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Synthetic studies toward the total synthesis of tedanolide: assembly of the C1–C23 carbon backbone

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Abstract—A stereoselective assembly of the C1–C23 fragment representing the carbon backbone of tedanolide was accomplished utilizing a chiral boron reagent to effect the aldol coupling of the C1–C12 diketoester fragment with the C13–C23 aldehyde fragment.
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Tedanolide (**1**) and 13-deoxytedanolide (**2**) are both polyketide macrolides found in marine organisms. Tedanolide (**1**) was isolated from *Tedania ignis*, a Caribbean sponge by Schmitz et al.[1] in 1984 and 13-deoxytedanolide (**2**) from *Mycale adhaerens*, a Japanese sea sponge by Fusetani et al.[2] in 1991, respectively. These compounds were found to exhibit very potent biological activities against certain tumor cell lines.[2,3] Complete structural elucidation of these two compounds by the two research groups revealed that both molecules were found to possess an 18-membered macrolide having a complex structural architecture. They contained a heavily substituted and highly oxygenated carbon backbone and a very crowded arrangement of contiguous stereocenters. Their complex chemical structures and antitumor properties have attracted a significant number of synthetic studies,[4] including the recent total syntheses of 13-deoxytedanolide (**2**) reported by Smith[4l] and Roush.[4w]

Our synthetic plan for the synthesis of tedanolide is outlined in Figure 1. Retrosynthetically, **1** can be synthesized from the seco-ester **3** after several forward transformations, including the key epoxidation of the C18–C19 olefin and lactonization at the C29 hydroxyl group. Retrosynthetic scission of the C12–C13 bond via an aldol disconnection dissected **3** into **4**, the C1–

C12 diketoester fragment and **5**, the C13–C23 aldehyde fragment.

Diketoester **4** can be derived from the aldol coupling of ketoester **6** and the α,β-unsaturated aldehyde **7** via the diastereoselective boron-mediated *syn* aldol reaction reported in our previous study for another enal.[4q] We anticipated that using enal **7** in the present strategy would improve convergency and efficiency. We planned to elaborate aldehyde **5** from compound **8**, a secondary alcohol intermediate in our preliminary synthetic study[4r] without installing the sensitive epoxide group. Here, we describe a revised strategy based on our previous synthetic studies to diketoester **4** and aldehyde **5**. Their subsequent aldol coupling to afford the desired stereochemistry at the newly formed 13-hydroxyl center in seco-ester **3** is also reported.

The synthesis of diketoester **4** began with silyl protection of the readily available hydroxy ester (*S*)-**9** using TBDPSCl in 99% yield (Scheme 1). The silyl protected ester was then converted to Weinreb amide **10** using a known procedure.[5] The crude amide was subsequently reacted with methylmagnesium bromide in THF at 0 °C to form the crude methyl ketone which was further reduced to a diastereomeric mixture of alcohols **11** in an almost quantitative yield. PMB (*p*-methoxybenzyl) ether formation from alcohol **11** with PMB trichloroacetimidate[6] and removal of the primary silyl protecting group using TBAF in THF (72% over the two steps) transformed alcohol **11** into primary alcohol **12**. Dess–Martin oxidation[7] of alcohol **12** to the corresponding aldehyde followed by Wittig olefination with the stabilized ylide
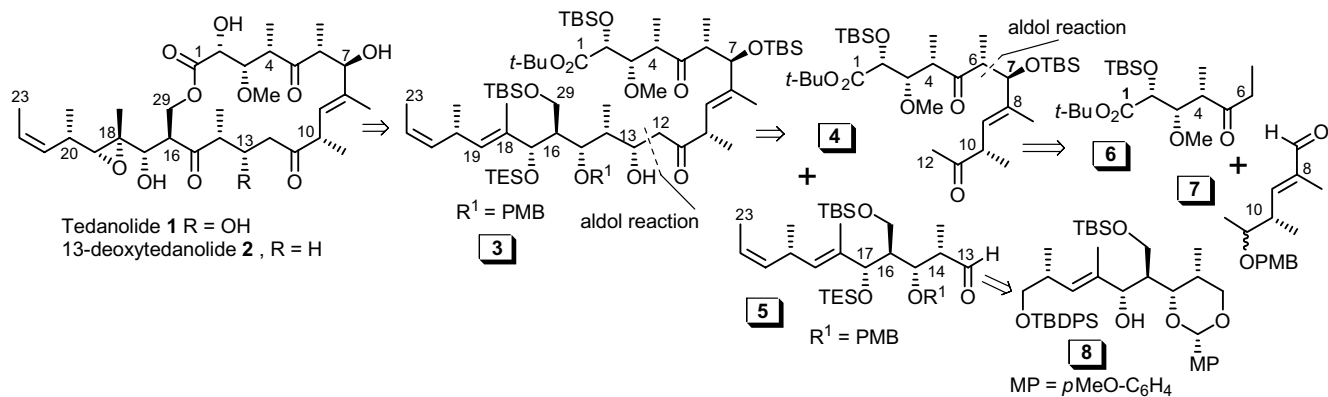
Figure 1. Retrosynthetic analysis.

