ORGANIC LETTERS

2007
Vol. 9, No. 8
1453−1456

An Efficient and Stereoselective Synthesis of the Monomeric Counterpart of Marinomycin A

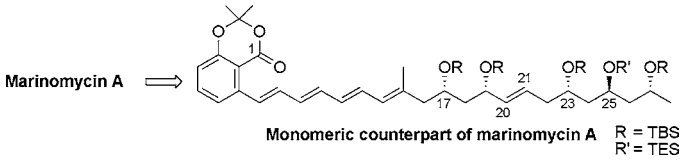
Dominique Amans, Véronique Bellosta, and Janine Cossy*

Laboratoire de Chimie Organique associé au CNRS, ESPCI, 10 rue Vauquelin, 75231 Paris Cedex 05, France

janine.cossy@espci.fr

Received January 30, 2007

ABSTRACT



The monomeric counterpart of marinomycin A, an antitumor–antibiotic marine natural product, was synthesized efficiently in 11 steps from the commercially available ethyl (*R*)-(–)-3-hydroxybutyrate. The strategy was highlighted by a crucial regio- and stereoselective cross-metathesis to form the C20–C21 double bond, enantioselective allyltitanations to control the configuration of the C17, C23, and C25 stereogenic centers, and a stereocontrolled construction of the tetraene moiety based on an original Horner–Wadsworth–Emmons olefination followed by a Pd-catalyzed cross-coupling.

Marinomycin A is a polyene macrodiolide which has been recently isolated by Fenical et al. from the saline culture of a new group of marine actinomycetes, named *Marinispora* strain CNQ-140, cultured from a sediment collected from the bottom of the ocean offshore of La Jolla, California (USA).[1] This novel macrodiolide exhibits significant antibiotic activity against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*. Along with these unusual biological properties, this naturally occurring molecule also demonstrated impressive and selective cancer cell cytotoxicities against 6 of the 8 melanoma cell lines of the National Cancer Institutes's 60 cancer cell line panel.[1] Marinomycin A is a 44-membered C_2-symmetrical dimeric macrodiolide constituted by a tetraene moiety conjugated with an aromatic unit derived from 2-hydroxybenzoic acid and connected to a pentahydroxylated polyketide chain. Only one total synthesis of marinomycin A has been reported recently by Nicolaou et al.[2] Challenged by the unique molecular architecture of this marine natural product and attracted by its impressive biological properties, we embarked on the synthesis of marinomycin A. In this context, we wish to report an efficient and highly convergent synthesis of the monomeric counterpart of marinomycin A, mainly based on the use of a stereoselective cross-metathesis of functionalized alkenes to construct the C20−C21 double bond of the polyol chain, enantioselective allyltitanations to control the configuration of three of the five stereogenic centers, and a Pd-catalyzed cross-coupling reaction to achieve the synthesis of the tetraene moiety.

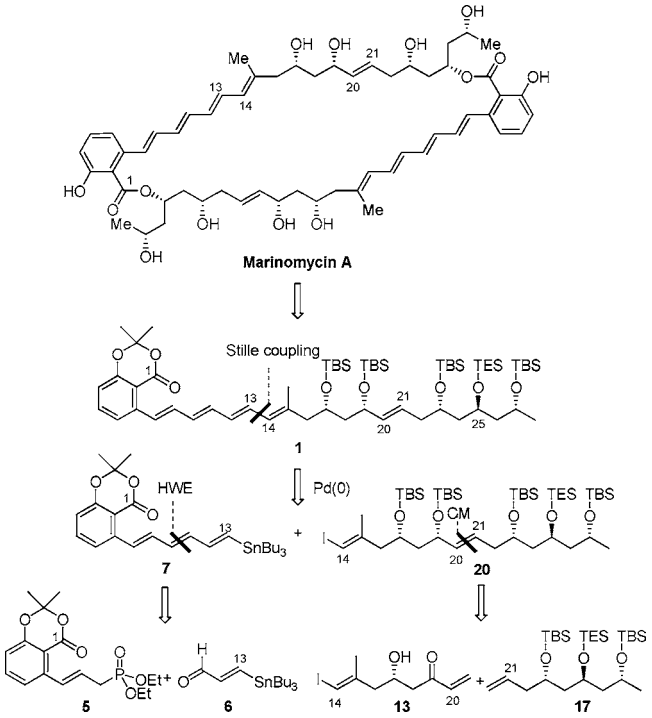
The retrosynthetic analysis of marinomycin A is depicted in Scheme 1. It relied on the synthesis of its monomer, compound **1**, which could be obtained by performing a pallado-catalyzed Stille cross-coupling reaction between alkenyl iodide **20** and the trienic vinyl stannane **7**, which in turn would result from a Horner−Wadsworth−Emmons olefination between the arylphosphonate **5** and the α,β-unsaturated aldehyde **6**. A stereo- and chemoselective cross-metathesis between vinyl ketone **13** and the trihydroxylated

(1) Kwon, H. C.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *J. Am. Chem. Soc.* **2006**, *128*, 1622−1632.

