Synthesis of the C1–C11 Segment of Tedanolide via Vinylogous Mukaiyama Aldol Reaction

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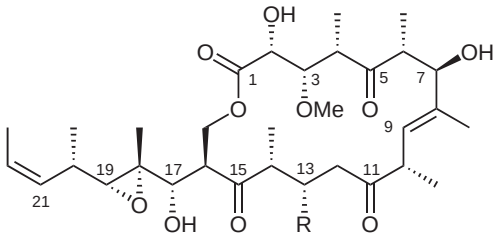
Abstract: The successful construction of complex natural products depends to a large extent on how efficiently key intermediates can be generated. Here we report our efforts towards the first total synthesis of tedanolide (**1**), employing Evans' aldol methodology in combination with a vinylogous Mukaiyama aldol reaction (VMAR) and Sharpless' asymmetric dihydroxylation. This protocol allows for rapid access to its numerous chiral centers.

Key words: aldol reactions, Mukaiyama, natural products, dihydroxylations, stereoselective synthesis

Tedanolide (**1**) and 13-deoxytedanolide (**2**) are two potent marine natural products that were isolated and whose structure was elucidated by Schmitz et al.[1] and Fusetani et al.,[2] respectively (Figure 1). Due to their challenging structure in combination with their promising anti-tumor activity, a variety of fragment syntheses have been put forward.[3]

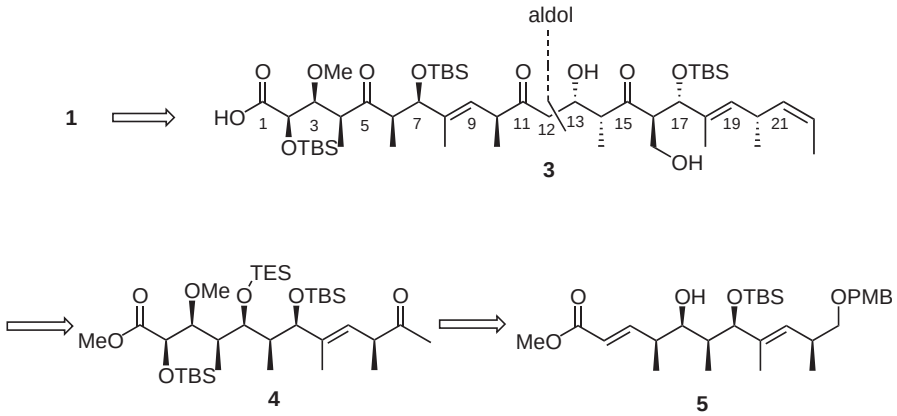
Our retrosynthetic analysis (Scheme 1) dissected tedanolide between C12 and C13. In synthetic direction, this coupling could be performed by an aldol reaction. An elegant analysis of aldol reactions of such methyl ketones has been reported by Roush et al. who demonstrated that both the α-methyl group of the methyl ketone and the stereochemistry of the aldehyde direct the stereochemical outcome of the reaction towards the Felkin product.[3e,4] Another obvious problem in a total synthesis of **1** and **2** is the fact that the three ketone carbonyl groups in the natural product are sensitive to retro-aldol processes. We therefore decided to carry them through the synthesis as protected alcohols, which could be liberated and oxidized at a later stage. With theses prerequisites in mind we generated the C1–C11 segment as the all *syn*-polyketide in which the C5-ketone was the TES-protected alcohol.



1 R = OH Tedanolide
2 R = H 13-Deoxytedanolide

Figure 1 Tedanolide and 13-deoxytedanolide.

Fueled by our work on the synthesis of ratjadone,[5] we focused on the vinylogous Mukaiyama aldol reaction as a method for the rapid access to aldol segments. The use of silyl ketene acetal **12** substitutes the sequence of a propionate aldol reaction followed by Wittig olefination and circumvents functional group manipulations. In earlier



Scheme 1 Retrosynthetic analysis of tedanolide.

