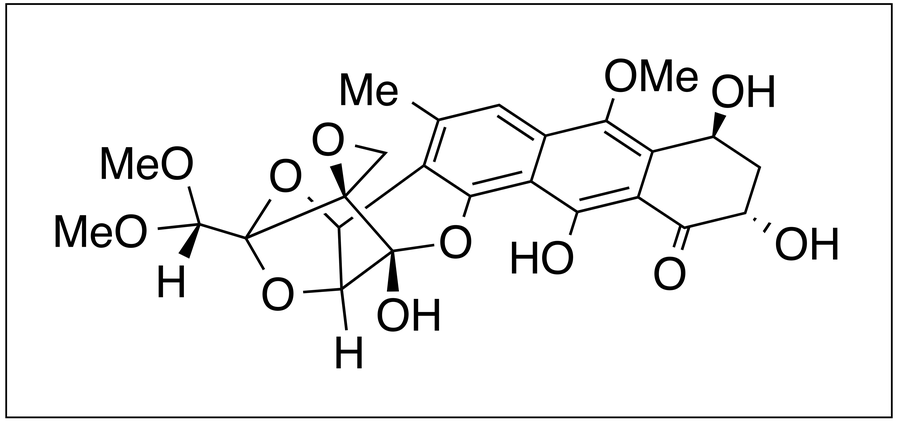
Total Synthesis of Trioxacarcin DC-45-A2



Nicolaou, K. C.; Cai, Q.; Qin, B.; Petersen, M. T.; Mikkelsen, R. J. T.; Heretsch, P.
Angew. Chem. Int. Ed. Engl. **2015**, *54*, 3074–3078.
DOI : 10.1002/anie.201410369

Valentin Soulard - Group Renaud
Journal Club - March, 12 2015

UNIVERSITÄT BERN

K. C. Nicolaou

> Born in Cyprus and emigrate then to England (University of London)

> PhD University of London (1972, Professors F. Sondheimer and P. J. Garratt)

> Postdoc at Columbia University (1972-1973, Professor T.J. Katz) and Harvard University (1973-1976, Professor E.J. Corey)

> Since 2013 : Professor at Rice University (Houston, Texas)

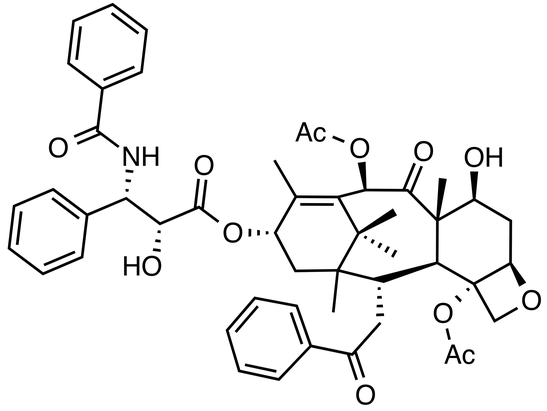
> Reasearch interest : Total synthesis of architecturally novel and biologically important natural products.

> Author or co-author of more than 725 publications, 67 patents and 6 books.

List of books :
- Classics in Total Synthesis I, II, III (respectively 1993, 2003, 2011)
- Molecules That Changed the World (2008)
- Handbook of Combinatorial Chemistry: Drugs, Catalysts, Materials, (2002)
- Selenium in Natural Products Synthesis (1984)

http://www.scripps.edu/nicolaou/kcn.html

K. C. Nicolaou : Natural Product Synthesis



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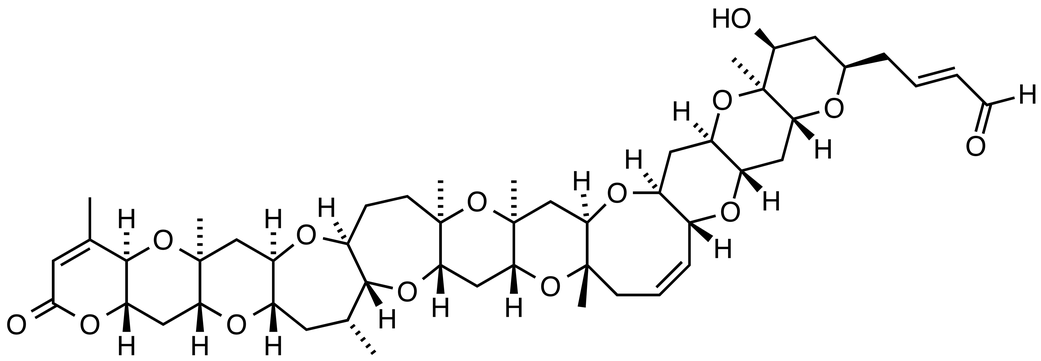
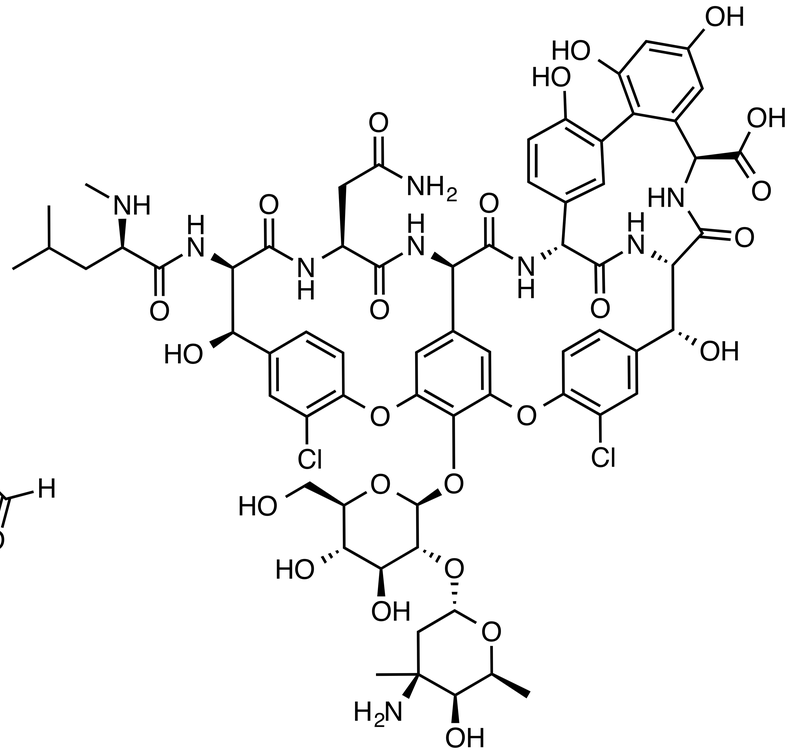


Brevetoxin B (1995)



Vancomycin (1998)

Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1995**, *117*, 624.
Nicolaou, K. C.; Liu, J. J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C. K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634.
Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Nantermet, P. G.; Claiborne, C. F.; Renaud, J.; Guy, R. K.; Shibayama, K. *J. Am. Chem. Soc.* **1995**, *117*, 645.
Nicolaou, K. C.; Ueno, H.; Liu, J. J.; Nantermet, P. G.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R. *J. Am. Chem. Soc.* **1995**, *117*, 653.

Nicolaou, K. C. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 588.

