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Progress towards the total synthesis of tedanolide: an efficient assembly of the C_1–C_{11} subunit

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Abstract—The C_1–C_{11} subunit of tedanolide was constructed using a boron-mediated *syn* aldol reaction as the key step to control the C_6 and C_7 stereocenters. Other features of this work include the asymmetric Sharpless dihydroxylation to incorporate the C_2, C_3 hydroxyl groups, selective protection of the hydroxyl group at C_2 as well as the usage of a *tert*-butyl ester to tolerate the attack of Grignard and enolate reagents. © 2001 Elsevier Science Ltd. All rights reserved.

Tedanolide was isolated from a prevalent Caribbean sponge *Tedania ignis* by Schmitz and co-workers[1] in 1984. As a member of the macrolide group, tedanolide **1** shows very good biological activity as well as a very interesting chemical structure,[1,2] which has initiated extensive synthetic studies towards its total synthesis.[3–15] Recently, we have established an elegant and efficient construction of the C_{13}–C_{23} fragment of tedanolide.[3] In this article, we present our assembly of the C_1–C_{11} subunit **4** of tedanolide.

As a synthetic target, tedanolide poses numerous challenges, including the assembly of two groups of crowded contiguous chiral centers (C_{16} to C_{19} and C_2 to C_4) as well as the control of the stereochemistry of the C_6, C_7, C_{16} and C_{17} chiral centers. Retrosynthetically, tedanolide can be disconnected into two subunits **2** and **3** via disconnection at the C_{29} lactone and the C_{12}, C_{13} aldol unit, as outlined in Fig. 1. The subunit **2** was envisioned to derive from the intermediate **4**, which could be obtained from the coupling between precursors **5** and **6**. Precursor **6** can be easily synthesized according to the reported procedure.[3,16] Our synthesis focuses on the preparation of the precursor **5**. As shown in Fig. 2, the precursor **5** can be traced back to the readily available aldehyde **9**. The key features of our strategy involve the *syn–syn* selective boron-mediated aldol reaction, as developed by Paterson,[17,18] to

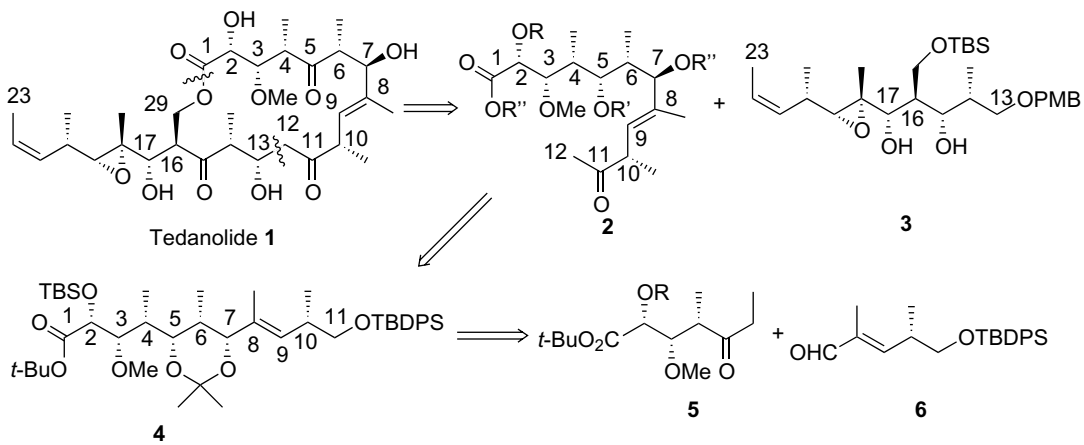

Figure 1.

