Synthesis of \((R)\)-Sitagliptin

**Significance:** The key step in the synthesis of \((R)\)-sitagliptin depicted is an asymmetric Mannich reaction of dithiomalonate \(B\) with bench-stable \(\alpha\)-amidosulfone \(A\) catalyzed by quinidine-derived squaramide catalyst \(C\) (2 mol%). The reaction proceeds at 0 °C under aqueous biphasic conditions to give Mannich adduct \(D\) in 72% yield and 95% ee. A single recrystallization affords \(D\) in >99% ee.

**Comment:** The superior reactivity of dithiomalonate \(B\) compared with monothiomalonates and malonates as Mannich donors is attributed to the higher acidity of its \(\alpha\)-hydrogen. Under the reaction conditions, the \(\alpha\)-amidosulfone undergoes elimination of sodium benzenesulfinate to an \(N\)-Boc-protected imine which reacts before tautomerization to the enamine can occur. Sitagliptin (Januvia) is a DPP-4 inhibitor that is prescribed for the treatment of type 2 diabetes.

**Category**

- Synthesis of Natural Products and Potential Drugs

**Key words**

- sitagliptin
- DPP-4 inhibitor
- asymmetric Mannich reaction
- \(\beta\)-amino acids
- dithiomalonates
- organocatalysis

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