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An Alternative Scalable Process for the Synthesis of a Key Intermediate of Omarigliptin
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Synthesis of a Key Intermediate of Omarigliptin

Synthesis of fragment A:

Significance: Wang and co-workers describe a kilogram-scale asymmetric synthesis of intermediate **H** en route to omarigliptin, a DPP-4 inhibitor that is of interest for the treatment of diabetes. The key steps in the synthesis depicted are (1) the diastereoselective substrate-controlled Meerwein-Ponndorf-Verley reduction of α -aminoketone **C** and (2) the stereoselective intramolecular 5-exo-dig iodoetherification of alkynol **E**.

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Comment: Synthesis of **A** began with the asymmetric α -alkylation of nickel(II) complex **I** with 3-chloro-1-propyne. The choice of solvent and temperature was critical to achieve a reproducible conversion and high stereoselectivity for this alkylation. Best results were obtained using sodium hydroxide in DMF at $-10\text{ }^{\circ}\text{C}$. At the end of the reaction, water was added to the reaction mixture, and product **J** crystallized out from the aqueous media.

Category

Synthesis of Natural Products and Potential Drugs

Key words

omarigliptin

DPP-4 inhibitor

Meerwein-Ponndorf-Verley reduction

asymmetric enolate alkylation

iodoetherification

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