Synthetic Studies of Tedanolide. 4. Stereoselective and Efficient Synthesis of the C13-C23 Part

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Received 8 March 1999

Abstract: The C13-C23 part (**5**) of tedanolide (**1**) was synthesized starting from enantiomeric methyl (*R*)- and (*S*)-3-hydroxy-2-methylpropionates (**8**) *via* coupling between the C13-C17 aldehyde (**6**) and the C18-C21 iodoalkene (**7**).

Key words: macrolide, cytotoxic activity, aldol reaction, benzyl protecting group

Tedanolide (**1**) is a potent cytotoxic macrolide isolated from a Caribbean sponge, *Tedania ignis*, by Schmitz *et al.* in 1984, and its structure was elucidated by X-ray analysis.[1a] Its related compound 13-deoxytedanolide (**2**), isolated later from a Japanese marine sponge, *Mycale adhaerens*, showed more potent cytotoxicity against P388 murine leukemia cells.[1b] This significant biological activity, along with unusual structural features, four labile aldol units, an α-epoxy alcohol, and an 18-membered lactone constructed with the C16 primary (not the usual secondary) hydroxy group, has prompted considerable synthetic interest.[2]

Recently, we reported the synthesis of the 18-membered lactone (**3**), a key intermediate to **1**, *via* highly efficient lactonization of the corresponding seco-acid (**4**), which was designed with the aid of molecular mechanics (MM) calculations, and synthesized *via* condensation of the C1-C7, C8-C11, C13-C17, and C18-C21 fragments, although the procedure required considerable improvement.[2a]

The selective protection strategy of different hydroxy groups usually plays a key role in the successful synthesis of polyol-containing compounds, and a variety of selective protecting groups such as silyl ethers and benzyl ethers has been reported.[3] Among the benzyl ethers, 4-methoxybenzyl (MPM) and 3,4-dimethoxybenzyl (DMPM) ethers[4] were highlighted, because they can be selectively cleaved[5] or converted with a neighboring hydroxy group to a benzylidene acetal,[6] which on regioselective reductive opening[7] gives an MPM or DMPM ether.

The advantage of this MPM methodology was demonstrated in the recent synthesis of the C1-C12 part of **1**.[2c] In this paper, we report a stereoselective and practical synthesis of the C13-C23 part (**5**), almost a half molecular of **4,** achieved successfully again, by taking advantage of the DMPM protecting group.

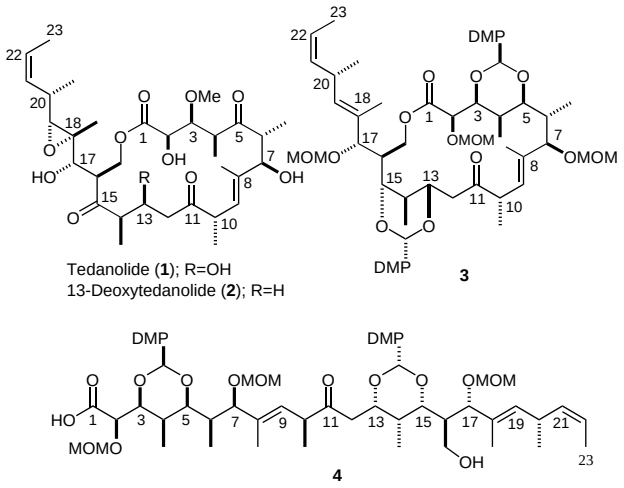
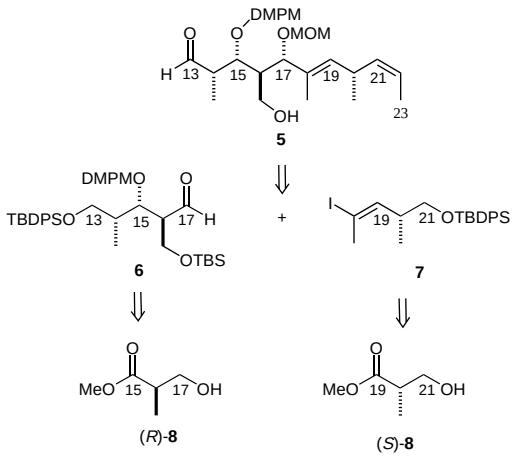


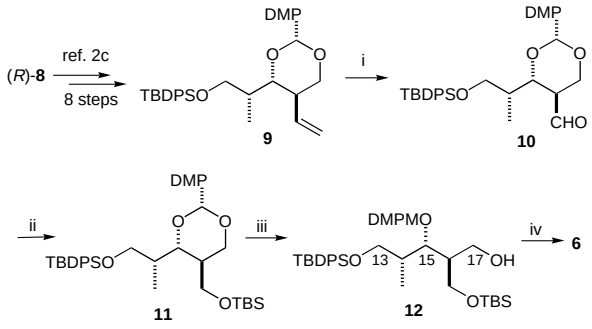
Figure 1 DMP: 3,4-$(MeO)_2C_6H_3$- MOM: $MeOCH_2$-

Scheme 1 outlines the synthesis plan. The C13-C23 part (**5**) would be synthesized by coupling between the C13-C17 (**6**) and C18-C21 (**7**) fragments, which were obtained from enantiomeric (*R*) and (*S*)-methyl 3-hydroxy-2-methylpropionates (*R*- and *S*-**8**), respectively.



