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A Divergent Approach to the Myriaporones and Tedanolide: Enantioselective Preparation of the Common Intermediate[1]

Richard E. Taylor,* Jeffrey P. Ciavarri, and Brian R. Hearn

Department of Chemistry and Biochemistry,
251 Nieuwland Science Hall
University of Notre Dame, Notre Dame, IN 46556

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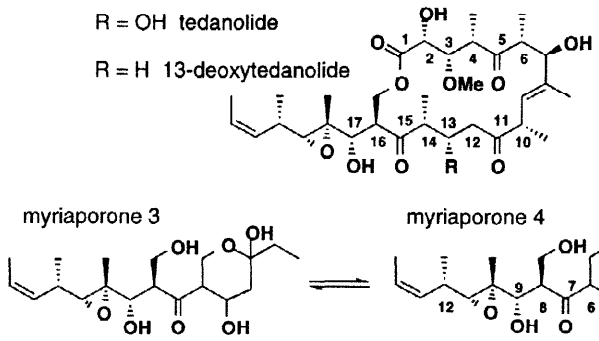
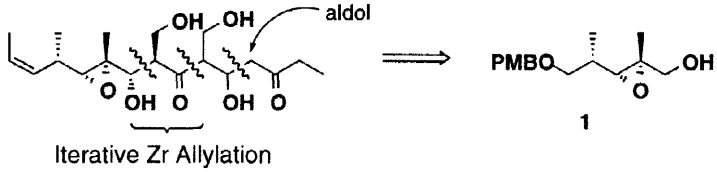
Abstract: The tedanolide and myriaporone classes of natural products represent interesting targets for synthesis because of their structural similarity and biological activity. The asymmetric preparation of a potential common intermediate in the total synthesis of each of these targets is presented. The key step, a Zr-mediated allylation, allows for the efficient preparation of the hydroxypropionate structural unit.



Tedanolide is a potent cytotoxic macrolide isolated from the Caribbean sponge *Tedania ignis*.[2] In addition, cell-flow cytofluorometry analysis revealed that tedanolide causes accumulation of cells at the S phase of the cell cycle. More recently, Fusetani and coworkers reported the isolation of 13-deoxytedanolide from the marine sponge *Mycale adhaerens*.[3] This related molecule also showed extraordinary biological activity exhibiting an IC_{50} of 94 pg/mL against P388 murine leukemia cell lines. Surprisingly, despite their interesting biological activity and structural novelty, only a few publications to date have focused on synthetic efforts towards the tedanolide class of natural products.[4] Our interest in tedanolide began when we learned of the isolation of a potential analogue, myriaporone 4.[5] In 1995, Rinehart reported the isolation of this interesting compound which, in addition to its structural similarity to the C10-C23 of tedanolide, had an IC_{50} = 100 ng/mL in L-1210 cells. As the first step in the elucidation of the molecular basis of its biological activity, we have begun synthetic studies toward the development of a practical total synthesis of myriaporone 4 which would also set the foundation for a synthesis of tedanolide.

Enantiomerically pure epoxide **1** was chosen as an initial goal. Figure 1 outlines the connectivity analysis which guides our synthetic plan for myriaporone 4. Two successive aldehyde allylation reactions should allow the incorporation and stereochemical control necessary for the preparation of the hydroxypropionate portion (C13-C17). The final carbon-carbon bond-forming step (C12-C13) will be accomplished through a kinetic enolate aldol reaction.