Scheme 1. Synthesis of aldehyde 7.
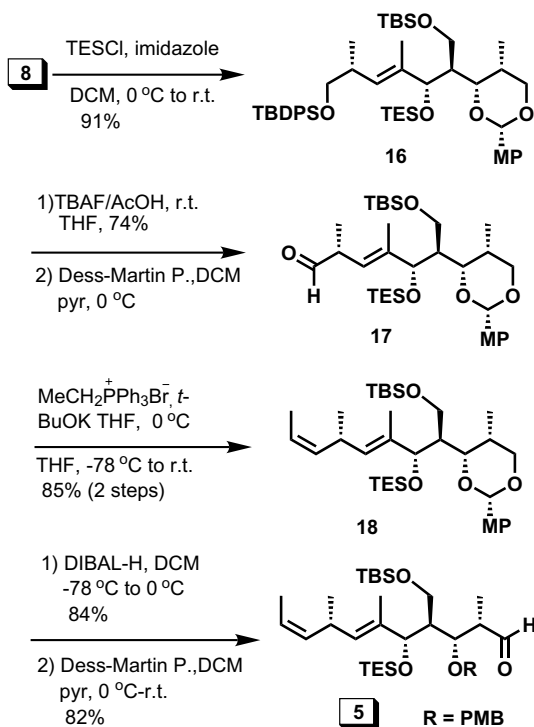

Scheme 2. Synthesis of diketoester 4.

$Ph_3P=CH(Me)CO_2Me$ yielded the α,β-unsaturated methyl ester **13** with high *E*-selectivity in an 86% yield (two steps). DIBAL-H reduction of ester **13** in DCM (CH_2Cl_2) and Dess–Martin oxidation of the allylic alcohol provided the desired enal **7** in an 85% yield (two steps).

With enal **7** in hand, the boron-mediated *syn* aldol reaction[8] with ketoester **6** was performed following a similar procedure to that reported in our previous study.[4q] In our initial attempt, the desired hydroxy ketoester **14** was obtained in a 60% isolated yield (74% conversion yield based on recovered **6** selectivity at C6, C7, dr C6:C7 = 94:6) along with recovered **6** (26%) and **7** (20%) when ketoester **6** (1 equiv) was treated with *n*-Bu$_2$-BOTf, Et$_3$N in DCM at −78 °C followed by the addition of enal **7** (1 equiv). On optimization, the yield of **14** was increased to 88% when 1.5 equiv of **6** was used in the reaction (Scheme 2) while still giving an excellent

diastereoselectivity (along with 39% of recovered **6**). The hydroxy functionality of **14** was then silyl protected using TBSCl and 2,6-lutidine in CH_2Cl_2 at −78 °C to afford **15** in 78% yield. Deprotection of the PMB ether of the C11 hydroxy group of **15** followed by Dess–Martin oxidation gave the desired diketoester **4** in 71% yield (two steps).

