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Total Synthesis of Marinomycins A−C and of Their Monomeric Counterparts Monomarinomycin A and *iso*-Monomarinomycin A

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Abstract: Marinomycins A−C (**1**−**3**), and their monomeric analogues monomarinomycin A (**m-1**) and *iso*-monomarinomycin A (**m-2**), were synthesized by a convergent strategy from key building blocks ketophosphonate **5**, aldehyde **6**, and dienyl bromide carboxylic acid **7**. The first attempt to construct marinomycin A [**1**, convertible to marinomycins B (**2**) and C (**3**) by light] by direct Suzuki-type dimerization/cyclization of boronic acid dienyl bromide **4** led to premature ring closure to afford, after global desilylation, monomarinomycin A (**m-1**) and *iso*-monomarinomycin A (**m-2**) in good yield and only small amounts (≤2%) of the desired product. A subsequent stepwise approach based on Suzuki-type couplings improved considerably the overall yield of marinomycin A (**1**), and hence of marinomycins B (**2**) and C (**3**). Alternative direct dimerization approaches based on the Stille and Heck coupling reactions also led to monomarinomycins A (**m-1** and **m-2**), but failed to deliver useful amounts of marinomycin A (**1**).

Introduction

The need for new antibiotics has never been greater since the discovery of penicillin,[1] owing to the rather dramatic proliferation of drug-resistant bacteria and the frequent occurrence of untreatable infections. Actinomycetes have provided more than 10000 bioactive compounds and have generated more than 70% of the antibacterial natural products found to date.[2] However, the discovery of new antibiotics, especially those with novel mechanisms of action, has been steadily declining.[3] Many groups have shifted their efforts from terrestrial actinomycetes toward those of the ocean, which have, until now, been largely overlooked.[4] The Fenical group in particular has been successful in cultivating new colonies of actinomycetes from marine deep sea sediment samples, efforts that resulted in the isolation of several biologically active natural products.[5] Marinomycins A−C (**1**−**3**, Figure 1) have recently been isolated from a novel marine actinomycete, *Marinispora* strain CNQ-140, collected offshore of La Jolla, California.[6] Possessing novel molecular architectures, these natural products exhibit potent antibiotic activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VREF), with MIC_{90} values ranging from 0.1 to 0.6 μM, with marinomycin A (**1**) being the most active.[6] In addition to their significant antibacterial activity, the marinomycins show potent cytotoxicities against the National Cancer Institute's panel of 60 cell lines, with an average LC_{50} value of 2.7 μM, and remarkable selectivity against six of the eight melanoma cell lines, where SK-MEL-5 is about 500 times more sensitive than the other cell lines, with an LC_{50} value of 5.0 nM.[6] Because of this selectivity, it has been suggested that these secondary metabolites inhibit tumor proliferation by a novel mode of action.[6] The marinomycins were also suspected, because of their polyene functionalities, and hence resemblance to amphotericin B,[7] to be potent antifungal agents. However, only marinomycin A (**1**) showed activity against *Candida albicans* (MIC_{90} = 10 μM).[6] These important biological activities of the marinomycins, combined with their challenging structures, elicited our attention with regards to their total synthesis. Herein, we describe the full account of our total synthesis of marinomycins A−C (**1**−**3**)[8] as well as their unnnatural monomeric homologues, monomarinomycin A (**m-1**) and *iso*-monomarinomycin A (**m-2**).