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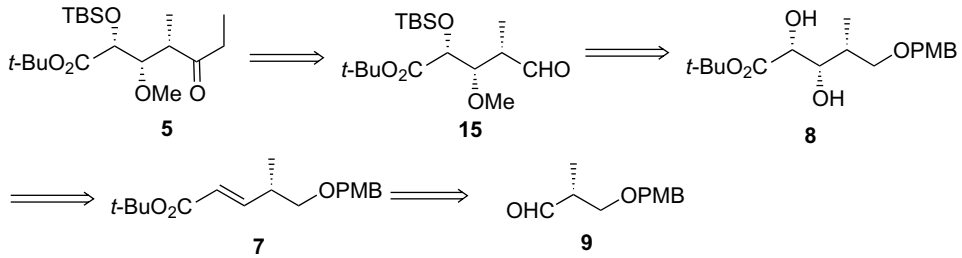


Figure 2.

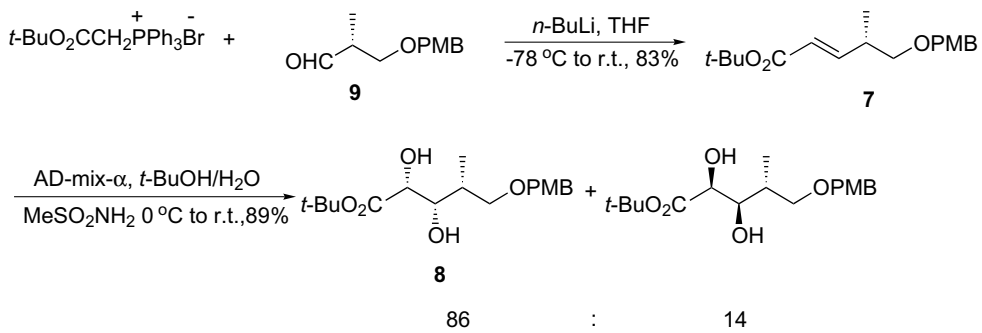
control the C_6, C_7 stereochemistry, the asymmetric Sharpless dihydroxylation to incorporate the C_2, C_3 hydroxyl groups, selective protection of the hydroxyl group at C_2 as well as the use of a *tert*-butyl ester to tolerate the attack of Grignard and enolate reagents.

The synthesis of precursor **5** commenced with the preparation of the conjugated *tert*-butyl ester **7**, which was easily obtained as a single isomer in 83% yield via a Wittig reaction of aldehyde **9** with the stabilized Wittig reagent t-$BuO_2CCH{=}PPh_3$.[19–21] Next, Sharpless asymmetric dihydroxylation using AD-mix-α was explored to incorporate the C_2, C_3 hydroxyl groups (Scheme 1).[10,22,23]

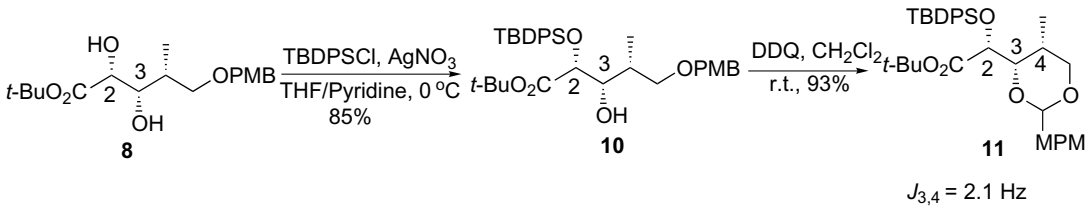
It can be seen from the results that the expected diol **8** was obtained in excellent yield with very good selectivity (86:14) when AD-mix-α was employed. The two diastereoisomers can be easily separated by flash silica gel column chromatography. The stereochemistry of the desired *syn* dihydroxylation product was established as shown in Scheme 2 by analysis of the coupling constant between the protons H_3 and H_4 of the acetal **11** (a mixture of two isomers, ratio: 77:23), which was prepared from diol **8** through selective protection of the vicinal diol[24] and acetal formation mediated by DDQ. The formation of acetal **11** confirmed the selective protection of the hydroxyl group at C_2.

