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A Concise Synthesis of (-)-Cytoxazone *via* Regioselective and Stereoselective Introduction of Amino Group using Chlorosulfonyl Isocyanate

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In 1998, Osada and co-workers isolated 140 mg of a novel cytokine modulator from 18 L of the culture broth of *Streptomyces* RK95-31 isolated from a soil sample in Hiroshima Prefecture. This new immunosuppressant was named (-)-cytoxazone and its absolute configuration was determined on the basis of its NMR, CD and X-ray analysis. It interferes with cytokine IL4, IL10 and IgG production by selective inhibition of the signaling pathway of Th2 cells, but not Th1 cells. Inhibitors of Th2-dependent cytokine production have potential as potent chemotherapeutic agents in the field of immunotherapy. The (-)-cytoxazone is different from known immunomodulators such as FK 506 and rapamycin in respect of structure and biological activity. As such cytoxazone should be a useful tool for understanding signaling pathways in Th2 cells, the synthesis of (-)-cytoxazone is of interest for the development of new cytokine modulators.

Because of these biological properties, several total syntheses of (-)-cytoxazone have been published in the last four years.

Recently, we have developed the novel one-pot synthetic methods for regioselective and stereoselective N-protected amines through the reaction of various ethers with chlorosulfonyl isocyanate (CSI) and established that our CSI reaction is a competitive reaction of SN*i* and SN1 reaction according to the stability of carbocation intermediate.

Herein, we report a stereoselective total synthesis of the (-)-cytoxazone, base on the regioselective and stereoselective CSI reaction we developed.