C. R. Zwick, III, H. Renata* (The Scripps Research Institute, Jupiter, USA)
Remote C–H Hydroxylation by an α-Ketoglutarate-Dependent Dioxygenase Enables Efficient Chemoenzymatic Synthesis of Manzacidin C and Proline Analogs

**Chemoenzymatic Distal C–H Hydroxylation**

**Significance:** Zwick and Renata report the chemoenzymatic hydroxylation of the δ-position of aliphatic amino acids. By using an α-ketoglutarate-dependent dioxygenase, the desired products could usually be obtained in high yield and with high selectivity. This novel methodology was applied to the formal total synthesis of manzacidin C and proline analogues.

**Comment:** C–H bond functionalization of distal bonds within amino acids represents a major challenge in organic synthesis. Transition-metal-catalyzed systems are typically limited to functionalization of the β-position whereas the δ-position can be functionalized by Hofmann–Löffler–Freytag-type reactions.

**Selected examples:**

- 7800 TTN 90% yield dr >99:1
- >10000 TTN 54% yield
- 190 TTN 23% yield
- 1900 TTN 88% yield dr >99:1
- 490 TTN 92% yield dr = 3:1

**Synthetic application:**

- **NH₂CO₂H**
- **OH**
- **R₁**
- **R₂**
- **R₃**
- **GriE (0.01–0.2 mol%)**
- **FeSO₄ (5 mol%)**
- **αKG (1.2–4.0 equiv)**
- **O₂**
- **kPi buffer (pH = 7.0)**
- **5 h, 20 °C**
- **NH₂CO₂H**
- **OH**
- **R₁**
- **R₂**
- **R₃**

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