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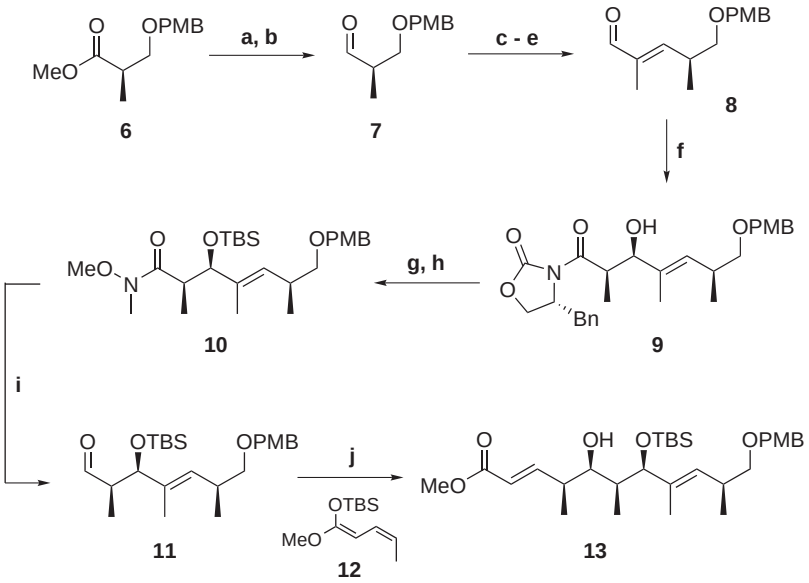
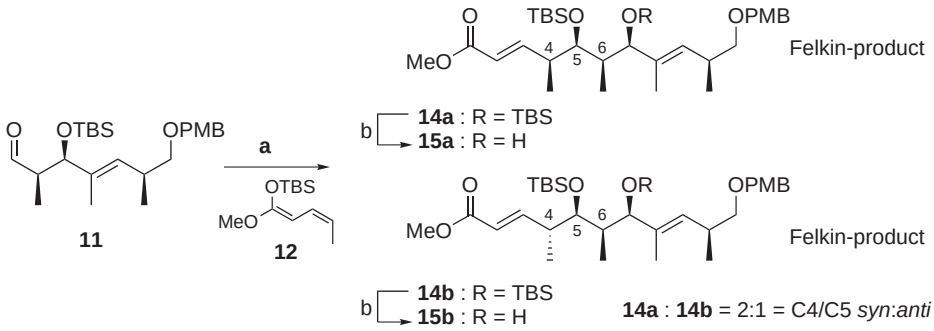
studies from our group, the use of a sterically demanding Lewis acid such as tris(pentafluorophenyl)borane (TPPB) was shown to be essential for achieving high *syn*-selectivity and Felkin control (Scheme 2).[6]

The synthesis started from enantiomerically pure PMB-protected methyl-hydroxyisobutyrate (**6**) that was converted to aldehyde **7** under standard conditions (Scheme 2). Wittig-olefination generated the α,β-unsaturated ester in 95% yield. DIBALH reduction followed by oxidation with MnO_2 furnished aldehyde **8** in 88% yield over two steps. The remaining propionate subunit of aldehyde **11** was introduced by an Evans aldol reaction, which was followed by transamination and TBS-protection (77% yield over two steps). The Weinreb amide (**10**) was directly reduced to aldehyde **11** by the aid of DIBALH. This sets the stage for the pivotal vinylogous Mukaiyama aldol reaction.