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(3) A notable example of an antibiotic with a new mechanism of action is the recently discovered platensimycin. Isolation and biology: (a) Wang, J.; et al. *Nature,* **2006**, *441*, 358. (b) Singh, S. B.; et al. *J. Am. Chem. Soc.* **2006**, *128*, 11916. Total synthesis: (c) Nicolaou, K. C.; Li, A.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2006**, *45,* 7086.
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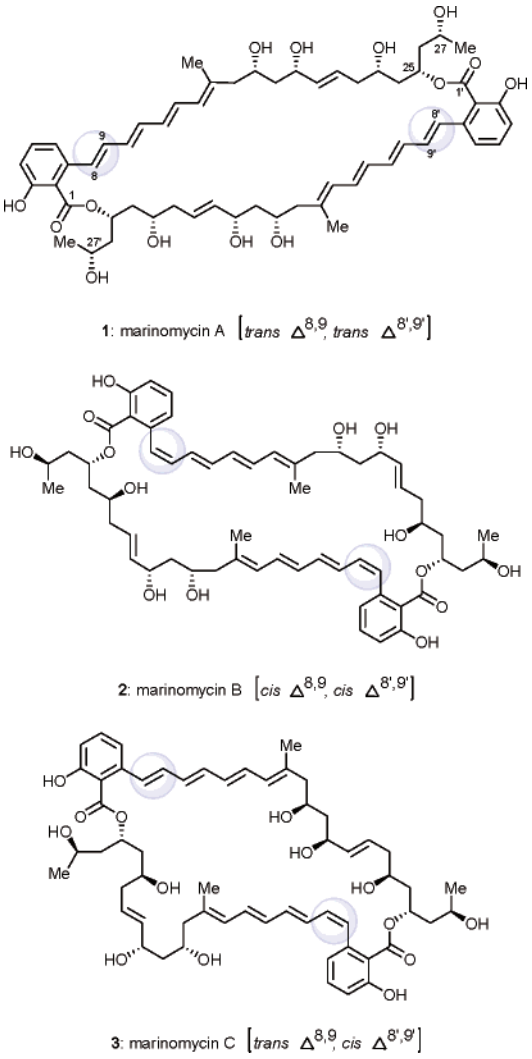

Figure 1. Structures of marinomycins A−C (**1**−**3**).

Results and Discussion

Retrosynthetic Design. In searching for a suitable strategy to deliver all three marinomycins (A−C, **1**−**3**) we were cognizant of the fact that a total synthesis of marinomycin A (**1**), the presumed true natural product,[6] would constitute a total synthesis of the others, in view of its known photoisomerization to marinomycins B (**2**) and C (**3**).[6] A cursory inspection of the structure of **1** reveals its many sites for retrosynthetic disconnection based on well-known processes such as the Suzuki, the Stille, and the Heck coupling reactions, the olefin metathesis reaction, the Mitsunobu reaction, and the Yamaguchi macrolactonization reaction. Taking advantage of the symmetry of the structure, our first retrosynthetic analysis of **1** (see Figure 2) relied on a dimerization strategy to construct the 44-membered macrocycle from two identical monomeric units. While any of the above-mentioned reactions could, in principle, achieve such a dimerization, we chose the Suzuki coupling as a possible means to achieve this goal, not only because of its reliability and the mild conditions it requires, but also because of its high stereoselectivity. Additional advantages included the fact that the required boronic acids could be generated stereoselectively from the corresponding terminal acetylenes and the opportunity to explore the applicability of the Suzuki reaction in forming challenging macrocyclic systems, an area where it

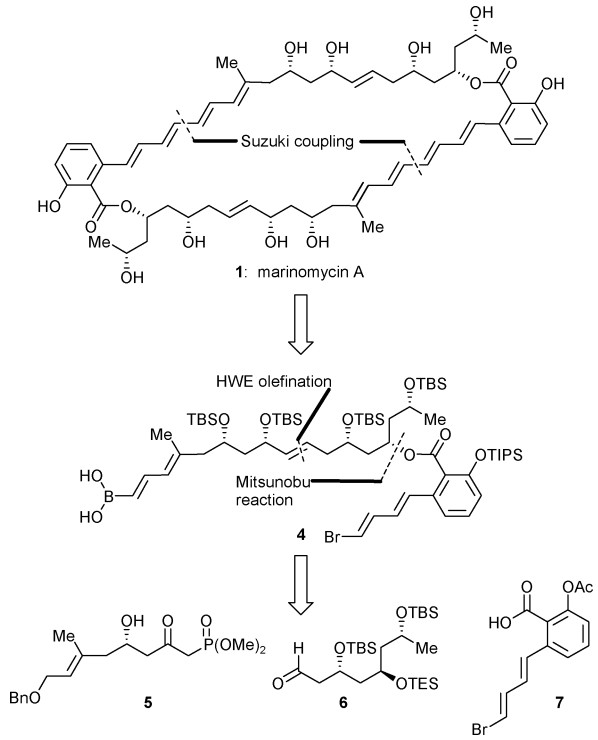

Figure 2. Retrosynthetic analysis of marinomycin A (**1**). Abbreviation: HWE, Horner−Wadsworth−Emmons.