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Trioxacarcin DC-45-A2

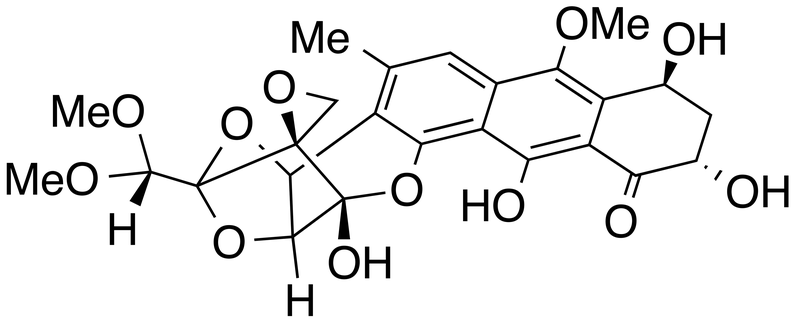
> Naturally occurring antitumor antibiotic

> Bacterial and eukaryotic cells metabolite

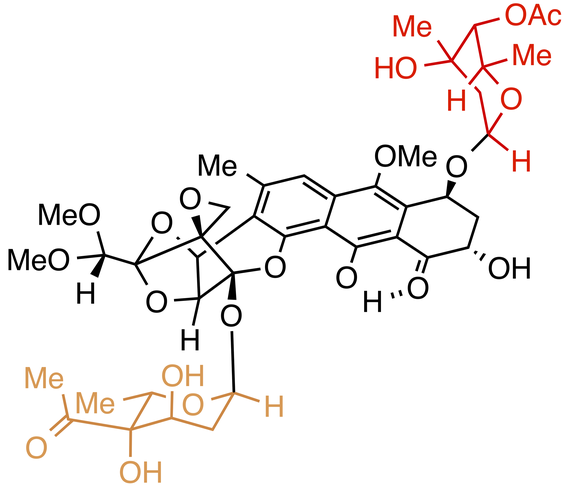
> Biosynthetic precursor to other biologically active member of the family

> Highly oxygenated and complex architecture

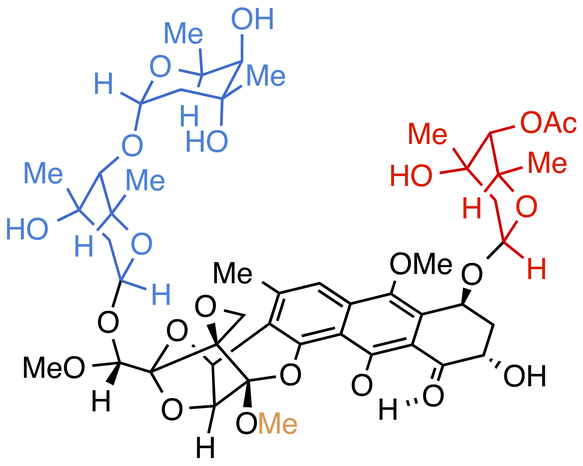
> Third synthesis of the compound



DC-45-A2



Trioxacarcin A



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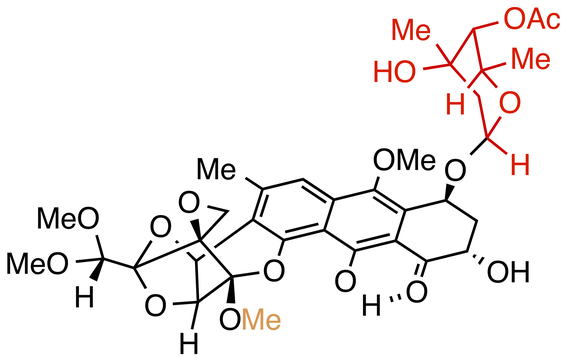
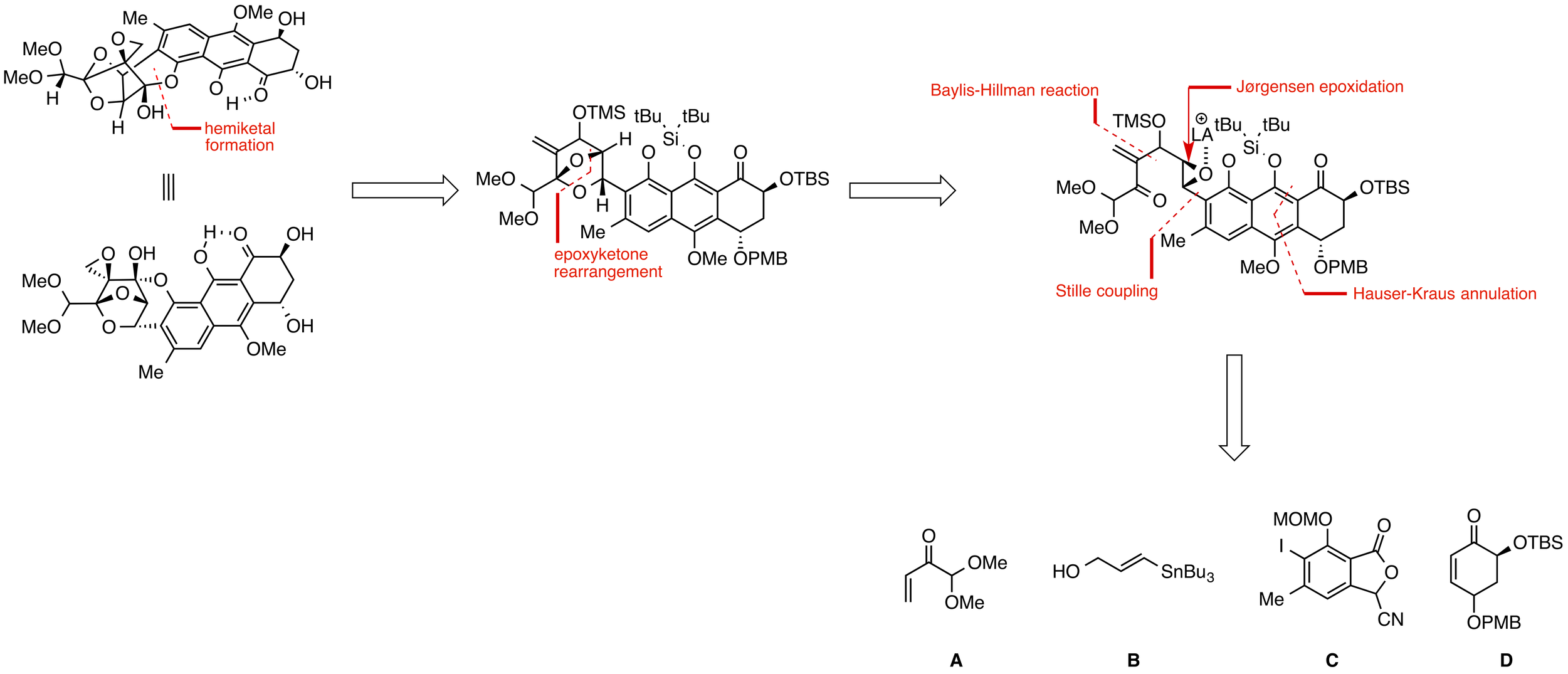


