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Studies toward the total synthesis of tedanolide: stereoselective synthesis of the C(8)–C(17) segment☆

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Abstract—The stereoselective synthesis of the C(8)–C(17) sub-unit (−)-**5** of tedanolide (**1**), which involves iterative Evans aldol reactions as the key steps, is described.

Tedanolide (**1**), an antitumor macrolide, was isolated from a prevalent Caribbean sponge, *Tedania ignis*, by Schmitz et al.[1] Tedanolide is highly cytotoxic, exhibiting ED_{50} values of 250 pg/mL in KB cell lines and 16 pg/mL in PS cell lines.[1] It also shows in vivo antitumor activity increasing the lifespan of mice implanted with lymphocytic leukemia cells (23% at 1.56 μg/kg).[2] In 1991, 13-deoxytedanolide (**2**) was discovered from the Japanese sponge *Mycale adhaerens*, and was also found to exhibit strong antitumor activity.[3] Their potent antitumor activity in combination with their very low natural abundance prompted several research groups to investigate synthetic access to these natural products.[4–12] However, to date, there is still no reported total synthesis of tedanolide, except for the recent total synthesis of (+)-13-deoxytedanolide by Smith[6a,b] and very recently by Roush.[9a]

The main approach of most of the synthetic studies is an aldol reaction between the C1–C12 and C13–C23 segments. Here we have devised an altogether new approach, and our retrosynthesis of tedanolide (**1**) is shown in Scheme 1.

Our retrosynthetic strategy for tedanolide (**1**) involves disconnections leading to three fragments, namely **3** (C18–C23), **5** (C8–C17), and **6** (C1–C9) as shown in Scheme 1.

Fragments **5** and **6** were designed to be connected by Yamaguchi esterification followed by RCM cyclization. Subsequently, fragment **3** is planned to be introduced through its vinyl anion. This approach may be useful in generating analogues of this macrolide by introducing various side chains in the form of fragment **3.** In continuation of our efforts on the total synthesis of tedanolides,[13] we report herein the stereoselective synthesis of the C(8)–C(17) segment **5** having six stereogenic carbon centers.

The synthesis of **5** began with achiral aldehyde **7**, available in two steps from 1,3-propanediol.[14] Evans aldol condensation with **8**,[15,16] followed by silyl protection (TBSCl/imidazole), afforded adduct (−)-**9** with very high diastereoselectivity.[17] Reductive removal of the chiral auxiliary ($NaBH_4$)[18] followed by Swern oxidation of the resulting primary alcohol gave the corresponding aldehyde (−)-**10** in excellent yield (Scheme 2). Subsequently, the deconjugative Evans aldol reaction using crotonoyl chiral auxiliary **11**[19] and (−)-**10** afforded the corresponding aldol adduct (+)-**12**, which upon reduction ($NaBH_4$) followed by silyl protection (TBDPSCl, Py, and 4-DMAP) afforded (+)-**13**.