was only rarely employed in the past.[9] Our intended Suzuki dimerization envisioned boronic acid vinyl bromide **4** as the precursor monomeric unit, an intermediate whose origin was traced back to building blocks ketophosphonate **5**, aldehyde **6**, and carboxylic acid **7** (Figure 2). It was expected that these three units could be assembled into the desired boronic acid bromide (**4**) through the indicated Horner−Wadsworth−Emmons (HWE) and Mitsunobu reactions. This strategy was flexible enough to allow for modifications as deemed appropriate, in the event of problems in the synthetic direction, a facet that was comforting and added to its attractiveness.

Construction of Building Blocks 5−7. The syntheses of the required, enantiomerically pure, building blocks **5**−**7** are summarized in Schemes 1−3. Beginning with the synthesis of ketophosphonate **5**, as shown in Scheme 1, a regioselective opening of enantiomerically pure epoxide **9**,[10] with the lithium species derived from propargyl ether **8**[11] and *n*-BuLi at −78 °C, in the presence of $BF_3{\cdot}OEt_2$, provided secondary alcohol **10** in 89% yield. Silylation (TBSCl, imid, 96% yield) of secondary alcohol **10**, followed by PMB-removal (DDQ, 79% yield), furnished primary allylic alcohol **12**. The latter compound was then used for the *trans*-stereoselective installment of the $\Delta^{14,15}$

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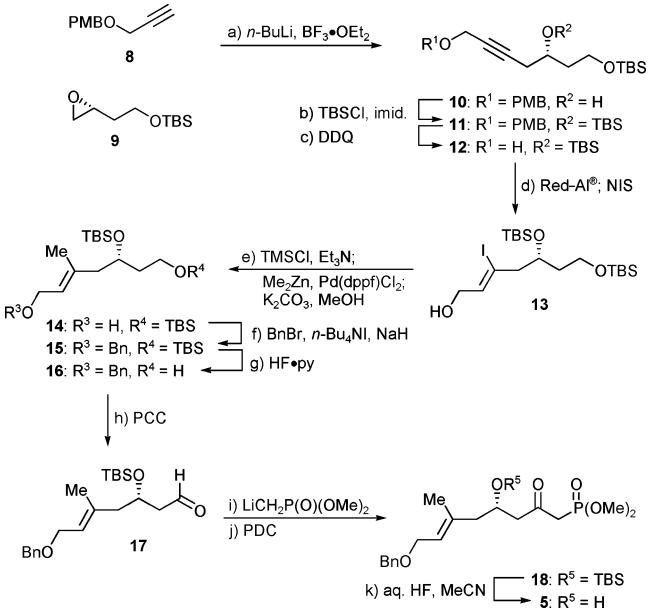
Scheme 1. Preparation of Ketophosphonate **5**[a]

