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Total Syntheses of (+)-Tedanolide and (+)-13-Deoxytedanolide

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Abstract: Convergent total syntheses of the potent cytotoxins (+)-tedanolide (**1**) and (+)-13-deoxytedanolide (**2**) are described. The carbon framework of these compounds was assembled via a stereoselective aldol reaction that unifies the C(1)−C(12) ketone fragment **5** with a C(13)−C(23) aldehyde fragment **6** (for 13-deoxytedanolide) or **52** (for tedanolide). Multiple obstacles were encountered en route to (+)-**1** and (+)-**2** that required very careful selection and orchestration of the stereochemistry and functionality of key intermediates. Chief among these issues was the remarkable stability and lack of reactivity of hemiketals **33b** and **34** that prevented the tedanolide synthesis from being completed from aldol **4**. Key to the successful completion of the tedanolide synthesis was the observation that the 13-deoxy hemiketal **36** could be oxidized to C(11,15)-diketone **38** en route to 13-deoxytedanolide. This led to the decision to pursue the tedanolide synthesis via C(15)-(*S*)-epimers, since this stereochemical change would destabilize the hemiketal that plagued the attempted synthesis of tedanolide via C(15)-(*R*) intermediates. However, use of C(15)-(*S*)-configured intermediates required that the side-chain epoxide be introduced very late in the synthesis, owing to the ease with which the C(15)-(*S*)-OH cyclized onto the epoxide of intermediate **50**.

Introduction

The tedanolides are a group of 18-membered macrolactones that display remarkable biological activity. (+)-Tedanolide (**1**, Figure 1), reported by Schmitz and co-workers in 1984 after isolation from the Caribbean fire sponge *Tedania ignis*, is highly cytotoxic against human nasopharynx carcinoma (ED_{50} = 250 pg/mL) and lymphocytic leukemia (ED_{50} = 16 pg/mL) cell lines and causes cell accumulation in the S phase at concentrations as low as 10 ng/mL.[1] In addition, tedanolide has been shown to increase the lifespan of mice implanted with lymphocytic leukemia by 23% at 1.5 μg/kg of body weight.[2] The closely related macrolide (+)-13-deoxytedanolide (**2**, Figure 1) was isolated by Fusetani and co-workers in 1991 from the Japanese sponge *Mycale adhaerens* and demonstrates potent cytotoxicity against P388 murine leukemia cells (IC_{50} = 94 pg/mL).[3] In an elegant study designed to probe the mechanism of 13-deoxytedanolide activity, Fusetani and co-workers demonstrated that the macrolide binds to the eukaryotic 60S ribosomal subunit[4a] and identified the C(11)−C(23) region of the natural product as the pharmacophore.[4b,5] A third member of this macrolide family, (+)-tedanolide C (**3**, Figure 1), was reported by Ireland and co-workers in 2006 from the extract of Papua New Guinea marine sponge *Ircinia* sp.[6] The reported structure of tedanolide C has different stereochemistry and a different methylation and oxygenation pattern than the two older congeners. Nevertheless, tedanolide C exhibits strong activity (IC_{50} = 57 ng/mL) against the HTC-116 colorectal cancer cell line.

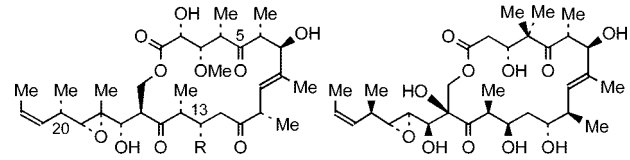

Figure 1. Tedanolide natural products.

The impressive biological profiles and the synthetic challenges presented by the tedanolides have encouraged researchers in our laboratory[7,8] and others to pursue their synthesis.[9−17] The complex architecture of tedanolide (**1**) is underscored by a heavily oxygenated and methylated carbon skeleton containing 13 stereocenters and two polysubstituted olefins—one of which

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(6) Chevallier, C.; Bugni, T. S.; Feng, X.; Harper, M. K.; Orendt, A. M.; Ireland, C. M. *J. Org. Chem.* **2006**, *71*, 2510.
(7) Total synthesis of (+)-13-deoxytedanolide: Julian, L. D.; Newcom, J. S.; Roush, W. R. *J. Am. Chem. Soc.* **2005**, *127*, 6186.
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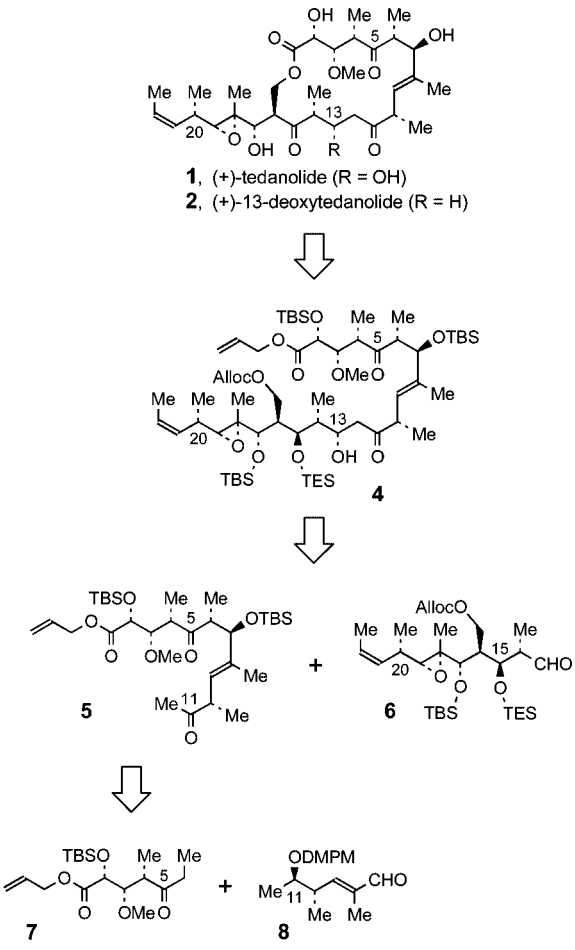
is incorporated into a β,γ-unsaturated ketone with the potential to migrate into conjugation with the carbonyl. In addition, tedanolide possesses a sensitive α-hydroxy trisubstituted epoxide and four β-hydroxy ketone units that are potentially susceptible to retro aldol decomposition. Total syntheses of tedanolide were recently completed by Kalesse[9a,b] (2006) and Smith[10a] (2007); a few years earlier, Smith[10c,d] (2003) and our group[7] (2005) reported total syntheses of 13-deoxytedanolide.

Results and Discussions

In planning our synthetic approach to tedanolide and 13-deoxytedanolide, we initially envisioned that **4** would serve as a common intermediate that would permit entry into both macrolides (Scheme 1). We planned to assemble **4** from the convergent aldol coupling of methyl ketone **5** and aldehyde **6**, which would establish the C(13)-alcohol stereochemistry of tedanolide via Felkin addition of **5** to **6**. We chose the (*R*)-configuration for the C(15)-position of **6** after previous studies from our group demonstrated that the lithium enolates of methyl ketone models of **5** add to 2,3-*anti* aldehydes (e.g., **6**) with greater Felkin selectivity than additions to 2,3-*syn* aldehydes (e.g., **39**, vide infra).[18] We envisaged that aldol **4** could be converted to tedanolide via a sequence involving C(15)-oxidation to the requisite carbonyl and macrolactonization. After considerable experimentation,[8b] we decided to mask the C(1)-acid in **5** as an allyl ester and the C(16)-hydroxymethyl group in **6** as an allyl carbonate (Alloc), motivated by our desire to remove both protection groups simultaneously prior to macrolactonization. We envisioned that aldol adduct **4** could also be converted to 13-deoxytedanolide by using a similar sequence that also included deoxygenation of the C(13)-alcohol.

