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Studies on the Synthesis of Tedanolide. 2. Stereoselective Synthesis of a Protected C(1)–C(12) Fragment

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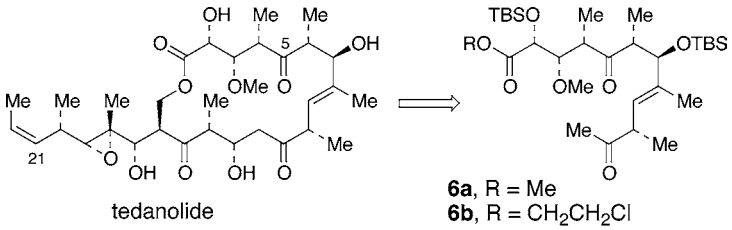
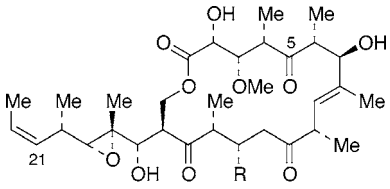
ABSTRACT



Highly diastereoselective syntheses of diketo esters 6a and 6b are described. These intermediates undergo efficient aldol reactions with protected C(13)–C(21) aldehydes 3 and 23, thereby providing advanced C(1)–C(21) tedanolide seco ester precursors 9a and 9b.

Tedanolide (**1**, Scheme 1) is a highly cytotoxic macrolide that was isolated from a Caribbean sponge species, *Tedania ignis*, by Schmitz and co-workers in 1984.[1] A structurally related congener, 13-deoxytedanolide (**2**), was subsequently isolated by Fusetani from a sponge species (*Mycale adhaerens*) obtained from the western Pacific Ocean.[2] The remarkably potent cytotoxicities of these compounds against a number of tumor cell lines has stimulated considerable interest in their synthesis. Thus far, studies on the synthesis of tedanolide and 13-deoxytedanolide have been reported by Yonemitsu,[3] Taylor,[4] Smith,[5,6] Jung,[7] Loh,[8] and Masamune.[9] In 1999 we described a highly stereoselective synthesis of

Scheme 1



1, tedanolide, R = OH
2, 13-deoxytedanolide, R = H

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(2) Fusetani, N.; Sugawara, T.; Matsunaga, S.; Hirota, H. *J. Org. Chem.* **1991**, *56*, 4971.

(3) (a) Katsuya, M.; Zhen, B.-Z.; Kusaka, S.-I.; Kuroda, M.; Yoshimoto, K.; Yamada, H.; Yonemitsu, O. *Eur. J. Org. Chem.* **2001**, 3615. (b) Zheng, B.-Z.; Yamauchi, M.; Dei, H.; Kusaka, S.-i.; Matsui, K.; Yonemitsu, O. *Tetrahedron Lett.* **2000**, *41*, 6441. (c) Matsushima, T.; Nakajima, N.; Zheng, B.-Z.; Yonemitsu, O. *Chem. Pharm. Bull.* **2000**, *48*, 855. (d) Zheng, B.-Z.; Maeda, H.; Mori, M.; Kusaka, S.-I.; Yonemitsu, O.; Matsushima, T.; Nakajima, N.; Uenishi, J.-I. *Chem. Pharm. Bull.* **1999**, *47*, 1288. (e) Matsushima, T.; Zheng, B.-Z.; Madea, H.; Nakajima, N.; Uenishi, J.-I.; Yonemitsu, O. *Synlett* **1999**, 780. (f) Matsushima, T.; Mori, M.; Zheng, B.-Z.; Maeda, H.; Nakajima, N.; Uenishi, J.-I.; Yonemitsu, O. *Chem. Pharm. Bull.* **1999**, *47*, 308. (g) Matsushima, T.; Mori, M.; Nakajima, N.; Maeda, H.; Uenishi, J.-I.; Yonemitsu, O. *Chem. Pharm. Bull.* **1998**, *46*, 1335. (h) Matsushima, T.; Horita, K.; Nakajima, N.; Yonemitsu, O. *Tetrahedron Lett.* **1996**, *37*, 385.