(2) (a) Nicolaou, K. C.; Nold, A. L.; Milburn, R. R.; Schindler, C. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 6527−6532. (b) Nicolaou, K. C.; Nold, A. L.; Milburn, R. R.; Schindler, C. S.; Cole, K. P.; Yamaguchi, J. *J. Am. Chem. Soc.* **2007**, *129*, 1760−1768.

10.1021/ol070240k CCC: $37.00
Published on Web 03/14/2007

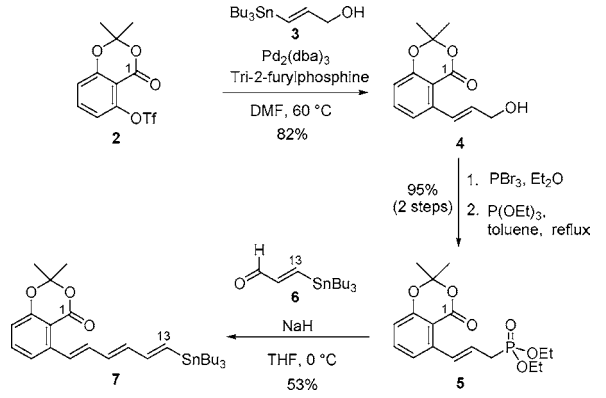
Scheme 1. Retrosynthetic Analysis



olefinic partner **17** orthogonally protected at C25 would allow the access to vinyl iodide **20** (Scheme 1).

The required trienic vinyl stannane **7** was synthesized from the known aryl triflate **2**,[3] readily accessible from commercially available 2-hydroxybenzoic acid (Scheme 2). The

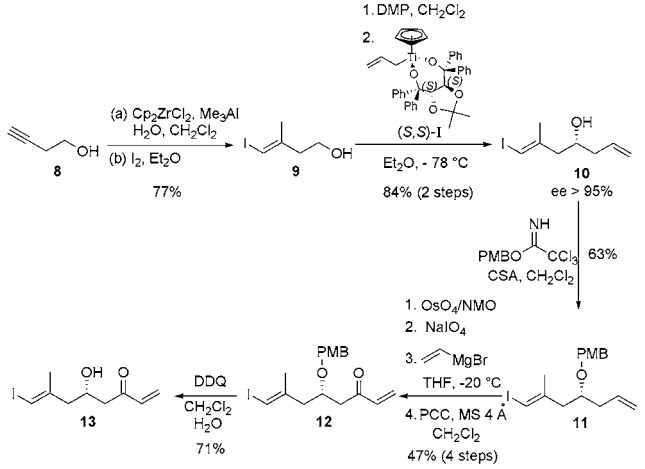
Scheme 2. Stereoselective Synthesis of Trienic Stannane **7**



latter was first converted into the allylic alcohol **4** by performing a $Pd_2(dba)_3$-catalyzed Stille cross-coupling with the organotin compound **3** (82% yield).[4] The resulting allylic alcohol **4** was subsequently subjected to bromination using PBr_3, and the phosphonation of the resulting allylic bromide under Michaelis−Arbuzov conditions provided the diethyl allylphosphonate **5** (95% yield from **4**, two steps). A Horner−Wadsworth−Emmons olefination between the obtained allylphosphonate and the α,β-unsaturated aldehyde **6**[5] successfully led to the required (*E*,*E*,*E*)-trienic vinyl stannane **7** in 53% yield. Therefore, the trienic alkenyl stannane **7**, precursor of the tetraenic moiety, was prepared efficiently in four steps from aryl triflate **2** in 40% overall yield (Scheme 2).

Then, we turned our attention toward the synthesis of vinyl iodide **13**, which commenced from a Negishi zirconium-assisted carboalumination applied to 3-butyn-1-ol **8** (cat. Cp_2ZrCl_2, Me_3Al, H_2O),[6] thus affording the alkenyl iodide **9** in 77% yield. Oxidation of the resulting primary alcohol with Dess−Martin periodinane (DMP) and subsequent treatment of the obtained aldehyde with the highly face-selective optically active allyltitanium complex (*S*,*S*)-**I**[7] led to the homoallylic alcohol **10** in 84% yield and with high enantioselectivity (ee > 95%).[8] The latter enantiopure secondary alcohol was then protected as a PMB ether using *p*-methoxybenzyl trichloroacetimidate, in the presence of camphorsulfonic acid (CSA), to furnish compound **11** in 63% yield. A regioselective oxidative cleavage of the terminal double bond (OsO_4/NMO, then $NaIO_4$) produced the corresponding chiral β-alkoxyaldehyde, which in turn could be directly converted into vinyl ketone **12** by a series of classical transformations (addition of vinylMgBr followed by oxidation with PCC; 47% yield, four steps). Finally, cleavage of the PMB ether with DDQ afforded the desired β-hydroxy vinyl ketone **13** in 71% yield (Scheme 3).

