ORGANIC LETTERS

1999
Vol. 1, No. 1
95−98

Studies on the Synthesis of Tedanolide: Synthesis of the C(5)–C(21) Segment via a Highly Stereoselective Fragment Assembly Aldol Reaction of a Chiral β,γ-Unsaturated Methyl Ketone

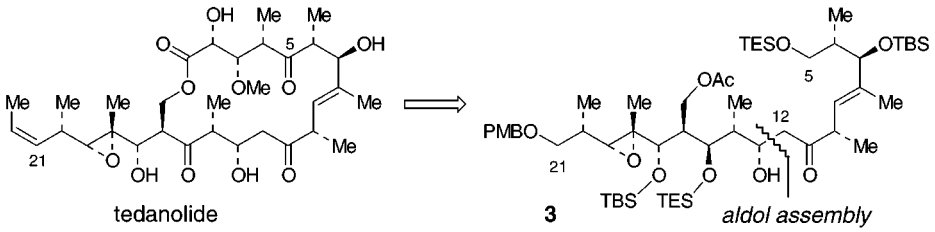
William R. Roush*[,1] and Gregory C. Lane

Departments of Chemistry, University of Michigan, Ann Arbor, Michigan 48109, and Indiana University, Bloomington, Indiana 47405

roush@umich.edu

Received April 9, 1999

ABSTRACT



A highly diastereoselective synthesis of 3, corresponding to the C(5)–C(21) segment of tedanolide, has been accomplished by a route utilizing the aldol reaction of aldehyde 4 and the β,γ-unsaturated methyl ketone 5.

Tedanolide, **1**, a highly cytotoxic macrolide, was isolated in 1984 from the Caribbean sponge *Tedania ignis*[2] (Figure 1). The structurally related macrolide 13-deoxytedanolide (**2**) was subsequently isolated from *Mycale adhaerens*, a sponge species from the western Pacific Ocean.[3] Tedanolide displays significant cytotoxicity against KB and PS tumor cell lines in vivo, with ED_{50}'s of 16 pg/mL in the PS assay and 250 pg/mL in the KB assay.[2] 13-Deoxytedanolide is also highly cytotoxic, with a reported IC_{50} of 94 pg/mL vs P388 murine leukemia cells.[3] These potent biological properties have stimulated interest in the synthesis of these molecules, especially tedanolide, whose stereostructure has been determined by X-ray analysis.[4−10] We report herein a highly stereoselective synthesis of the C(5)−C(21) segment **3** of tedanolide, via the fragment assembly aldol reaction of the chiral aldehyde **4** and the β,γ-unsaturated methyl ketone **5**.

In planning this approach to the synthesis of **3**, we relied on earlier studies from our laboratory which indicated that the diastereofacial selectivity of **4** should favor production of the C(13,14)-syn (i.e., Felkin) stereochemistry of **3**[11,12] and that the intrinsic diastereofacial bias of **5**, although

(1) Address correspondence to this author at the Department of Chemistry, University of Michigan, Ann Arbor, MI 48109-1055.

(2) Schmitz, F. J.; Gunasekera, S. P.; Yalamanchili, G.; Hossain, M. B.; van der Helm, D. *J. Am. Chem. Soc.* **1984**, *106*, 7251.
(3) Fusetani, N.; Sugawara, T.; Matsunaga, S.; Hirota, H. *J. Org. Chem.* **1991**, *56*, 4971.
(4) Yonemitsu, O. *J. Synth. Org. Chem. Jpn.* **1994**, *52*, 946.
(5) Matsushima, T.; Horita, K.; Nakajima, N.; Yonemitsu, O. *Tetrahedron Lett.* **1996**, *37*, 385.
(6) *Chem. Pharm. Bull.* **1998**, *46*, 1135.
(7) Liu, J.-F.; Abiko, A.; Pei, Z. H.; Buske, D. C.; Masamune, S. *Tetrahedron Lett.* **1998**, *39*, 1873.
(8) Taylor, R. E.; Ciavarri, J. P.; Hearn, B. R. *Tetrahedron Lett.* **1998**, *39*, 9361.
(9) Jung, M. E.; Karama, U.; Marquez, R. *J. Org. Chem.* **1999**, *64*, 663.
(10) Matsushima, T.; Mori, M.; Zheng, B. Z.; Maeda, H.; Nakajima, N.; Uenishi, J.; Yonemitsu, O. *Chem. Pharm. Bull.* **1999**, *47*, 308.
(11) Roush, W. R.; Bannister, T. D.; Wendt, M. D. *Tetrahedron Lett.* **1993**, *34*, 8387.
(12) Gustin, D. J.; VanNieuwenhze, M. S.; Roush, W. R. *Tetrahedron Lett.* **1995**, *36*, 3443.

