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

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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 crossmetathesis between vinyl ketone 13 and the trihydroxylated

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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



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 PBr₃, 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 zirconiumassisted carboalumination applied to 3-butyn-1-ol 8 (cat. Cp_2ZrCl_2 , Me₃Al, H₂O),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 allylitanium complex (S,S)- \mathbf{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 (OsO₄/NMO, then NaIO₄) 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).



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

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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 $(CH_2Cl_2, -78 \ ^{\circ}C)^9$ 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 (OsO₄/NaIO₄/2,6-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 tertbutyldimethylsilyl ether (TBSCl, imidazole) resulted in the

formation of the desired 1,3,5-triol **17** with the required *antianti*-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 crossmetathesis 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-III¹¹ in CH₂Cl₂ 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 (Et₂BOMe, NaBH₄)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



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.

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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.

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