Scheme 3. Stereoselective Synthesis of Vinyl Iodide **13**



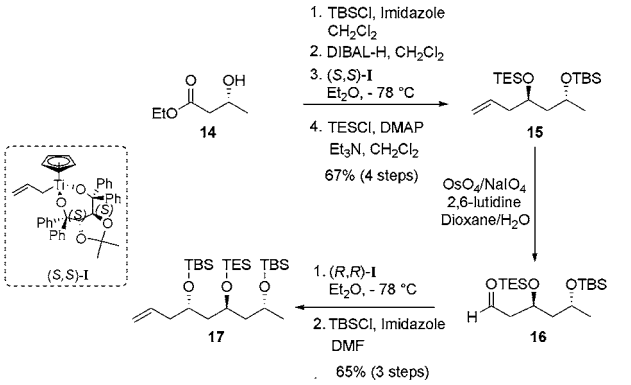
The last required fragment, that is, the optically active 1,3,5-triol **17**, was synthesized in seven steps from the

(3) (a) Hadfield, A.; Schweitzer, H.; Trova, M. P.; Green, K. *Synth. Commun.* **1994**, *24*, 1025−1028. (b) Dushin, R. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1992**, *114*, 655−659. (c) Fürstner, A.; Konetzki, I. *Tetrahedron* **1996**, *52*, 15071−15078.

(4) Wang, X.; Bowman, E. J.; Bowman, B. J.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2004**, *43*, 3601−3605.

(5) β-Stannylacrolein **6** was synthesized by performing a regio- and stereoselective stannylcupration of commercially available propiolaldehyde diethylacetal followed by acetal hydrolysis according to: (a) Lipshutz, B. H.; Lindsley, C. *J. Am. Chem. Soc.* **1997**, *119*, 4555−4556. (b) Lipshutz, B. H.; Ullman, B.; Lindsley, C.; Pecchi, S.; Buzard, D. J.; Dickson, D. *J. Org. Chem.* **1998**, *63*, 6092−6093.