Keywords: Tedanolide; Stereoselective; Aldol; Boron reagent.
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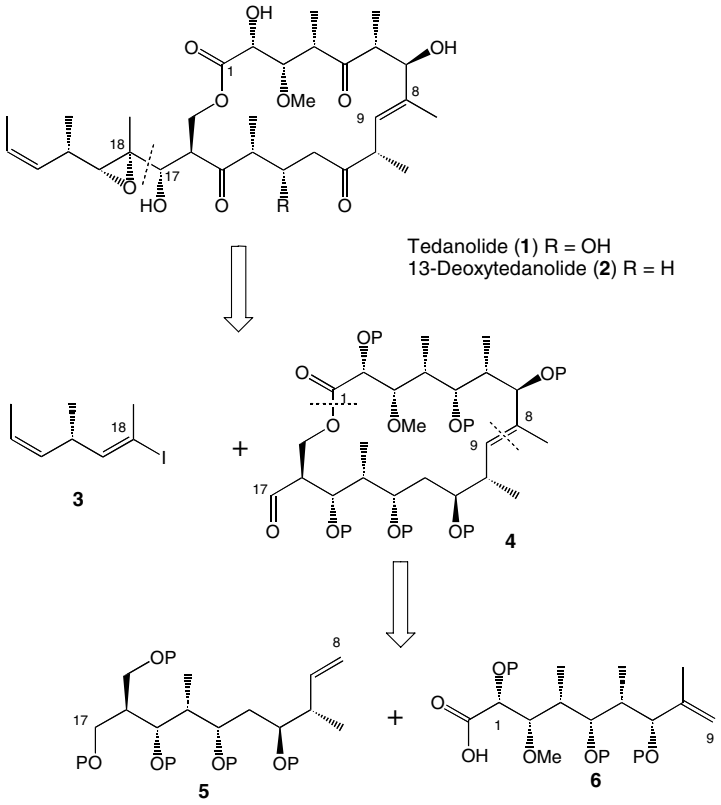
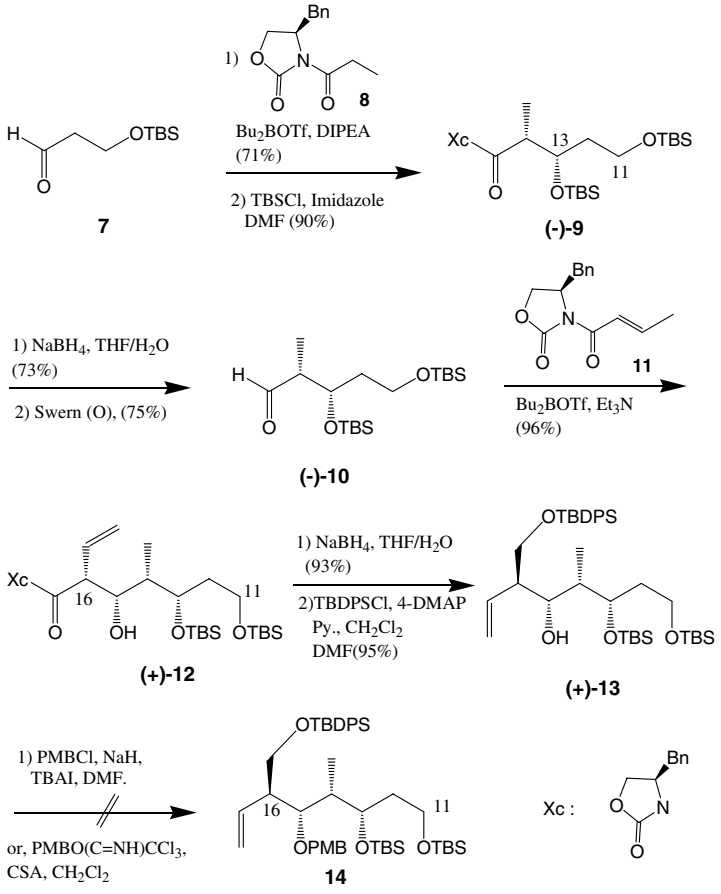
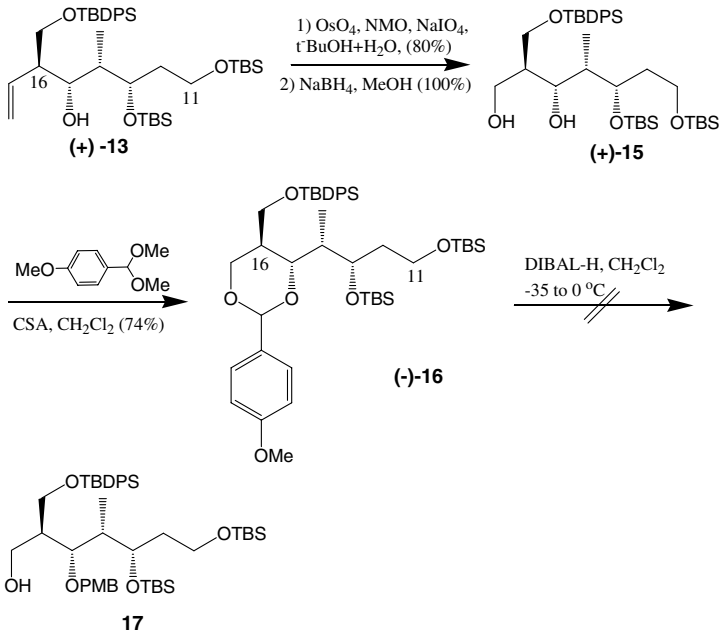