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(5) Smith, A. B.; Lodise, S. A. *Org. Lett.* **1999**, *1*, 1249.

(6) While this manuscript was in preparation, Prof. Amos Smith informed us that he had completed the first total synthesis of 13-deoxytedanolide. We thank him for making this information available to us prior to publication.

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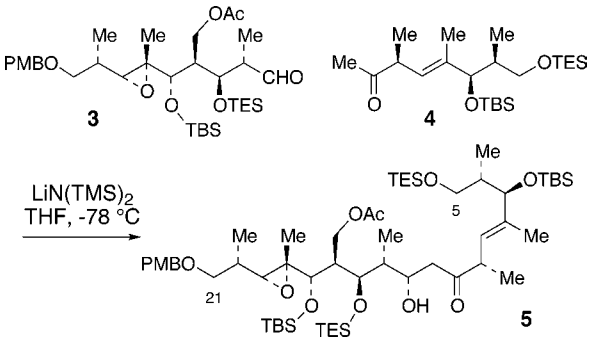
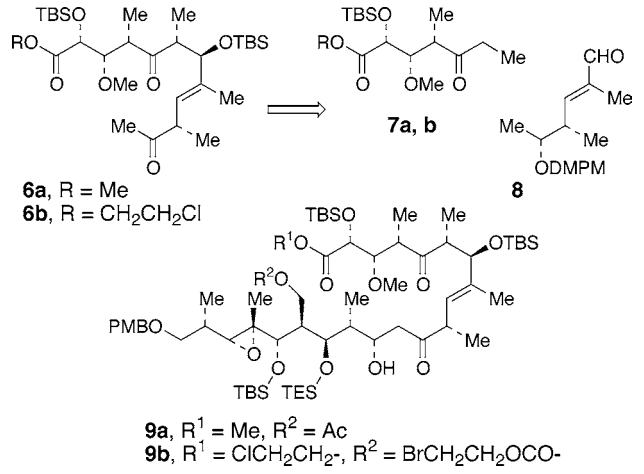
the tedanolide C(5)−C(21) fragment **5** via a highly stereoselective fragment assembly aldol reaction of chiral aldehyde **3** and the chiral β,γ-unsaturated methyl ketone **4** (Scheme 2).[10] We report herein a highly stereoselective synthesis of

Scheme 2



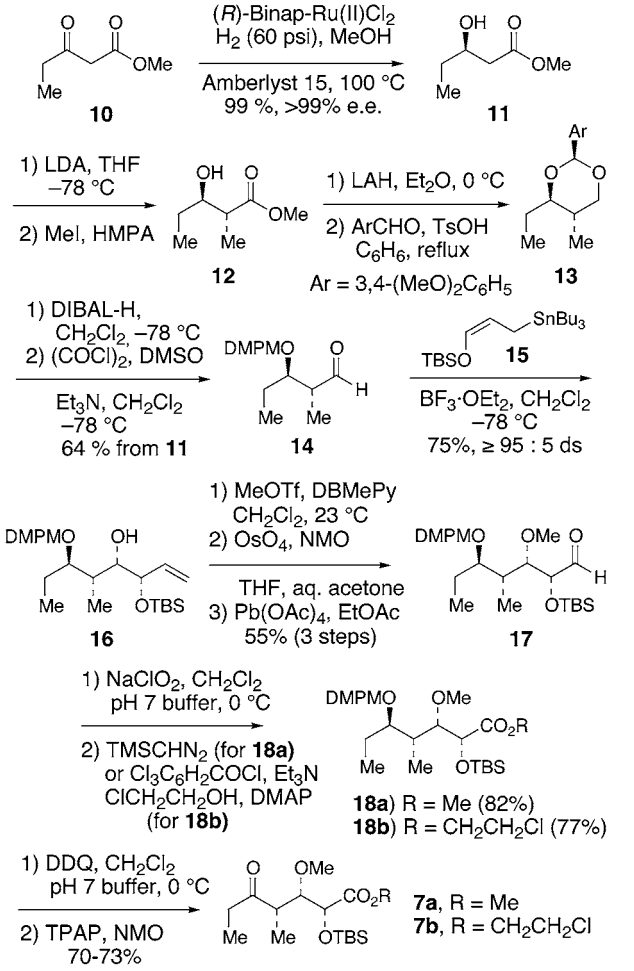
fully functionalized C(1)−C(12) methyl ketone fragments **6a**,**b** and their elaboration to advanced tedanolide seco acid precursors (**9a** and **9b**) (Scheme 3).