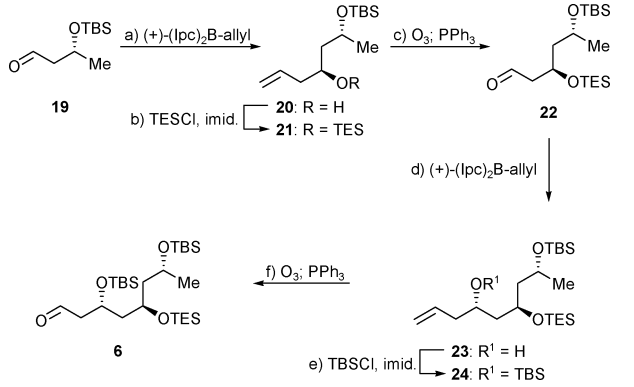


[a] Reagents and conditions: (a) **8** (2.0 equiv), *n*-BuLi (2.5 M in hexanes, 2.0 equiv), THF, −78 °C, 45 min; then $BF_3{\cdot}OEt_2$ (1.2 equiv), **9** in THF, −78 °C, 4 h, 89%; (b) TBSCl (1.2 equiv), imid. (3.0 equiv), DMF, 25 °C, 6 h, 96%; (c) DDQ (1.5 equiv), CH_2Cl_2, pH 7 phosphate buffer, 25 °C, 3 h, 79%; (d) Red-Al (3.33 M in toluene, 1.7 equiv), THF, 25 °C, 45 min; then NIS (1.8 equiv), THF, −78 °C, 30 min, 66%; (e) TMSCl (2.0 equiv), Et_3N (5.0 equiv), THF, 25 °C, 2 h; then $Pd(dppf)Cl_2$ (0.05 equiv), Me_2Zn (2.0 equiv), THF, 65 °C, 12 h; then K_2CO_3 (0.1 equiv), MeOH, 25 °C, 4 h, 81%; (f) NaH (1.6 equiv), THF, 0 → 25 °C, 30 min; then BnBr (1.7 equiv), *n*-Bu_4NI (0.1 equiv), 6 h, 88%; (g) HF•py, THF, 0 °C, 3 h, 77%; (h) PCC (2.0 equiv), $NaHCO_3$ (0.5 equiv), 25 °C, 3 h, 73%; (i) $CH_3P(O)(OMe)_2$ (4.0 equiv), *n*-BuLi (2.5 M in hexanes, 4.0 equiv), THF, −78 °C, 2 h; then **17** in THF, −78 °C, 2 h; (j) PDC (2.1 equiv), 4 Å MS, DMF, 25 °C, 12 h, 64% over two steps; (k) HF (48% aq), MeCN, 25 °C, 3 h, 92%. Abbreviations: THF, tetrahydrofuran; TBS, *tert*-butyldimethylsilyl; imid., imidazole; DMF, dimethylformamide; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; NIS, *N*-iodosuccinimide; TMS, trimethylsilyl; dppf, bis-(diphenylphosphino)ferrocene; PCC, pyridinium chlorochromate; PDC, pyridinium dichromate; MS, molecular sieves.

alkene in the presence of Red-Al, followed by quenching with NIS, a sequence that generated hydroxyvinyl iodide **13** in 66% yield. A Negishi coupling[12] of vinyl iodide **13**, after temporary silylation (TMSCl, Et_3N) of the free alcohol, with Me_2Zn in the presence of $Pd(dppf)Cl_2$ (catalyst) provided, after TMS-ether removal (K_2CO_3, MeOH), primary allylic alcohol **14** in 81% yield. This allylic alcohol was then protected as the benzyl ether (BnBr, NaH, *n*-Bu_4NI, 88% yield), and the primary TBS group was removed under the influence of HF•py to provide hydroxy compound **16** (77% yield), which was subsequently oxidized with PCC to afford aldehyde **17** in 73% yield. Lithiated dimethyl methyl phosphonate (*n*-BuLi, −78 °C) was then reacted with aldehyde **17**, and the resulting mixture of alcohol epimers were oxidized (PDC), to provide ketophosphonate **18** in 64% yield over the two steps. Finally, desilylation of **18** with 48% aqueous HF in MeCN at ambient temperature led to the desired hydroxy ketophosphonate (**5**) in 92% yield.

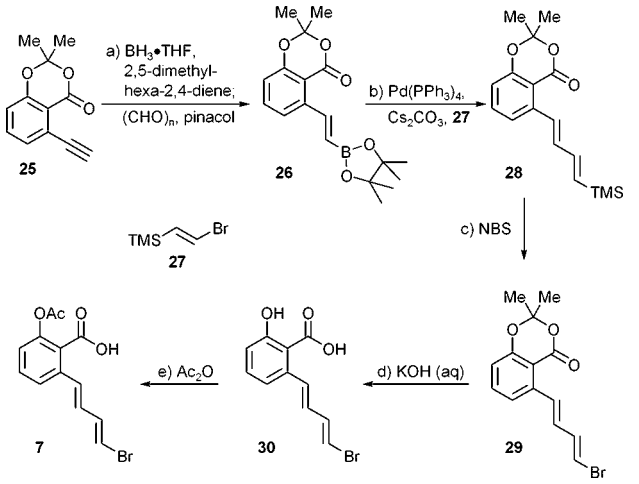
The required aldehyde **6** was prepared in short order from the readily available aldehyde **19**[13] in good overall yield (47% over the six steps involved) and with high diastereoselectivity (>40:1 dr) as shown in Scheme 2. Thus, Brown allylation[14] [(+)-$(ipc)_2$B-allyl, generated from (−)-$B(Ipc)_2OMe$ and allyl magnesium bromide] of **19** furnished allylic alcohol **20** in a highly stereoselective manner and in high yield (>40:1 dr, 95%