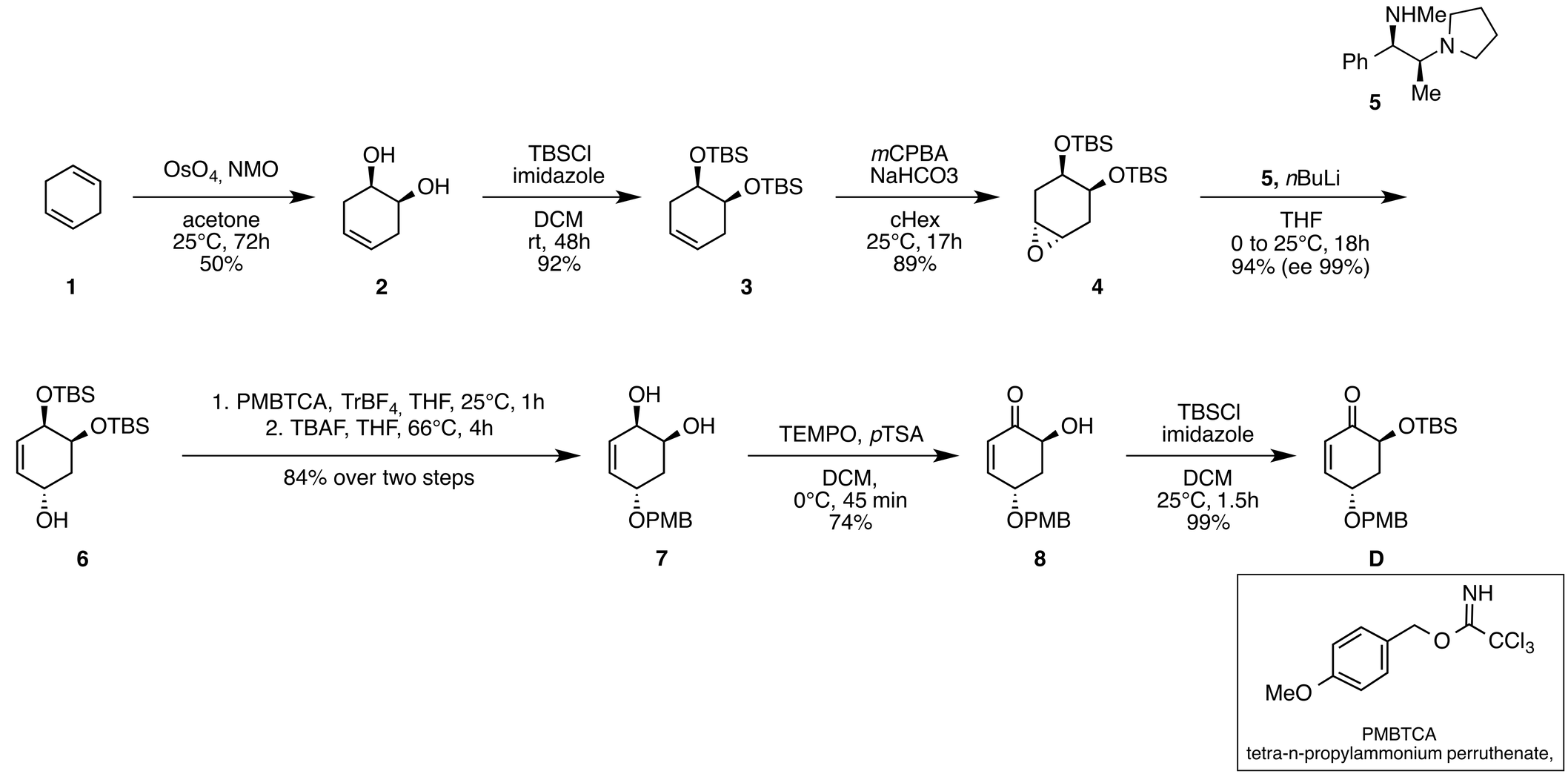
DC-45-A1

Švenda, J.; Hill, N.; Myers, A. G. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 6709.
Magauer, T.; Smaltz, D. J.; Myers, A. G. *Nat Chem* **2013**, *5*, 886.