Scheme 3



Our strategy for synthesis of the C(1)−C(12) methyl ketone unit called for **6a** to be assembled via the aldol coupling of ethyl ketone **7a** and α,β-unsaturated aldehyde **8**. The synthesis of methyl ester **6a** (Scheme 4) commenced with the enantioselective hydrogenation[11] of β-keto ester **10** using Taber's protocol,[12] which provided β-hydroxy ester **11** in almost quantitative yield and with ≥99% ee. Frater−Seebach alkylation of **11** then provided the *anti* α-methyl-β-hydroxy ester **12** in good yield and selectivity (≥95:5 ds).[13]

Scheme 4



Reduction of **12** with $LiAlH_4$ in THF at −78 °C provided the corresponding 1,3-diol, which was converted to the 3,4-dimethoxybenzylidene acetal **13** upon treatment with 3,4-dimethoxylbenzaldehyde and catalytic *p*-TsOH in benzene. DIBAL reduction[14] of acetal **13** cleanly provided the primary alcohol, which was oxidized to give aldehyde **14** using the standard Swern protocol (64% overall yield from **11**).[15] Treatment of **14** with 3 equiv each of allylstannane **15** and $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at −78 °C provided the 3,4-*syn*-4,5-*syn* homoallylic alcohol **16** in 75% yield with ≥95:5 ds.[16,17]

Conversion of the hydroxyl group of **16** to a methyl ether (MeOTf, 2,6-di-*tert*-butyl-4-methylpyridine (DBMePy), CH_2Cl_2, 23 °C)[18] followed by standard oxidative cleavage of the vinyl group provided aldehyde **17** (55% yield from **16**). Oxidation of the aldehyde to the corresponding carboxylic acid was best accomplished by using the sodium chlorite

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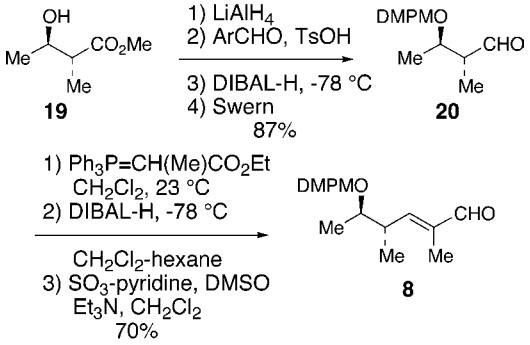
procedure.[19] It was essential that this oxidation be performed at 0 °C and for the oxidation to be quenched with the addition of Me_2S in order to avoid competitive chlorination of the dimethoxybenzyl (DMBM) ether. Esterification of the crude (and relatively unstable) carboxylic acid with trimethylsilydiazomethane then provided methyl ester **18a** in 82% yield. Deprotection of the DMPM[20] ether and oxidation (TPAP, NMO)[21] of the alcohol (which is sensitive to lactonization) to the ketone then completed the synthesis of the originally targeted C(1)−C(6) methyl ester fragment **7a** (70−73% yield). Spectroscopic analysis of the lactone generated from the alcohol prepared from **18a** allowed us to verify the stereochemistry of **16** and all intermediates derived therefrom.