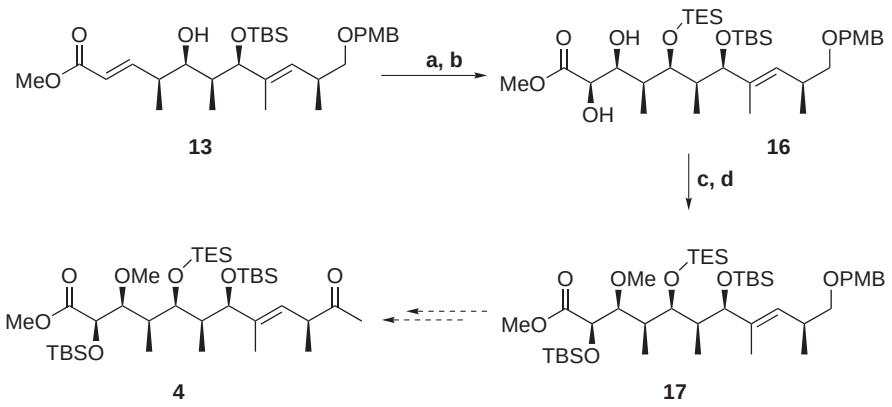
When aldehyde **11** was reacted with 2 equivalents of ketene acetal **12** using 0.6 equivalents of tris(pentafluorophenyl)borane (TPPB) at –78 °C in CH_2Cl_2/diethyl ether (9:1), two products, **14a** and **14b** were isolated (Scheme 3). Studies from Hoffmann et al.[7] have shown that the ^{13}C chemical shift for the methyl groups in the all *syn* stereotriad is significantly high-field shifted (δ<10 ppm) compared to structures with at least one *anti* relationship (δ>10 ppm). This analysis requires a hydrogen bond between the two adjacent oxygen functionalities. These bis-TBS ethers (**14a** and **14b**) were therefore converted to mono-TBS protected ethers **15a** and **15b** by selective deprotection at the C7 hydroxy group. This was achieved by using HF·pyridine in pyridine/THF. The ^{13}C NMR spectrum showed the signal for the C6 methyl groups at δ-values of 9.51 ppm and 9.14 ppm for the major (**15a**) and minor isomer (**15b**), respectively, thus indicating the all-*syn* stereochemistry in both cases (Felkin control, Scheme 3).



Scheme 2 Synthesis of **13**. *Reagents and conditions*: a) DIBALH, CH_2Cl_2, 93%; b) Dess–Martin-periodinane, CH_2Cl_2, 90%; c) $Ph_3P{=}C(CO_2Et)Me$, CH_2Cl_2, 95%; d) DIBALH, CH_2Cl_2, 90%; e) MnO_2, CH_2Cl_2, 98%; f) (*R*)-4-benzyl-3-propionyl-2-oxazolidinone, $(n\text{-Bu})_2BOTf$, NEt_3, CH_2Cl_2, 82%; g) $AlMe_3$, *N,O*-dimethyl-hydroxylamine hydrochloride, CH_2Cl_2; h) TBSOTf, 2,6-lutidine, CH_2Cl_2, 77% over 2 steps; i) DIBALH, THF, 89%; j) tris(pentafluorophenyl)borane (TPPB), ketene acetal **12**, isopropyl alcohol, Et_2O, 62%.



Scheme 3 *Reagents and conditions*: a) **12** (2 equiv), TPPB (0.6 equiv), CH_2Cl_2/Et_2O (9:1), –78 °C, r.t, 2 h, 72%; b) HF·pyridine, THF/pyridine (1:1), r.t., 30 h, 56%.



Scheme 4 *Reagents and conditions*: Synthesis of **16**: a) TESOTf, 2,6-lutidine, CH_2Cl_2, 93%; b) AD-mix-α, *t*-BuOH-H_2O, 88% (94% de); c) TBSCl, imidazole, DMF, 91%; d) MeOTf, 2,6-di-*t*-butylpyridine, $CHCl_3$, 60%.