The synthesis of the C13–C23 aldehyde **5** from compound **8**[4r] is depicted in Scheme 3. The C17 secondary hydroxy group in **8** was protected with TESCl[9] and imidazole in CH_2Cl_2 to afford the fully protected benzylidene acetal **16** in 91% yield. Selective removal of the primary TBDPS silyl protecting group of **16** was achieved using TBAF/AcOH[10] in THF at room temperature to give a primary alcohol in good yield (74%). Dess–Martin oxidation of this alcohol provided aldehyde **17** which was immediately subjected to a non-stabilized Wittig olefination with $CH_3CH=PPh_3$ in THF to give the *Z,E*-diene **18** as the major isomer (>10:1, 85% yield over the two steps). The *p*-methoxybenzylidene acetal of diene **18** was then reductively opened using DIBAL-H in DCM from −78 to 0 °C to provide the C15 PMB protected *Z,E*-diene primary alcohol in good yield (84%). Finally, Dess–Martin oxidation of this alcohol gave

available aldol reagents were tested to probe the diastereoselectivity of the newly formed C13 carbinol center. The results of this study are summarized in Table 1. As revealed in Table 1, the two fragments were coupled using all the reagents listed, giving various yields (not optimized) and selectivities.

The lithium and sodium enolates of methyl ketone 4, obtained using LiHMDS and NaHMDS, gave moderate stereoselectivities on aldol addition to aldehyde 5, favoring the desired diastereomer 3 (entries 1, 2). Addition of HMPA eroded the stereoselectvity for the lithium enolate reaction (entry 3). Reaction of 5 with the dibutylboron[8] and 9-BBN enolates[8a,11] of 4 provided similar levels of selectivity (entries 4 and 6) as the lithium enolate, while the dicyclohexylboron enolate[12] gave a slight improvement in favor of 3 (3a:3 = 26:74, entry 5). Attempts to increase the stereoselectivity of the aldol reaction via triple asymmetric induction[13] proved fruitful as treatment of aldehyde 5 with a chiral boron enolate generated from 4 and (−)-Ipc$_2$BCl according to Paterson's protocol[14] resulted in an improvement of the stereoselectivity in favor of 3a (3a:3 = 85:15, entry 7). Enolization employing the enantiomeric (+)-Ipc$_2$BCl[14] effected a reversal of stereoselectivity to give a 17:83 mixture of 3a and 3 in 34% yield (entry 8).

However, an aldol reaction with the chlorotitanium enolate[15] gave a mixture of aldol products modestly favoring diastereomer 3a (entry 9). The stereochemistry of the C13 center in diastereomers 3a[16] and 3[17] was determined according to a reported method by ^{1}H NMR analysis of the characteristic ABX pattern of the C12 methylene protons.[18] In addition, the recovery of diketoester 4 and aldehyde 5 were generally quite satisfactory. The recovered starting materials showed no epimerization
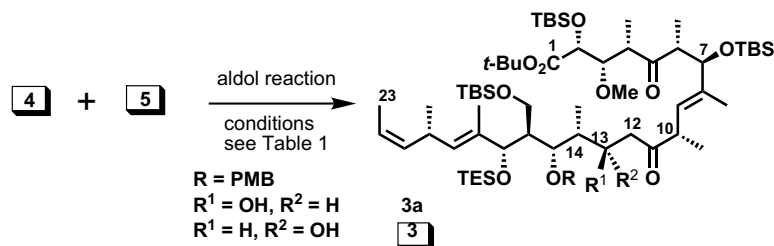
Scheme 3. Synthesis of diene-aldehyde 5.

the desired Z,E-dienal 5 in very good overall yield (38%, six steps from 8).