The C(7)−C(12) enal **8** was synthesized starting from the readily available *anti*-β-hydroxy-α-methylbutyrate **19**[13] as summarized in Scheme 5. Ester **19** was elaborated to the

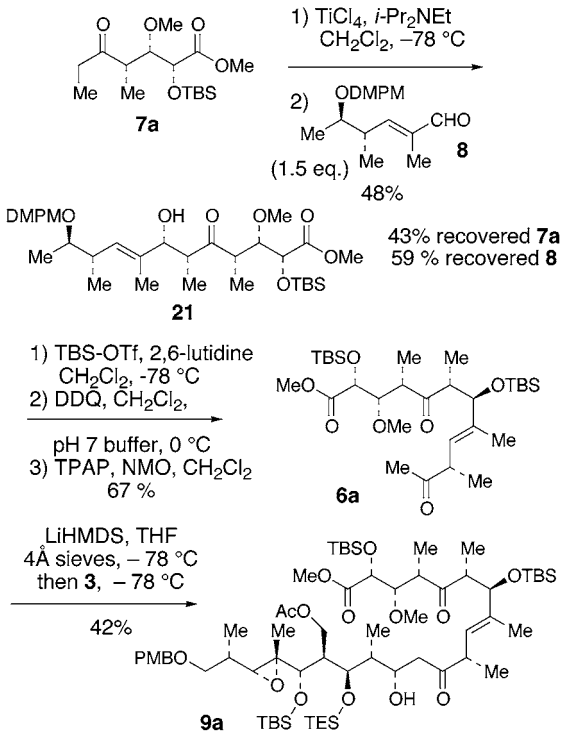
Scheme 5



β-alkoxy aldehyde **20** in 87% overall yield by using a sequence analogous to that described for the conversion of **12** to **14**. Treatment of **20** with the stabilized ylid, $Ph_3P{=}CH(Me)CO_2Me$, gave the α,β-unsaturated ester with excellent selectivity. Reduction of the ester using DIBAL-H in a mixture of CH_2Cl_2 and hexane at −78 °C and then Parikh−Doering oxidation[22] of the allylic alcohol provided enal **8** in 70% overall yield.

Aldol coupling of **7a** and **8** (1.5 equiv) was best accomplished by using the chlorotitanium enolate generated by treatment of **7a** with $TiCl_4$ and *i*-Pr_2NEt in CH_2Cl_2 at −78 °C (Scheme 6).[23] Under these conditions, aldol **21** was obtained in 48% yield.[24] Protection of **21** as a TBS ether

Scheme 6



followed by deprotection[20] of the DMPM ether and oxidation of the resulting alcohol to the β,γ-unsaturated ketone using TPAP and NMO[21] then provided **6a** in 67% overall yield. Treatment of **6a** with lithium hexamethyldisilazide (LiHMDS) in THF at −78 °C followed by addition of aldehyde **3**[10] (1 equiv) proved to be highly stereoselective and provided the Felkin aldol **9a** as the only observed aldol product. The stereochemistry of the new hydroxyl group of **9a** was assigned by application of our recently described NMR method.[25]

Intermediate **9a** represents the C(1)−C(21) fragment of the natural product, with all functionality in the correct oxidation state except for C(15), which ultimately must be oxidized to a ketone. However, all attempts to deprotect the methyl ester and the C(16)-acetoxymethyl groups were unsuccessful, owing to the base sensitivity of **9a** and intermediates derived therefrom. Therefore, ongoing efforts are focusing on the identification of a suitable set of protecting groups for the C(1)-carboxylic acid and C(16)-CH_2OH groups that can be unmasked under mild conditions. Toward this end, we have developed a synthesis of the C(1)−C(21) aldol **9b**, which possesses 2-chloroethyl ester at C(1) and a 2-bromoethyl carbonate protecting group for C(16)−CH_2OH (see Scheme 7).