Having successfully incorporated the C_2 and C_3 chiral centers, we carried on with the synthesis of precursor **5** from **10**, starting with the methyl protection of the hydroxyl group. Due to the crowded environment around the hydroxyl group, strong reaction conditions (Ag_2O, MeI, CH_3CN, reflux) were employed. However, this led to the cleavage of the TBDPS protecting group and none of the desired product. In order to circumvent this, TBDMS was introduced as a protecting group and alternative methylation conditions[25,26] were explored (Scheme 3). From these conditions, AgOTf/MeI[26] was found to be more desirable, providing the expected product **13** in 50% yield.

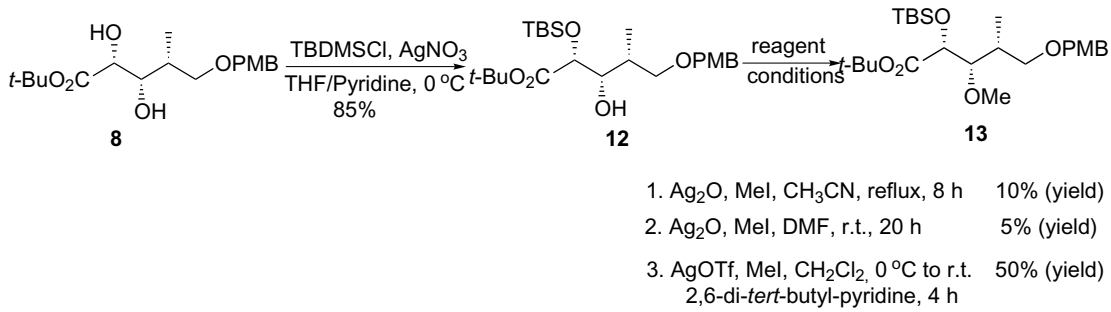
Further elaboration of precursor **5** began with the removal of the PMB protecting group of the *tert*-butyl ester **13** (Scheme 4). Treatment of **13** with DDQ (1.1 equiv.) provided the alcohol **14** cleanly in 85% yield. Dess–Martin oxidation of alcohol **14** afforded aldehyde **15** in excellent yield (97%). Grignard reaction of aldehyde **15** with ethylmagnesium bromide was then successfully carried out in Et_2O at −78°C to give the desired alcohol **16**, which was subjected to another



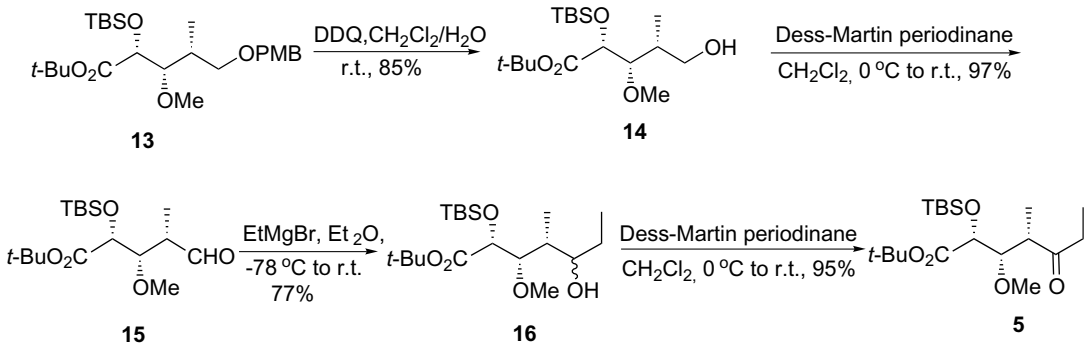
Scheme 1.



Scheme 2.



Scheme 3.