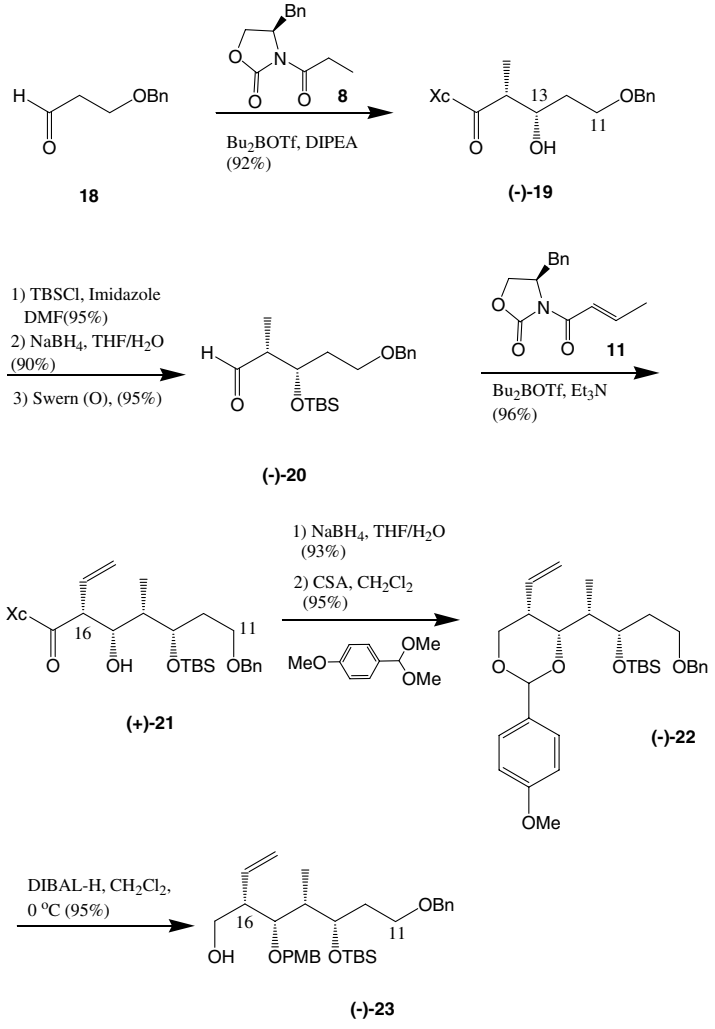
Scheme 1. Retrosynthesis of tedanolide (**1**).



Scheme 2.



Scheme 3.



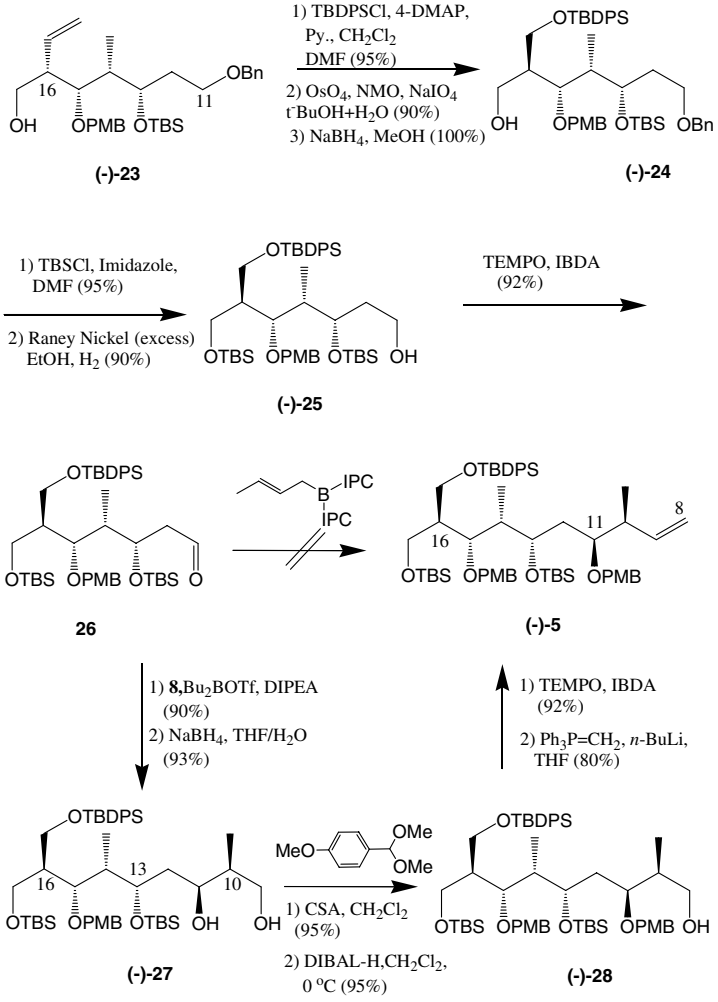
Scheme 4.