Scheme 1. Retrosynthetic Analysis of the Tedanolides



We developed a convergent route that assembles the C(1)−C(12) ketone **5** via the aldol reaction of ethyl ketone **7** and aldehyde **8**. The synthesis of ethyl ketone **7** began with asymmetric hydrogenation[19] of β-keto ester **9**, followed by alkylation of the β-hydroxy ester under Fráter conditions[20] to access the 2,3-*anti* ester **10** (Scheme 2). The hydroxyl group of **10** was protected as a DMPM ether in **11** through a sequence involving ester reduction with $LiAlH_4$, conversion of the 1,3-diol to the 3,4-dimethoxybenzylidene acetal, and regioselective acetal reductive opening with DIBAL. The primary alcohol of **11** was oxidized under Swern conditions,[21] and the resulting aldehyde was treated with 3 equiv of γ-siloxy allylstannane **12**[22a] and BF_3-OEt_2 in CH_2Cl_2 at −78 °C[22b] to afford the 3,4-*syn*-4,5-*syn*-homoallylic alcohol with >95:5 diastereomeric ratio (dr). Methylation of the alcohol (MeOTf, 2,6-di-*tert*-butyl-4-

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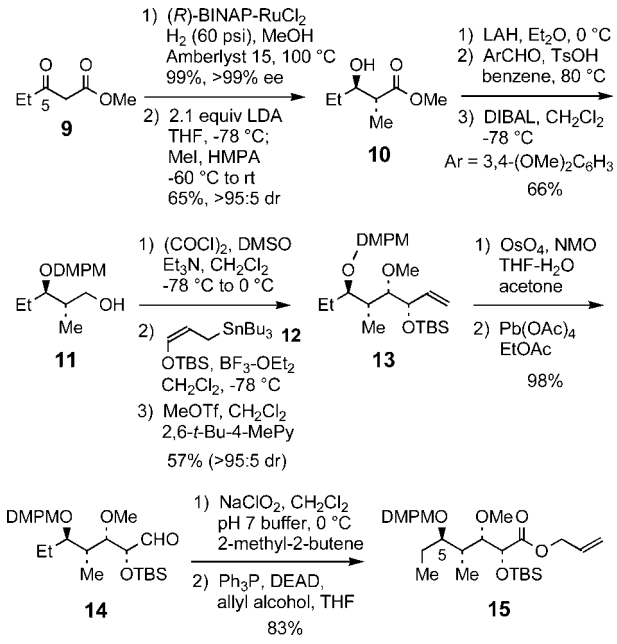
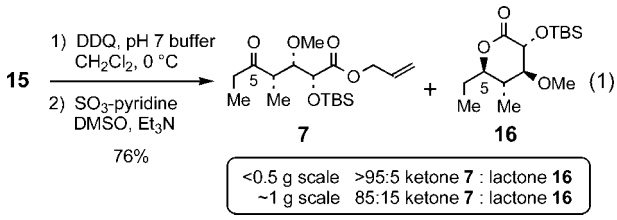
(21) For a review: Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
(22) (a) Keck, G. E.; Abbott, D. E.; Wiley, M. R. *Tetrahedron Lett.* **1987**, *28*, 139. (b) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322.

Scheme 2. Preparation of Allyl Ester **15**



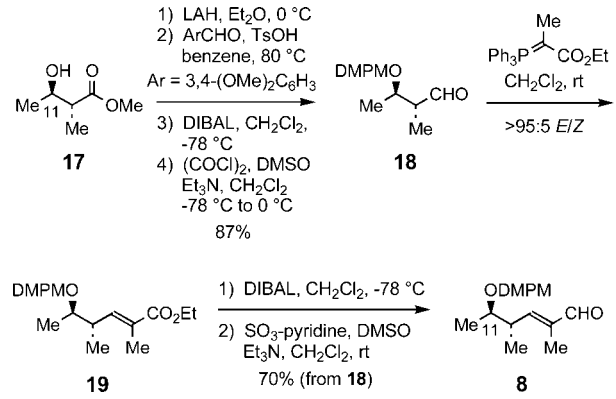
methylpyridine)[23] and oxidative cleavage of the olefin provided aldehyde **14**, which in turn was converted to allyl ester **15** via chlorite oxidation to the carboxylic acid[24] and esterification with allyl alcohol under Mitsunobu conditions.[25]

The conversion of allyl ester **15** to the ethyl ketone **7** was complicated by the competitive formation of lactone **16** when **15** was treated with dichlorodicyanoquinone (DDQ)[26] followed by oxidation of the resulting secondary alcohol via the Parikh−Doering method (eq 1).[21] Lactone **16** is produced during isolation of the C(5)-alcohol after DDQ-mediated benzyl ether cleavage. This side reaction became more prominent when the debenzylation−oxidation sequence was performed on a gram scale. The alcohol intermediate proved very sensitive to acid,[27] and great care was taken to minimize the formation of lactone **16** by removing the mildly acidic dihydroquinone (DDQ byproduct) with aqueous sodium bicarbonate extractions.



Aldehyde **8** (to be coupled with ethyl ketone **7** en route to C(1)−C(12) ketone **5**) was synthesized from the readily

Scheme 3. Synthesis of Unsaturated Aldehyde **8**



available *anti*-β-hydroxy-α-methylbutyrate **17**[28] as shown in Scheme 3. Ester **17** was converted to aldehyde **18** via ester reduction with $LiAlH_4$, dimethoxybenzylidene acetal formation, regioselective acetal reductive opening, and Swern oxidation of the resulting primary alcohol. Wittig olefination of **18** with the stabilized ylide $Ph_3P{=}C(Me)CO_2Et$ provided the α,β-unsaturated ester **19** with excellent selectivity (>95:5 *E*/*Z*). Reduction of **19** to the allylic alcohol, followed by Parikh–Doering oxidation[21] of the primary alcohol, furnished aldehyde **8** in 70% yield over three steps.

The stereoselective aldol coupling of ethyl ketone **7** and aldehyde **8** was effected by using $TiCl_4$ and *i*-Pr_2NEt and provided **20** in 73% yield with 10:1 diastereoselectivity (Scheme 4).[29] The selectivity of this transformation stems from a transition state, **TS**, in which the C−O bond of the titanium enolate eclipses the α'-C−H bond, allowing the aldehyde to approach from the less-hindered face of the enolate.[29] Extensive optimization was required to minimize the formation of **21** via intramolecular cyclization of the titanium enolate onto the allyl ester. This competitive pathway was suppressed by treating ketone **7** with $TiCl_4$ and *i*-Pr_2NEt for a maximum of 8 min at −78 °C longer exposure times led to substantially lower yields (<30%) of **20** and correspondingly increased amounts of **21**. The synthesis of C(1)−C(12) ketone **5** was completed in three steps with the silylation of the C(7)-alcohol of **20**, DDQ cleavage of the dimethoxybenzyl ether,[26] and TPAP oxidation[30] of the liberated secondary alcohol.