Figure 1. Connectivity Analysis for Myriaporone 4



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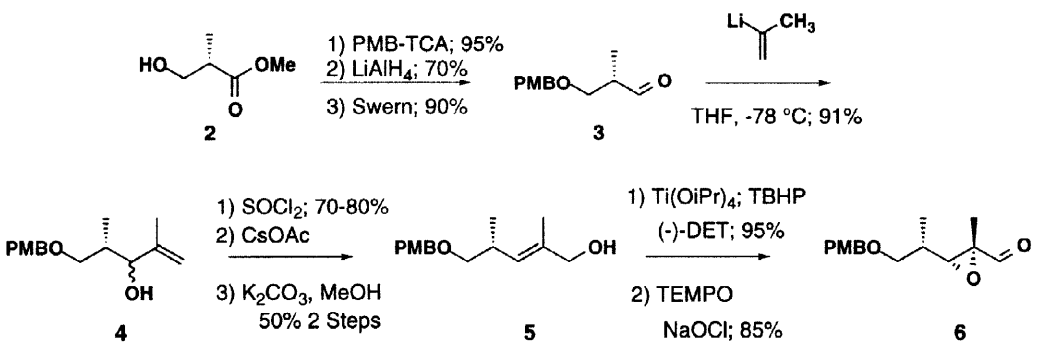
The enantiomer of chiral epoxide **1** has been synthesized previously by Meyers et al.[6] We have successfully developed two alternative approaches each starting from the identical chiral hydroxyester **2**. Our initial approach is outlined in Scheme I. Commercially available hydroxyester **2**, a common chiral starting material, was protected as a *p*-methoxybenzyl ether with PMB-trichloroacetimidate under standard conditions. After a reduction-oxidation sequence to furnish the aldehyde **3**, condensation with 2-lithiopropene provided the allylic alcohol **4** as a mixture of diastereomers in 91% yield. The two stereoisomers were then subjected to thionyl chloride in methylene chloride at -78 °C to provide selectively the rearranged primary allylic chloride.[7] Performing the reaction at higher temperature can produce substantial amounts of the secondary allylic chloride from S_Ni substitution. Displacement of the chloride with cesium acetate followed by saponification provided the desired epoxidation precursor **5** in moderate yield. ^{1}H NMR of the crude reaction mixtures suggests that the reaction was stereoselective providing exclusively the *E*-trisubstituted olefin (confirmed by NOE experiments). An alternative sequence from aldehyde **3** has allowed for the preparation of alcohol **5** with greater throughput. A Wittig reaction between aldehyde **3** and (carboethoxyethylidene)triphenylphosphorane provided the homologated ester in good yield with excellent stereocontrol. Reduction of the ester was then accomplished with DIBAL to provide the allylic alcohol **5** necessary to direct a Sharpless asymmetric epoxidation reaction.[8] Exposure of alcohol **5** to $Ti(OiPr)_4$/TBHP and (-)-diethyl tartrate provided the desired epoxide **3** in good yield. The diastereoselectivity of the process was >20:1 by ^{1}H NMR. In contrast, titanium or vanadium directed epoxidation without tartrate was stereorandom, and mCPBA provided exclusively the undesired diastereomer.

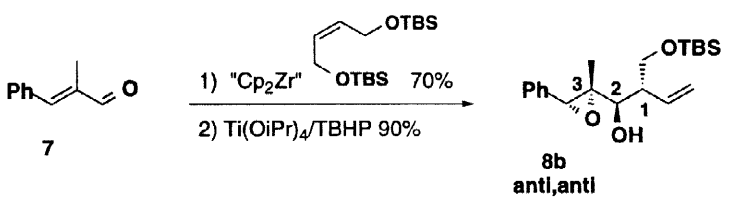
Scheme I



At this point in the sequence it was desired to have the α,β-epoxyaldehyde control the relative stereochemistry of a zirconium-mediated allylation to form the repeating hydroxypropionate functionality. This type of structural unit is actually quite difficult to synthesize since enolates with β-alkoxy groups are prone to elimination.[9] Clark has recently reported the successful allylation of benzaldehyde to provide the hydroxypropionate unit with almost exclusive formation of *anti*-stereochemistry.[10] The preference for *anti*-stereochemistry can be rationalized by proposing an *E*-allyl zirconium species and a Zimmerman-Traxler cyclic transition state.[11]

