Tedanolide, a highly cytotoxic 18-membered macrolide, was isolated in 1984 by Schmitz and co-workers from the Caribbean sponge *Tedania ignis*, also known as fire sponge. Its structure was assigned by X-ray crystal structure analysis. Because of their significant antitumor activity and their complex structure, tedanolide and its 13-deoxy analogue have attracted considerable synthetic attention over the past decade.

Here we report the first total synthesis of tedanolide. The synthetic approach to tedanolide is based on the aldol coupling of a C1-C12 ketone fragment and a C13-C23 aldehyde. Both are synthesized using a wide range of aldol coupling and olefination methods. After assembly of the complete C1-C23 backbone, Mitsunobu lactonization yielded the desired macrolactone. A combination of stepwise deprotection and oxidation generated the fully functionalized hydroxy keto lactone which was epoxidized selectively using *m*-CPBA, thus concluding the total synthesis of (+)-tedanolide.