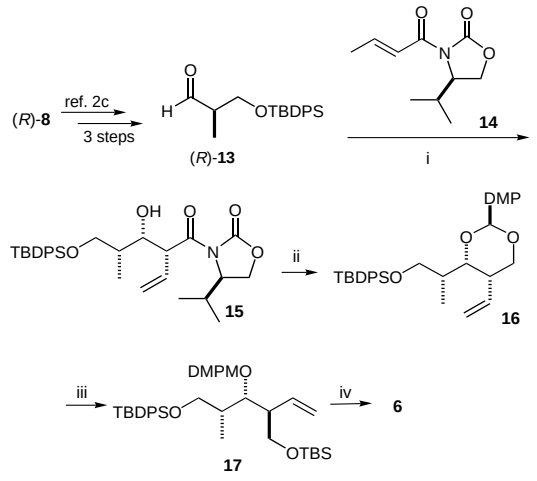
Scheme 1 DMPM: 3,4-$(MeO)_2C_6H_3CH_2$-

The synthesis of **6** from (*R*)-**8** is shown in Scheme 2. (*R*)-**8** was first converted to the alkene (**9**), a common synthetic intermediate to the C1-C12 part, by using the procedure described in our previous report.[2c] Oxidative cleavage of the double bond of **9** gave the aldehyde (**10**), which was then reduced with $LiBH_4$, and protection of the resulting hydroxy group as a *tert*-butyldimethylsilyl (TBS) ether gave **11**. Regioselective reductive cleavage of the benzylidene acetal of **11** with DIBAH[7] gave the primary alcohol (**12**) in 54% yield, albeit accompanied with a by-product with loss of the TBS group in 30% yield. Subsequent Swern oxidation of **12** completed the synthesis of **6**.



Scheme 2 i. a) OsO_4, NMO, acetone-H_2O (3 : 1), rt, 95%; b) $NaIO_4$, THF-H_2O (1 : 1), rt, 100%. ii, a) $LiBH_4$, Et_2O, rt, 93%; b) TBSCl, imidazole, CH_2Cl_2, rt, 100%. iii. DIBAH, CH_2Cl_2, -20°C, 54%. iv. DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, 98%.

A shorter and efficient synthesis of **6** was accomplished by using Evans' asymmetric aldol reaction.[8] Thus, treatment of (*R*)-**13** with titanium enolate of the Evans auxiliary (**14**)[8a] gave the desired syn adduct (**15**) in high diastereoselectivity (>95% d.e.). Reduction of **15** with $LiBH_4$[9] and protection of the resulting diol as a DMPM acetal gave **16**, which was transformed to **6** in the usual manner as described above.



Scheme 3 i. $TiCl_4$, *i*-Pr_2EtN, CH_2Cl_2, -76~0°C, 70%. ii, a) $LiBH_4$, cat. H_2O, Et_2O-THF, 87%; b) $DMPCH(OMe)_2$, CSA, CH_2Cl_2, rt, 99%. iii, a) DIBAH, toluene, -30°C; b) TBSCl, imidazole, CH_2Cl_2, 0°C, 92%, in two-steps. iv, a) OsO_4, NMO, acetone-H_2O (3 : 1), rt; b) $NaIO_4$, THF-H_2O (1 : 1), rt, 90%, in two-steps.

Coupling of **6** and **7**[10] was next carefully examined. Excess (1.5 equiv) **7** was first lithiated with *tert*-BuLi and allowed to react with **6** at –78 ~ –30 °C. The coupling proceeded smoothly to give **18** as a 7.5 : 1 mixture of C17-isomers, but unfortunately the major product was the undesired Cram adduct (**18b**). All attempts to selectively get the desired chelation- controlled adduct (**18a**) by the addition of $MgBr_2OEt_2$ and $ZnCl_2$ were unsuccessful. In order to convert the C17 configuration, selective reduction of the corresponding ketone (**19**), readily available by Dess-Martin oxidation[11] of **18**, was examined. However, reduction with $LiAlH_4$ gave a 1 : 2 mixture (82%) of the desired **18a** and the diol (**21**) deprotecting the TBS group, and hence **19** was firstly subjected to selective deprotection of the TBS group. Treatment of **19** with PPTS gave the ketol (**20**) in 99% yield. Subsequent reduction of **20** with $Zn(BH_4)_2$[12] proceeded with complete stereoselectivity due to β-chelation of zinc with the C16 carbinol to give the desired **21** as a single product in 96% yield. The C17 configuration was confirmed by NOE studies of the corresponding 3,4-dimethoxybenzylidene acetal (**22**), which was obtained by protection of the primary hydroxy group of **21** with a pivaloyl group followed by oxidation with DDQ.[6] Protection of the diol of **21** by acetylation and removal of the two TBDPS groups gave a new diol (**23**), which was then treated with DDQ to selectively protect the C13 hydroxy group as a benzylidene acetal[6] and the alcohol (**24**) was isolated in excellent yield. Dess-Martin oxidation of the C21 hydroxy group of **24** and subsequent Wittig reaction with ethyltriphenyl-phosphonium bromide and *tert*-BuOK led to the (*Z*)-alkene (**25**) with excellent selectivity (15 : 1). Deprotection of the diacetyl groups of **25** with $LiAlH_4$ gave the diol (**26**). Protection of the primary alcohol of **26** as a TBS ether and the secondary alcohol as a methoxymethyl (MOM) ether formed **27**. Selective cleavage of the benzylidene acetal of **27** with DIBAH provided the alcohol (**28**), which was finally subjected to Dess-Martin oxidation to achieve the synthesis of the title compound (**5**). Coupling of **5** with the C1-C12 part, followed by macrolactonization to the lactone (**3**) will be reported soon.

