ORGANIC LETTERS

2002
Vol. 4, No. 17
2953−2955

A Divergent Approach to the Myriaporones and Tedanolide: Completion of the Carbon Skeleton of Myriaporone 1

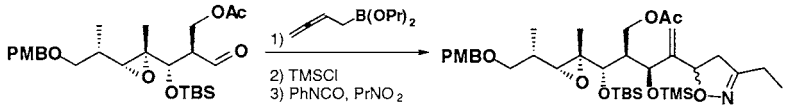
Richard E. Taylor,* Brian R. Hearn, and Jeffrey P. Ciavarri

Department of Chemistry and Biochemistry and the Walther Cancer Center, University of Notre Dame, 251 Nieuwland Science Hall, Notre Dame, Indiana 46556-5670

taylor.61@nd.edu

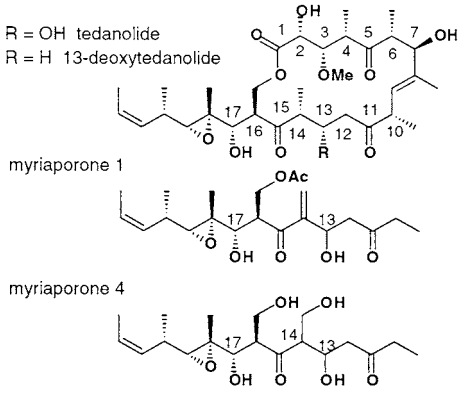
Received June 12, 2002

ABSTRACT



A linear but concise synthetic approach toward the structurally related natural products myriaporone and tedanolide is reported. The route is highlighted by a stereoselective homoallenylboration and a regio- and chemoselective nitrile oxide cycloaddition. Installation of the (*Z*)-olefin completed the carbon skeleton of myriaporone 1.

Natural products can serve as valuable mechanistic tools in unraveling the role of aberrant cellular signal transduction in cancer. Tedanolide, a polyketide macrolide, was isolated from the Caribbean sponge *Tedania ignis* and found to be cytotoxic to KB and PS tumor cell lines in the picomolar range.[1] More recently, Fusetani reported 13-deoxytedanolide that also showed significant biological activity.[2] In neither case was sufficient material obtained to perform experiments capable of determining their mode of action at the molecular level. The combination of their interesting structure and potent biological activity has made them a target of the synthetic community.[3] Our interest in tedanolide began when we learned of the isolation of the structurally related myriaporone natural products. In 1995, Rinehart reported the isolation of these interesting compounds that, in addition to their structural similarity to the C10−C23 region of tedanolide, had an $IC_{50} = 100$ ng/mL in L-1210 cells.[4] Synthetic and biological studies of the simpler myriaporones may provide insight into the mode of action as well as provide a foundation for the total synthesis of tedanolide. Herein, we report the second installment of our efforts and the preparation of the carbon skeleton of myriaporone 1.

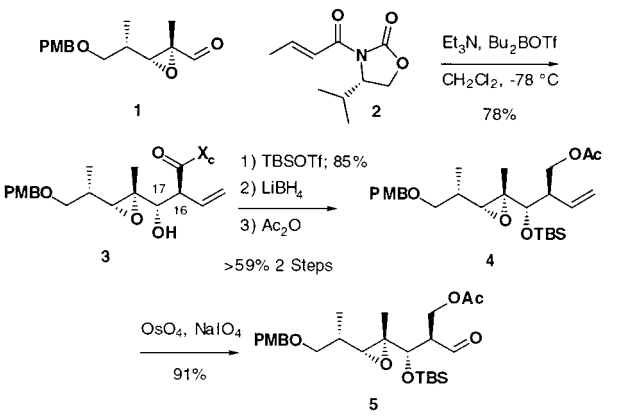


Previously, we reported the synthesis of the common intermediate to these two classes of natural products exploiting a novel zirconium allylation of aldehyde **1** to generate the C16,C17 anti stereochemical relationship.[5] However, with this reaction we were unable to find conditions that provided

10.1021/ol026356s CCC: $22.00 © 2002 American Chemical Society
Published on Web 08/02/2002

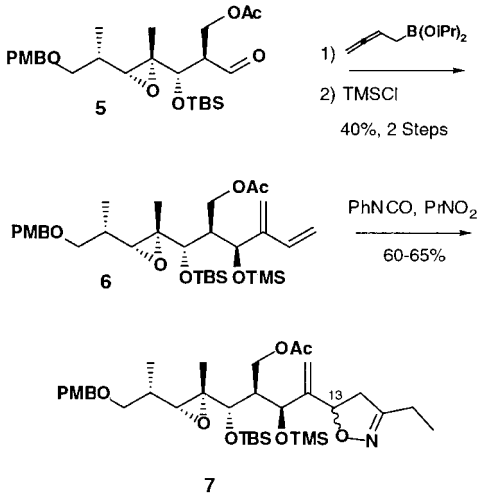
both high aldehyde facial selectivity and the desired anti relative stereochemistry. It therefore became necessary to use an external auxiliary, Evans' oxazolidinone **2**, which provided the desired aldol adduct in high yield as shown in Scheme 1.[6] After protection of the C17-hydroxyl as a TBS ether, the auxiliary was reductively removed and the resulting primary alcohol was protected as an acetate as in the target, myriaporone 1. The common synthetic intermediate to both classes of natural products was then completed by oxidative cleavage of the terminal olefin.