Chloroethyl ester **7b** was prepared by Yamaguchi esterification[26] of the carboxylic acid derived from **17** with

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(23) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047.
(24) The stereochemistry of aldol **21** was assigned by 1,3-anti reduction (tetramethylammonium triacetoxyborohydride, CH_3CN, HOAc, −10 °C, 86%) followed by conversion of the diol to the corresponding 1,3-anti acetonide derivative. For the 1,3-anti reduction, see: Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560. For the 1,3-diol stereochemical assignment, see: Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.
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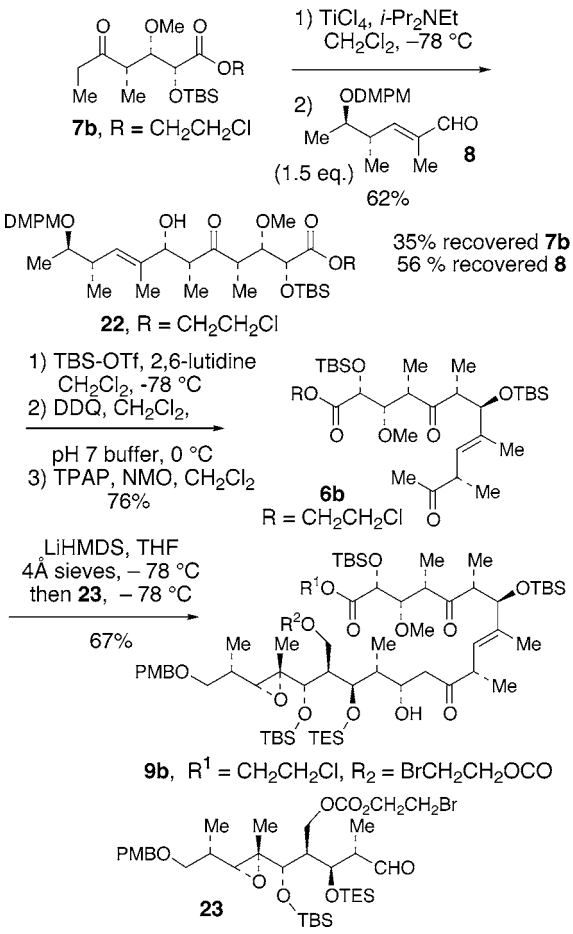
(26) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Chem. Bull. Jpn.* **1979**, *52*, 1989.

Scheme 7



2-chloroethanol (77%), followed by deprotection of the DMPM ether and oxidation of the C(5)-hydroxyl group (Scheme 4). Aldol coupling of **7b** and **8** (1.5 equiv) using the chlorotitanium enolate technology provided **22** in 62% yield; 35% of **7b** and 56% of **8** were recovered. Conversion of **22** to **6b** proceeded uneventfully (76% for the three steps). The key aldol reaction of the lithium enolate generated from **9b** and aldehyde **23**[27] (with a bromoethyl carbonate protecting group for C(16)−CH_2OH) then provided the Felkin aldol **9b** in 67% yield along with 20% of recovered **6b** and 17% of recovered **8**. However, we have not been able to develop a workable procedure to generate the targeted seco acid by deprotection of seco ester **9b**. Consequently, efforts to identify an appropriate protecting group combination for the advanced seco ester intermediate are continuing.

In summary, we have developed a highly stereoselective syntheses of the C(1)−C(12) fragments **6a** and **6b** of tedanolide and have demonstrated that these diketo esters undergo efficient and stereoselective fragment coupling with aldehydes **3** and **23**, respectively. Further progress toward completion of the total synthesis of tedanolide will be reported in due course.

Acknowledgment. Support provided by the National Institutes of Health (Grant GM 38436 to W.R.R. and Training Grant GM 07767) is gratefully acknowledged. We also thank Ms. Lisa Julian for providing samples of aldehyde **23** used in this work.

Supporting Information Available: Tabulated spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) The synthesis of **23** was performed by Lisa Julian, by appropriate modifications of our previously published synthesis of **3** (ref 10).