Scheme 2. Preparation of Aldehyde **6**[a]



[a] Reagents and conditions: (a) (−)-$B(Ipc)_2OMe$ (1.7 equiv), allylMgBr (1.0 M in Et_2O, 1.7 equiv), Et_2O, −78 → 25 °C, 2 h; then **19** in Et_2O, −78 °C, 4 h; −78 → 25 °C, 1 h, 95% (>40:1 dr); (b) TESCl (1.8 equiv), imid. (4.0 equiv), DMF, 25 °C, 4 h; (c) O_3, CH_2Cl_2, −78 °C, 4 h; then PPh_3 (1.3 equiv), −78 °C, 2 h; −78→25 °C, 1 h, 64% over two steps; (d) (−)-$B(Ipc)_2OMe$ (1.7 equiv), allylMgBr (1.0 M in Et_2O, 1.7 equiv), Et_2O, −78 → 25 °C, 2 h; then **22** in Et_2O, −78 °C, 4 h; −78→25 °C, 1 h, 85% (>40:1 dr); (e) TBSCl (2.0 equiv), imid. (5.0 equiv), DMF, 25 °C, 4 h; (f) O_3, CH_2Cl_2, −78 °C, 4 h; then PPh_3 (1.3 equiv), −78 °C, 2 h; −78 → 25 °C, 1 h, 91% over two steps. Abbreviations: Ipc, isopinocamphenyl; TES, triethylsilyl.

Scheme 3. Preparation of Dienyl Bromide Carboxylic Acid Fragment **7**[a]



[a] Reagents and conditions: (a) 2,5-dimethylhexa-2,4-diene (5.5 equiv), $BH_3{\cdot}THF$ (2.5 equiv), THF, 0 °C, 3 h; then **25**, 0 °C, 1.5 h; then H_2O, 0 → 25 °C, 1 h; then $(CH_2O)_n$, 25 °C, 12 h; then pinacol (1.1 equiv), $MgSO_4$ (5.0 equiv), 25 °C, 12 h, 87%; (b) $Pd(PPh_3)_4$ (0.1 equiv), Cs_2CO_3 (10 equiv), **27** (1.3 equiv), THF/H_2O (5:1), 55 °C, 1 h, 89%; (c) NBS (1.2 equiv), MeCN, 25 °C, 15 min, 88%; (d) KOH (5.0 equiv), THF/H_2O (1:1), 55 °C, 18 h, 87%; (e) $Mg(ClO_4)_2$ (0.03 equiv), Ac_2O (1.1 equiv), 25 °C, 48 h, 96%. Abbreviation: NBS, *N*-bromosuccinimide.

yield). Silylation (TESCl, imid.) of the latter compound, followed by ozonolysis (O_3, PPh_3) gave aldehyde **22** in 64% overall yield for the two steps. A second Brown allylation, now on **22** [(+)-$(ipc)_2$B-allyl], led to the allylic alcohol **23** (85% yield, >40:1 dr) which was silylated with TBSCl and imidazole to afford, after ozonolysis (O_3; PPh_3), the targeted aldehyde **6** in 91% overall yield from **23**.