Scheme 4. Stereoselective Synthesis of Triol **17**

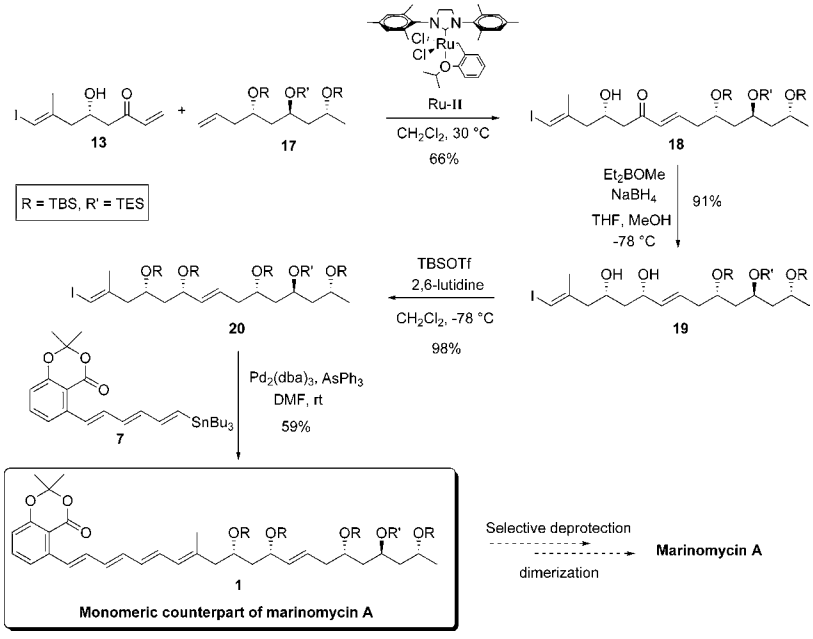


commercially available ethyl (*R*)-(−)-3-hydroxybutyrate **14** (Aldrich, 99% ee), and its preparation involved two consecutive allyltitanations to control the configuration of the secondary alcohols at C23 and C25 (Scheme 4). After protection of alcohol **14** as a *tert*-butyldimethylsilyl ether (TBSCl, imidazole), the ester functionality was transformed into the corresponding aldehyde by reduction with DIBAL-H (CH_2Cl_2, −78 °C)[9] and then directly treated with the allyltitanium complex (*S*,*S*)-**I** followed by protection of the free secondary alcohol as a triethylsilyl (TES) ether to give the 1,3-diol **15** with the suitable *anti*-relative configuration (dr > 95/5).[7c] Oxidative cleavage of the terminal double bond (OsO_4/$NaIO_4$/2,6-lutidine)[10] generated aldehyde **16**, which was directly treated with the (*R*,*R*)-**I** complex to afford the corresponding optically active homoallylic alcohol. Subsequent protection of the latter secondary alcohol as a *tert*-butyldimethylsilyl ether (TBSCl, imidazole) resulted in the formation of the desired 1,3,5-triol **17** with the required *anti*-*anti*-relative configuration (65% overall yield from **17**, three steps, Scheme 4).

At this juncture, the stage was set to probe the envisaged coupling reactions, and we faced the challenge to join fragments **13** and **17** by using a Ru-catalyzed cross-metathesis reaction. Gratifyingly, treatment of an equimolar amount of vinyl ketone **13** and olefin **17**, in the presence of 10 mol % of the second generation Grubbs−Hoveyda catalyst Ru-**II**[11] in CH_2Cl_2 at 30 °C, successfully produced the desired enone **18** in 66% yield and with complete (*E*)-stereoselectivity (Scheme 5). Enone **18** was subsequently reduced diastereoselectively (Et_2BOMe, $NaBH_4$)[12] thus leading to the *syn*-diol **19** in 91% yield containing the five required stereogenic centers. Protection of the two hydroxy groups at C17 and C19 as TBS ethers (TBSOTf, 2,6-lutidine) led to the fully protected pentaalkoxylated vinyl iodide **20** (98% yield). The completion of the synthesis of the monomeric counterpart of the natural product marinomycin A, compound **1**, was achieved by performing a $Pd_2(dba)_3$-catalyzed Stille cross-coupling,[13] in degassed DMF, between vinyl iodide **20** and the trienic vinyl stannane **7**, which successfully produced tetraene **1** in 59% yield (Scheme 5).

Thus, we have achieved an efficient and highly convergent stereoselective synthesis of the fully protected monomer of marinomycin A in 11 linear steps from the commercially available ethyl (*R*)-(−)-3-hydroxybutyrate **14**, in 15% overall yield. Synthetic highlights include enantioselective allyltitanations to create the stereogenic centers, a cross-metathesis to form the (*E*)-C20−C21 double bond, and a Pd-catalyzed cross-coupling to introduce the tetraene moiety. A selective deprotection of the TES group followed by a dimerization reaction should lead to the biologically active natural product

Scheme 5. Stereoselective Synthesis of Compound **1**, the Monomeric Counterpart of Marinomycin A



marinomycin A. This rapid and flexible synthetic approach should also allow access to a wide variety of analogues for biological evaluation. The synthesis of the naturally occurring marine macrodiolide marinomycin A, as well as its synthetic analogues, will be reported in due course.

Acknowledgment. The Société de Chimie Thérapeutique/Servier is gratefully acknowledged for financial support, and for a grant to one of us (D.A.).

Supporting Information Available: General experimental procedure and characterization data of the described compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL070240K

(6) (a) Wipf, P.; Lim, S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1068−1071. (b) Marshall, J. A.; Eidam, P. *Org. Lett.* **2004**, *6*, 445−448.

(7) (a) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, J.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321−2336. (b) Duthaler, R. O.; Hafner, A. *Chem. Rev.* **1992**, *92*, 807−832. (c) Cossy, J.; BouzBouz, S.; Pradaux, F.; Willis, C.; Bellosta, V. *Synlett* **2002**, 1595−1606.

(8) The (*R*) absolute configuration of **1** was confirmed by examination of the ^{1}H NMR spectra of the two corresponding mandelates, following the procedure described by: Seco, J. M.; Quiñoa, E.; Riguera, R. *Tetrahedron: Asymmetry* **2001**, *12*, 2915−2925.

(9) Wattanasereekul, S.; Maier, M. E. *Adv. Synth. Catal.* **2004**, *346*, 855−861.

(10) Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217−3219.

(11) (a) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. *J. Am. Chem. Soc*. **1999**, *121*, 791−799. (b) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360−11370.

(12) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repič, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155−158.

(13) (a) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636−3638. (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl*. **1986**, *25*, 508−524. (c) Coleman, R. S.; Walczak, M. C. *Org. Lett.* **2005**, *7*, 2289−2291.