The Hajos–Parrish–Eder–Sauer–Wiechert Reaction

**Significance:** In the early 1970s, Hajos and Parrish at Hoffmann-La Roche, and Eder, Sauer, and Wiechert at Schering independently developed a proline-catalyzed intramolecular aldol cyclization of substituted cyclic 1,3-diones toward the corresponding aldol products. The desired carbocycles are obtained in good to excellent yields with moderate to excellent enantioselectivities. Acid-catalyzed dehydration delivers tetrahydroindanediones and octahydronaphthalenediones, which can also be obtained in a single step by using a combination of proline and a Brønsted acid co-catalyst. The developed reaction provides important intermediates for the synthesis of pharmaceutically relevant steroids and other natural products in an economic and efficient manner even though the reaction has never been used on an industrial scale.

**Comment:** Although the potential and generality of chiral amine catalysis was not realized until the early 2000s (B. List, R. A. Lerner, C. F. Barbas *J. Am. Chem. Soc.* 2000, 122, 2395), the Hajos–Parrish–Eder–Sauer–Wiechert reaction is considered a milestone in the field of organocatalysis. Although Hajos and Parrish rejected the correct aldolase-type enamine mechanism (L. Hoang, S. Bahmanyar, K. N. Houk, B. List *J. Am. Chem. Soc.* 2003, 125, 16) at the time, they recognized that proline might constitute a simplified model of an enzyme. Thirty years later, the seminal work of both groups stimulated further studies on the similarity between aldolase enzymes and small-molecule catalysts that led to the ‘enamine catalysis’ concept and, ultimately, culminated in the establishment of organocatalysis as the third pillar of catalysis, complementing metal catalysis and biocatalysis.