The synthesis of C(13)−C(23) aldehyde **6** is summarized in Scheme 5. Wittig olefination of the known aldehyde **22**[31] with the stabilized ylide $Ph_3P{=}C(Me)CO_2Et$ furnished the α,β-unsaturated ester in excellent selectivity (97:3 *E*/*Z*), and DIBAL reduction provided the allylic alcohol. Subsequent Sharpless epoxidation[32] of the allylic alcohol (>18:1 dr) and Parikh−Dosering oxidation of the hydroxyl group afforded epoxyaldehyde **23**. Evans aldol reaction[33a] of **23** with the chiral crotonate

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(24) (a) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888. For a modification using 2-methyl-2-butene as chlorine scavenger: (b) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175.
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(27) A sample of secondary alcohol in $CDCl_3$ (treated with K_2CO_3) completely converted to lactone **16** within 20 min, as observed by ^1H NMR analysis.
(28) Available from methyl acetoacetate (see ref 20) via a sequence of asymmetric hydrogenation and alkylation that parallels the conversion of **9** to **10** (Scheme 2).
(29) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047.
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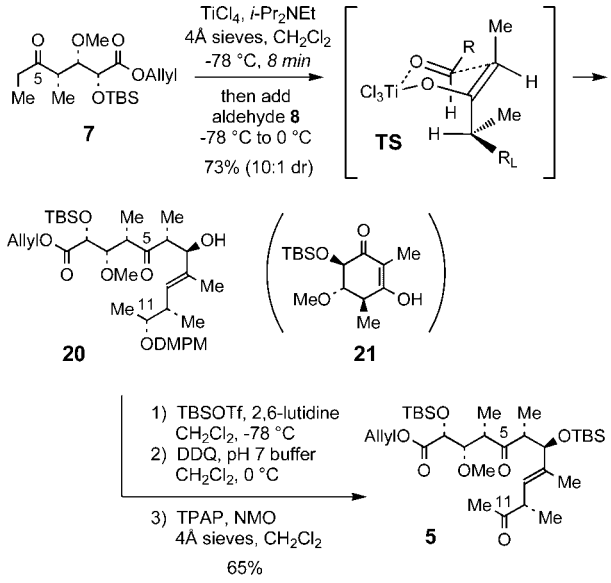
Scheme 4. Completion of the Synthesis of C(1)−C(12) Ketone **5**

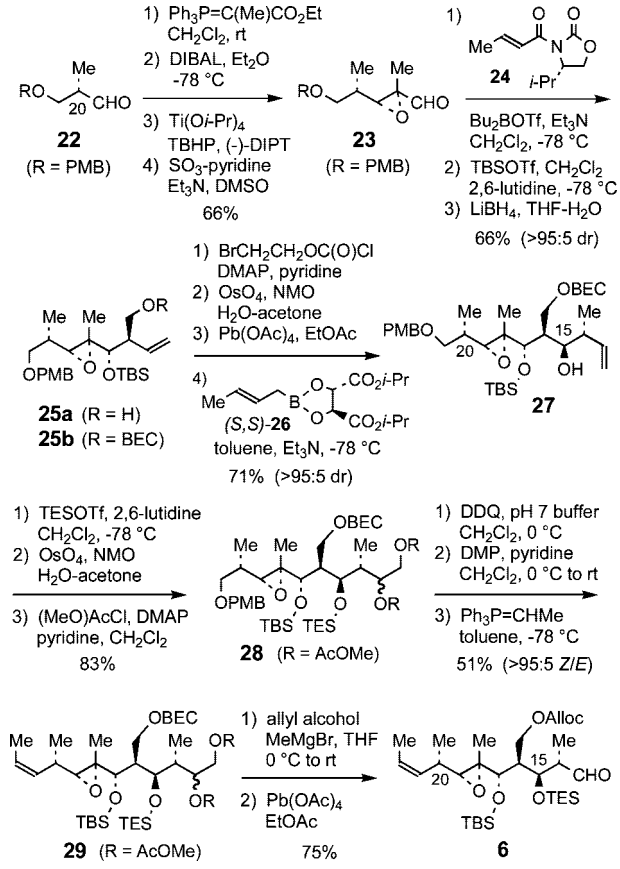


imide **24**,[33b] silylation of the newly formed alcohol, and reduction of the acyl oxazolidinone with $LiBH_4$ in aqueous tetrahydrofuran (THF)[34] provided homoallylic alcohol **25a**. The primary alcohol of **25a** was temporarily protected as a 2-bromoethyl carbonate (BEC); unfortunately, the Alloc group we desired at this position in **6** could not be directly installed due to its incompatibility with subsequent olefin oxidative cleavage steps. Standard oxidative cleavage of the vinyl group of BEC-protected **25b** furnished an aldehyde that was converted to **27** via asymmetric crotylboration with (*S*,*S*)-**26**.[35]

The conversion of **27** to the targeted aldehyde **6** required the installation of the C(21)−C(22) (*Z*)-olefin and conversion of the terminal C(13)-alkene to the aldehyde. Our initial efforts to chemoselectively functionalize the C(13)-alkene in the presence of the C(21)−C(22) olefin were unsuccessful; as a result, it was necessary to functionalize the terminal alkene before introducing the C(21)−C(22) olefin. This was accomplished by silylation of the secondary alcohol of **27**, dihydroxylation of the terminal alkene, and protection of the resulting diol as two α-methoxyacetate esters in **28**. The C(21)−C(22) (*Z*)-olefin was installed upon DDQ oxidative cleavage of the PMB ether of **28**, Dess−Martin oxidization[36] of the primary alcohol, and Wittig olefination of the resulting aldehyde. Treatment of **29** with allyl alcohol and MeMgBr, which generates the magnesium alkoxide in situ, converted the BEC to the Alloc and also cleaved the two α-methoxyacetate esters. Treatment of the liberated diol with $Pb(OAc)_4$ then furnished the targeted C(13)−C(23) aldehyde **6**.

Completion of the synthesis of the tedanolide backbone was accomplished by converting methyl ketone **5** to its lithium enolate with LHMDS followed by the addition of aldehyde **6** (Scheme 6). This aldol reaction provided adduct **4** as a single

Scheme 5. Synthesis of C(13)−C(23) Aldehyde **6**



diastereomer[37] in 59% yield, along with recovered ketone **5** (27%) and aldehyde **6** (11%). Surprisingly, our efforts to protect the newly formed C(13)-alcohol as a trimethylsilyl (TMS) or triethylsilyl (TES) ether or as an acetate ester (Ac or AcOMe) were unsuccessful, and we carried the unprotected aldol **4** forward. Cleavage of the allyl ester and allyl carbonate units by treatment with $Pd(PPh_3)_4$ and *n*-Bu_3SnH[38] liberated the seco-acid for macrolactonization;[39] however, efforts to obtain macrolactone **30**were complicated by the formation of 14-membered macrolactone **31** via competitive cyclization onto the unprotected C(13)-alcohol. We did not observe equilibration of **30** and **31** upon treatment of these macrolactones with titanium isopropoxide.

In an attempt to circumvent the competitive formation of **31**, we tried to alter the conformation of the seco-acid by installing the C(15)-ketone prior to macrolactonization. Selective cleavage of the C(15)-TES ether of **4** with aqueous AcOH in THF led to secondary alcohol **32a** that cyclized onto the C(11)-carbonyl to form hemiketal **33a** (Scheme 7). Silylation of the C(13)-alcohol of **33a** with TESCl provided the hemiketal **33b**, which proved to be remarkably stable and unreactive toward oxidants. Extensive efforts to intercept the ring-opened isomer **32b** with oxidants (Dess−Martin periodinane,[36] SO_3−pyridine in dimethylsulfoxide (DMSO),[21] H_2CrO_6 (Jones oxidation),[40] PDC,[41]

