



April 21, 2009

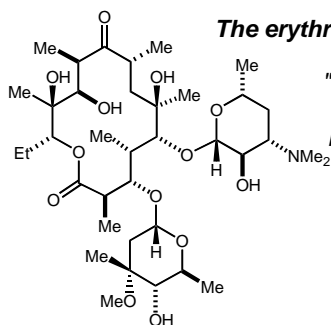
**“The Expanding Universe of Chemical Synthesis. Is it Dead or Alive?”**

David A. Evans

*Harvard University, Department of Chemistry & Chemical Biology  
12 Oxford Street, Cambridge MA, 02138***Abstract**

Organic chemists are frequently invited to speculate on the next frontiers in organic synthesis. It is evident from trends in the chemical literature that the field is moving in a number of directions. One frontier is concerned with the application of the tools of chemical synthesis to solving problems in biology. The application of chemical synthesis to the construction of new materials with tailored physical properties represents another direction. What about organic synthesis?

The *Complexity Criterion* may be used to evaluate the state of advancement of the synthesis activity. For example, the condition of the field may be assessed on the basis of the *Architectural Complexity* that may be achieved in the synthesis of molecular targets with the latest reaction-based tools. Woodward's rumination on the architectural complexity embodied in the erythromycin structure signaled that this molecular target was beyond the reach of organic chemists and their reaction tools at that point in time.

**The erythromycin-A structure, as viewed by Woodward in the '50s**

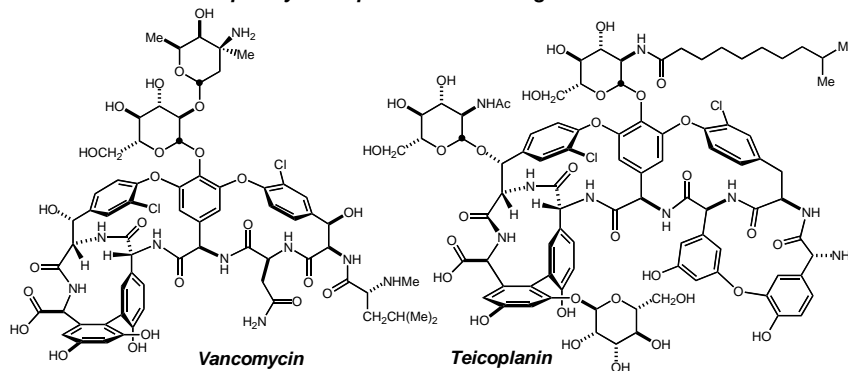
"Erythromycin, with all of our advantages, looks at present quite hopelessly complex, particularly in view of its plethora of asymmetric centers."

R. B. Woodward, 1956

At the personal level, the vancomycin and teicoplanin structures have provided me with a similar visceral response. At the outset of our studies in this area some years ago, these structures also appeared to us to be "hopelessly complex" as well. Accordingly, such structures become ideal targets for synthesis since the undertaking will drive the development of new reactions that must perform in an architecturally complex molecular environment.

The complexity criterion may also be used in the evaluation of reaction development. For example, the number of competing rate constants that might be associated with a given chemical process may be used as a gauge of the inherent complexity of the overall transformation. In this instance one is dealing with the issue of *Dynamic Complexity*. For the purpose of illustration, the pictured imide alkylation may be viewed as a four-rate constant problem wherein both enolization and enolate face selectivities must be constrained to collectively contribute to the overall stereoselectivity of the desired bond construction. If the requirements for the hydrolysis event are included, the complexity of the process further escalates. Nevertheless, in this example, the chemical events are regulated by reagent addition.

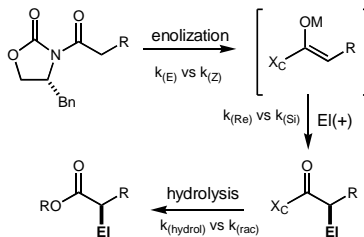
**Architectural Complexity: Complex molecular targets define limitations of the field**



**Chiral Enolate Design: A six rate constant problem**

Overall enantioselection will be the sum total of the defects introduced through:

- (A) Enolization selectivity:  $k_{(E)}$  vs  $k_{(Z)}$
- (B) Enolate-EI(+) face selectivity:  $k_{(Re)}$  vs  $k_{(Si)}$
- (C)  $X_C$  removal vs racemization  $k_{(hydroly)}$  vs  $k_{(rac)}$

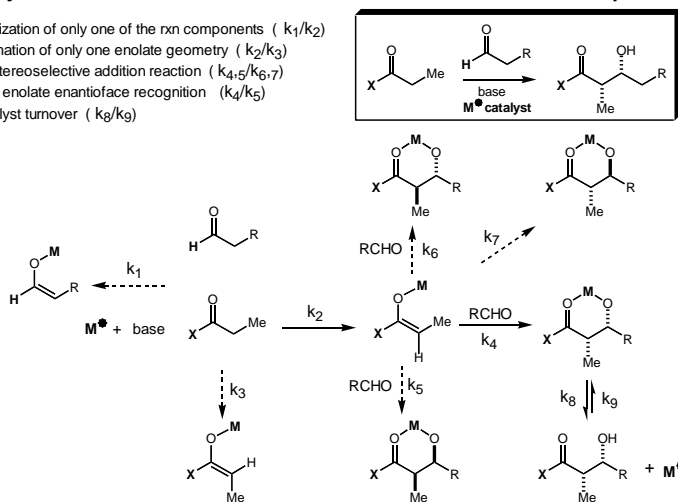


with Bartroli, Shih, *JACS* **1981**, 103, 2127; with Ennis, Mathre, *JACS* **1982**, 104, 1737

The *Dynamic Complexity* associated with catalytic enantioselective processes is invariably large, and the frontiers of reaction design currently encompass transformations that fall into this general family. As the graphic below illustrates, approximately nine rate constants must be appropriately tailored for an acceptable outcome.

**Catalyzed Enantioselective Aldol Reactions: An nine rate constant problem**

- Enolization of only one of the rxn components ( $k_1/k_2$ )
- Formation of only one enolate geometry ( $k_2/k_3$ )
- Diastereoselective addition reaction ( $k_4,5/k_6,7$ )
- High enolate enantioface recognition ( $k_4/k_5$ )
- Catalyst turnover ( $k_8/k_9$ )



This lecture will focus on the issues of architectural and dynamic complexity in the continued development of the field of organic synthesis.

Sincerely yours,

David A. Evans