Having established an efficient route to both diketoester 4 and aldehyde 5, we examined the crucial aldol reaction required to effect the generation of the desired C13 center of the tedanolide skeleton (see Fig. 1). Various

Table 1. Aldol reaction of diketoester 4 and aldehyde 5

Entry	Aldol reaction conditions[a]	Yield[b] (%)	3a:3[c]	Recovered (%) 4	Recovered (%) 5
1	LiHMDS, −78 °C, THF	26	32:68	66	59
2	NaHMDS, −78 °C, THF	30	36:64	57	43
3	LiHMDS, 9% HMPA, −78 °C, THF	27	47:53	54	29
4	n-Bu$_2$BOTf, Et$_3$N, −78 °C, CH$_2$Cl$_2$	24	34:66	79	53
5	(c-hex)$_2$BCl, Et$_3$N, Et$_2$O, 0 °C, 1 h then 5, −78 to −20 °C	47	26:74	59	∼1
6	9-BBNOTf, Et$_3$N, Et$_2$O, −78 to −20 °C	52	40:60	14	6
7	(−)-Ipc$_2$BCl, Et$_3$N, Et$_2$O, 0 °C, 1 h then 5, −78 to −20 °C	19	85:15	62	56
8	(+)-Ipc$_2$BCl, Et$_3$N, Et$_2$O, 0 °C, 1 h then 5, −78 to −20 °C	34	17:83	37	17
9	TiCl$_4$, i-Pr$_2$EtN, DCM, −78 °C	24	59:41	46	0

[a] The reactions were typically carried out using 1.4–1.8 equiv of diketoester 4 and 1 equiv of aldehyde 5.
[b] Combined isolated yields of 3a and 3 (unoptimized) after silica gel chromatography.
[c] Ratio was determined from ^{1}H NMR of the purified diastereomers in a mixture.

or isomerization under the aldol conditions used or during the subsequent purification.

In conclusion, we have developed convergent routes to synthesize both diketoester **4** and aldehyde **5** and demonstrated their synthetic viability for an aldol coupling. The stereoselective assembly of the C1–C23 carbon backbone of tedanolide was accomplished using a chiral boron reagent with good selectivity. The desired diastereomer **3** represents the carbon framework of tedanolide with all the required chiral centers installed with the exception of the epoxide functionality. Efforts directed at further synthetic exploration to tedanolide are currently in progress.

Acknowledgments

References and notes

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16. Compound **3a** (mixture of 85:15 with **3**). $R_f = 0.63$ (*n*-hexane/EtOAc, 4:1); ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.23 (d, $J = 8.3$ Hz, 2H, Ph*H*), 6.86 (d, $J = 8.3$ Hz, 2H, Ph*H*), 5.32 (dq, $J = 10.6$, 6.9 Hz, 1H, MeC*H*=CH), 5.26 (dd, $J = 0.9$, 9.7 Hz, 1H, C=C*H*), 5.20 (dd, $J = 1.9$, 8.8 Hz, 1H, CHC*H*=CMe), 5.19 (ddd, $J = 1.9$, 9.3, 10.6 Hz, 1H, MeCH=C*H*CH), 4.52 (d, $J = 11.6$ Hz, 1H, OC*H*$_a$H$_b$PhOMe), 4.42 (d, $J = 11.1$ Hz, 1H, OCH$_a$*H*$_b$PhOMe), 4.33 (d, $J = 6.0$ Hz, 1H, C*H*O), 4.19 (d, $J = 9.2$ Hz, 1H, TBSOC*H*MeC=), 4.09 (d, $J = 5.1$ Hz, 1H, TBSOC*H*CO), 3.97 (dd, $J = 2.8$, 5.1 Hz, 1H, MeOC*H*), 3.95 (ddd, $J = 4.2$, 4.6, 6.0 Hz, 1H, C*H*OH), 3.84 (dd, $J = 4.2$, 4.2 Hz, 1H, C*H*O), 3.80 (s, 3H, PhO*Me*), 3.49 (d, $J = 6.9$ Hz, 1H, C*H*$_c$H$_d$O), 3.42 (s, 3H, *Me*OCH), 3.39 (m, 3H, =CHC*H*MeCH=, CH$_c$*H*$_d$O, MeC*H*C=O), 3.01 (dq, $J = 9.3$, 6.9 Hz, 1H, MeC*H*C=O), 2.72 (dq, $J = 2.3$, 6.9 Hz, 1H, MeC*H*C=O), 2.50 (d, $J = 6.0$ Hz, 2H, C*H*$_2$C=O), 2.17 (m, 1H, C*H*), 2.13 (m,