Scheme 1



The next stage of the synthetic route required generation of the C14−C15 bond through nucleophilic addition to aldehyde **5**. Facial selectivity was not essential here since the resulting C15 secondary alcohol would ultimately be oxidized to a ketone. Initially, we explored Nozaki−Hiyama−Kishi coupling reactions with highly functionalized vinyl halides representing the right-hand portion of the myriaporone 1 framework.[7] However, we found that this strategy led mostly to eliminated and/or epimerized products due to the hindered nature of the aldehyde. Scaling back our goals, we found that homoallenylboration[8] proceeded in moderate yield to provide, after protection as a silyl ether, diene **6**. A single diastereomer was isolated ,which we have tentatively assigned as shown in Scheme 2. Much to our delight, this compound underwent a chemoselective and regioselective nitrile oxide cycloaddition to provide isoxazoline **7**.[9] The masked β-hydroxyketone was obtained as a 3:1 mixture of C13 diastereomers. This strategy was conceived in order to provide both stereoisomeric alcohols at C13, a stereogenic center that was not unambiguously assigned in the original report.

Scheme 2



With a fully protected intermediate **7** in hand, we turned our attention toward the appropriate timing of the oxidation of C15 and reductive cleavage of the isoxazoline. Exposure of isoxazoline **7** to Raney nickel hydrogenation in the presence of boric acid conditions cleanly provided the corresponding β-hydroxyketone **8**, Scheme 3. The diastereomeric alcohols were easily separated at this stage by flash chromatography. The reductive hydrolysis proceeded in nearly quantitative yield despite initial concerns about the acid-sensitive nature of the trisubstituted epoxide. The C15 TMS ether was then selectively removed by treatment with TBAF at low temperatures. This was followed by selective protection of the C13 hydroxyl. Dess−Martin oxidation[10] then provided the α,β-unsaturated ketone in good yield.

The timing of these two functionalizations was critical. Attempted reductive cleavage of the isoxazoline in the presence of a C15 α,β-unsaturated carbonyl led to reduction

(1) Schmitz, F. J.; Gunasekera, S. P.; Yalamanchili, G.; Hossain, M. B.; van der Helm, D. *J. Am. Chem. Soc.* **1984**, *106*, 7251.

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

(3) (a) Matsushima, T.; Horita, K.; Nakajima, N.; Yonemitsu, O. *Tetrahedron Lett.* **1996**, *37*, 385. (b) Matsushima, T.; Mori, M.; Nakajima, N.; Maeda, H.; Uenishi, J.; Yonemitsu, O. *Chem. Pharm. Bull.* **1998**, *46*, 1335. (c) Liu, J. F.; Abiko, A.; Pei, Z.-H.; Buske, D. C.; Masamune, S. *Tetrahedron Lett.* **1998**, *39*, 1873. (d) Matsushima, T.; Mori, M.; Zheng, B. Z.; Maeda, H.; Nakajima, N.; Uenishi, J.; Yonemitsu, O. *Chem. Pharm. Bull.* **1999**, *47*, 308. (e) Zheng, B. Z.; Maeda, H.; Mori, M.; Kusaka, S.; Yonemitsu, O.; Matsushima, T.; Nakajima, N.; Uenishi, J. *Chem. Pharm. Bull.* **1999**, *47*, 1288. (f) Matsushima, T.; Zheng, B. Z.; Maeda, H.; Nakajima, N.; Uenishi, J.; Yonemitsu, O. *Synlett* **1999**, 780. (g) Roush, W. R.; Lane, G. C. *Org. Lett.* **1999**, *1*, 95. (h) Smith, A. B., Lodise, S. A. *Org. Lett.* **1999**, *1*, 1249. (i) Jung, M. E.; Marquez, R. *Org. Lett.* **2000**, *2*, 1669. (j) Matsushima, T.; Nakajima, N.; Zheng, B.-Z.; Yonemitsu, O. *Chem. Pharm. Bull.* **2000**, *48*, 855. (k) Zheng, B.-Z.; Yamauchi, M.; Dei, H.; Kusaka, S.; Matsui, K.; Yonemitsu, O. *Tetrahedron Lett.* **2000**, *41*, 6441. (l) Zheng, B.-Z.; Yamauchi, M.; Dei, H.; Yonemitsu, O. *Chem. Pharm. Bull.* **2000**, *48*, 1761. (m) Loh, T.-P.; Feng, L.-C. *Tetrahedron Lett.* **2001**, *42*, 3223. (n) Matsui, K.; Zheng, B.-Z.; Kusaka, S.; Kuroda, M.; Yoshimoto, K.; Yamada, H.; Yonemitsu, O. *Eur. J. Org. Chem.* **2001**, 3615.