10.1021/ol990572s CCC: $18.00
Published on Web 05/24/1999

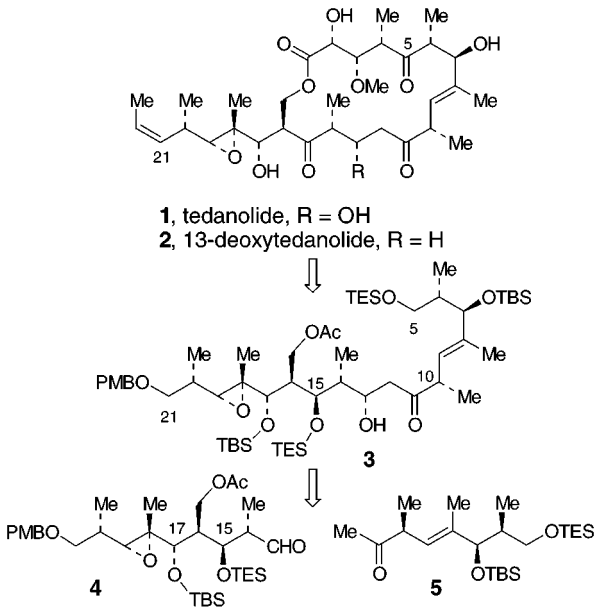
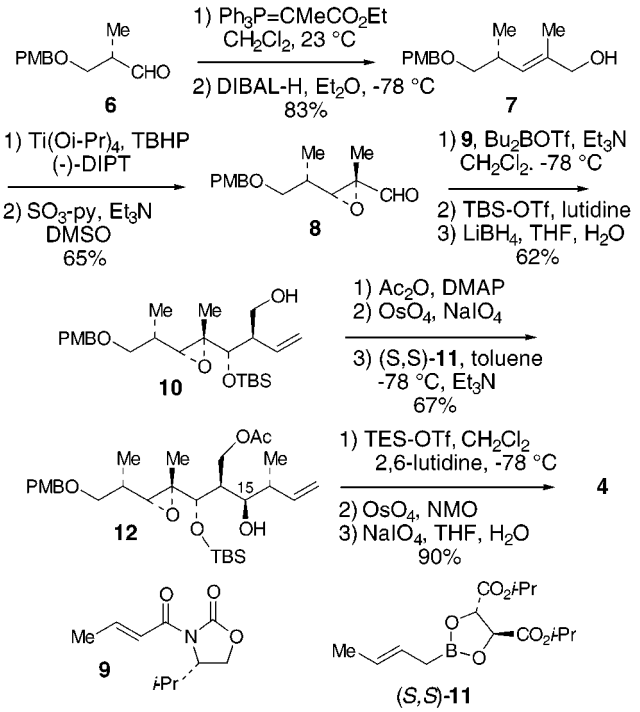


Figure 1. Retrosynthetic analysis.

expected to be relatively modest,[13] should reinforce that of **4** in a matched double asymmetric[14] fragment coupling process using the lithium enolate of **5**. However, we also recognized that successful implementation of this strategy would be dependent on two critical issues. The first was whether the potentially sensitive C(10) stereocenter of β,γ-unsaturated ketone **5** would survive the planned aldol coupling. The second concerned the definition of a suitable protecting group strategy for the C(15) hydroxyl group, since our earlier studies indicated that this unit would have a pronounced effect on the aldol reaction stereoselectivity.[12] While a C(15)-OTES ether was deemed appropriate for late-stage manipulations in our projected total synthesis, our earlier studies suggested that a β-TES ether would not be suitable for the proposed fragment assembly sequence. Fortunately, as described herein, the aldol reaction of **4** and **5** proved to be a highly stereoselective and synthetically useful transformation.