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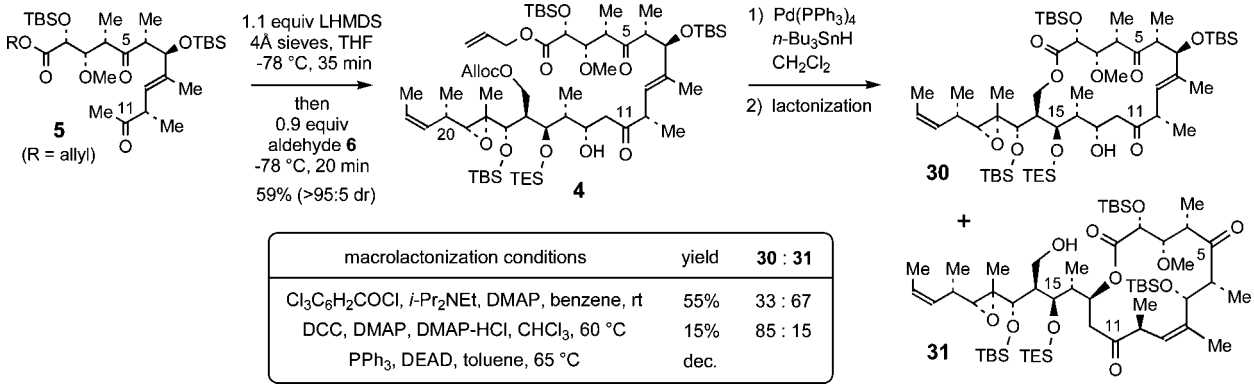
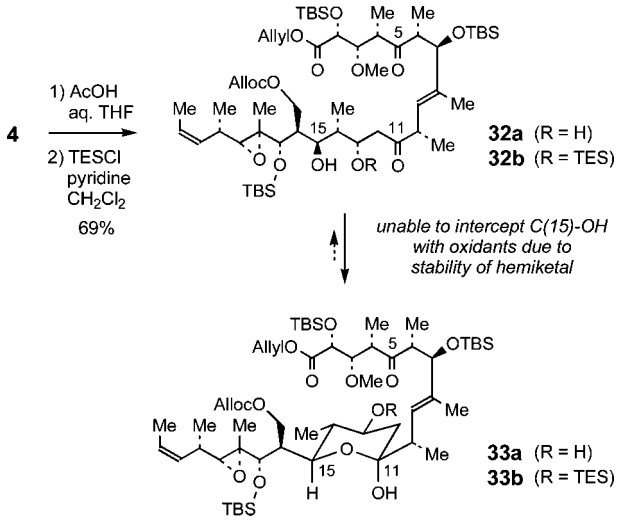
Scheme 6. Aldol Coupling and Macrolactonization

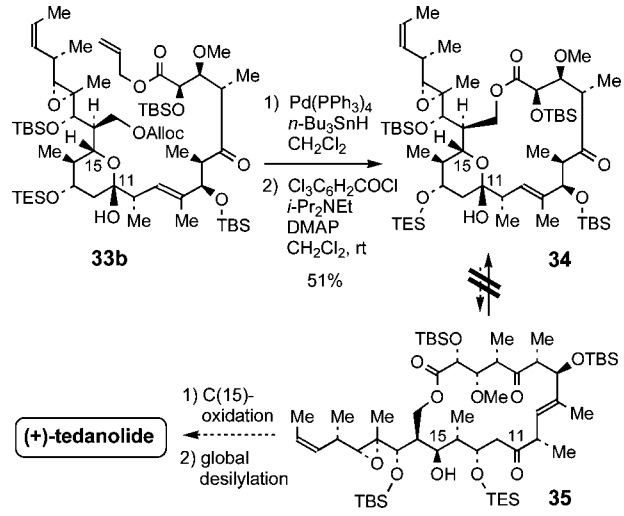


macrolactonization conditions	yield	30 : 31
$Cl_3C_6H_2COCl$, *i*-Pr_2NEt, DMAP, benzene, rt	55%	33 : 67
DCC, DMAP, DMAP-HCl, $CHCl_3$, 60 °C	15%	85 : 15
PPh_3, DEAD, toluene, 65 °C	dec.	

Scheme 7. Hemiketal Formation of C(11,15)-Hydroxy Ketone



Scheme 8. Hemiketal Stability in the Macrolactone



TPAP/NMO[30]) en route to the C(15)-ketone failed. We postulated that converting these intermediates to the macrolactone **34** might shift the hemiketal/hydroxy ketone equilibrium to the hydroxy ketone isomer **35** and permit C(15)-oxidation (Scheme 8). Therefore, conversion of **33b** to the seco-acid and then macrocyclization as described for **4** provided macrocyclic hemiketal **34**. However, the hydroxy ketone tautomer **35** could not be intercepted with oxidants to afford the targeted C(11,15)-dione, and under various oxidation conditions the hemiketal **34** was recovered intact. As a result, we were unable to elaborate **34/35** to tedanolide, even though these intermediates are only two synthetic steps from the natural product (i.e., C(15)-oxidation and global desilylation).

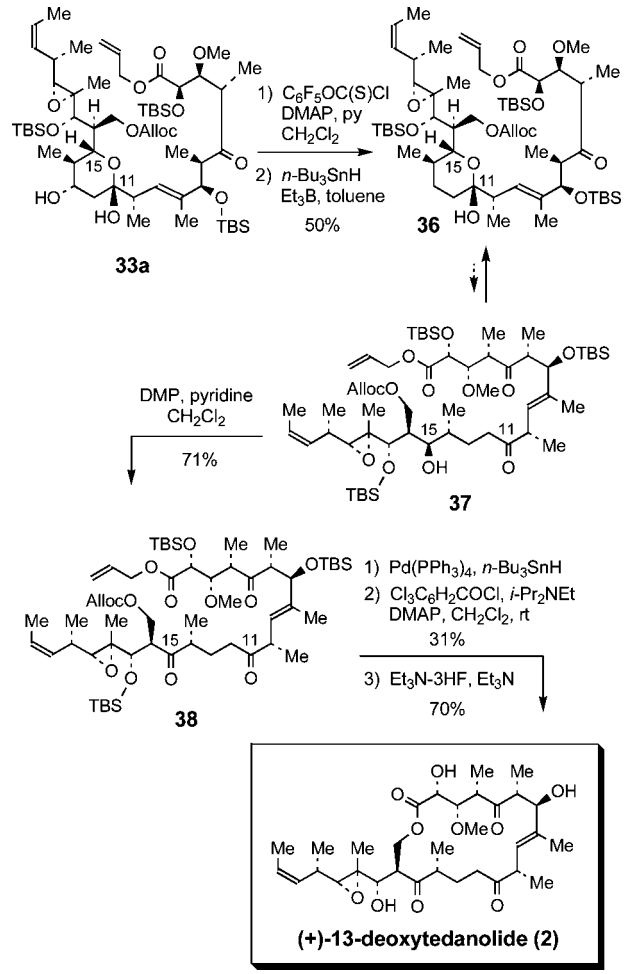
Although it was not possible to convert hemiketal **33b** or **34** to tedanolide, we were able to use **33a** for the synthesis of 13-deoxytedanolide (Scheme 9). By analogy to the principles of the Thorpe−Ingold effect,[42,43] which stipulates that increased numbers of substituents (typically in a geminal arrangement) between two reactive termini lead to an increased rate of ring formation, we speculated that removal of the C(13)-alcohol would decrease the stability of the hemiketal relative to the hydroxy ketone tautomer and enable oxidation of C(15)-OH to the C(11,15)-dione. Excision of C(13)-OH of **33a** was accomplished via conversion of the alcohol to the pentafluorophenylthiocarbonate[44] and subsequent treatment with Et_3B and *n*-Bu_3SnH.[45] Although the resulting hemiketal **36** did not appear to be in equilibrium with hydroxy ketone isomer **37** according to ^{1}H NMR analysis, we were gratified that treatment of **36** with Dess−Martin periodinane furnished the triketone **38** in 71% yield. Ketone **38** was converted to 13-deoxytedanolide (**2**) in three steps via seco-acid formation and Yonemitsu-modified Yamaguchi lactonization,[39] followed by removal of the three TBS ethers with Et_3N−buffered Et_3N−3HF (thereby generating Et_3N−2HF in situ).[46] Synthetic 13-deoxytedanolide was identical in all respects (^{1}H NMR, ^{13}C NMR, IR, optical rotation, HRMS) to an authentic sample.

Having completed the synthesis of the 13-deoxy congener, we continued our efforts to synthesize tedanolide, which had been thwarted by the stability of hemiketal intermediates **33b** and **34**. We hypothesized that inversion of the C(15)-(*R*)-alcohol stereochemistry in our first-generation intermediates to the C(15)-(*S*)-configuration would destabilize the corresponding

(41) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399.
(42) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080.
(43) Implicit to this assumption is the recognition that the equilibrium constant for cyclization of the hydroxy ketone to the hemiketal is determined by the ratio of the rates of formation and breakdown of the hemiketal intermediate. Thus, while the Thorpe−Ingold effect is kinetic in nature, it may also impact the equilibrium constant of reversible processes.