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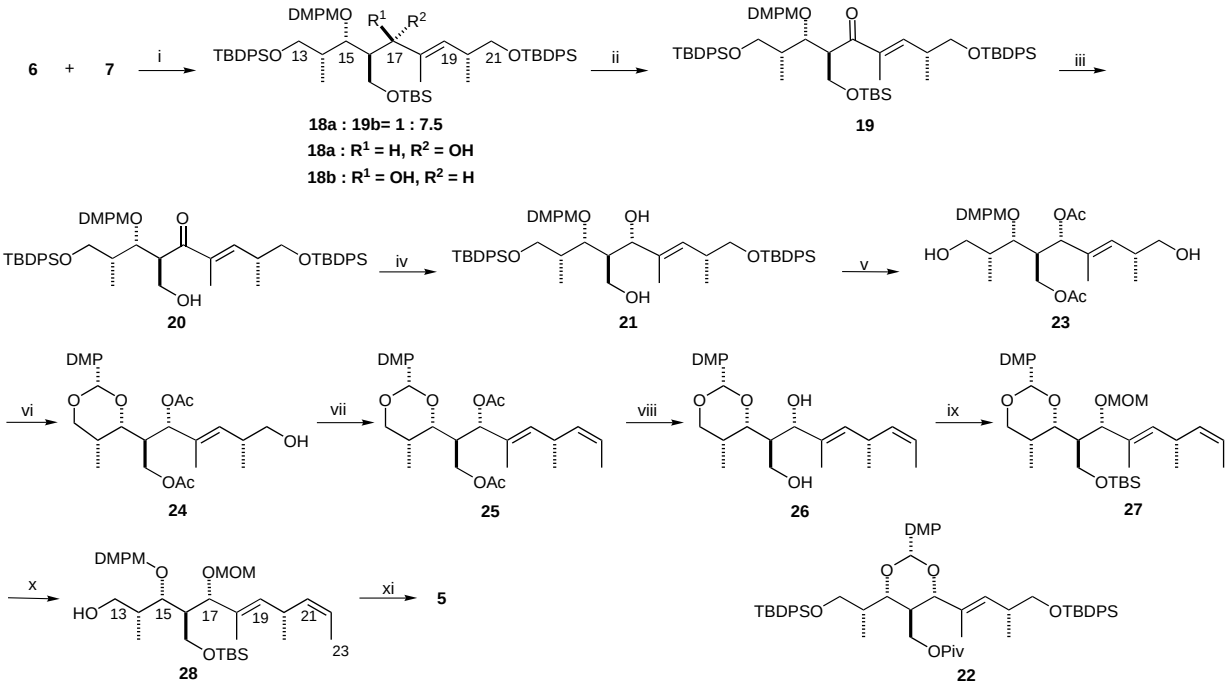

Scheme 4 i. *tert*-BuLi, Et_2O, -78 ~ -30°C, 85%. ii. Dess-Martin reagent, pyridine, CH_2Cl_2, 0°C, 91%. iii. PPTS, EtOH, 50°C, 99%. iv. $Zn(BH_4)_2$, Et_2O, 0°C, 96%. v, a) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 96%; b) *n*-Bu_4NF, AcOH, THF, rt, 100%. vi. DDQ, CH_2Cl_2, -10°C, 93%. vii, a) Dess-Martin reagent, pyridine, CH_2Cl_2, 0°C, 92%; b) $Ph_3PCH_2CH_3Br$, *tert*-BuOK, THF, rt. viii. $LiAlH_4$, Et_2O, rt, 74%, in two steps. ix, a) TBSCl, imidazole, CH_2Cl_2, rt, 86%; b) MOMCl, *i*-Pr_2EtN, CH_2Cl_2, rt, 100%. x. DIBAH, CH_2Cl_2, -50°C, 70%. xi. Dess-Martin reagent, pyridine, CH_2Cl_2, rt, 100%.

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Article Identifier:
1437-2096,E;1999,0,06,0780,0782,ftx,en;Y03699ST.pdf