Asymmetric Synthesis of FR900482

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The antitumor antibiotic natural products FR900482 (1) and FR66979 (2) were isolated from Streptomyces sandaensis No. 6897 by the Fujisawa Pharmaceutical Co. in 1987. Recent studies from our laboratory have demonstrated that FR900482 (1) and FK317 (4) cross-link the minor groove-binding HMGA1 oncoprotein to DNA in vivo, which has very significant implications for the mode of action of these agents. Both FK973 (3) and FK317 (4), semi-synthetic derivatives of FR900482 (1), have shown highly promising antitumor activity in human clinical trials in Japan.

Dimethyldioxirane effects the remarkable one-step deprotection/oxidative cyclization of an eight-membered ring amino-ketone to the unique hydroxylamine hemi-ketal ring system of FR900482, a clinically significant antitumor antibiotic. This reaction has been exploited in a concise thirty-three step enantioselective total synthesis of FR900482, which constitutes the shortest synthesis of this natural product reported to date.

Williams, R.M.; Rollins, S.B.; Judd, T.C., Tetrahedron, 2000, 56, 521~532.