(44) Barton, D. H. R.; Jaszberenyi, J. C. *Tetrahedron Lett.* **1989**, *30*, 2619.
(45) Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 6125.
(46) (a) Giudicelli, M. B.; Picq, D.; Veyron, B. *Tetrahedron Lett.* **1990**, *31*, 6527. (b) McClinton, M. A. *Aldrichimica Acta* **1995**, *28*, 31.

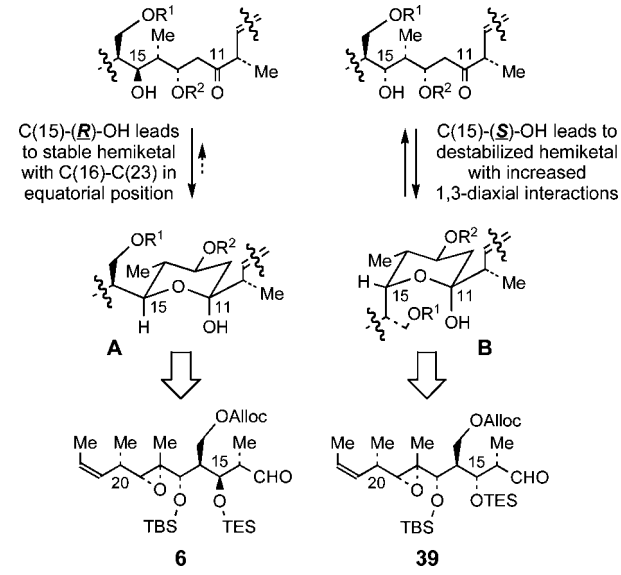
Scheme 9. Synthesis of (+)-13-Deoxytedanolide (**2**)



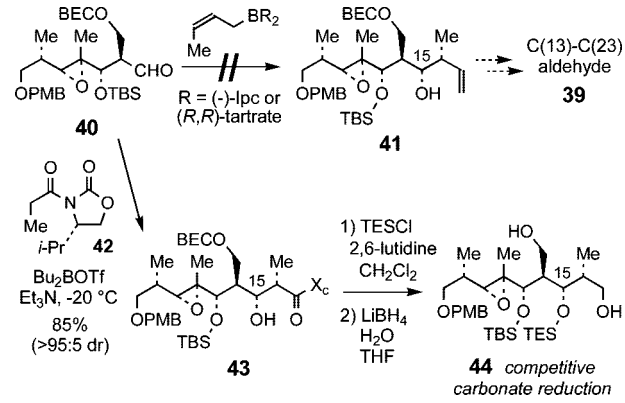
hemiketal **B** via increased 1,3-diaxial interactions and permit the requisite C(15)-oxidation (Scheme 10).[47,48] Thus, we targeted aldehyde **39** containing the (*S*)-configuration at the C(15)-position.

We were unable to install the C(15)-(*S*)-OH of **39** via crotylboration (Scheme 11) of **40** (the immediate precursor to **27**, Scheme 5), which was surprising since a similar crotylboration reaction set the C(15)-(*R*)-OH of aldehyde **6** (vide supra). The reactions of (*R*,*R*)-tartrate crotylboronate[35] or (−)-Ipc_2-(*Z*)-crotylboronane[49] with aldehyde **40** did not provide **41** but rather gave either the undesired C(15)-(*R*)-OH diastereomer (i.e., **27**) or unidentified products lacking the diagnostic olefin protons in the ^{1}H NMR spectrum. Alternatively, we pursued this key stereocenter using an Evans aldol approach.[33a] Reaction of aldehyde **40** with chiral imide **42** provided the aldol adduct **43** with excellent yield and selectivity. Treatment of the alcohol with TESCl afforded the silyl ether. However, efforts to cleave the acyl oxazolidinone unit of **43** led to competitive reduction of the 2-bromoethyl carbonate, and so we looked to replace the carbonate protection group with a silyl ether, as shown in Scheme 12. Aldol reaction of chiral imide **42** with aldehyde **45**

Scheme 10. Proposed Effect of C(15)-Configuration on Hemiketal Stability



Scheme 11. Unsuccessful Efforts toward Aldehyde **39**



and subsequent reduction of the acyl oxazolidinone provided 1,3-diol **47**. The primary alcohol of **47** was temporarily protected as a methoxyacetate ester before silylation of the secondary alcohol. Subsequent cleavage of the methoxyacetate ester followed by oxidation of the resulting alcohol completed the synthesis of aldehyde **49** with the desired (*S*)-configuration at the C(15)-position.

The aldol reaction of the lithium enolate generated from C(1)−C(12) ketone **5** and C(13)−C(23) aldehyde **49** led to the Felkin adduct **50** as the major product[37] with 78:22 diastereoselectivity (Scheme 13). The diminished diastereoselectivity (compared to >95:5 dr from the aldol coupling of **5** and 2,3-*anti* aldehyde **6**) was expected due to the mismatched 1,3-induction imparted by the 2,3-*syn* aldehyde **49**.[18,50] Specifically, the expected Felkin chair-like transition state (**TS-1**) for the aldol reaction of **5** with 2,3-*syn* aldehyde **49** is destabilized relative to the Felkin chair-like transition state (**TS-2**) for the 2,3-*anti* aldehyde **6** due to the stereoelectronic repulsion of interacting dipoles of the aldehyde carbonyl and C(15)-hydroxy TES ether.[50] In an attempt to move the synthesis forward, aldol product **50** was treated with aqueous AcOH in THF to cleave

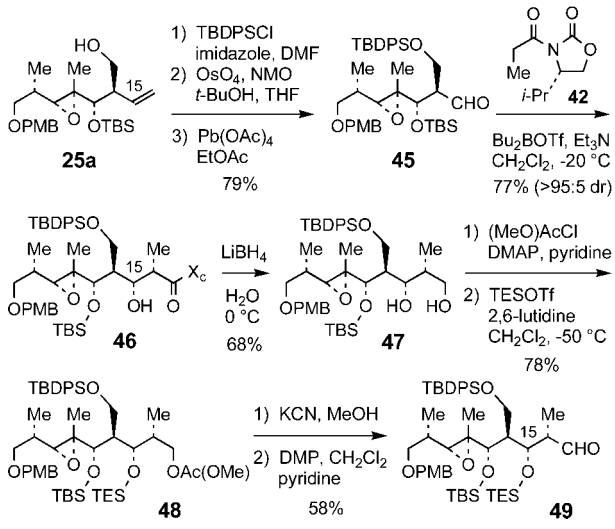
(47) Julian, L. D. Studies toward the total synthesis of the tedanolides: Total synthesis of 13-deoxytedanolide. Ph.D. thesis, University of Michigan, 2005.

(48) While this work was in progress, Kalesse reported experimental evidence for this hypothesis (refs 9a and 9b). Kalesse credits us for this analysis (ref 9b).

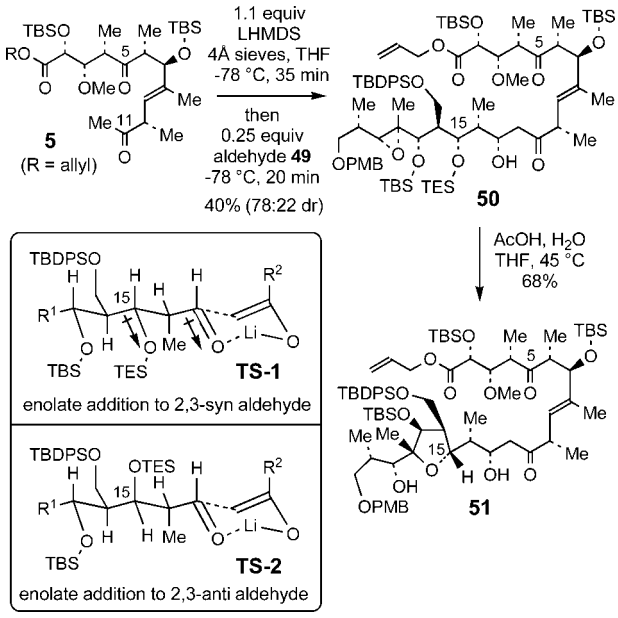
(49) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092.

