Synthetic Studies of 18-Membered Antitumor Macrolide, Tedanolide. 2. Stereoselective Synthesis of the C1—C7 Fragment *via* a Mismatched but Highly Efficient Sharpless Dihydroxylation

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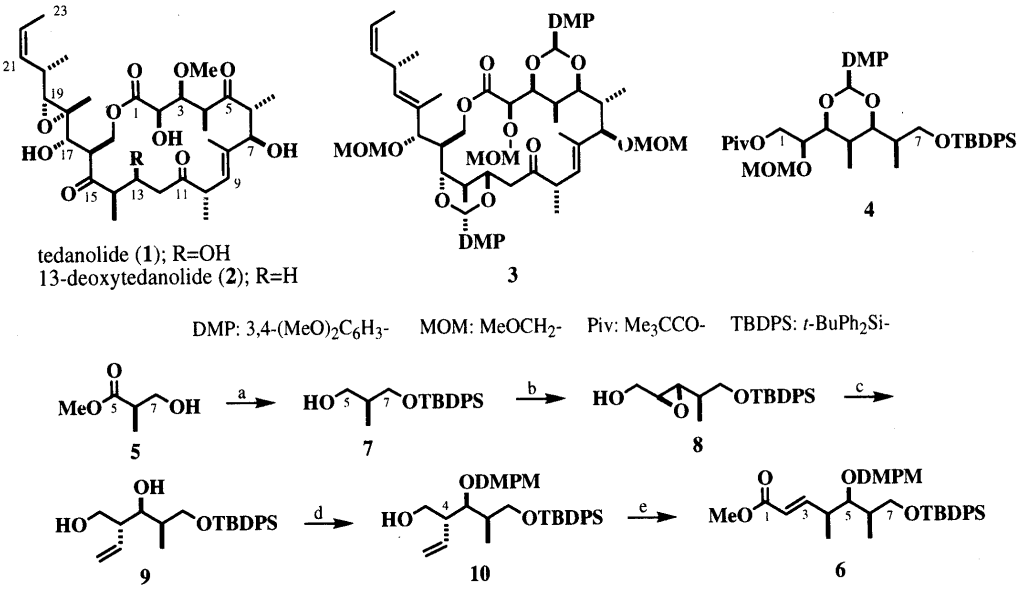
The C1—C7 fragment (4) of tedanolide (1) was synthesized starting from methyl (*R*)-3-hydroxy-2-methylpropionate *via* a mismatched but highly efficient Sharpless dihydroxylation of the C1—C7 α,β-unsaturated ester (6) with AD-mix-α.

Key words macrolide; stereoselective synthesis; Sharpless epoxidation; sonication; Sharpless dihydroxylation; AD-mix-α

Tedanolide (**1**) was isolated from a Caribbean sponge *Tedania ignis* as a tumor-inhibitory macrolide in extremely low yield, and its structure was elucidated by Schmitz *et al.* in 1984.[1,2] Because of the unusual structural feature having four labile aldol units, an α-epoxy alcohol, and an 18-membered lactone constructed with the C16 primary (not the usual secondary) hydroxy group, synthesis of **1** was presumed to be difficult. Recently, we reported the synthesis of the 18-membered lactone (**3**),[3] which is expected as a key intermediate to **1**, *via* highly efficient lactonization[4] of the corresponding seco-acid. In macrolide synthesis, the molecular design of a seco-acid suitable for macrolactonization is extremely important[4]; hence, after conformational analyses of seco-acid derivatives with the aid of molecular mechanics (MM) calculation[5] we designed the seco-acid, which was first synthesized *via* condensation of C1—C7 (**4**), C8—C11, C13—C17, and C18—C21 fragments,[6] although the procedure required many improvements. In this report we describe an efficient synthesis of **4**, the most important fragment, starting from methyl (*R*)-3-hydroxy-2-methylpropionate (**5**) *via* a mismatched but highly efficient Sharpless dihydroxylation of the α,β-unsaturated ester (**6**) using AD-mix-α.[7]

Compound **6** was smoothly synthesized from **5** as shown in the following scheme.

Dihydroxylation of **6** with OsO_4 was next carefully examined. The diastereoselective face selectivity of the double bond in this reaction is mainly governed by the conformation of **6**. Two favorable conformations, A and B, can be considered. A is the conformation controlled by the 1,3-allylic strain,[9] whereas in B-conformation a large R group is situated in an antiperiplanar position to the double bond. Osmylation is usually expected to proceed by an attack of OsO_4 to the A-conformation.[9] When **6** was treated with 5 mol% of OsO_4 and an excess of *N*-methylmorpholine *N*-oxide (NMO) at room temperature, a 1 : 3 mixture of diols, **11** and **12**, was obtained. The unexpected diol (**12**), formed by osmylation on the *si-re* face of the B-conformation, was disappointingly the main product. Therefore we had to switch the osmylation from



(a) 1) TBDPSCl, imidazole, CH_2Cl_2, 100%; 2) $LiBH_4$, Et_2O, 100%. (b) 1) Swern oxid; 2) $Ph_3P{=}CHCO_2Me$, C_6H_6, 2 steps 98%; 3) DIBAH, CH_2Cl_2, 99%; 4) (+)-DET, $(i\text{-PrO})_4Ti$, TBHP, CH_2Cl_2, 99%. (c) $CH_2{=}CHMgBr$, CuCN, Et_2O-THF, sonication, 86%. (d) 1) $DMPCH(OMe)_2$, CSA, CH_2Cl_2, 92%; 2) DIBAH, CH_2Cl_2, 85%. (e) 1) TsCl, Et_3N, DMAP, CH_2Cl_2; 2) $LiAlH_4$, THF, 2 steps 90%; 3) OsO_4, NMO, Me_2CO-H_2O, 98%; 4) $NaIO_4$, MeOH-H_2O; 5) $Ph_3P{=}CHCO_2Me$, C_6H_6, 2 steps, 98%.