Retrosynthetic analysis of Triocacarcin DC-45-A2

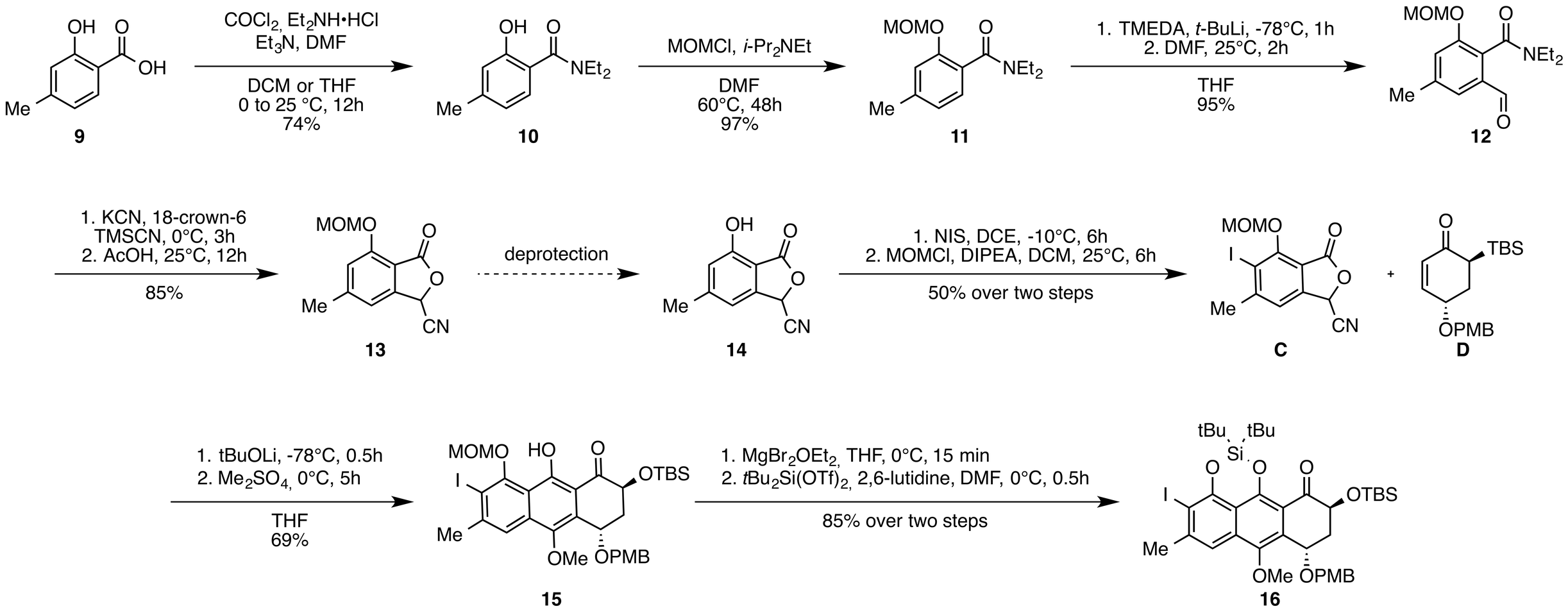


Synthesis of the key building block D



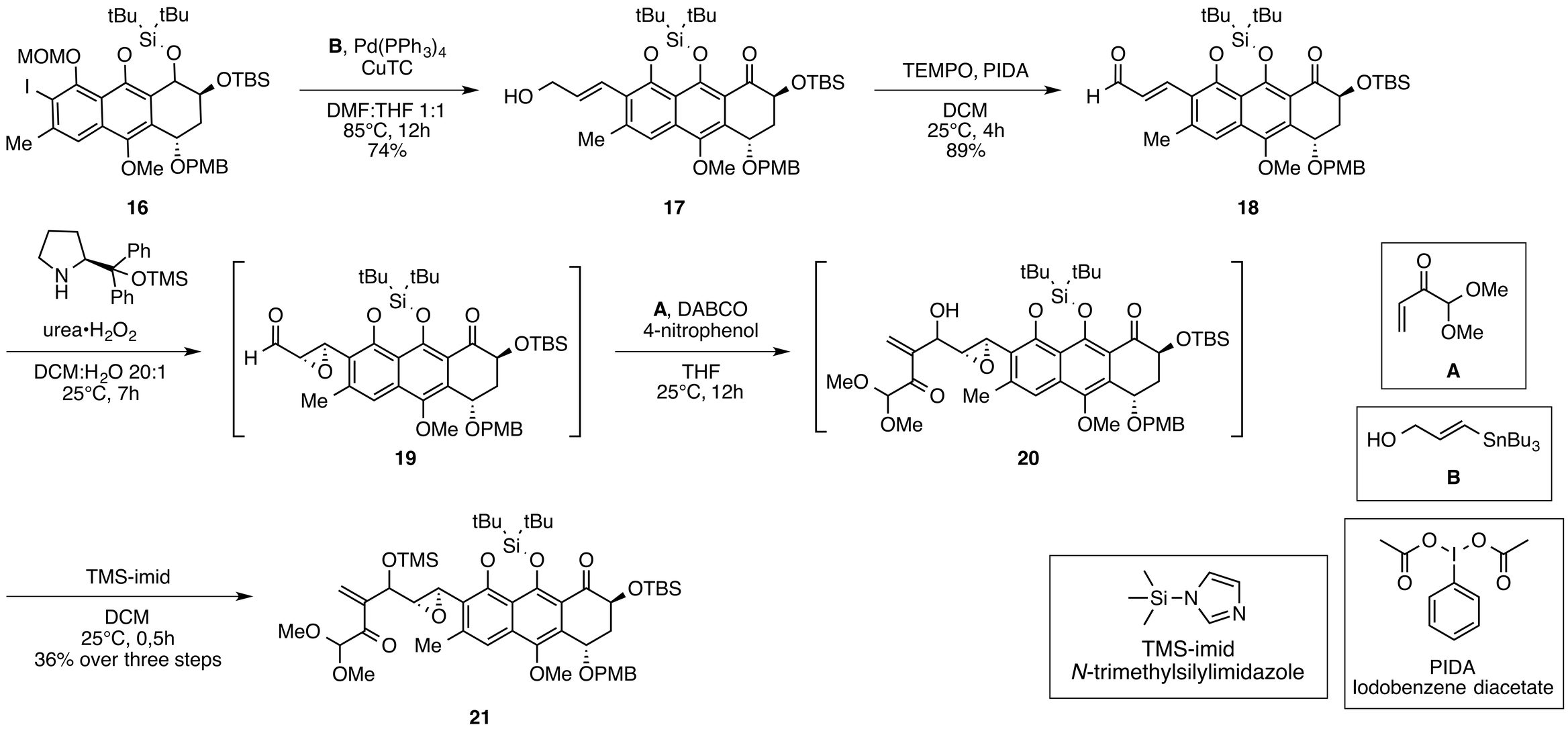
Bhuniya, D.; DattaGupta, A.; Singh, V. K. *J. Org. Chem.* **1996**, *61*, 6108.

Synthesis of the key building block C



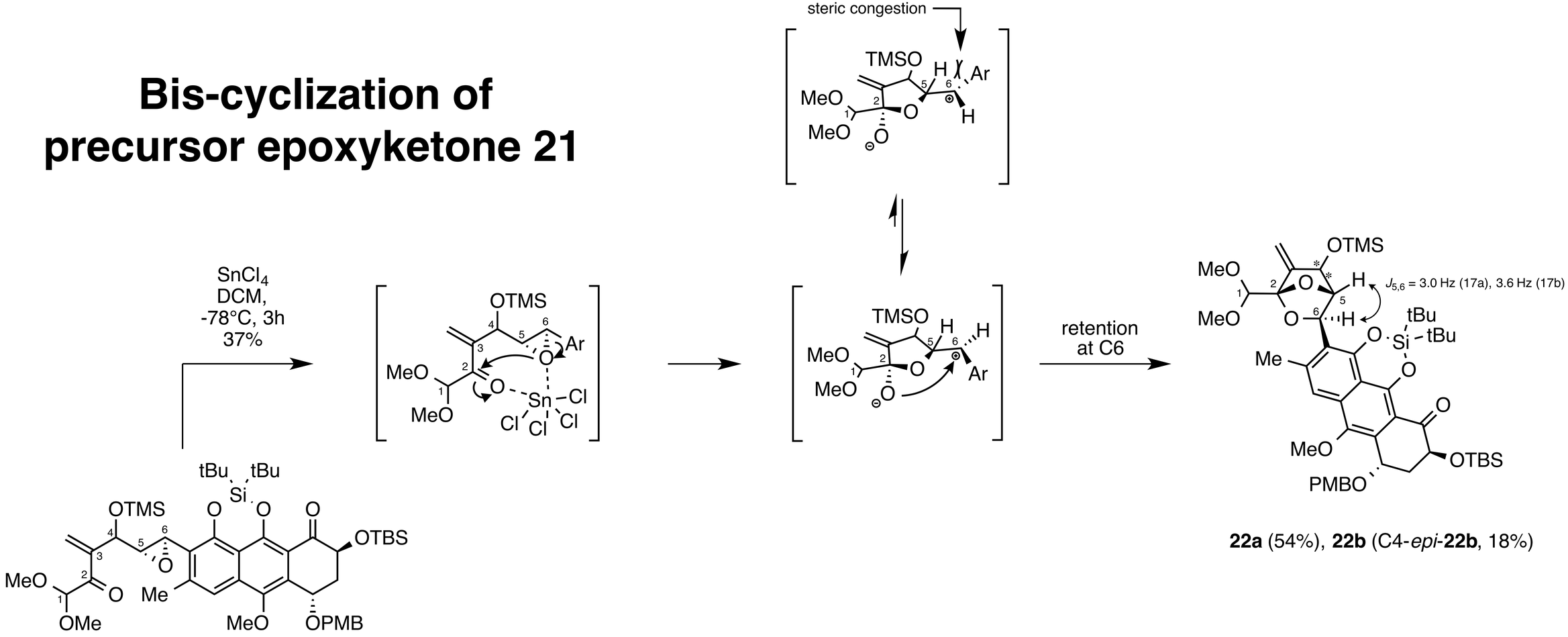
Nicolaou, K. C.; Becker, J.; Lim, Y. H.; Lemire, A.; Neubauer, T.; Montero, A. *J. Am. Chem. Soc.* **2009**, *131*, 14812.

