Synthetic Studies on Tedanolide: Stereoselective Synthesis of the C13-C21 Fragment

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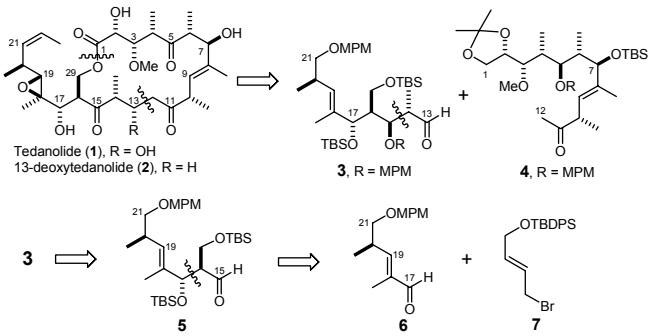
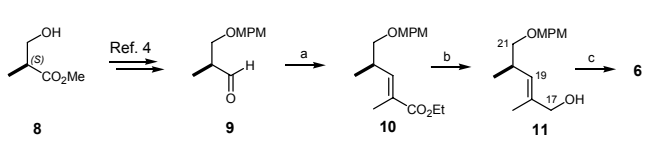
The highly cytotoxic macrolide tedanolide (**1**) was isolated by Schmitz and co-workers from the Caribbean sponge *Tedanis ignis* in 1984.[1] This antitumor macrolide features four labile aldol units, a side chain containing a hydroxy epoxide ring, an 18-membered lactone, and the crowded contiguous chiral centers at C16-C19. It also shows *in vitro* cytotoxicity against KB and PS cell lines (ED_{50}'s: 250 pg/mL and 16 pg/mL, respectively) and *in vivo* antitumor activity, increasing the lifespan of mice implanted with lymphocytic leukemia cells (23% at 1.56 μg/kg). Because of their unusual structural features and powerful biological activities, **1** and **2** have attracted considerable attention of synthetic chemists. Recently Kalesse[2a,b] and Smith[2c] have reported successful total synthesis of tedanolide (**1**), respectively. We have reported our synthetic studies on tedanolide (**1**).[3] As part of our synthetic studies toward **1**, we now report a concise and stereoselective synthesis of the C13-C21 fragment **3**.

Our retrosynthetic analysis of tedanolide (**1**) is outlined in Scheme 1. Disconnections at the lactonic C-O bond and a bond between C12 and C13 produce subunits of aldehyde **3** and ketone **4**. The C13-C21 aldehyde **3** can be prepared by the Roush asymmetric crotylation from aldehyde **5**. Our present synthesis focuses on the preparation of **5**. For the key stereoselective C-C bond formation of **5**, we relied on a metal-mediated allylation reaction between aldehyde **6** and allylic bromide **7** with the control of C16-C17 stereogenic centers. The aldehyde **6** was synthesized from (*S*)-methyl 3-hydroxy-2-methylpropionate as reported in the literature.[4]



Scheme 1. Retrosynthetic analysis

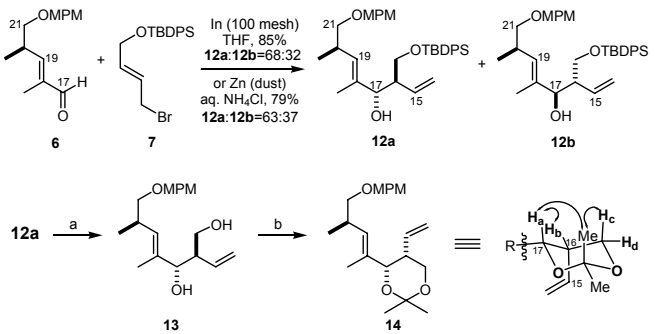
Our synthesis commenced with the preparation of aldehyde **6**. For the synthesis of aldehyde **6** (Scheme 2), aldehyde **9**, readily available from (*S*)-methyl 3-hydroxy-2-methylpropionate (**8**) in three steps, was subjected to the Wittig reaction to furnish α,β-unsaturated ester **10** (*E*/*Z* = 95:5). And then **10** was reduced regioselectively with DIBAL-H to give allylic alcohol **11** in good yield. The Swern oxidation[5] of **11** completed the synthesis of the desired aldehyde **6** in 75% overall yield from **9** in three steps.