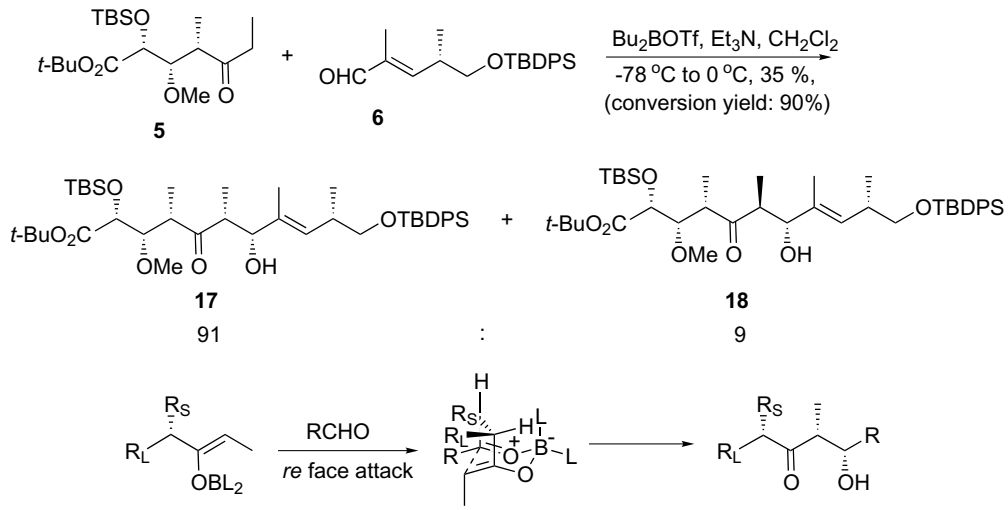


Scheme 4.

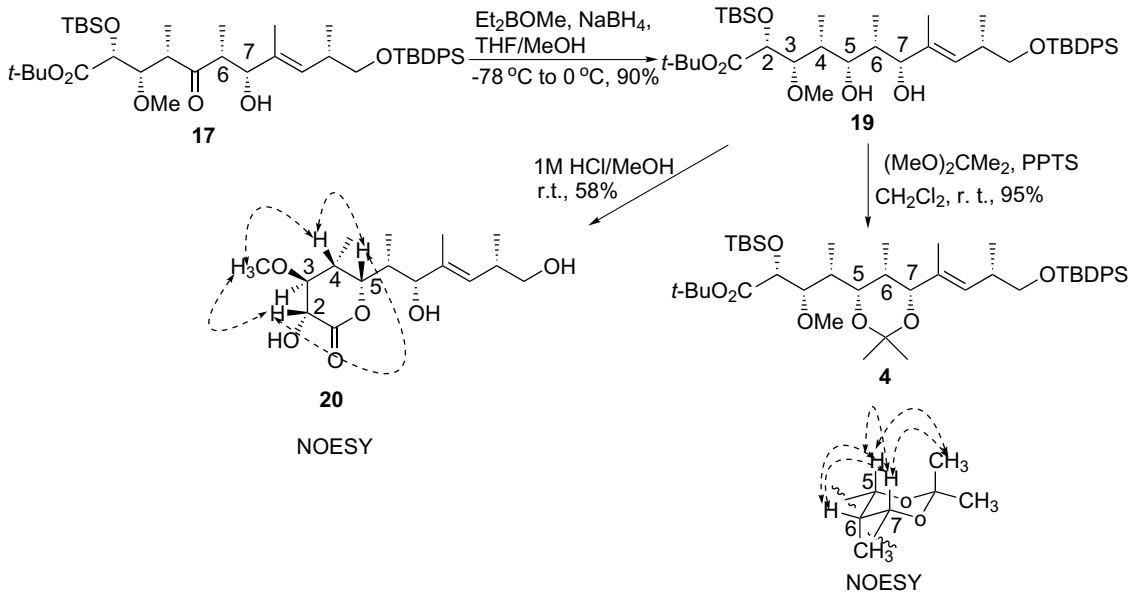
Dess–Martin oxidation to furnish the ketone **5** in 19% overall yield (eight steps).