Aldehyde **4** was synthesized starting from the readily available chiral aldehyde **6**[15] (Scheme 1). A Wittig reaction of **6** with $Ph_3P{=}CMeCO_2Et$ provided the targeted (*E*)-enoate in 85% yield following chromatographic separation of the minor *Z* isomer (97:3 selectivity). Reduction of the (*E*)-enoate with DIBAL then provided **7** in 83% yield from **6**.[16] Diastereoselective epoxidation of **7** was performed using the Sharpless asymmetric epoxidation,[17] and the resulting epoxy alcohol was oxidized to the aldehyde **8** in 65% overall yield by using the Parikh−Doering procedure.[18] Epoxyaldehyde **8** was elaborated to the homoallylic alcohol **10** via aldol reaction with the chiral crotonate imide **9**,[19] protection of the aldol product as a TBS ether, and then reduction of the acyl oxazolidinone using $LiBH_4$ (5 equiv) in THF containing 3 equiv of H_2O.[20] Acylation of the primary hydroxyl group of **10** followed by oxidative cleavage of the terminal olefin and asymmetric crotylboration[21] of the resulting aldehyde provided **12** with excellent stereoselectivity. Finally, protection of the C(15) alcohol as a TES ether followed by oxidative cleavage of the olefin completed the synthesis of **4**.

Scheme 1. Synthesis of Chiral Aldehyde **4**



The diastereofacial selectivity of **4** and the related aldehydes **13a** and **13b** was probed by studying their aldol reactions with enolates generated from methyl isopropyl ketone (3-methyl-2-butanone; Table 1 and Figure 2). The results of these reactions demonstrate once again that the

(13) For example, the chiral methyl ketones employed in the studies summarized in refs 10 and 11, which are more structurally complex than **5** in the present work, exhibited diastereofacial preferences ranging from 60:40 to 83:17, depending on the metal enolate employed (see footnote 10 in ref 11).

(14) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(15) Walkup, R. D.; Kane, R. R.; Boatman, P. D., Jr.; Cunningham, R. T. *Tetrahedron Lett.* **1990**, *52*, 7587.

(16) The spectroscopic and physical properties (e.g., ^{1}H NMR, IR, mass spectrum and/or C,H analysis) of all new compounds were fully consistent with the assigned structures.

(17) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1.

(18) Parikh, J. R.; von Doering, E. W. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

(19) Evans, D. A.; Sjogren, E. B.; Bartroli, J.; Dow, R. L. *Tetrahedron Lett.* **1986**, *27*, 4957.

(20) Pfenning, T. D.; Djuric, S. W.; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Synth. Commun.* **1990**, *20*, 307.

(21) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.

(22) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511.

(23) The stereochemistry of all other aldols was assigned via analysis of the characteristic ABX pattern for the C(12)−CH_2 and C(13)−H resonances, as previously described (see footnote 8 of ref 10).

Table 1. Aldol Reactions of Aldehydes **4** and **13** with 3-Methyl-2-Butanone

entry no.	RCHO	aldol reaction conditions (−78 °C)[a]	yield (%)[b]	major product	**14**:**15**
1	**4**	LHMDS, THF, −78 °C	83	**14a**	≥97:03
2	**4**	$TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, −78 °C	60	**14a**	77:23
3	**4**	Bu_2BOTf, *i*-Pr_2NEt, CH_2Cl_2, −78 °C	86	**14a**	59:41
4	**13a**	LHMDS, THF, −78 °C	79	**14b**	≥95:05
5	**13a**	NaHMDS, THF, −78 °C	76	**14b**	90:10
6	**13a**	KHMDS, THF, −78 °C	26	**14b**	80:20
7	**13a**	$TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, −78 °C	55	**14b**	85:15
8	**13a**	Bu_2BOTf, *i*-Pr_2NEt, CH_2Cl_2, −78 °C	85	**14b**	55:45
9	**13b**	LHMDS, THF, −78 °C	74	**14c**	93:7
10	**13b**	NaHMDS, THF, −78 °C	54	**14c**	≥95:05
11	**13b**	Bu_2BOTf, *i*-Pr_2NEt, CH_2Cl_2, −78 °C	61	**14c**	33:67