The synthesis of carboxylic acid **7** started from known acetonide acetylene **25**[9c] as shown in Scheme 3. Thus, reaction of **25** with the adduct of $BH_3{\cdot}THF$ and 2,5-dimethyl-hexa-2,4-diene,[15] provided boronic ester **26**, which was subsequently coupled with commercially available TMS vinyl bromide (**27**) under the catalytic influence of $Pd(PPh_3)_4$ and Cs_2CO_3 (10 equiv)

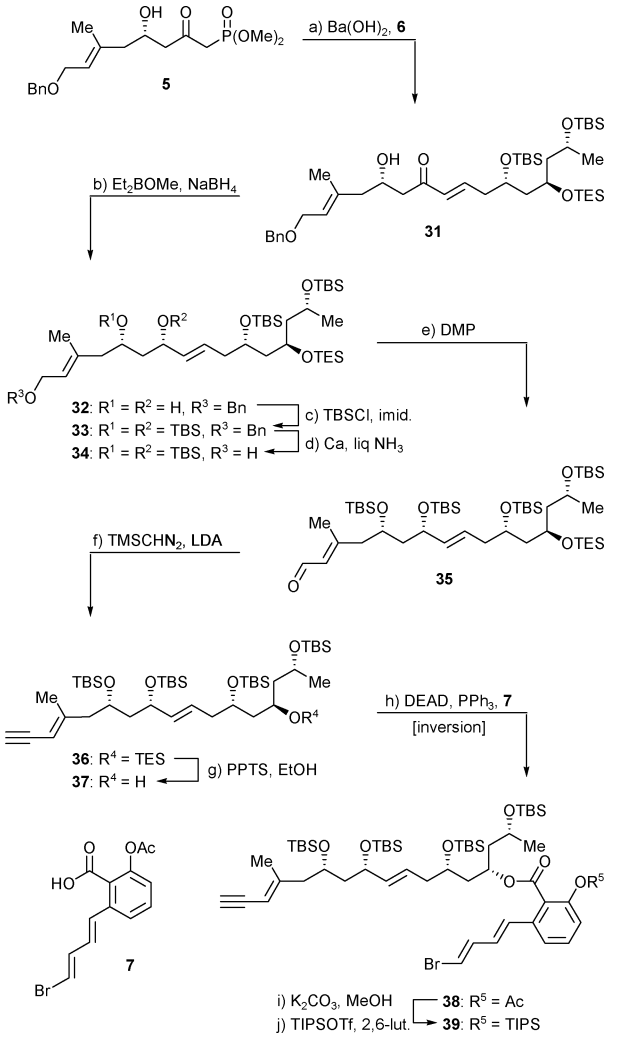
to give TMS diene **28** in 89% yield. *ipso*-Bromo desilylation of TMS diene **28** with NBS in MeCN afforded the all-*trans* bromo-diene **29** (88% yield), a compound that was stable to moderate light, unlike its iodide variant, in which the *trans* $\Delta^{10,11}$ double bond would rapidly isomerize to *cis*, even under low-light conditions. Saponification of **29** (KOH, 87% yield) provided the corresponding salicylic acid, which was protected as the acetate with acetic anhydride (1.1 equiv) in the presence of catalytic amounts of $Mg(ClO_4)_2$ (96% yield),[16] to yield the desired acetoxy carboxylic acid **7**, setting the stage for the upcoming Mitsunobu esterification.

Preparation of Dimerization Precursor 39. With all the key building blocks in hand, the assembly of desired dimerization precursor **39** could commence (Scheme 4). Thus, a Horner−Wadsworth−Emmons olefination reaction between ketophosphonate **5** and aldehyde **6** under the influence of $Ba(OH)_2$ proceeded smoothly to provide enone **31** in 95% yield. Before the HWE coupling was found to be the highest yielding method to prepare intermediate **31**, a study was undertaken to establish whether an olefin cross metathesis reaction could be employed to generate this enone as summarized in Table 1. Despite the initial success of this reaction between enone **40a** and the simple olefin **41** to furnish enone **42** (entry 1, Table 1), the adoption of the real, and more complex, olefin **23** or **24** led to unsatisfactory results (entries 2−5, Table 1). It is interesting to note that in this instance the Hoveyda−Grubbs catalyst **44**[17] proved slightly more efficient than the Grubbs second generation catalyst **43**[18] in generating the desired product, enone **31a** (entry 5, Table 1).

