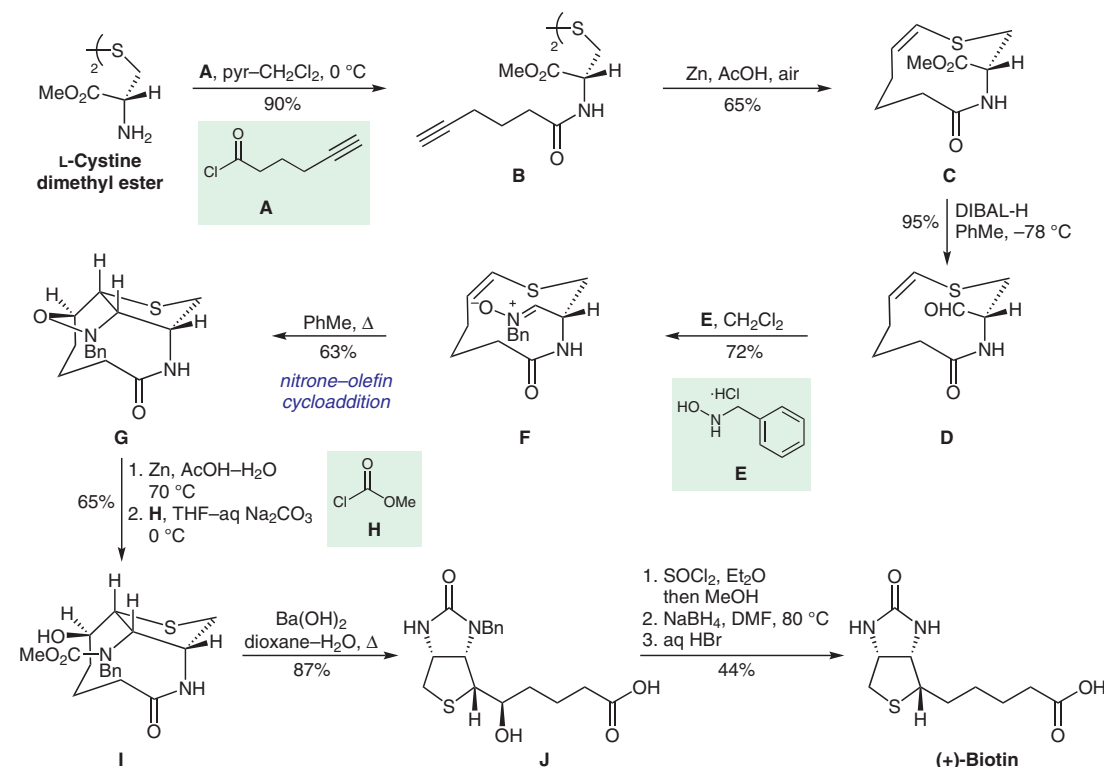


Synthesis of (+)-Biotin



Significance: (+)-Biotin is a vitamin involved in several biological processes including acetyl-CoA carboxylase mediated carboxylation of acetyl-CoA to malonyl-CoA. (+)-Biotin forms one of the strongest known non-covalent interactions with the protein streptavidin. In biotechnology, this binding is widely used for the labeling of proteins and small molecules and protein purification. Starting from L-cystine dimethyl ester, Baggiolini and co-workers reported an elegant synthesis of (+)-biotin, which features a highly diastereoselective intramolecular dipolar cycloaddition.

Comment: Acylation of L-cystine dimethyl ester with 5-hexynoyl chloride (**A**) afforded amide **B**. Treatment of **B** with zinc in AcOH under air atmosphere led to disulfide cleavage and subsequent cyclization to furnish **C**. DIBAL-H reduction of the ester moiety followed by condensation of the resulting aldehyde with hydroxylamine **E** gave nitron **F**. Nitron-olefin cycloaddition was induced by refluxing **F** in toluene. Reductive N–O cleavage followed by treatment with methyl chloroformate (**H**) afforded carbamate **I**. Ba(OH)₂-mediated amide hydrolysis led to concomitant urea formation. Dehydroxylation of **J** in two steps followed by global deprotection furnished (+)-biotin.

Category

Synthesis of Natural Products and Potential Drugs

Key words

(+)-biotin

disulfide cleavage

dipolar cycloaddition

nitron-olefin cycloaddition

Synfact Classic