(50) (a) Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537. (b) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322.

Scheme 12. Synthesis of C(13)−C(23) Aldehyde **49**

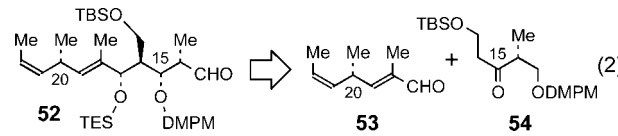


Scheme 13. Aldol Coupling of Ketone **5** and Aldehyde **49**



the TES ether. Unfortunately, these desilylation conditions led to the 5-*exo*-cyclization of the liberated C(15)-alcohol onto the epoxide[51] to form tetrahydrofuran **51**. *The analogous cyclization was **not** observed during manipulation of aldol **4** deriving from the 2,3-anti-aldehyde **6*** (Scheme 7). We hoped that cleavage of the C(15)-TES ether under buffered or basic conditions (Et_3N−3HF, tetrabutylammonium fluoride, TAS-F) might avoid the epoxide-opening, but these efforts led to competitive desilylation of the various TBS ethers. Nevertheless, even when these neutral or weakly basic conditions were used, evidence for cyclization of C(15)-OH onto the epoxide was observed (e.g., **51** and desilylated versions of **51** were detected). Thus, the change in stereochemistry of C(15)-OH significantly affected the reactivity of intermediate **50** (Scheme 13). As a result, we were unable to elaborate these intermediates to tedanolide.

At this point, we targeted aldehyde **52** as a third-generation coupling partner for ketone **5** en route to tedanolide (eq 2). The C(13)−C(23) fragment **52** maintains the (*S*)-configuration at the C(15)-position but lacks the epoxide. This revision to our approach to tedanolide would now require a late-stage, C(17)-OH-directed epoxidation of the C(18)−C(19) olefin,[12c,52] a strategy utilized by Smith[10c,d] in the synthesis of 13-deoxytedanolide and by Kalesse[9a,b] and Smith[10a] in their syntheses of tedanolide. Aldehyde **52** was designed with protecting groups for the C(15)- and C(17)-alcohols that could be selectively removed prior to C(15)-alcohol oxidation and C(17)-directed epoxidation, respectively, at appropriate junctions of the synthesis following the aldol coupling with **5**.



We sought to construct the C(13)−C(23) framework of aldehyde **52** via the anti-aldol reaction of aldehyde **53** and ketone **54** (eq 2) using conditions developed by Paterson (enol borinate formation with *c*-Hex_2BCl, Et_3N in Et_2O at 0 °C followed by aldehyde addition).[53] This convergent assembly would set the C(16)- and C(17)-stereocenters in a single operation through a transition state believed to minimize electronic repulsion between the oxygen lone pairs of the enol borinate and the benzyl ether.[53b] We were encouraged by literature precedent showing that β-siloxy ethyl ketones participate in the anti-aldol reaction under Paterson's conditions without β-elimination of the siloxy substituent.[12c] Furthermore, after the completion of this work,[8a] Kalesse and co-workers reported the successful anti-aldol coupling of aldehyde **53** with the C(13)-OPMB analogue of ketone **54** under similar conditions.[9a]

Fragments **53** and **54** were synthesized by using easily scalable routes (Scheme 14). The synthesis of **53**[9a,d] commenced with the Wittig olefination of trityl-protected aldehyde **55**, followed by cleavage of the trityl ether under acidic conditions. Swern oxidation of alcohol **56** afforded β,γ-unsaturated aldehyde **57**. The stabilized ylide $Ph_3P{=}C(Me)CO_2Et$ was added directly to the Swern reaction mixture to generate α,β-unsaturated ester **58** in a one-pot oxidation−olefination sequence. Reduction of the ester and subsequent MnO_2 oxidation of the allylic alcohol then provided aldehyde **53**. Ketone **54** was prepared from the DMPM-protected **60**[54] in four synthetic steps. Addition of the lithium enolate of *tert*-butyl acetate to **60** resulted in a β-hydroxy ester that was reduced to a 1,3-diol with $LiAlH_4$. Selective silylation of the primary alcohol and oxidation of the secondary alcohol furnished the requisite ketone **54**.

Our early efforts to unify aldehyde **53** and ketone **54** using Paterson's anti-aldol conditions led to **61** as the major of two diastereomers with 80:20 selectivity (Scheme 15). Literature precedent[9a,12c] suggested that **62** would be the minor product; however, Mosher ester analysis[55] revealed that the C(17)-alcohols of the major and minor aldols both have identical (*S*)-

(51) Loh and co-workers induced a similar cyclization to analyze epoxide stereochemistry in their tedanolide fragment synthesis (ref 12c).

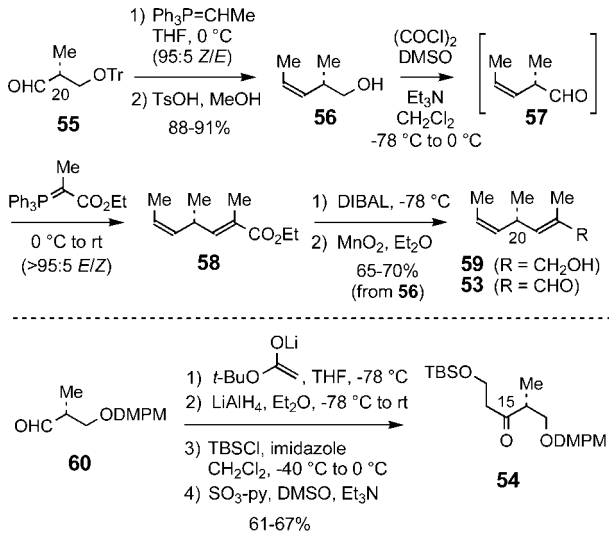
(52) For a review of hydroxy directed epoxidations of allylic alcohols: Adam, W.; Wirth, T. *Acc. Chem. Res.* **1999**, *32*, 703.

(53) (a) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121. Mechanistic discussion: (b) Vulpetti, A.; Bernardi, A.; Gennari, C.; Goodman, J. M.; Paterson, I. *Tetrahedron* **1993**, *49*, 685.

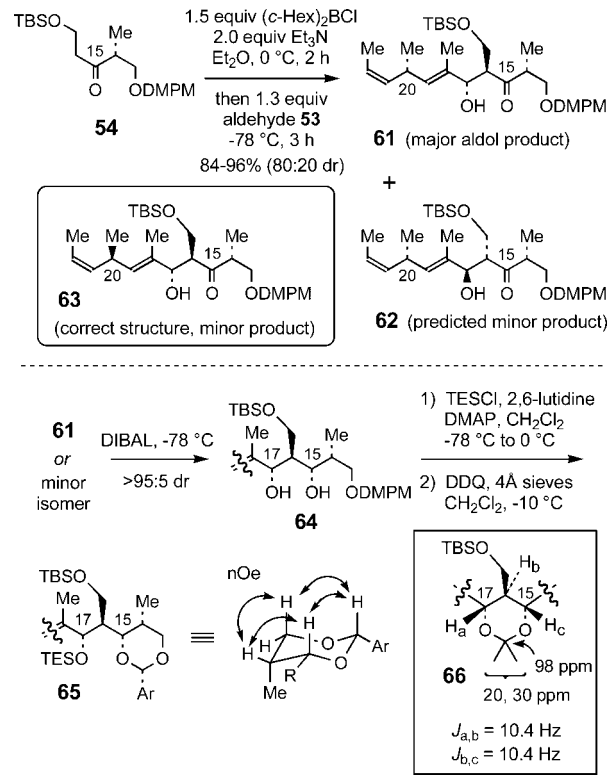
(54) Prepared in analogous fashion to the known PMB-protected aldehyde: Organ, M. G.; Wang, J. *J. Org. Chem.* **2003**, *68*, 5568.