[a] Aldol reactions were performed at −78 °C by adding 1.0 equiv of **4** or **13** to the enolate generated from 3 equiv of isopropyl methyl ketone. [b] The combined yields (unoptimized) of **14** and **15** isolated chromatographically.

aldehyde diastereofacial selectivity is enolate metal dependent, with the best selectivity for the Felkin diastereomer **14** being obtained with the lithium enolate. The stereochemistry of **14a** (R^1 = TBS, R^2 = TES) was assigned following removal of the TES ether (TBAF, $ClCH_2CH_2Cl$) and conversion of the resulting 1,3-diol to the 1,3-anti acetonide **16**.[22,23] However, in contrast to our earlier studies with aldehydes **17a** and **17b**, the reaction diastereoselectivity is not highly dependent on the identity of the C(15)-OR protecting group.[12] Our current working hypothesis is that the bulky C(7)-OTBDPS substituent of **17** induces the C(5)-OTBS group to adopt a conformation anti to the C(5,6)-bond which, in turn, forces the C(3)-OTES unit to be anti to C(3,4). In this particular conformation, the TES ether is

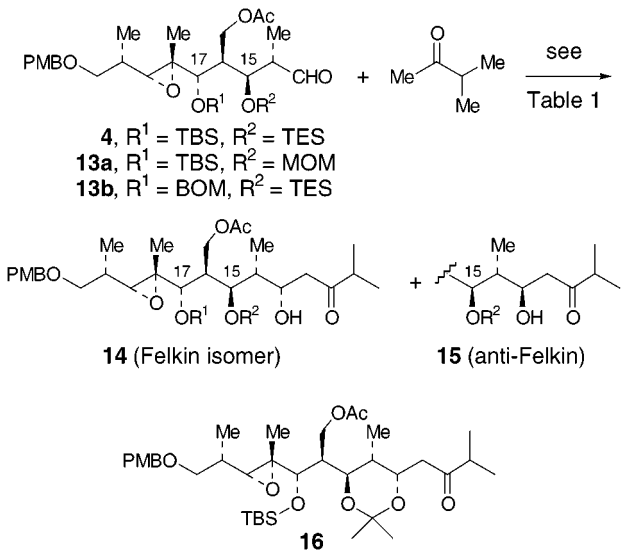


Figure 2. Structures of products of aldol reactions of aldehydes **4** and **13** with 3-methyl-2-butanone.

positioned relatively close to the aldehyde, where it can destabilize the otherwise favored chairlike transition state.[12] However, the gearing effects that dominate the conformational preferences of **17** are not operational, or at least are not as prevalent in **4,** since the C(18−19)-epoxide unit is less sterically demanding than the C(8)−OTBDPS unit of **17** (the conformation of the backbone of **4** should be as shown in Figure 3 in order to minimize gauche interactions;

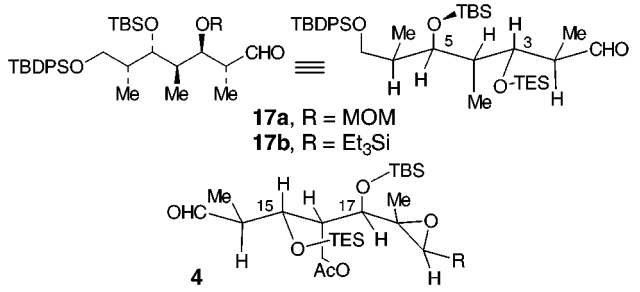
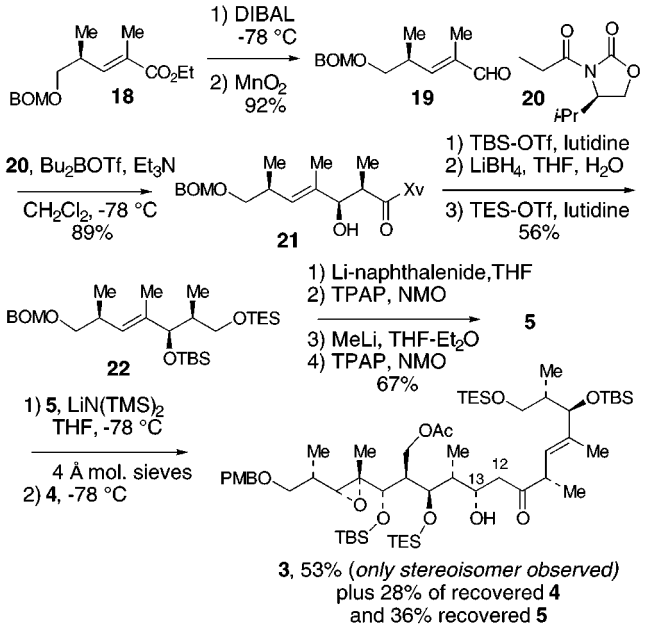