1H, C*H*), 1.64 (dd, $J = 1.9, 6.5$ Hz, 3H, *Me*CH=CH), 1.64 (d, $J = 0.9$ Hz, 3H, *Me*C=CH), 1.60 (s, 3H, =C*Me*), 1.48 (s, 9H, *t-Bu*O), 1.28 (d, $J = 7.4$ Hz, 3H, *Me*CH), 1.10 (d, $J = 6.9$ Hz, 3H, CH*Me*), 0.99 (d, $J = 6.9$ Hz, 3H, *Me*CH), 0.94 (s, 9H, *t-Bu*SiMe$_2$), 0.92 (t, $J = 7.9$ Hz, 9H, (*Me*CH$_2$)$_3$Si), 0.88 (s, 9H, *t-Bu*SiMe$_2$), 0.86 (d, $J = 6.9$ Hz, 3H, *Me*CH), 0.80 (s, 9H, *t-Bu*SiMe$_2$), 0.78 (d, $J = 7.4$ Hz, 3H, CH*Me*), 0.57 (q, $J = 7.9$ Hz, 6H, (MeC*H$_2$*)$_3$Si), 0.12 (s, 3H, *t*-Bu*Me*SiMe), 0.08 (s, 3H, *t*-BuMeSi*Me*), 0.01 (s, 6H, Si*Me$_2$*) −0.04 (s, 3H, *t*-BuMeSi*Me*); −0.05 (s, 3H, *t*-BuMeSi*Me*); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 215.6, 213.0, 171.4, 159.7, 138.5, 135.6, 134.6, 132.2, 131.9, 129.4, 128.4, 122.3, 114.3, 82.0, 81.5, 78.7, 76.7, 73.4, 71.7, 61.1, 61.0, 56.0, 49.8, 47.8, 47.7, 47.7, 46.5, 42.5, 31.1, 28.7, 26.6, 26.6, 26.5, 21.8, 19.1, 18.8, 18.7, 17.0, 15.1, 13.7, 13.6, 12.9, 11.7, 11.3, 7.6, 5.6, −3.9, −4.0, −4.3, −4.4, −4.6, −4.7; FTIR (thin film, KBr plate) cm^{-1}: 3538 (br), 3007, 2956, 2930, 2883, 2856, 1748, 1715, 1614, 1586, 1515, 1472, 1463, 1407, 1390, 1368, 1336, 1301, 1251, 1172, 1147, 1100, 1062, 1041, 1005, 963, 939, 896, 838, 817, 779, 741, 726, 669; HRMS (ESI) calcd. For C$_{68}$H$_{126}$O$_{12}$Si$_4$Na [M+Na$^+$]: 1269.8224. Found: 1269.8237.

