Synthetic Studies on Tedanolide: Stereoselective Synthesis of the C1-C7 Fragment

Se Hwan Park and Hyo Won Lee*

*Department of Chemistry, Chungbuk National University, Cheongju, Chungbuk 361-763, Korea. *E-mail: hwnlee@chungbuk.ac.kr*

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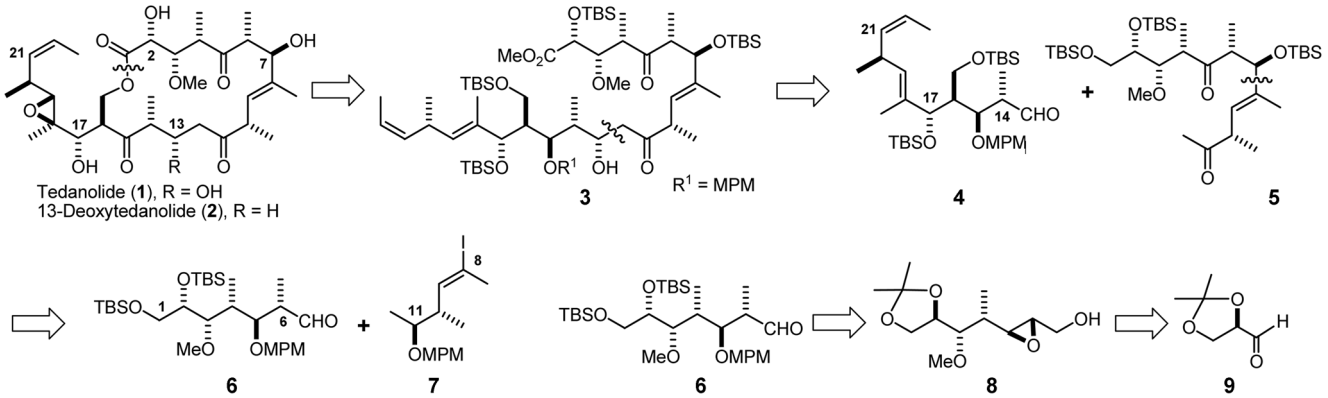
Tedanolide (**1**), an 18-membered macrolide, was isolated by Schmitz *et al.*[1a] in 1984 from the Caribbean sponge *Tedania ignis* and structurally related 13-deoxytedanolide (**2**) was isolated from a Japanese sea sponge, *Mycale adhaerens*, by Fusetani *et al.*[1b] in 1991. Both tedanolide (**1**) and 13-deoxytedanolide (**2**) exhibit very potent biological activities against certain tumor cell lines.[1a] Their complex structures and distinctive biological properties make them extremely attractive targets for synthetic chemists.[2] Recently Kalesse[3a,b] and Smith[3c] have reported successful total syntheses of tedanolide (**1**).

As shown in Scheme 1, our retrosynthetic strategy for tedanolide (**1**) was the disconnection to two subunits **4** and **5** *via* cleavage at ester C-O bond and the aldol condensation transformation. The subunit **5** was envisioned to be obtained from the coupling between precursors **6** and **7**. Herein we disclose our efforts in the construction of the C1-C7 fragment **6** of tedanolide (**1**).

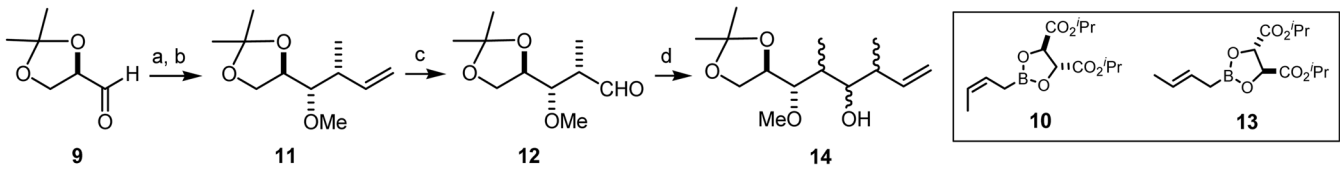
At first stage, we have utilized the Roush protocol as a key methodology toward fragment **6**. The synthesis began with the known aldehyde **9**.[4] The Roush asymmetric crotylation upon **9** with **10** gave the desired product in 80% yield as a 92:8 mixture of two diastereomers,[5] which was methylated to the methyl ether **11** in good yield. Ozonolysis of **11** furnished aldehyde **12**. The second Roush crotylation on **12** did not yield the desired product. Instead we obtained a mixture of diastereomers (Scheme 2).