The fragment (+)-**13** had all the correct chiral centers as present in the natural product, however, we were unable to protect the C-15 hydroxy as O-PMB using a variety of conditions. We then turned our attention to manipulate the double bond in (+)-**13** to give a primary hydroxyl group which could then be protected in the form of a cyclic acetal using the C-15 and C-17 hydroxyl groups.

Accordingly, (+)-**13** was treated with OsO_4–$NaIO_4$ followed by reduction to afford the diol (+)-**15** in high yield and purity. The 1,3-diol in (+)-**15** was converted into the corresponding cyclic acetal (−)-**16** (PMP-acetal-CSA) in good yield. At this stage we attempted to unmask the primary alcohol of the acetal in (−)-**16** using the literature procedure (DIBAL-H)[20] to access **17**, however, no trace of the latter product was obtained under these conditions. A careful analysis of the reaction mixture revealed that DIBAL-H reduction of (−)-**16** gave a mixture of compounds which lacked the TBS group at C-11.[21]

This observation prompted us to realize that hydride attack at the acetal carbon may be hindered due to the presence of a bulky TBDPS group. To circumvent the problem arising due to the presence of silicon groups at C-11 and C-16 in (−)-**16**, we changed the protecting group on **7** to a benzyl group. Thus repeating the synthetic sequence using **18** as described in Scheme 2, we synthesized the intermediates (−)-**19**, (−)-**20**, and (+)-**21** in good yields and optical purity (Scheme 4).[22] To avoid the presence of a bulky silicon protecting group (cf. (+)-**13**, Scheme 3), prior to cyclic acetal formation, we converted (+)-**21** to the corresponding cyclic acetal (−)-**22**[23] by reductive removal of the chiral auxiliary ($NaBH_4$) followed by cyclic acetal formation (CSA, PMP acetal) on the resulting diol. Selective unmasking of the primary hydroxyl group of the cyclic acetal in (−)-**22** was achieved on DIBAL-H reduction to give (−)-**23** in excellent yield.

The success in selective unmasking of the primary alcohol in (−)-**22** compared with (−)-**16** clearly accounted for our observation that the steric bulk of the TBDPS group prevents hydride reduction of the acetal carbon in (−)-**16**. The primary alcohol group in (−)-**23** was protected (TBDPSCl, Py, and 4-DMAP) and the double bond was oxidatively cleaved using OsO_4 followed by reduction to give (−)-**24** (Scheme 5). Subsequently, protection of the hydroxyl group in (−)-**24** followed by removal of the benzyl group (Ra–Ni) afforded (−)-**25**.



Scheme 5.

At this stage the primary hydroxyl group of (−)-**25** was oxidized (TEMPO) to give the corresponding aldehyde which was reacted with the crotyl borane reagent to install the other two chiral centers (C-10, C-11) as present in the target fragment **5**. However, several attempts using this reaction gave unacceptably low yields of the expected fragment. The failure of the crotyl boration led us to follow an alternative approach and completion of the synthesis of fragment **5** was straightforward as described in Scheme 5.