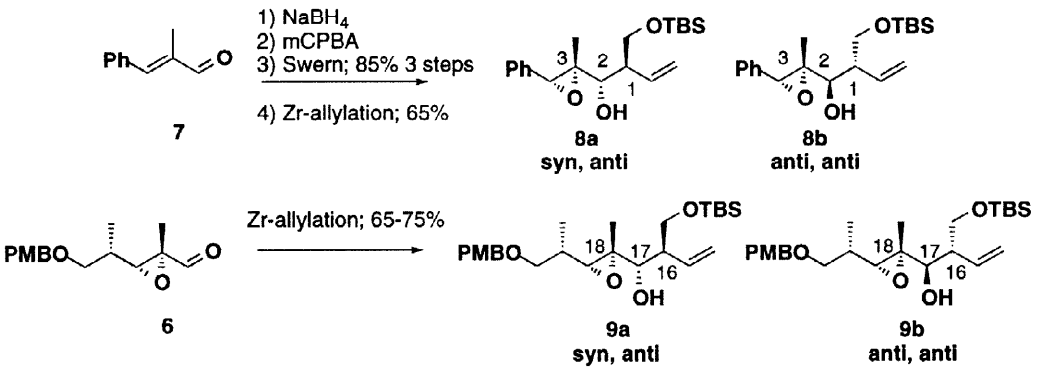
Initial studies were performed on a model system as shown in Scheme II. To assist in the stereochemical assignments of these addition products the first reaction we attempted was the zirconium-mediated allylation of aldehyde **7**. This reaction proceeded in good yield to provide the desired *anti*-hydroxypropionate addition product which after $Ti(OiPr)_4$/TBHP epoxidation provided exclusive formation of the *anti-anti* diastereomer **8b.**

Scheme II



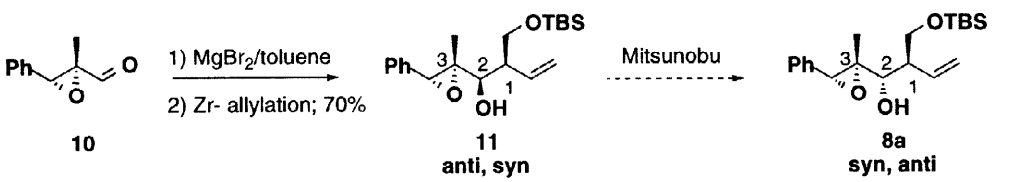
With full characterization of the undesired *anti-anti*-**8b** in hand we next turned to the Zr-mediated allylation of the racemic epoxyaldehyde derived from commercially available aldehyde **7**. The aldehyde was reduced with $NaBH_4$ and after isolation the crude material was subjected to peracid epoxidation. The purified epoxyalcohol was then oxidized to the racemic aldehyde with Swern conditions. Exposure of this model system to the identical Zr-allylation conditions provided a ~1:1 mixture of desired diastereomer *syn-anti*-**8a** and the previously identified **8b**, Scheme III. A similar diastereorandom allylation resulted from the Zr-mediated allylation of the aldehyde **6**. In each case the combined yield of the allylation products were 65-75%. Although far from ideal, this sequence has already provided substantial quantities of the myriaporone 4 intermediate **9a** for further synthetic studies toward tedanolide and the myriaporone class of natural products.

Scheme III



We have been able to rationalize the lack of stereocontrol in the allylation of epoxyaldehyde **6** by the presence of the α-methyl substituent which hinders the approach of the nucleophile in both the chelated and Felkin-Anh transition states. Therefore, we began exploring modifications of the reaction conditions with hopes of influencing the stereoselectivity. In fact we have recently found an interesting effect of external Lewis acids. When epoxyaldehyde model system was pre-incubated with magnesium bromide and the reaction carried out in a non-polar solvent such as toluene a single diastereomeric addition product was isolated, the anti,syn-hydroxypropionate **11** in 70% yield, Scheme IV. The interesting change in preference to *syn*-1,2 stereochemistry can be rationalized by proposing an acyclic transition state where the presence of the external Lewis acid obviates the need for internal Zr-activation of the aldehyde.