(55) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. For a useful explanation and examples of Mosher ester analysis: (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

Scheme 14. Synthesis of Aldehyde **53** and Ketone **54**

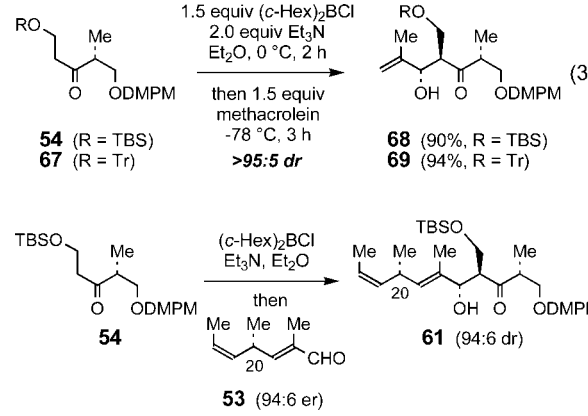


Scheme 15. Aldol Coupling of **53** and **54**



configurations. Independent conversion of the two aldol products to their corresponding benzylidene acetals (of type **65**) and acetonides (of type **66**) revealed, through spectroscopic analysis,[56] that both aldol adducts have identical stereochemistry within the C(14)−C(17) positions; that is, both aldol diastereomers are anti-aldol products with (*S*)-configurations at C(17)-OH.

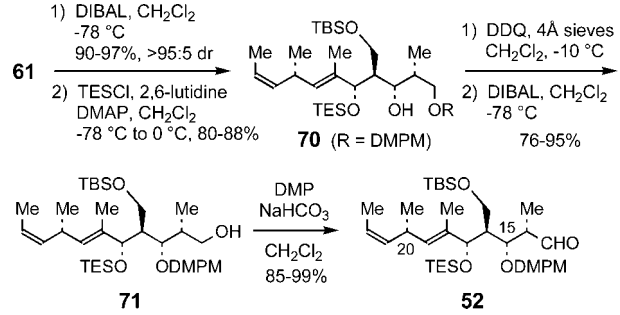
We speculated that **63** (Scheme 15) might be the correct structure of the minor aldol product and that it might arise from epimerization of the bisallylic C(20)-stereocenter during the synthesis of aldehyde **53**. This hypothesis was supported by our observation that only one diastereomer is formed from the aldol coupling of ketones **54** or **67** with methacrolein under identical conditions (eq 3). Furthermore, Mosher ester analysis of the primary alcohol **59** (precursor to aldehyde **53**, Scheme 14) *revealed an 80:20 ratio of diastereomers at the C(20)-bisallylic stereocenter.* We concluded that C(20)-epimerization was occurring during the oxidation−olefination sequence used in the conversion of alcohol **56** (>95:5 enantiomeric ratio (er) as determined by Mosher ester analysis) to α,β-unsaturated ester **58**. After vigorously investigating different oxidation and olefination conditions,[8a] we found that treatment of **56** with Dess−Martin periodinane at 0 °C, followed by ylide addition and olefination at 0 °C, provided ester **58** (and subsequently aldehyde **53**) with 94:6 er. When aldehyde **53** (of 94:6 er) was used in the anti-aldol reaction with **54**, we obtained a 94:6 mixture of aldol diastereomers **61** and **63** (eq 4). It is remarkable that the aldol selectivity perfectly matched the enantiomeric purity of aldehyde **53**. These experiments were also crucial to our ability to bring sufficient material forward en route to tedanolide.



The synthesis of C(13)−C(23) aldehyde **52** from **61** was completed in five steps (Scheme 16). Reduction of the β-hydroxy ketone **61** to the *syn*-1,3-diol with DIBAL and selective silylation[57] of the allylic alcohol provided TES ether **70**. The dimethoxybenzyl ether of **70** was transferred to the secondary alcohol via benzylidene acetal formation, followed by regioselective acetal reductive opening with DIBAL. Finally, oxidation of primary alcohol **71** using the Dess−Martin periodinane provided aldehyde **52** in excellent yield.

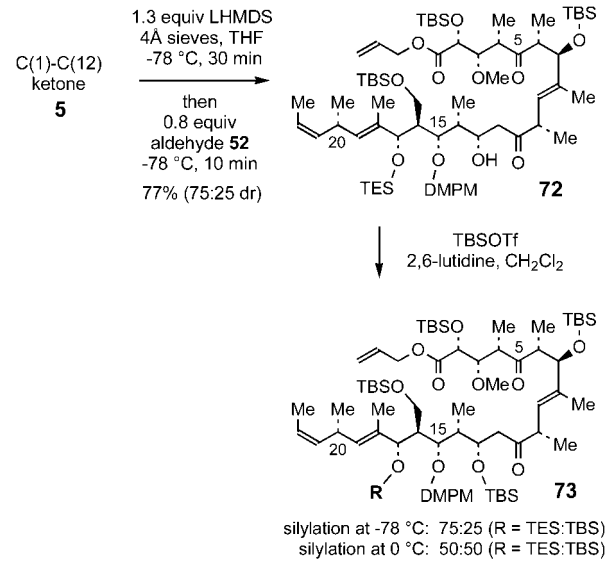
Addition of the lithium enolate of ketone **5** to aldehyde **52** provided Felkin adduct **72** (as determined by NMR analysis[37] and Mosher ester analysis[55]) in 77% yield with 75:25 selectivity (Scheme 17). The diastereomeric ratio for this transformation is similar to that observed previously for the aldol reaction of

Scheme 16. Completion of the Synthesis of Aldehyde **52**



(56) Acetonide analysis: Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res.* **1998**, *31*, 9.

Scheme 17. Aldol Coupling of Ketone **5** and Aldehyde **52**

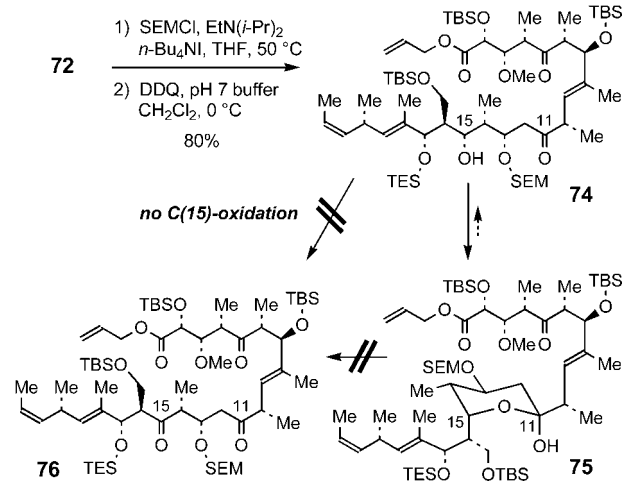


2,3-*syn* aldehyde **49** (vide supra), and variations to the stoichiometry of aldehyde **52** (0.8−1.4 equiv) relative to ketone did not affect the yield (based on limiting reagent) or selectivity. At this point, we looked to protect the C(13)-alcohol of **72** before further elaborating the intermediate to the natural product. Treatment of **72** with TBSOTf and 2,6-lutidine in CH_2Cl_2 led to the product **73** as a mixture of TES and TBS ethers at the C(17)-position. It seemed unlikely that this substitution is due to the direct silylation of the C(17)-OTES oxygen, as the TES:TBS ratio at this position was unchanged when a mixture of products **73**−TES and **73**−TBS was resubjected to the silylation reaction conditions. However, attempts to suppress the scrambling of the silyl ether protecting group at this position were unsuccessful.

Instead, protection of the C(13)-OH of **72** as a SEM ether proceeded without complication in quantitative yield (Scheme 18). At this point, we planned to convert the C(15)-dimethoxybenzyl ether to the C(15)-ketone via cleavage of the DMPM group and subsequent oxidation. Treatment of SEM-protected **72** with DDQ liberated the C(15)-(*S*)-OH of **74**; however, hemiketal **75** was observed as the exclusive product by spectroscopic analysis. Furthermore, efforts to intercept the hydroxy ketone isomer **74** with oxidants (e.g., DMP, SO_3−pyridine in DMSO) were unsuccessful, and we were unable to obtain the desired C(15)-ketone **76**.