Synthesis of the bis-cyclization precursor epoxyketone 21



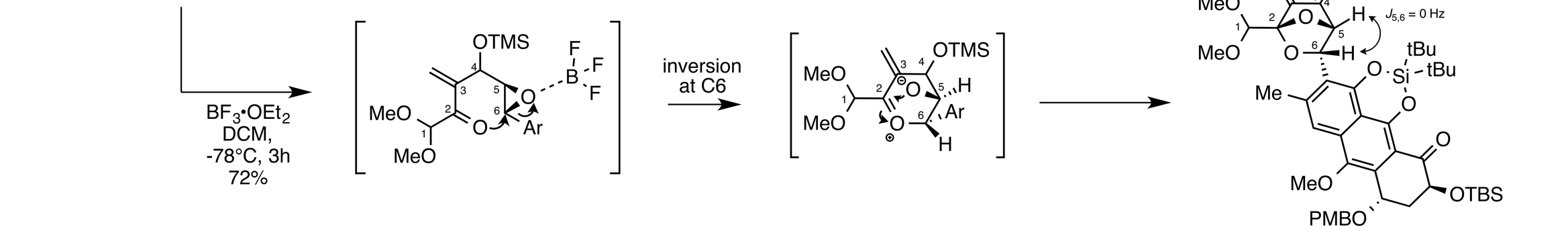
Marigo, M.; Franzén, J.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 6964.
M. L. Edwards, P. J. Cox, S. Amendola, S. D. Deprets, T. A. Gillespy, A. Timothy, C. D. Christopher, A. D. Morley, C. J. Gardner, B. Pedgrift, H. Bouchard, D. Babin, L. Gauzy, A. Le Brun, T. N. Majid, J. C. Reader, L. J. Payne, N. M. Khan, M. Cherry, WO 2003035065, 2003.

Bis-cyclization of precursor epoxyketone 21



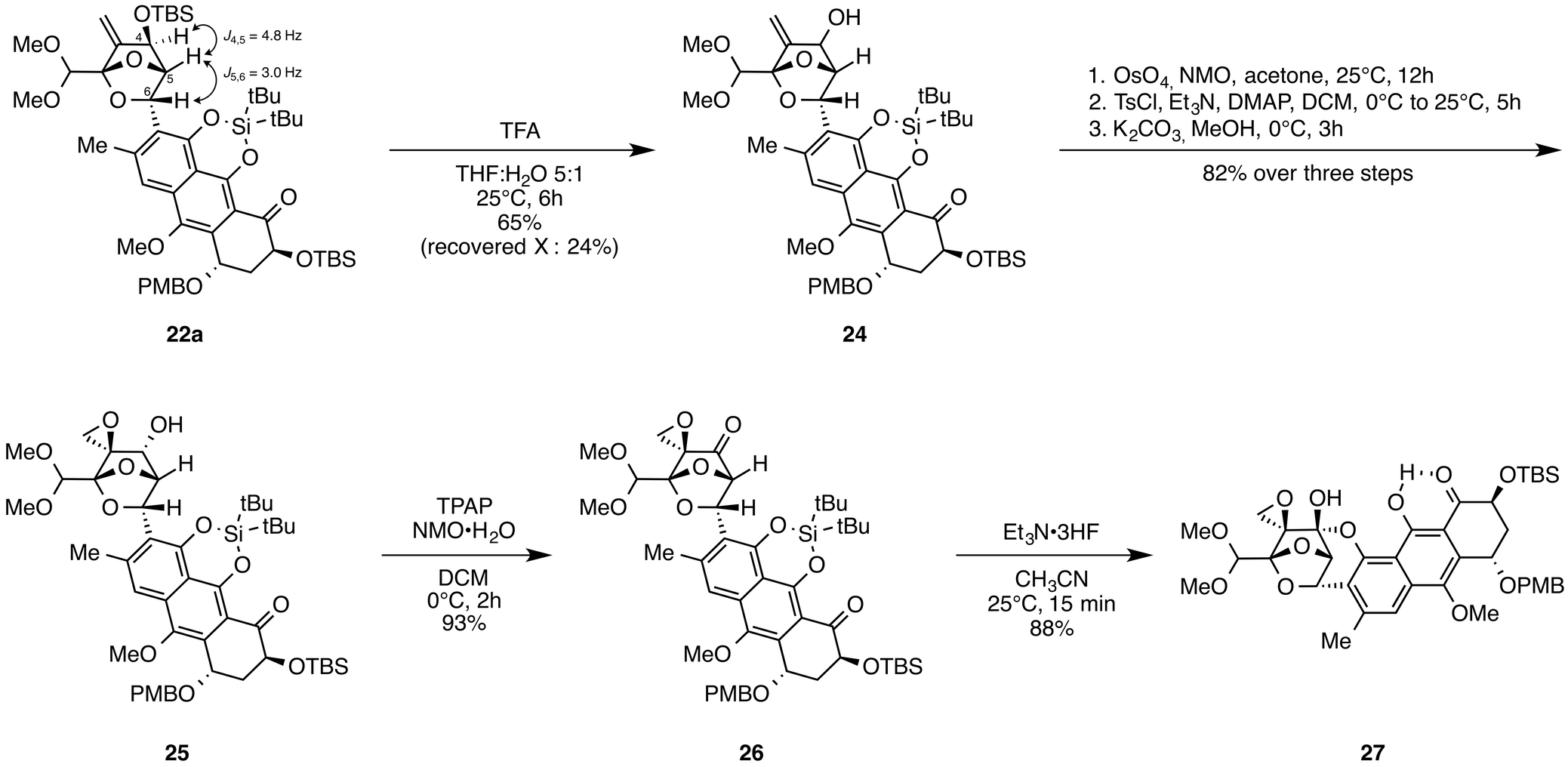
21, (+C4-*epi*-**21**, d.r. ca. 3:1)

22a (54%), **22b** (C4-*epi*-**22b**, 18%)