Since aldehyde **6** can be easily synthesized from the commercially available (*R*)-methyl 3-hydroxy-2-methylpropionate as reported in the literature,[3,16] we proceeded to effect C–C bond formation at C_6, C_7 via a boron-promoted *syn* aldol reaction (Scheme 5).[17,18,27–31] To our delight, in the presence of Bu_2BOTf, the reaction proceeded in 35% isolated yield (90% conversion yield) and excellent diastereoselectivity (91:9), favoring the desired C_6, C_7 *syn* product. In order to determine the relative stereochemistry of the major product, **17** was first selectively reduced to the *syn* diol **19** as a >20:1 diastereomeric mixture using $Et_2BOMe/NaBH_4$,[32] which was then converted into acetonide **4** as well as lactone **20**. The stereochemistries at C_6 and C_7 were confirmed by NOESY studies of both lactone **20** and acetonide **4** (Scheme 6). This result is also in accordance with the predicted stereochemistry based on the transition state proposed by Paterson (Scheme 5).[33]

In summary, the assembly of the C_1–C_{11} subunit of tedanolide has been achieved using very few steps. The C_2 and C_3 hydroxyl groups were incorporated using Sharpless asymmetric dihydroxylation. The stereochemistry of the C_6 and C_7 stereocenters were established via the Bu_2BOTf-mediated *syn* selective aldol reaction.



Scheme 5.



Scheme 6.

Besides, a *tert*-butyl ester was employed to tolerate the attack of Grignard and enolate reagents. The assembly of subunit **2** and its combination with subunit **3** are in progress.

Acknowledgements

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33. Bernardi, A.; Capelli, A. M.; Comotti, A.; Gennari, C.; Gardner, M.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1991**, *47*, 3471. Data for compound **4**: R_f 0.86 (*n*-hexane/EtOAc, 4:1); $[\alpha]_D^{29}$+19 (*c* 0.3, ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.62–7.59 (m, 4H, Ph), 7.34–7.27 (m, 6H, Ph), 5.24 (d, J=9.4 Hz, 1H, =CH), 4.09 (d, J=8.0 Hz, 1H, CHOTBS), 4.08 (br, 1H, =CCHO), 3.68 (dd, J=1.4, 9.4 Hz, 1H, CHO), 3.46 (s, 3H, OMe), 3.47 (dd, J=6.0, 9.4 Hz, 1H, CH_2OTBDPS), 3.39 (dd, J=7.3, 9.4 Hz, 1H, CH_2OTBDPS), 3.29 (dd, J=1.2, 8.0 Hz, 1H, CHOMe), 2.64–2.54 (m, 1H, $CHCH_3$), 1.68–1.60 (m, 1H, $CHCH_3$), 1.43–1.33 (m, 1H, $CHCH_3$), 1.42 (s, 3H, =CCH_3), 1.39 (s, 9H, *t*-BuO), 1.32 (s, 3H, CCH_3), 1.31 (s, 3H, CCH_3), 0.97 (s, 9H, *t*-BuSi(Ph)$_2$), 0.95 (d, J=6.6 Hz, 3H, $CHCH_3$), 0.89 (d, J=6.6 Hz, 3H, $CHCH_3$), 0.85 (s, 9H, *t*-BuSi(Me)$_2$), 0.58 (d, J=6.6 Hz, 3H, $CHCH_3$), 0.04 (s, 3H, CH_3Si), 0.02 (s, 3H, CH_3Si); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ (ppm): 170.8, 135.6 (2), 134.1, 132.3, 129.4, 127.5, 127.1, 98.8, 81.4, 81.3, 75.7, 74.9, 68.5, 61.4, 55.5, 36.4, 35.0, 31.9, 30.0, 27.8, 26.8, 25.7, 19.5, 19.2, 18.1, 17.5, 13.6, 9.7, 4.9, −5.0 (2); IR (neat, KBr plate) cm^{-1}: 3072, 3051, 2960, 2931, 2858, 1739, 1463, 1428, 1368, 1256, 1113, 1008, 838, 780, 758, 703, 505; HRMS (ESI) calcd for $C_{45}H_{74}O_7Si_2Na$ [M+Na$^+$]: 805.4873; Found: 805.4874.