Remote C–H Hydroxylation by an α-Ketoglutarate-Dependent Dioxygenase Enables Efficient Chemoenzymatic Synthesis of Manzacidin C and Proline Analogs

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**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.

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**Synthetic application:**

1. **A**
   - **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

2. **Selected examples:**
   - **NH₂-CO₂H**
     - R¹ = H, Me, SMe, N₃, CO₂Me, OH
     - R² = H, Me
     - R³ = H, Me
     - 13 examples up to 92% yields, up to >10000 TTN, dr from 3:1 to >99:1

3. **Synthetic application:**
   - **A**
     - **TBADT**
     - **hv (365 nm)**
     - 49% yield
     - **GriE (0.25 mol%)**
     - **FeSO₄ (10 mol%)**
     - αKG (2.0 equiv)
     - **O₂**
     - **kPi buffer (pH = 7.0)**
     - then NH₃-BH₃

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