Scheme IV



This interesting result appears to be general. We have observed a similar preference to *syn*-hydroxypropionate formation with a number of simple aldehydes.[14] However, treatment of aldehyde **6** with the modified conditions again provided a mixture of hydroxypropionate diastereomers. The lack of stereoselectivity (compared to model system) may be attributed to competing chelation with the distal PMB-ether. Alternative protecting groups as well as Lewis acids are currently been investigated to overcome this lack of stereoselectivity.

Herein we have reported an efficient route to the common intermediate in our synthetic approach to tedanolide and myriaporone 4.[15] The route is highlighted by a thionyl chloride based rearrangement to control trisubstituted olefin geometry and a zirconium-mediated allylation to prepare the hydroxypropionate structural unit. The generality of each these interesting reactions is currently under investigation. Conversion of the intermediate **9a** to myriaporone 4 and ultimately tedanolide is also being pursued and results will be reported in due course.

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REFERENCES AND NOTES

1. Presented at the 35th National Organic Chemistry Symposium, June 22-26, 1997, Trinity University San Antonio, TX; abstract No. M71.
2. a) Schimtz, F. J.; Gunasekera, S. P.; Yalamanchili, G.; Hossain, M. B.; van der Helm, D. *J. Am. Chem. Soc.* **1984**, *106*, 7251-7252. b) O'Hagan, D. *Nat. Prod. Reports* **1993**, 593-625.
3. Fusetani, N.; Sugawasara, T.; Matsunaga, S. *J. Org. Chem.* **1991**, *56*, 4971-4973.
4. a) Matsushima, T.; Horita, K.; Nakajima, N.; Yonemitsu, O. *Tetrahedron Lett.* **1996**, *37*, 385-388. b) Matsushima, T.; Mori, M.; Nakajima, N.; Maeda, H.; Uenishi, J.; Yonemitsu, O. *Chem. Pharm. Bull.*. **1998**, *46*, 1335-1336. C) Liu, J.-F.; Abiko, A.; Pei, Z.; Buske, D.; Masamune, S. *Tetrahedron Lett.* **1998**, *39*, 1873-1876.
5. Rinehart, K. L.; Tachibana, K. *J. Nat. Prod.* **1995**, *58*, 344-358.
6. a) Meyers, A. I.; Hudspeth, J. P. *Tetrahedron Lett.* **1981**, *22*, 3925-3928. b) Meyers, A. I.; Babiak, K. A.; Campbell, A. L.; Comins, D. L.; Fleming, M. P.; Henning, R.; Heuschmann, M.; Hudspeth, J. P.; Kane, J. M.; Reider, P. J.; Roland, D. M.; Shimizu, K.; Tomioka, K.; Walkup, R. D. *J. Am. Chem. Soc.* **1983**, *105*, 5015-5024.
7. Caserio, F. F.; Dennis, G. E.; DeWolfe, R. H.; Young, W.G *J. Am . Chem. Soc.* **1955**, *77*, 4182-4183. From a mechanistic perspective, this reaction has been restudied on numerous occasions. However, to the best of our knowledge only Johnson has exploited the stereoselectivity of this interesting reaction from a synthetic perspective; Johnson, W. S.; Li, T.-T.; Harbert, C. A.; Bartlett, W. R.; Herrin, T. R.; Staskun, B.; Rich, D. H. *J. Am . Chem. Soc.* **1970**, *92*, 4461-4463.
8. Katsuki, T.; Sharpless, K. B. *J. Am . Chem. Soc.* **1980**, *102*, 5974-5976.
9. Masamune, S.; Kaibo, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521-5523.
10. Clark, A. J.; Kasujee, I.; Peacock, J. L. *Tetrahedron Lett.* **1995**, *36*, 7137-7140.
11. Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920-1922.
12. Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.
13. Mitsunobu, O. *Synthesis.* **1980**, 1-27.
14. Hearn, B. R.; University of Notre Dame, unpublished results.
15. Satisfactory spectral and HRMS data has been obtained on all new compounds.