

Published on Web 10/06/2006

The Total Synthesis of (+)-Tedanolide

Gunnar Ehrlich, Jorma Hassfeld,[†] Ulrike Eggert, and Markus Kalesse*

Institut für Organische Chemie, Leibniz Universität Hannover, Schneiderberg 1B, D-30167 Hannover, Germany

Received August 23, 2006; E-mail: markus.kalesse@oci.uni-hannover.de

(+)-Tedanolide (1) was isolated from the Caribbean sponge *Tedania ignis* by Schmitz and co-workers¹ in 1984. In 1991, Fusetani and co-workers² reported the isolation of (+)-13-deoxy-tedanolide (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).³ Recently, the isolation of a third metabolite, tedanolide C (Scheme 1), was reported by Ireland et al.⁴ The challenging structural complexity of the tedanolides in combination with the promising biological profile has initiated several synthetic studies⁵ resulting in a variety of fragment syntheses of (+)-13-deoxytedanolide (2) were reported in 2003 and 2005 by Smith and Roush, respectively.⁶

Here we report the first total synthesis of (+)-tedanolide (1). Even though both compounds (+)-tedanolide (1) and (+)-13deoxytedanolide (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 Roush⁷ at the ORCHEM meeting in 2004.

Our synthesis utilized an aldol coupling between the methyl ketone **4**⁸ and aldehyde **5**. The synthesis of aldehyde **5** began with known ketone **6**,⁹ 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,¹⁰ and the liberated primary hydroxyl group was subsequently oxidized with TPAP/NMO¹¹ 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,⁸ 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.¹² The subsequent ester cleavage was

[†] Present address: Schering AG, Müllerstr. 178, D-13342 Berlin, Germany.

Scheme 1



 $\begin{array}{l} \mathsf{R} = \mathsf{OH} \ (\texttt{+}) \text{-tedanolide} \ (\texttt{1}) \\ \mathsf{R} = \mathsf{H} \quad (\texttt{+}) \text{-13-deoxytedanolide} \ (\texttt{2}) \end{array}$



Scheme 2



achieved in quantitative yield with $Pd(PPh_3)_2Cl_2$ and Bu_3SnH . The elegant use of the allyl protecting group for the carboxylate was also presented in the synthesis of (+)-13-deoxytedanolide (2) by

Scheme 4



Roush.^{6c,7} For the subsequent macrolactonization, best yields were observed when *seco*-acid **9** was subjected to the Mitsunobu protocol¹³ directly after Pd-catalyzed deprotection of the allyl ester. Other lactonizations, such as the Keck–Boden protocol¹⁴ or the Yamaguchi esterification,¹⁵ did not generate comparable yields.

To establish the remaining two ketones, the PMB group was removed with DDQ followed by Dess-Martin oxidation.¹⁶ These two transformations could only be performed with moderate yields. Next, the TES group was selectively deprotected with PPTS¹⁷ in the presence of four TBS ethers, and again a Dess-Martin oxidation provided triketone 11 (Scheme 4). The last steps to be accomplished were the global TBS deprotection and the critical final step epoxidation. Thorough experimentation using combinations of fluoride and proton sources revealed the combination of HF-Et₃N to be the superior combination for the TBS deprotection, as described by Roush.6c Under these conditions, the deprotection of four silvl ethers only proceeded sluggishly to half-conversion after 4 days. By separation of the partial deprotected material through column chromatography and re-subjecting to the deprotection conditions, full conversion was achieved. Finally, the last step epoxidation remained to be accomplished. Since Smith and coworkers^{6a} had shown that a late-stage epoxidation of (+)-13deoxytedanolide (2), with the C7 hydroxyl protected, occurs with the desired face selectivity, we were encouraged to take on this transformation as the final step. Additionally, Taylor and co-workers reported on the epoxidation of myriaporone, a related natural product.¹⁸ Following their experimental procedure, using mCPBA (-40 °C, 2 days) gave clean conversion of the C18-C19 double bond to the monoepoxide and traces of the diepoxide. The spectroscopic data (¹H NMR, ¹³C NMR, HRMS, optical rotation) were in all respect identical to the data originally reported by Schmitz and co-workers.¹

In summary, the first total synthesis of (+)-tedanolide has been achieved through a convergent route using an aldol reaction, a Mitsunobu lactonization, and a final step epoxidation.

Acknowledgment. This work was supported by the DFG (KA 913/9-1, KA 913/9-2). The authors thank Myriam Roy (Taylor group, University of Notre Dame) for helpful discussions.

Supporting Information Available: Spectroscopic and analytical data for compounds **1**, **10**, and **11**, and selected experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA0659572