With enone **31** in hand (Scheme 4), a 1,3-*syn* reduction of the carbonyl group (Et_2BOMe, $NaBH_4$, −78 °C)[19] set the final stereocenter within the growing substrate, furnishing diol **32** as a single stereoisomer and in high yield (89%), which was silylated (TBSCl, imid.) to generate the fully protected hexaol **33** in 89% yield. Cleavage of the benzyl group (Ca, liq NH_3)[20] from the latter compound provided primary allylic alcohol **34** in 75% yield, which was subsequently oxidized to enal **35** with Dess−Martin periodinane (87% yield). Reaction of this aldehyde with the lithiated species from TMS−diazomethane and LDA[21] resulted in acetylene formation, providing enyne **36** in high yield (85% yield). The TES−ether of the latter compound was then selectively cleaved by the action of catalytic amounts of PPTS in EtOH at ambient temperature to provide the alcohol coupling partner for the Mitsunobu reaction (**37**, 77% yield).

Despite literature precedent[22] for the participation of salicylic acid derivatives in Mitsunobu-type reactions, the Mitsunobu reaction of alcohol **37** and carboxylic acid **45** under standard conditions (i.e., DEAD, PPh_3) failed to produce the expected product, even after 20 h at ambient temperature (Scheme 5). To develop suitable conditions to accomplish the coupling of these two compounds, a model study was undertaken in which readily available alcohol **47** was employed in coupling reactions with the simple salicylic acids **48a** and its derivatives **48b** and **48c** as shown in Scheme 5. Interestingly, a notable rate enhancement was observed when the phenolic group of the salicylic acid component was protected (e.g., **48b** and **48c**), as opposed to salicylic acid itself (i.e., **48a**), in which the phenolic group was free. Furthermore, it was found that the acetoxy derivative (i.e., **48c**) reacted significantly faster (complete conversion in 1 vs 3 h) than its methoxy counterpart (i.e., **48b**). Proceeding in 81% yield, the Mitsunobu reaction of the acetoxy salicylic acid derivative **50** provided further encouragement, and when we finally attempted the coupling of our two real partners

Scheme 4. Preparation of Suzuki Coupling Precursor **39**[a]



[a] Reagents and conditions: (a) **5** (1.0 equiv), **6** (1.1 equiv), $Ba(OH)_2 \cdot H_2O$ (0.75 equiv), THF/H_2O (20:1), 25 °C, 1 h, 95%; (b) Et_2BOMe (1.0 M in THF, 1.1 equiv), THF/MeOH (4:1), −78 °C, 15 min; then $NaBH_4$ (1.1 equiv), 3 h, 89%; (c) TBSCl (4.0 equiv), imid. (8.0 equiv), DMF, 25 °C, 8 h, 89%; (d) **33** in THF/ *i*-PrOH (3:1); then liq NH_3; then Ca (30 equiv), −78 °C, 1 h, 75%; (e) DMP (1.6 equiv), $NaHCO_3$ (10 equiv), CH_2Cl_2, 25 °C, 30 min, 87%; (f) *i*-Pr_2NH (1.8 equiv), *n*-BuLi (2.5 M in hexanes, 1.5 equiv), THF, −78 → 0 °C, 30 min; then $TMSCHN_2$ (1.5 equiv), THF, −78 °C, 30 min; then **35**, −78 °C, 1 h, −78 → 25 °C, 2 h, 85%; (g) PPTS (0.1 equiv), EtOH, 25 °C, 3 h, 77%; (h) DEAD (6.0 equiv), PPh_3 (6.0 equiv), **7** (6.0 equiv), THF, 25 °C, 1 h, 93%; (i) K_2CO_3 (0.05 equiv), MeOH, 25 °C, 15 min; (j) TIPSOTf (30 equiv), 2,6-lut. (60 equiv), CH_2Cl_2, 25 °C, 18 h, 92% over two steps. Abbreviations: DMP, Dess−Martin periodinane; PPTS, pyridinium *p*-toluenesulfonate; DEAD, diethyl azodicarboxylate; TIPS, triisopropylsilyl; Tf, trifluoromethanesulfonyl; lut., lutidine.