Thus, Evans aldol reaction between chiral auxiliary **8** and aldehyde **26** gave the desired adduct[17] which upon reduction with $NaBH_4$ yielded (−)-**27**. The C-11 PMB protection was carried out by cyclic acetal formation with anisaldehyde dimethyl acetal followed by regioselective opening with DIBAL-H (90%, two steps) to give (−)-**28**. Finally oxidation of alcohol **28** with TEMPO followed by a Wittig reaction on the resulting aldehyde with $Ph_3P=CH_2$ and *n*-BuLi in THF afforded the target C(8)–C(17) segment **5**[24] in 75% yield.

In summary, we have carried out a highly stereoselective synthesis of the C(8)–C(17) segment of tedanolide where all six stereogenic centers were generated using the Evans chiral auxiliary in an iterative fashion. Continued advancement of this intermediate toward tedanolide (**1**) will be reported in due course.

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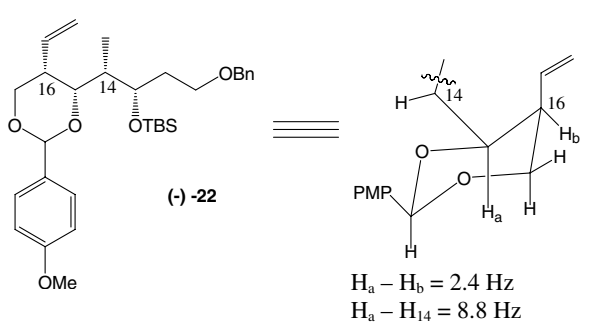
23.



24. *Spectral data for* (−)-**5**: $[\alpha]_D^{23}$ −41.0 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.66–7.63 (m, 4H), 7.40–7.30 (m, 6H), 7.21 (d, $J = 8.8$ Hz, 2H), 7.12 (d, $J = 8.4$ Hz, 2H), 6.82–6.78 (m, 4H), 5.76 (ddd, $J = 17.2$ Hz, 10.8 Hz, 6.4 Hz, 1H), 4.93 (d, $J = 9.6$ Hz, 1.6 Hz, 1H), 4.90 (dd, $J = 17.2$ Hz, 1.2 Hz, 1H), 4.56 (d, $J = 4.0$ Hz, 1H), 4.54 (d, $J = 4.0$ Hz, 1H), 4.46 (d, $J = 11.2$ Hz, 1H), 4.30 (d, $J = 11.2$ Hz, 1H), 3.93 (dd, $J = 10.0$ Hz, 2.8 Hz, 1H), 3.84−3.70 (m, 4H), 3.78 (s, 3H), 3.76 (s, 3H), 3.54 (dd, $J = 10.0$ Hz, 6.0 Hz, 1H), 3.43 (dd, $J = 8.0$ Hz, 4.0 Hz, 1H), 2.59–2.57 (m, 1H), 1.95 (m, 1H), 1.72–1.70 (m, 1H), 1.64 (m, 1H), 1.47 (m, 1H), 1.05 (s, 9H), 0.89 (d, $J = 7.2$ Hz, 3H), 0.87 (s, 9H), 0.85 (s, 9H), 0.77 (d, $J = 6.8$ Hz, 3H), 0.01 (s, 3H), −0.005 (s, 3H), −0.01 (s, 3H), −0.09 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.8, 158.6, 140.0, 135.6, 135.5, 133.8, 133.7, 131.7, 131.3, 129.5, 129.4, 128.7, 128.5, 128.4, 127.5, 114.4, 113.6, 113.5, 80.3, 75.0, 72.6, 70.1, 62.0, 59.0, 55.2, 55.1, 47.4, 41.4, 39.0, 35.2, 26.9, 26.1, 25.8, 19.1, 18.1, 18.0, 15.0, 10.9, 0.9, −3.5, −4.3, −5.3, −5.4; IR (KBr, cm^{-1}) 3072, 2930, 2857, 1614, 1587, 1514, 1471, 1428, 1389, 1360, 1301, 1248, 1172, 1070, 1006, 835, 774, 740, 702, 504; *m*/*z* (ESMS) 969 (M^++1, 100%), HRMS calcd for $C_{57}H_{89}O_7Si_3$ $(M+H)^+$ 969.5916, found 969.5925.