

## The Total Synthesis of (+)-Tedanolide

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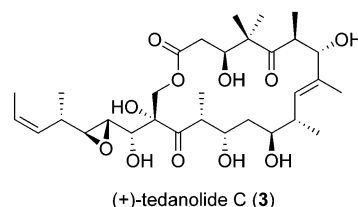
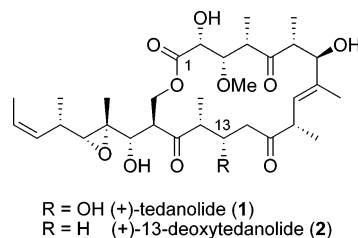
(+)-Tedanolide (**1**) was isolated from the Caribbean sponge *Tedania ignis* by Schmitz and co-workers<sup>1</sup> in 1984. In 1991, Fusetani and co-workers<sup>2</sup> reported the isolation of (+)-13-deoxytedanolide (**2**) from the sponge *Mycale adhaerens*. These two closely related polyketides exhibit remarkable cytotoxicity against P388 murine leukemia cells at pico- to nanomolar ranges, and Fusetani et al. were able to identify the 60S large ribosomal subunit as the molecular target of (+)-13-deoxytedanolide (**2**).<sup>3</sup> Recently, the isolation of a third metabolite, tedanolide C (Scheme 1), was reported by Ireland et al.<sup>4</sup> The challenging structural complexity of the tedanolides in combination with the promising biological profile has initiated several synthetic studies<sup>5</sup> resulting in a variety of fragment syntheses as well as fundamental studies. Consequently, two total syntheses of (+)-13-deoxytedanolide (**2**) were reported in 2003 and 2005 by Smith and Roush, respectively.<sup>6</sup>

Here we report the first total synthesis of (+)-tedanolide (**1**). Even though both compounds (+)-tedanolide (**1**) and (+)-13-deoxytedanolide (**2**) differ only in the presence of one hydroxyl group at carbon 13, the concomitant retro aldol processes and elimination, due to the 1,3 functional group distance of the hydroxy ketone, are one major obstacle that requires substantial strategy changes. Our retro synthetic analysis dissects tedanolide (**1**) such that an aldol reaction between C12 and C13 serves as the juncture between both key fragments **4** and **5** (Scheme 2). One key issue responsible for the successful synthesis is the choice of the *S* configuration at C15. This configuration prevents unfavorable hemiacetal formation as already analyzed by Roush<sup>7</sup> at the ORCHEM meeting in 2004.

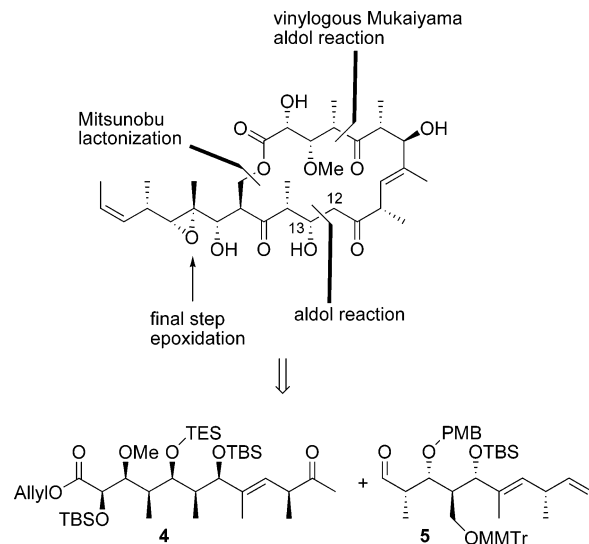
Our synthesis utilized an aldol coupling between the methyl ketone **4**<sup>8</sup> and aldehyde **5**. The synthesis of aldehyde **5** began with known ketone **6**,<sup>9</sup> which can be accessed in large quantities starting from the Roche ester. Before introducing the acid labile monomethoxy trityl group (MMTr), the carbonyl group in **6** was reduced stereoselectively with the aid of DIBAL-H followed by removal of the TBS group. Protection of the allylic hydroxyl group was achieved using TBSCl, and treatment with DDQ in the absence of water produced the corresponding acetal. Reductive acetal opening with DIBAL-H furnished the PMB-protected secondary alcohol,<sup>10</sup> and the liberated primary hydroxyl group was subsequently oxidized with TPAP/NMO<sup>11</sup> to establish aldehyde **5** for the pivotal aldol coupling (Scheme 3).

The aldol coupling between ketone **4** and aldehyde **5** gave best selectivity (7:1) in favor of the Felkin product when KHMDS was used as the base. As described earlier for a model aldehyde,<sup>8</sup> the selectivity was governed by the methyl ketone and varied depending on the counterion used with the base. The synthesis continued by protecting the secondary alcohol as the TBS ether. This step induced a retro aldol reaction, which is responsible for the low yield observed in this transformation. Next, the MMTr group was removed with hexafluoroisopropanol and MeOH in order to trap the liberated MMTr cation.<sup>12</sup> The subsequent ester cleavage was

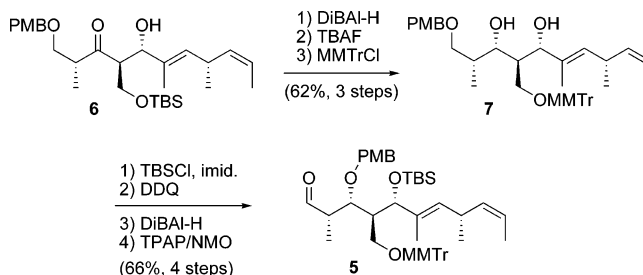
Scheme 1



Scheme 2



Scheme 3



achieved in quantitative yield with Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> and Bu<sub>3</sub>SnH. The elegant use of the allyl protecting group for the carboxylate was also presented in the synthesis of (+)-13-deoxytedanolide (**2**) by

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