17. Compound **3** (mixture of 83:17 with **3a**). $R_f = 0.64$ (*n*-hexane/EtOAc, 4:1); ^{1}H NMR (500 MHz, CDCl$_3$) δ (ppm): 7.25 (d, $J = 8.8$ Hz, 2H, Ph*H*), 6.86 (d, $J = 8.8$ Hz, 2H, Ph*H*), 5.33 (dd, $J = 1.4, 9.2$ Hz, 1H, C=C*H*), 5.31 (dq, $J = 10.6, 6.9$ Hz, 1H, Me*CH*=CH), 5.20 (ddd, $J = 1.9, 9.2, 11.1$ Hz, 1H, MeC*H*=CHCH), 5.17 (d, $J = 8.8$, 1H, CHC*H*=CMe), 4.51 (d, $J = 11.1$ Hz, 1H, OC*H$_a$*H$_b$PhOMe), 4.44 (d, $J = 11.1$ Hz, 1H, OCH$_a$*H$_b$*-PhOMe), 4.28 (d, $J = 6.9$ Hz, 1H, C*H*O), 4.19 (d, $J = 9.7$ Hz, 1H, TBSOC*H*MeC=), 4.09 (d, $J = 5.1$ Hz, 1H, TBSOC*H*CO), 3.98 (dd, $J = 2.8, 5.1$ Hz, 1H, MeOC*H*), 3.83 (dd, $J = 2.3, 6.5$ Hz, 1H, C*H*O), 3.79 (s, 3H, PhO*Me*), 3.42 (s, 3H, *Me*OCH), 3.39 (m, 5H, C*H*O, =CHC*H*MeCH=, C*H$_2$*O, MeC*H*C=O), 3.01 (dq, $J = 9.7, 6.9$ Hz, 1H, MeC*H*C=O), 2.72 (dq, $J = 2.3, 7.4$ Hz, 1H, MeC*H*C=O), 2.65 (dd, $J = 9.2, 16.2$ Hz, 1H, C*H$_c$*H$_d$C=O), 2.33 (dd, $J = 3.2, 16.2$ Hz, 1H, CH$_c$*H$_d$*C=O), 2.18 (m, 1H, C*H*), 2.16 (m, 1H, C*H*), 1.64 (d, $J = 0.9$ Hz, 3H, *Me*C=CH), 1.63 (dd, $J = 1.9, 6.5$ Hz, 3H, *Me*CH=CH), 1.60 (d, $J = 0.9$ Hz, 3H, =C*Me*), 1.47 (s, 9H, *t-Bu*O), 1.28 (d, $J = 7.4$ Hz, 3H, *Me*CH), 1.12 (d, $J = 6.9$ Hz, 3H, CH*Me*), 1.01 (d, $J = 6.9$ Hz, 3H, *Me*CH), 0.93 (s, 9H, *t-Bu*SiMe$_2$), 0.90 (d, $J = 6.9$ Hz 3H, *Me*CH), 0.89 (t, $J = 7.9$ Hz, 9H, (*Me*CH$_2$)$_3$Si), 0.88 (s, 9H, *t-Bu*SiMe$_2$), 0.80 (s, 9H, *t-Bu*SiMe$_2$), 0.79 (d, $J = 6.9$ Hz, 3H, CH*Me*), 0.54 (q, $J = 7.9$ Hz, 6H, (MeC*H$_2$*)$_3$Si), 0.12 (s, 3H, *t*-Bu*Me*SiMe), 0.08 (s, 3H, *t*-BuMeSi*Me*), 0.01 (s, 6H, Si*Me$_2$*), −0.03 (s, 3H, *t*-BuMeSi*Me*); −0.04 (s, 3H, *t*-BuMeSi*Me*); ^{13}C NMR (125 MHz, CDCl$_3$) δ (ppm): 215.6, 211.5, 171.4, 159.7, 138.2, 135.7, 134.6, 132.3, 131.9, 129.8, 128.9, 122.3, 114.3, 82.1, 82.0, 81.5, 81.0, 77.1, 76.7, 73.4, 70.3, 61.7, 61.0, 55.9, 49.9, 47.7, 46.9, 46.5, 46.1, 41.1, 31.1, 28.7, 26.6, 26.6, 26.5, 21.8, 19.1, 18.9, 18.8, 17.2, 15.2, 13.7, 13.0, 11.7, 11.3, 10.6, 7.6, 5.5, −3.9, −4.0, −4.4, −4.5, −4.7, −4.8; FTIR (thin film, KBr plate) cm^{-1}: 3531(br), 2955, 2931, 2883, 2858, 1749, 1715, 1614, 1587, 1515, 1472, 1463, 1404, 1390, 1368, 1302, 1251, 1172, 1147, 1099, 1061, 1039, 1005, 963, 939, 896, 838, 810, 779, 740, 726, 670; HRMS (ESI) calcd. For C$_{68}$H$_{126}$O$_{12}$Si$_4$Na [M+Na$^+$]: 1269.8224. Found: 1269.8234.

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