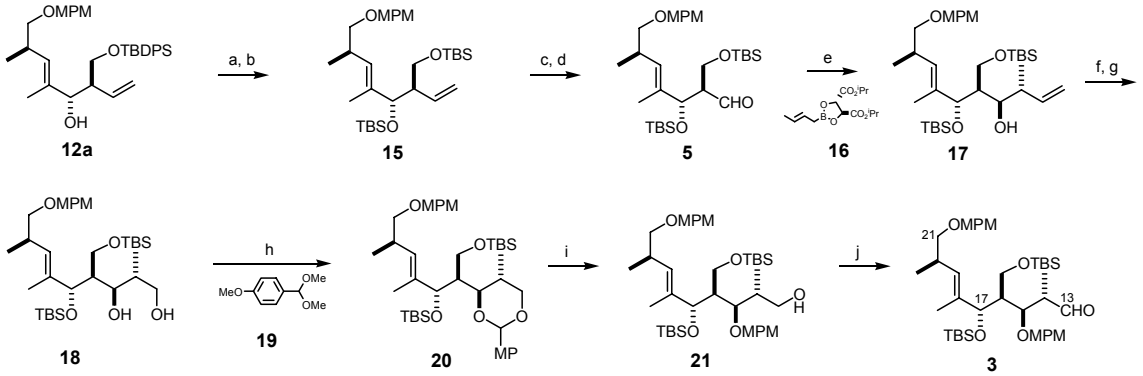
Scheme 2. a) $Ph_3PCCH_3CO_2Et$, CH_2Cl_2, rt, 24h, 85%; b) DIBAL-H, THF, -78 °C, 1h, 96%; c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to 0 °C, 1h, 92%.

With aldehyde **6** in hand, we carried out metal-catalyzed allylation reaction.[6] Several kinds of metals have been employed as mediators for the allylations of aldehyde **6** with allylic bromide **7** (Scheme 3). Among these, indium and zinc are widely utilized. The use of indium metal as a mediator under the Barbier-type conditions was first reported in 1988.[6a] Compared to other metals, indium offers a number of advantages, including its low toxicity, tolerance toward air and moisture and, due to its low ionization potential, a high reactivity in the absence of external activators and proton sources. Zinc was also employed in the Barbier-type allylations and it has been likewise proved to be a highly useful mediator for the allylation of various substrates.[6b] In contrast to indium-mediated allylations, which are commonly carried out in THF/water mixtures without additives, the use of zinc generally requires the presence of saturated aqueous NH_4Cl as a proton source together with the organic solvent.

Indium or zinc mediated coupling of aldehyde **6** and allylic



Scheme 3. a) TBAF, THF, rt, 1h, 96%; b) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2, 0 °C, 2h, 95%.



Scheme 4. a) TBAF, THF, rt, 1h, 96%; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 2h, 80%; c) OsO_4, NMO, acetone, rt, 3h, 75%; d) $NaIO_4$, THF:H_2O=4:1, rt, 1h; e) **16**, 4A MS, toluene, -78 °C, 3h, 90%; f) OsO_4, NMO, acetone, rt, 4h, 88%; g) $NaIO_4$, THF:H_2O=4:1, rt, 3h; $NaBH_4$, 0 °C, 1h, 87%; h) **19**, CSA, CH_2Cl_2, 0 °C, 3h, 83%; i) DIBAL-H, THF, -78 °C, 1h, 71%; j) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C, 1h, 85%.

bromide **7** produced a ~2:1 mixture of diastereomeric alcohols at C17 (Scheme 3). Although no excellent selectivity was observed, the two diastereomers could be easily separated by flash column chromatography. In order to determine the relative stereochemistry of the major product **12a**, the removal of a TBDPS silyl group of **12a** with TBAF furnished the diol **13**. The 1,3-diol **13** was then converted into acetonide **14**. The configurations at C16 and C17 were confirmed by the Mosher's method[7] and NOE analysis of acetonide **14**, respectively.

The next step along the sequence was the introduction of a C13-C15 homoallylic alcohol unit using the Roush asymmetric crotylation[8] (Scheme 4). Deprotection of TBDPS silyl ether **12a** with TBAF furnished the intermediate 1,3-diol. The next step was the protection of two hydroxy groups as TBS silyl ethers. The treatment of the intermediate diol with TBSOTf in the presence of 2,6-lutidine provided compound **15**. The terminal vinyl group in **15** was converted into the corresponding aldehyde **5** by initial osmium-mediated dihydroxylation followed by oxidative cleavage with $NaIO_4$. The subsequent Roush asymmetric allylation reaction upon aldehyde **5** gave predominantly the desired homoallylic alcohol **17** (95:5 dr by ^{1}H NMR analysis) with the requisite stereochemistry at C14 and C15 of tedanolide (**1**) as we expected. Homoallylic alcohol **17** was treated with OsO_4-$NaIO_4$ followed by reduction to afford the diol **18** in high yield. The 1,3-diol **18** was protected as 4-methoxybenzylidene (MPM) acetal **20**, which was then reduced regioselectively with DIBAL-H in CH_2Cl_2 to give primary alcohol **21** in good yield. Finally the Dess-Martin oxidation[9] of **21** completed the synthesis of the desired aldehyde **3**.

In conclusion, the C13-C21 segment **3** of tedanolide (**1**) was obtained in 20% yield over 14 steps from the aldehyde **9**. The key steps were metal-mediated allylation and the Roush asymmetric crotylation. Ongoing efforts toward the completion of tedanolide (**1**) are currently in progress and will be reported in due course.

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