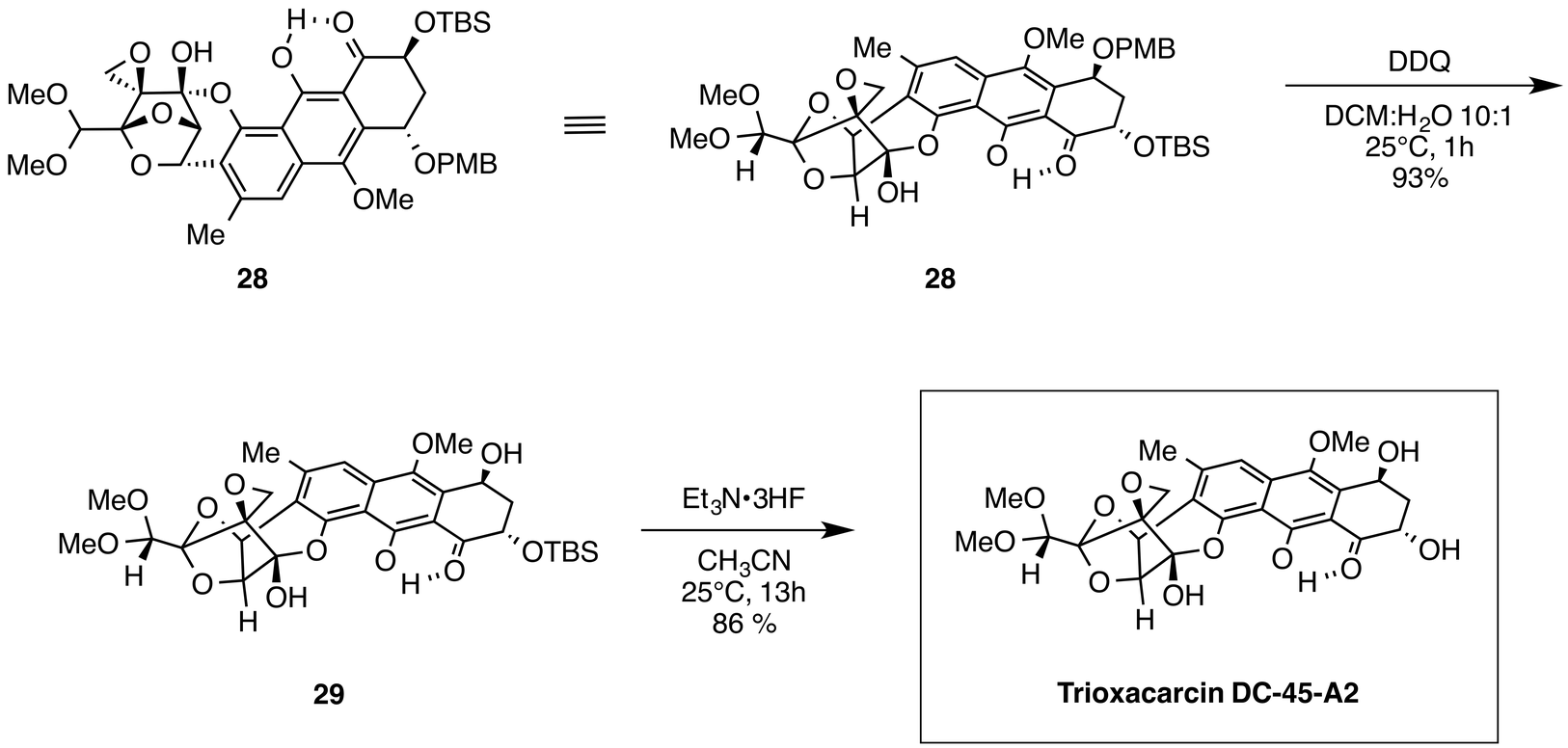


23 (+C4-*epi*-**23** : d.r. ca. 13:1 37%)

Completion of the total synthesis of trioxacarcin DC-45-A2



Completion of the total synthesis of trioxacarcin DC-45-A2



Conclusion

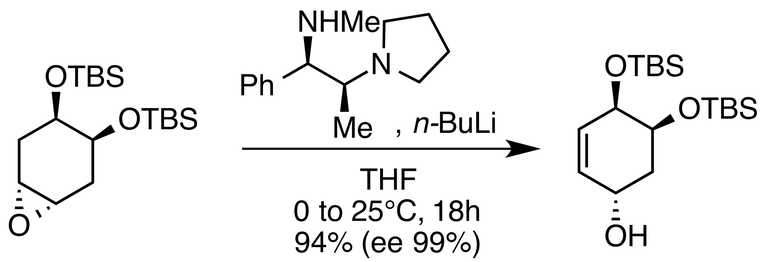
> Novel Lewis acid-induced cascade rearrangement of epooxyketone to forge the polyoxygenated 2,7-dioxabicyclo(2.2.1)heptane core

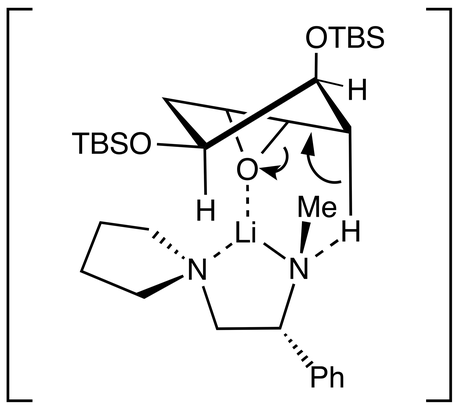
> Provide a rapid access to the trioxacarcin DC-45-A2

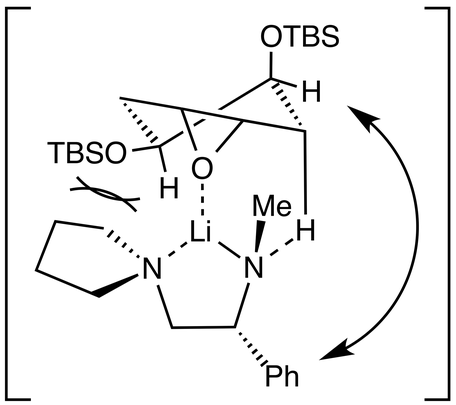
> Application in the construction of designed analogues

Thank you for your attention

Supplementary information : Regioselective opening of the epoxyde

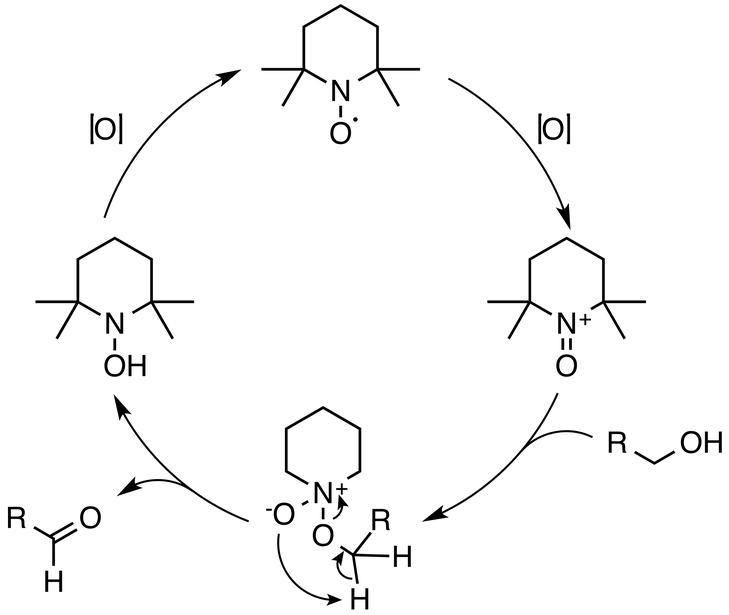






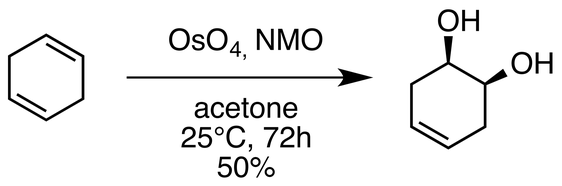
Bhuniya, D.; DattaGupta, A.; Singh, V. K. *J. Org. Chem.* **1996**, *61*, 6108.

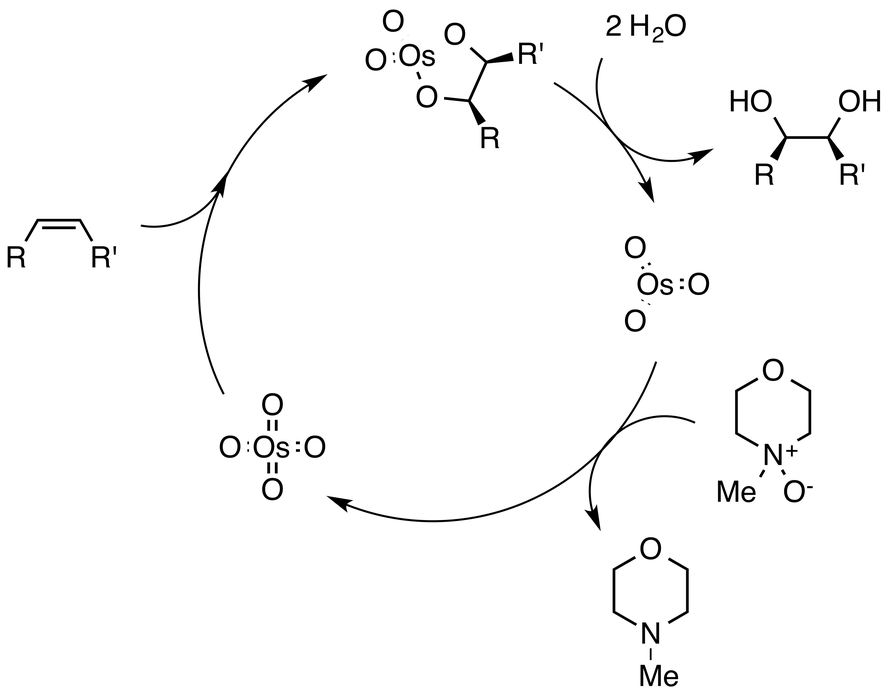
Supplementary information : Tempo Oxydation