(4) Rinehardt, K. L.; Tachibana, K. *J. Nat. Prod.* **1995**, *58*, 344.

(5) Taylor, R. E.; Ciavarri, J. P.; Hearn, B. R. *Tetrahedron Lett.* **1998**, *39*, 9361.

(6) Evans, D. A.; Sjorgren, E. B.; Bartoli, J.; Dow, R. L. *Tetrahedron Lett.* **1986**, *27*, 4957.

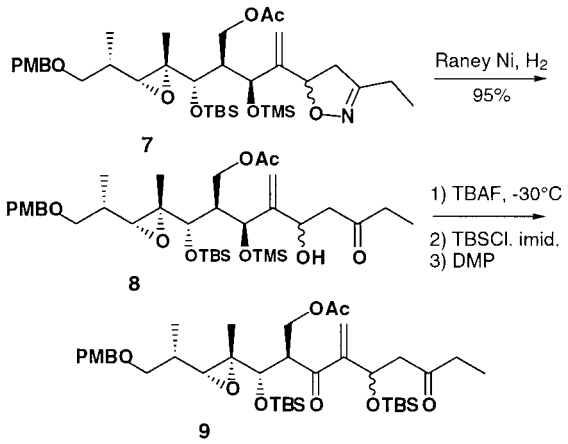
(7) Taylor, R. E; Ciavarri, J. P. *Org. Lett.* **1999**, *1*, 467.

(8) Soundararajan, R.; Li, G.; Brown, H. C. *J. Org. Chem.* **1996**, *61*, 100.

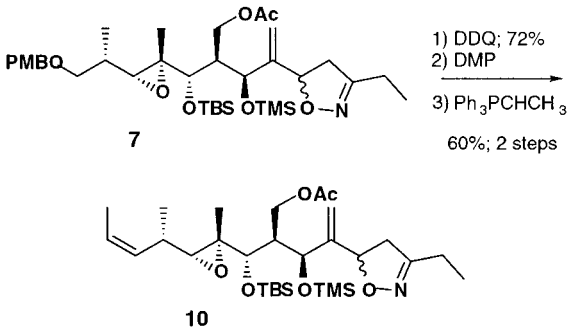
(9) For recent work exploiting nitrile oxide cycloaddition as an alternative to aldol chemistry, see: (a) Bode, J. W.; Carreira, E. M. *J. Org. Chem.* **2001**, *66*, 6410. (b) Bode, J. W.; Fraefel, N.; Muri, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2001**, *40* , 2082. (c) McGarvey, G. J.; Mathys, J. A.; Wilson, K. J. *Tetrahedron Lett.* **2000**, *41*, 6011.

(10) Dess, D. B.; Martin. J. C. *J. Org. Chem.* **1983**, *48*, 4155.

Scheme 3



Scheme 4



of the 1,1-disubstituted olefin. Attempted deprotection of the silyl ethers of advanced intermediate **9** led to decomposition. The sensitivity of these compounds was presumably due to the reactivity of the C15 carbonyl and the epoxide since the C17 TBS ether could be deprotected before oxidation at C15. Alternative strategies toward exposure of this key functionality are currently being pursued.

Frustrated by the instability of the intermediates along this sequence, we then chose to investigate the installation of the C21−C22 (*Z*)-olefin and completion of the carbon skeleton of myriaporone 1, Scheme 4. Oxidative deprotection of the PMB group was accomplished with DDQ, and the resulting primary alcohol was oxidized with Dess−Martin periodinane. The aldehyde was then reacted with an in situ-generated Wittig reagent from ethyltriphenyl phosphonium bromide and potassium *t*-butoxide. The desired (*Z*)-olefin **10** was isolated in good yield. Base-induced fragmentation of the epoxide to form the corresponding α,*β*-unsaturated aldehyde was observed only if the reaction temperature was not carefully monitored.

In summary, we have developed a synthetic route that provides access to structures with the complete carbon skeleton of the myriaporone class of natural products. Despite the inability to provide the natural product, biological evaluation of key intermediates available from this route may provide insight into the myriaporone pharmacophore and allow an attempted isolation of the biological receptor through affinity chromatographic techniques. Efforts to reorder the installation of sensitive functionalities are currently underway, and results along these lines will be reported in due course.

Acknowledgment. Dr. Mostofa Hena is thanked for assistance with the homoallenylboration. Kristen Fleming is thanked for assistance with the Wittig olefination. Support was provided by the National Cancer Institute/National Institutes of Health (Grant CA 81128). J.P.C. and B.R.H. thank the University of Notre Dame for support through J. Peter Grace Prize Fellowships. R.E.T. acknowledges support from Eli Lilly through the Lilly Grantee award program.

Supporting Information Available: Experimental and characterization data for the preparation of **6**−**8** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026356S