

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 .

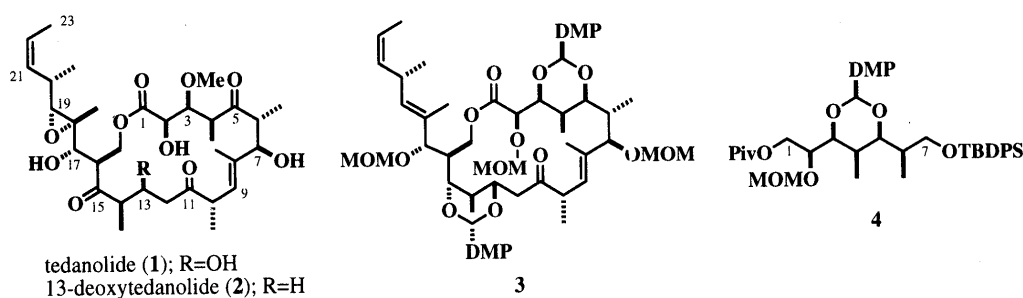
Key words macrolide; stereoselective synthesis; Sharpless epoxidation; sonication; Sharpless dihydroxylation; AD-mix- α

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 lactonization⁴⁾ of the corresponding seco-acid. In macrolide synthesis, the molecular design of a seco-acid suitable for macrolactonization is extremely important⁴⁾; hence, after conformational analyses of seco-acid derivatives with the aid of molecular mechanics (MM) calculation⁵⁾ 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

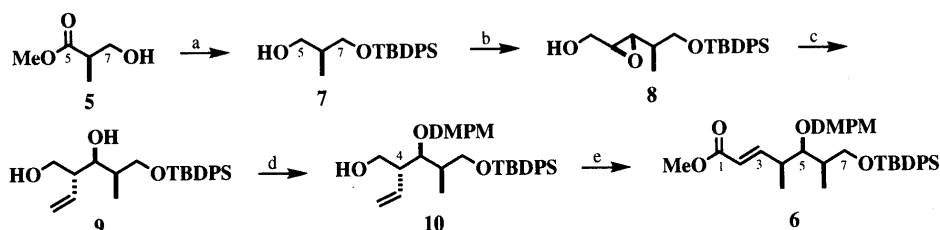
methyl (R)-3-hydroxy-2-methylpropionate (5) *via* a mismatched but highly efficient Sharpless dihydroxylation of the α,β -unsaturated ester (6) using AD-mix- α .⁷⁾

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

Dihydroxylation of 6 with OsO₄ 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 OsO₄ to the A-conformation.⁹⁾ When 6 was treated with 5 mol% of OsO₄ 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

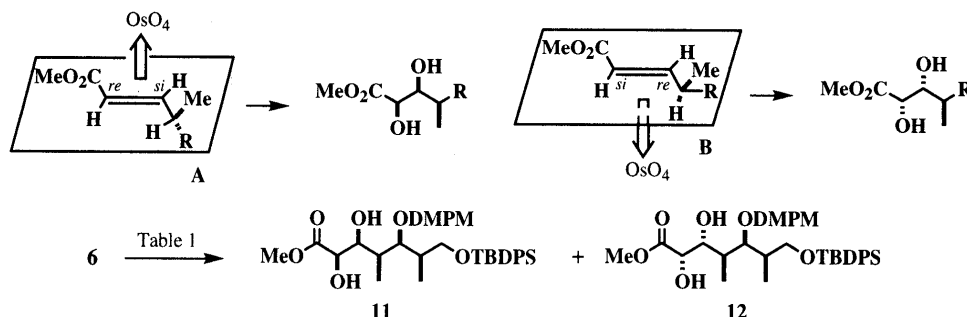


DMP: 3,4-(MeO)₂C₆H₃- MOM: MeOCH₂- Piv: Me₃CCO- TBDPS: *t*-BuPh₂Si-



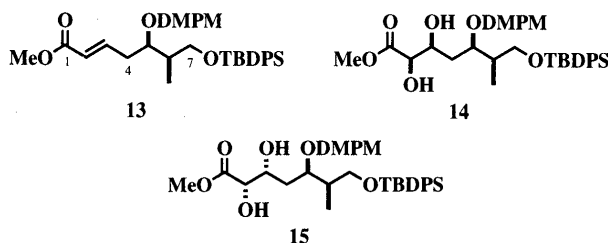
(a) 1) TBDPSCl, imidazole, CH₂Cl₂, 100%; 2) LiBH₄, Et₂O, 100%. (b) 1) Swern oxid; 2) Ph₃P=CHCO₂Me, C₆H₆, 2 steps 98%; 3) DIBAH, CH₂Cl₂, 99%; 4) (+)-DET, (*i*-PrO)₄Ti, TBHP, CH₂Cl₂, 99%. (c) CH₂=CHMgBr, CuCN, Et₂O-THF, sonication, 86%. (d) 1) DMPCH(OMe)₂, CSA, CH₂Cl₂, 92%; 2) DIBAH, CH₂Cl₂, 85%. (e) 1) TsCl, Et₃N, DMAP, CH₂Cl₂; 2) LiAlH₄, THF, 2 steps 90%; 3) OsO₄, NMO, Me₂CO-H₂O, 98%; 4) NaIO₄, MeOH-H₂O; 5) Ph₃P=CHCO₂Me, C₆H₆, 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 ₂ CO-H ₂ O, rt	78	1 : 3
AD-mix α (0.02 eq), MSA ^{b)} (1.0 eq), <i>t</i> -BuOH-H ₂ O, rt	95	>99 : <1

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



diastereoselective to enantioselective. An AD-mix⁷⁾ 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 OsO₄ 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 model¹²⁾ 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

Table 2. Asymmetric Dihydroxylation of **6** and **13**^{a)}

Substrate	AD-mix	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 μ mol), AD-mix (0.01 eq), MeSO₂NH₂ (0.02 eq), *t*-BuOH-H₂O (1 : 1), rt, 6 h.

acetal formation with DDQ¹³⁾; protection with a MOM group; LiAlH₄ reduction; and protection with a pivaloyl group. The overall yield for 19 steps starting from **5** to the title compound (**4**) was 32.2%.

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