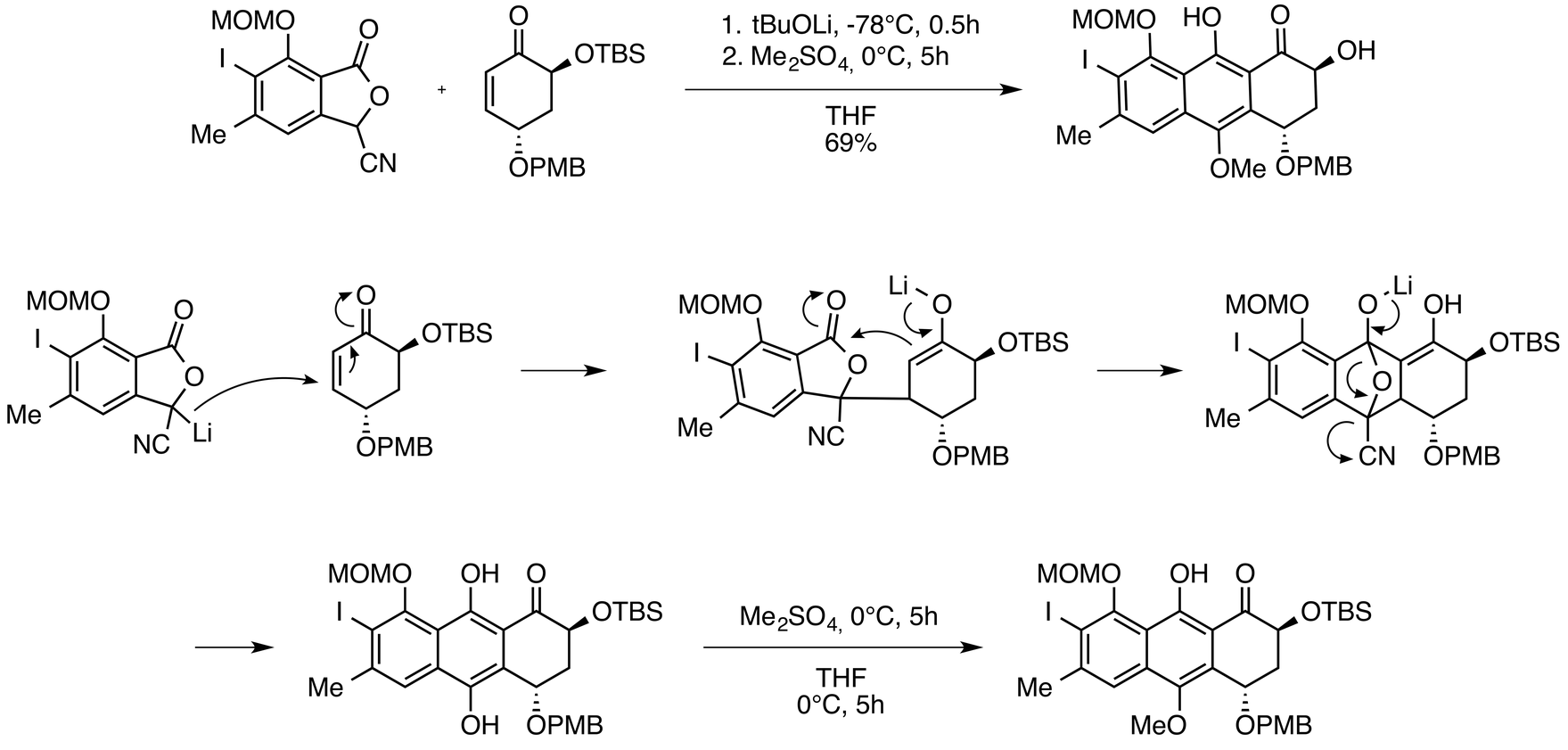
Li, X.-Q.; Zhang, C. *Synthesis* **2009**, *2009*, 1163.
Banwell, M. G.; Bridges, V. S.; Dupuche, J. R.; Richards, S. L.; Walter, J. M. *J. Org. Chem.* **1994**, *59*, 6338.

Supplementary information : Up-John dihydroxylation



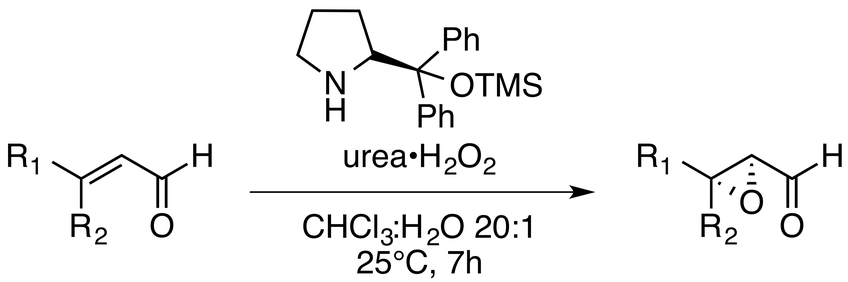


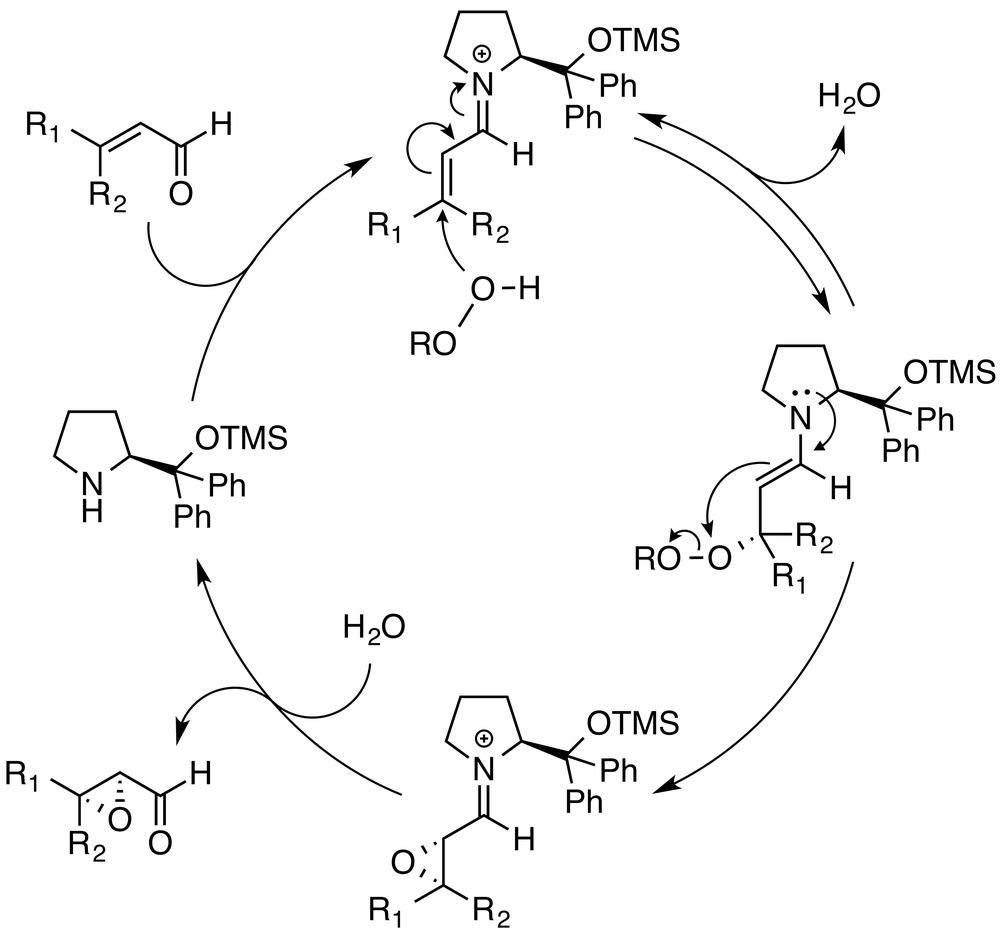
Supplementary information : Hauser-Kraus annulation