Figure 3. Conformational analysis of **4** and **17**.

note also that **4** and **17** are in opposite absolute stereochemical series).[24] Consequently, the C(17)-OTBS ether can adopt a position anti to the C(15,16) bond, which in turn allows the C(15)-OTES ether to move away from aldehyde unit in the reaction transition state.

The synthesis of the chiral β,γ-unsaturated ketone **5** commenced with enal **19**, which was prepared by standard procedures from enoate **18** (Scheme 2). The diastereoselective aldol reaction of **19** with the D-valine derived acyl oxazolidinone **20**[25] provided **21** with excellent selectivity

Scheme 2. Synthesis of Chiral β,γ-Unsaturated Ketone **5** and Its Aldol Reaction with **4**



(89% yield). Protection of the hydroxyl group as a TBS ether (96%) followed by reduction of the acyl unit (62%) and protection of the primary hydroxyl group as a TES ether then provided **22** in 95% yield. The BOM ether was then removed via reduction with lithium naphthalenide (87%).[26] The primary alcohol was oxidized to the sensitive β,γ-unsaturated enal by using catalytic TPAP and NMO (96% yield),[27] which was dissolved in THF and added to a solution of MeLi in Et_2O at −78 °C. The resulting secondary alcohol was then oxidized, again by using the catalytic TPAP protocol,[27] to give the targeted methyl ketone **5** in 67% overall yield for this final four-step sequence.

To our considerable delight, treatment of 1.9 equiv of **5** with 2.1 equiv of LiHMDS in THF at −78 °C followed by addition of 1.0 equiv of aldehyde **4** provided aldol **3** in 53% yield, *as the only observed aldol diastereomer*. In addition, 28% of aldehyde **4** and 36% of β,γ-unsaturated ketone **5** were recovered, along with ca. 8% of a compound tentatively identified as the aldol dimer of **5**. The stereochemistry of the newly formed C(13) hydroxyl group of **3** was assigned by spectroscopic correlation with **14a**, using the characteristic and diagnostic[11,23] ABX pattern for the C(12)−C(13) spin system in the ^{1}H NMR spectrum as a specific point of comparison. Remarkably, both methyl ketone **5** and aldol **3** are stable to silica gel chromatography, and the potentially sensitive C(10) stereocenter exhibits no tendency to epimerize under normal handling conditions.[28]

In conclusion, we have demonstrated that the aldol reaction of aldehyde **4** and the chiral β,γ-unsaturated methyl ketone **5** is a synthetically viable strategy for construction of the C(5)−C(21) segment of tedanolide. Further progress toward completion of a total synthesis of this highly bioactive marine macrolide will be reported in due course.

Acknowledgment. Support provided by the National Institutes of Health (Grant No. GM 38436) is gratefully acknowledged.

Supporting Information Available: Figures giving ^{1}H NMR spectra of **3**, **14a**−**c**, and **15a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL990572S

(24) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1124.
(25) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.
(26) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924.
(27) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.

(28) A mixture of C(10) epimers of **3** was observed in one initial aldol experiment in which a sub-stoichiometric amount of LiHDMS was accidentally used. A small amount (ca. 10%) of epimerization of C(10) of recovered methyl ketone **5** is also observed if the aldol reactions are quenched by addition of saturated aqueous NH_4Cl to the −78 °C reaction mixture (the NH_4Cl solution immediately freezes). However, if the −78 °C reaction mixture is poured directly into aqueous NH_4Cl solution at ambient temperature, recovered **5** is completely stereochemically homogeneous. Epimerization of the aldol product **3** was not observed under either of these sets of workup conditions.