Our next course of action was to form the macrolactone prior to C(15)-oxidation (Scheme 19). We postulated that conformational constraints imposed by the macrocycle might destabilize the hemiketal or even disfavor hemiketal formation from the hydroxy ketone. Therefore, the C(13)-alcohol of aldol adduct **72** was protected as a SEM ether, and the seco-acid was liberated via stepwise cleavage of the primary TBS ether (along with the C(17)-TES ether[58]) to provide **77**, followed by removal of the allyl ester. Macrolactonization of this seco-acid was effected at room temperature using the Yonemitsu modification of the Yamaguchi protocol.[39] The cyclization was completely selective for the primary alcohol (no reaction at the secondary C(17)-OH was observed),[59] and the macrolactone was obtained in 32% overall yield from **72** (four steps). Finally, the C(17)-OH was protected as a SEM ether to provide **78**.

Scheme 18. Attempted C(15)-Oxidation of Hemiketal **75**



Treatment of **78** with DDQ liberated the C(15)-alcohol. *Spectroscopic analysis revealed that **79** exists as the open-chain hydroxy ketone, and we did not detect the hemiketal isomer*. We were gratified that treatment of **79** with Dess−Martin periodinane afforded the C(11,15)-dione **80** in 71% yield over two steps from DMPM ether **78**. The synthesis of (+)-tedanolide (**1**) was then completed in three steps. Removal of the two SEM ethers was accomplished by using $MgBr_2$ and EtSH in Et_2O[60] (as previously demonstrated by Smith[10a]). C(17)-Hydroxyl-directed epoxidation of the C(18)−C(19) olefin with *m*-CPBA[12c] gave a single epoxide diastereomer in 54% yield. Finally, global desilylation of the penultimate intermediate with Et_3N−buffered Et_3N−3HF[46] provided synthetic (+)-tedanolide. The spectroscopic data (^1H NMR, ^{13}C NMR, IR, optical rotation, HRMS) from our synthetic tedanolide were in excellent agreement with data published for an authentic sample,[1] as well as with data reported by Kalesse[9a,b] and Smith[10a] for synthetic tedanolide.

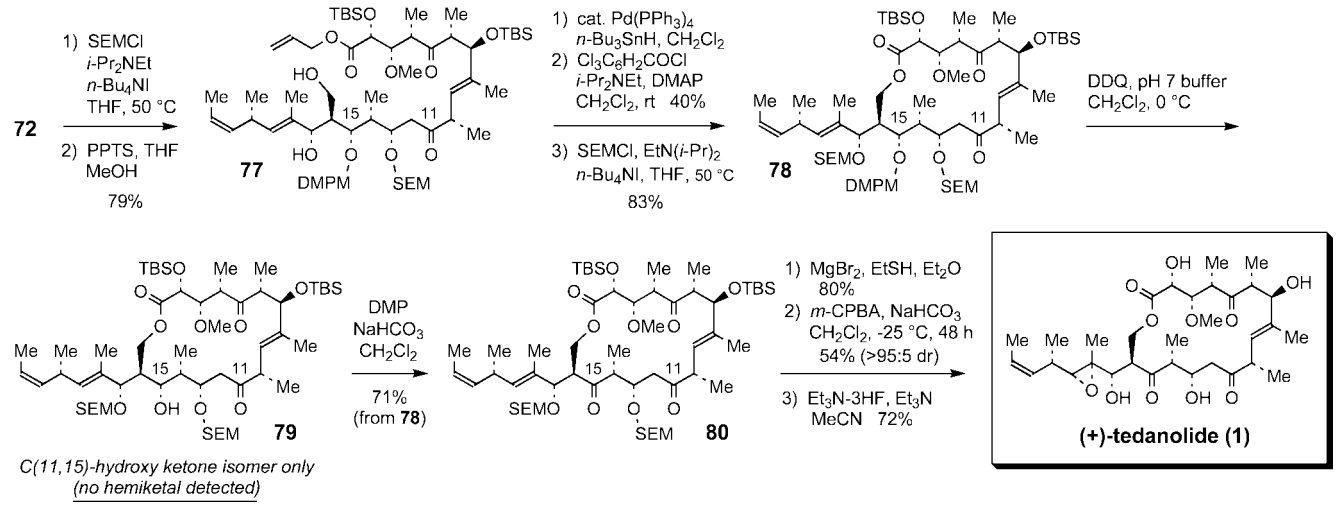
Summary

Convergent, stereocontrolled total syntheses of (+)-tedanolide and (+)-13-deoxytedanolide have been accomplished. A key transformation for the assembly of both natural products is the aldol coupling of the C(1)−C(12) methyl ketone **5** with a C(13)−C(23) aldehyde partner. Aldehyde **6**, with 2,3-*anti* stereochemistry, was initially employed, and its aldol reaction with the lithium enolate generated from **5** proceeded with >95:5 selectivity for the Felkin aldol **4**. However, it proved impossible to elaborate **4** to tedanolide owing to the remarkable stability of hemiketals **33b** and **34** and especially their lack of reactivity toward oxidants. Deoxygenation of hemiketal **33a** provided the 13-deoxy hemiketal **36**, which was successfully oxidized to the C(11,15)-diketone **38** by using the Dess−Martin periodinane reagent. The later intermediate was smoothly elaborated to (+)-13-deoxytedanolide.

Recognition that 13-deoxy hemiketal **36** could be oxidized by way of its hydroxy ketone tautomer **37** suggested that the remarkable stability and lack of reactivity of hemiketals **33b**

(57) Hicks, J. D.; Huh, C. W.; Legg, A. D.; Roush, W. R. *Org. Lett.* **2007**, *9*, 5621.
(58) We were unable to remove the primary TBS ether without also cleaving the TES ether.
(59) Similar selectivity was also observed by Smith and co-workers in their syntheses of tedanolide and 13-deoxytedanolide (refs 10a, 10c, 10d).
(60) Kim, S.; Kee, I. S.; Park, Y. H.; Park, J. H. *Synlett* **1991**, 183.

Scheme 19. Completion of the Total Synthesis of (+)-Tedanolide (**1**)



and **34** might be due to the equatorial conformation of ring substituents in **33b** and **44**, which stabilizes the hemiketal relative to the acyclic hydroxy ketone isomer. This then led to the decision to redesign the synthesis of tedanolide to proceed by way of the stereochemically inverted C(15)-(*S*)-alcohol intermediates, since hemiketal intermediates with C(15)-(*S*) series would be destabilized by having at least one large substituent in an axial position (Scheme 10). However, use of C(15)-(*S*)-configured intermediates also required that the side-chain epoxide unit be introduced very late in the synthesis, owing to the ease with which C(15)-(*S*)-OH cyclized onto the epoxide in intermediate **50** (Scheme 13).

Therefore, 2,3-*syn* aldehyde **52** was employed in the aldol coupling with methyl ketone **5** which gave the Felkin aldol **72** with 75:25 selectivity. Elaboration of Felkin aldol **72** to macrolactone **78** set the stage for removal of the C(15)-DMPM ether and oxidation of the C(15)-OH to the required ketone in **80**. Fortunately, the hemiketal that plagued the unsuccessful tedanolide syntheses via C(15)-(*R*)-configured intermediates **33b** and **34** was not observed for the C(15)-(*S*)-hydroxy ketone **79** derived from **78**. Intermediate **80** was smoothly elaborated to tedanolide via deprotection of C(17)-OH, which was used to direct the epoxidation of the adjacent C(18,19)-olefin. Final, global cleavage of all silyl ethers then completed the total synthesis of (+)-tedanolide.

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Supporting Information Available: Experimental procedures, spectroscopic data, and spectra for selected intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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