Mal, D.; Pahari, P. *Chem. Rev.* **2007**, *107*, 1892.

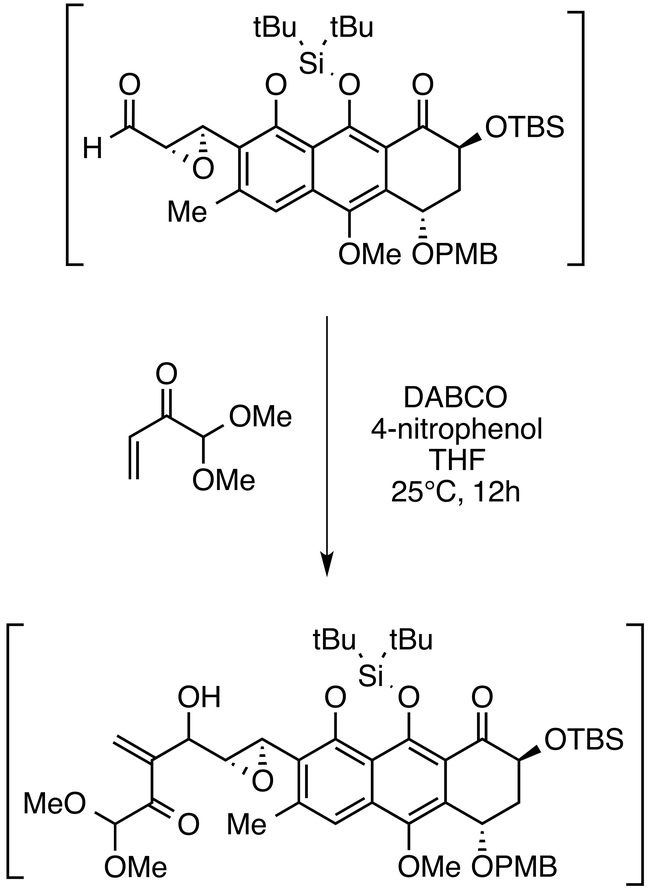
Supplementary information : Jørgensen epoxidation

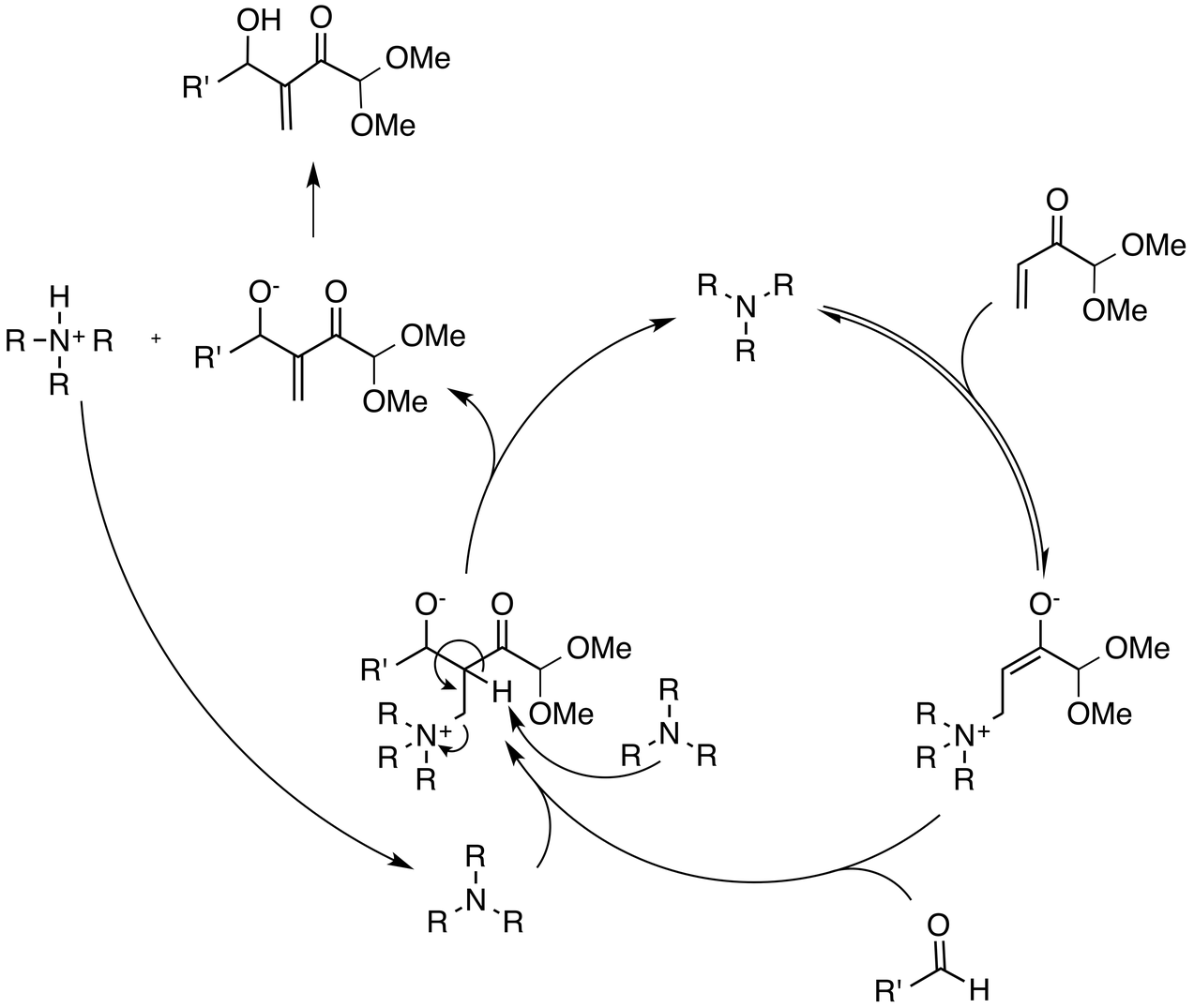




Marigo, M.; Franzén, J.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 6964.

Supplementary information : Baylis-Hillman reaction





M. L. Edwards, P. J. Cox, S. Amendola, S. D. Deprets, T. A. Gillespy, A. Timothy, C. D. Christopher, A. D. Morley, C. J. Gardner, B. Pedgrift, H. Bouchard, D. Babin, L. Gauzy, A. Le Brun, T. N. Majid, J. C. Reader, L. J. Payne, N. M. Khan, M. Cherry, WO 2003035065, 2003.