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 nitroso F. Nitroso-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.