In optimization studies for this pivotal reaction, when aldehyde **11** was treated with 2 equivalents of ketene acetal **12** using 1 equivalent of TPPB and 1 equivalent of isopropanol in diethyl ether, only aldol product **13** was isolated. (Scheme 2).[8] As before, its stereochemistry was assigned unambiguously using ^{13}C NMR data. A stoichiometric amount of alcohol is necessary in order to trap reactive silicon species liberated in the course of the reaction. It is known that these R_3Si^+ species can catalyze aldol reactions albeit with little or no stereocontrol. Failure to quench them leads to the formation of isomer **14b**. Interestingly, use of $BF_3{\cdot}OEt_2$ as sterically less demanding Lewis acid exclusively alkylates the ketene acetal at the α-position.

Continuing with the synthesis of tedanolide, the newly generated secondary alcohol was TES-protected and subsequent Sharpless dihydroxylation to **16** stereoselectively established the remaining stereocenters of the all-*syn* polyketide fragment (Scheme 4).[3b,f] The alcohol at C2 could be selectively protected as TBS-ether and the remaining hydroxyl group at C3 was transformed into the methyl ether **17** using MeOTf and di-*tert*-butylpyridine for the O-alkylation. These transformations completed the synthesis of the C1–C11 segment in which 6 chiral centers were selectively generated in 14 steps and 9.6% overall yield. Additionally, the hydroxyl groups have been differentially protected thus allowing for selective removal followed by functional group transformations in the endgame of the synthesis. Progress on the total synthesis will be reported in due course.

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(8) Aldehyde **11** (92 mg, 0.218 mmol) dissolved in diethyl ether (2 mL) was cooled to –78 °C under an argon atmosphere. Tris(pentafluorophenyl)borane (110 mg, 0.217 mmol) was added and a mixture of ketene acetal **12** (100 mg, 0.438 mmol) and isopropyl alcohol (17 μL, 0.24 mmol) dissolved

in diethyl ether (1 mL) was added via syringe pump over 6 h. An additional equivalent of ketene acetal **12** (100 mg, 0.438 mmol) was added in diethyl ether (1 mL) over 4 h. After complete addition, the reaction was quenched by sat. aq $NaHCO_3$ (2 mL), slowly warmed to r.t. and stirred overnight. Water (3 mL) was added and the mixture was extracted with ether (2 × 15 mL). The organic layer was separated, dried with $MgSO_4$ and evaporated in vacuo. Flash column chromatography using petroleum ether/ethyl acetate (4:1) as eluent afforded **13** (73 mg, 62%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8.78 Hz, 2 H), 6.85 (d, *J* = 8.78 Hz, 2 H), 6.70 (dd, *J* = 15.69, 9.29 Hz, 1 H), 5.80 (dd, *J* = 15.69, 0.75 Hz, 1 H), 5.16 (d, *J* = 9.54 Hz, 1 H), 4.38 (s, 2 H), 3.87 (d, *J* = 7.44 Hz, 1 H), 3.77 (s, 3 H), 3.70 (s, 3 H), 3.28 (dd, *J* = 8.90, 5.90 Hz, 1 H), 3.28–3.24 (m, 1 H), 3.18 (dd, *J* = 8.90, 8.03 Hz, 1 H), 2.77–2.66 (m, 1 H), 2.44–2.36 (m, 2 H), 1.59–1.51 (m, 1 H), 1.53 (d, *J* = 1.25 Hz, 3 H), 0.97 (d, *J* = 6.52 Hz, 3 H), 0.90 (d, *J* = 6.77 Hz, 3 H), 0.85 (d, *J* = 6.90 Hz, 3 H), 0.85 (s, 9 H), 0.02 (s, 3 H), –0.05 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9, 159.2, 151.0, 136.2, 130.8, 130.3, 129.2, 120.7, 113.8, 82.4, 75.1, 72.7, 55.2, 51.4, 40.8, 39.7, 32.5, 26.9, 25.9, 18.1, 17.1, 16.7, 11.9, 8.1, –4.4, –5.1; HRMS calcd for $C_{30}H_{50}O_6Si$: 534.3377. Found: 534.3371.