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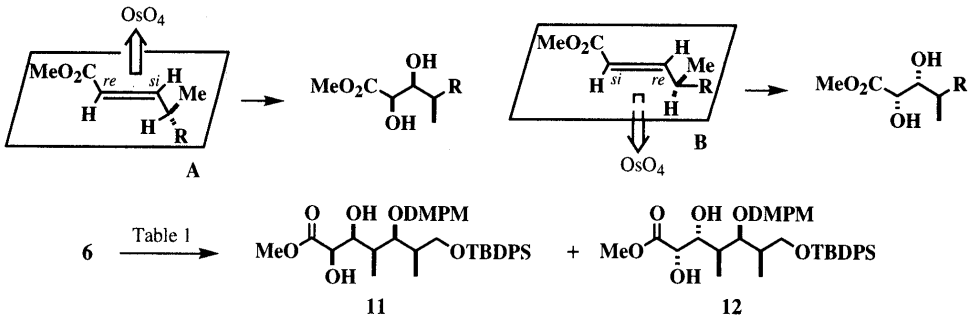
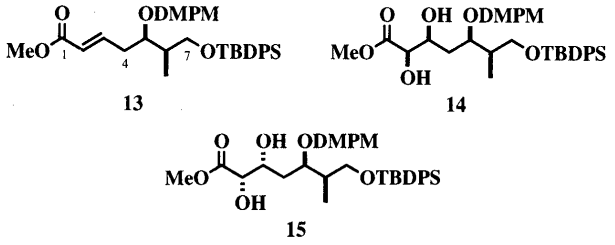


Table 1. Dihydroxylation of **6**

Conditions	Yield (%)	Ratio
OsO_4 (0.05 eq), NMO[a] (2.0 eq), Me_2CO–H_2O, rt	78	1 : 3
AD-mix α (0.02 eq), MSA[b] (1.0 eq), *t*-BuOH–H_2O, rt	95	>99 : <1

a) *N*-methylmorpholine *N*-oxide. *b*) methanesulfonic amide.



diastereoselective to enantioselective. An AD-mix[7] is the most convenient reagent for this purpose, and the osmylation on the *re-si* face of α,β-unsaturated esters can be achieved with AD-mix-α.[10] This is, unfortunately, a mismatched case.[11]

When **6** was treated with AD-mix-α (2.0 mol%) at room temperature, surprisingly, the expected diol (**11**) was obtained in excellent yield (95%) with almost complete selectivity (>99% de). This result clearly shows that a conformational change from B to A occurred in this reaction. For this type of cinchona-catalyzed enantioselective dihydroxylation, a mechanism (Criegee-Corey-Noe model) *via* a [3+2] cycloaddition of OsO_4 to an olefin in a U-shaped binding pocket of catalysts composed of the two parallel methoxyquinoline units was proposed.[12] If the 3,4-dimethoxybenzene part of **6** comes between the methoxyquinoline units, the olefin in the A-conformation, not in the B-conformation, can fit into the binding pocket. This may provide a reason why the face-selectivity changes from *si-re* to *re-si*. Inspection of CPK molecular models reveals that **6** in the A-conformation can bind smoothly to AD-mix-α, but only slightly to AD-mix-β because of steric hindrance caused by the bulky C6—C7 portion of **6**. The C4 demethyl compound (**13**) is present in two A-type conformations, which fit into AD-mix-α and -β; hence, **13** should be smoothly oxidized by AD-mix-β as well as -α.

Both **6** and **13** were treated with the two reagents under the same conditions. The results shown in Table 2 are consistent with our prediction, probably supporting the CCN model[12] for Sharpless asymmetric dihydroxylation, although more conclusive evidence is still required.

Finally, **11** was readily converted to the C1—C7 fragment (**4**) through four conventional reactions; oxidative acetal formation with DDQ[13]; protection with a MOM group; $LiAlH_4$ reduction; and protection with a pivaloyl group. The overall yield for 19 steps starting from **5** to the title compound (**4**) was 32.2%.

Table 2. Asymmetric Dihydroxylation of **6** and **13**[a]

Substrate	AD-mix	Product Yield (%)	Product Ratio
6	α	78	**11** (99) : **12** (1)
6	β	39	**11** (1) : **12** (8)
13	α	83	**14** (6) : **15** (1)
13	β	93	**14** (1) : **15** (12)

a) Reaction conditions: **6**, **13** (50 μmol), AD-mix (0.01 eq), $MeSO_2NH_2$ (0.02 eq), *t*-BuOH–H_2O (1 : 1), rt, 6 h.

References and Notes

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