Because of the observed lability of aldehyde **12** during the second crotylation, we considered the modification of the synthetic pathway. As a replacing measurement for the second Roush crotylation, we devised the combined application of Sharpless asymmetric epoxidation[6] and Gilman cuprate reaction.[7]

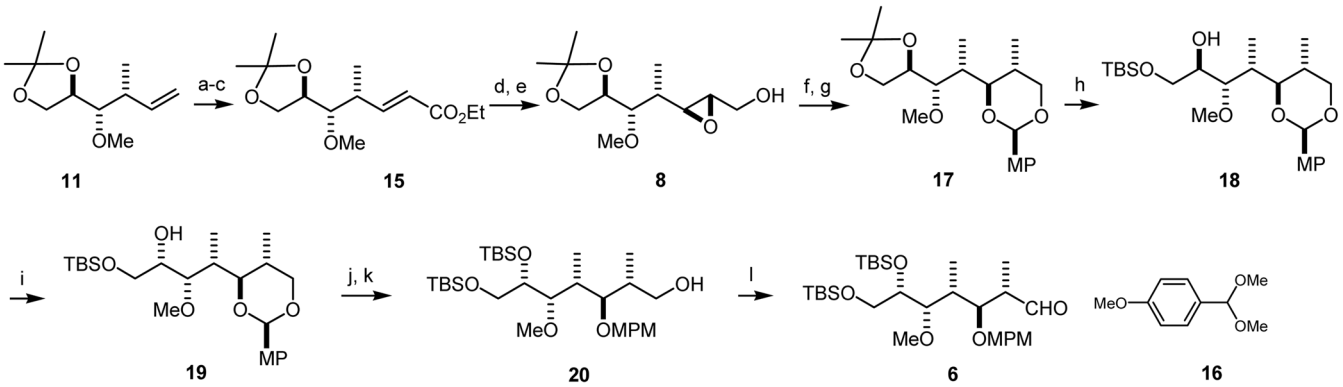
As shown in Scheme 3, we established a highly stereoselective synthesis of precursor **6** *via* epoxide ring-opening and Mitsunobu reaction.[8] The oxidative cleavage of the terminal vinyl group of **11** followed by immediate Horner-Wadsworth-Emmons reaction provided α,β-unsaturated ester **15** in 75% yield over two steps (*trans*:*cis* = 96:4). Subsequent reduction of ester **15** using DIBAL-H gave the intermediate allylic alcohol and Sharpless epoxidation upon this alcohol with $Ti(O^iPr)_4$, L-DET and TBHP afforded stereoselectively epoxide **8** in nearly quantitative yield ($\beta/\alpha \geq 30$). Epoxide ring opening of **8** by the treatment with MeLi and CuI furnished the intermediate 1,3-diol (1,3-diol:1,2-diol = 88:12) and the exposure of the resulting 1,3-diol to **16** with PPTS yielded *p*-methoxyphenyl acetal **17** in 70% yield. To introduce the requisite stereochemistry at C2, the



Scheme 1. Retrosynthetic Analysis.



Scheme 2. Stereoselective Control *via* Roush Crotylation. (a) **10**, 4A MS, PhMe, −78 °C, 3 h, 80%. (b) NaH, MeI THF, 0 °C, 3 h, 90%. (c) O_3, MeOH, −78 °C, 30 min; Me_2S. (d) **13**, 4A MS, PhMe, −78 °C, 3 h, 82%.



Scheme 3. Synthesis of the precursor **6**. (a) OsO_4, NMO, Me_2CO:H_2O (5:1), rt, 6 h. (b) $NaIO_4$, THF:H_2O (5:1), 0 °C, 30 min. (c) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, −78 °C, 2 h, 53% over three steps from **11**. (d) DIBAL-H, THF, 0 °C, 2 h, 88%. (e) $Ti(O^iPr)_4$, L-DET, TBHP, CH_2Cl_2, −78 °C, 3 h, 94%. (f) Me_2CuLi, Et_2O, −78 °C, 2 h; $NaIO_4$, 82%. (g) **16**, PPTS, CH_2Cl_2, 0 °C, 2 h, 70%. (h) TBSOTf, $^iPr_2NEt$, DCE, 80 °C, 48 h; I_2, $NaHCO_3$, THF:H_2O (4:1), rt, 30 min, 84%. (i) Ph_3P, DIAD, PhCOOH, THF, rt, 12 h; K_2CO_3, MeOH, 0 °C, 3 h, 68%. (j) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 30 min, 97%. (k) DIBAL-H, CH_2Cl_2, 0 °C, 2 h, 85%, (l) SO_3·py, Et_3N, CH_2Cl_2, DMSO, 0 °C, 1 h, 88%.

acetonide group in **17** was treated with TBSOTf and iodine in sequence and the consequent inversion of the hydroxyl group at C2 *via* Mitsunobu reaction provided the desired alcohol **19** in 57% yield over two steps from **17**. Subsequently the protection of a hydroxyl group of **19** by treatment with TBSOTf and 2,6-lutidine and regioselective opening of the intermediary *p*-methoxyphenyl acetal using DIBAL-H provided the bis(TBS) ether **20** in good yield. Finally, the target precursor **6** was successfully afforded from Parikh-Doering oxidation upon alcohol **20**.

In summary, we have developed an efficient synthetic pathway of the C1-C7 fragments **6** of tedanolide (**1**). Successfully we introduced the stereogenic centers at C2 and C6 using Mitsunobu and epoxide ring-opening reactions. Continued advancement of precursor **6** toward the total synthesis of tedanolide (**1**) will be reported in due course.

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