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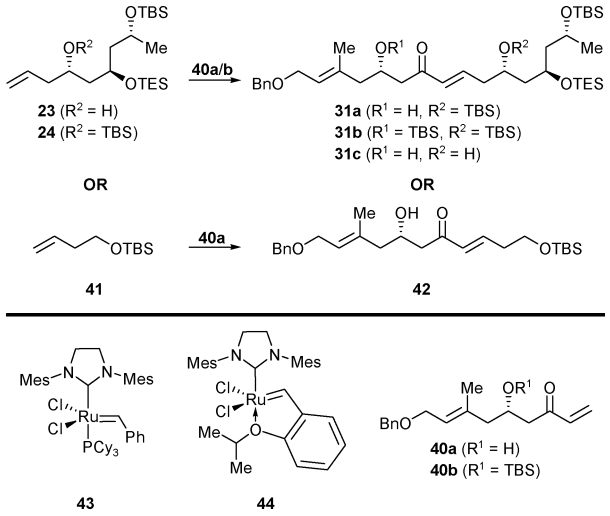
Table 1. Olefin Cross-Metathesis Forays toward Enone **31**



entry[a]	substrate (R^2)	substrate (R)	catalyst	product (% yield)[b]
1	**41**	**40a** (H)	**43**	**42** (80)
2	**24** (TBS)	**40a** (H)	**43**	**31a** (36, 72[c])
3	**24** (TBS)	**40b** (TBS)	**43**	**31b** (20, 65[d])
4	**23** (H)	**40a** (H)	**43**	**31c** (42)
5	**24** (TBS)	**40a** (H)	**44**	**31a** (44, 80[e])

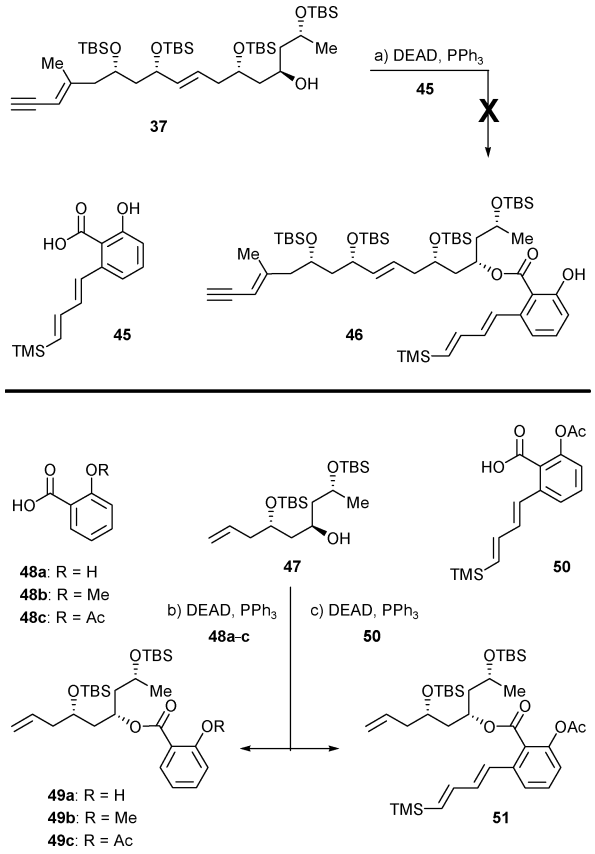
[a] All reactions carried out on 0.07 mmol scale at 25 °C for 18 h with 1.0 equiv of enone and 2.0 equiv of alkene, except in entry 5, where 3.0 equiv of enone and 1.0 equiv of alkene were used. [b] Isolated yield. [c] Based on 50% recovered starting material. [d] Based on 69% recovered starting material. [e] Based on 45% recovered starting material.

under the Mitsunobu conditions, as shown in Scheme 4, we were pleasantly surprised. Indeed, the Mitsunobu reaction between alcohol **37** and acetoxy carboxylic acid **7** (DEAD, PPh_3) proceeded to completion within 1 h at ambient temperature, smoothly producing ester **38** in 93% yield. Having served its facilitating purpose, and observing its vulnerability to cleavage in subsequent steps, the acetoxy group of **38** was then replaced with a TIPS group by a two-step procedure (K_2CO_3, MeOH; TIPSOTf, 2,6-lut., 25 °C), leading to precursor **39** in 92% overall yield.

Direct Dimerization Attempts toward the Marinomycins. With acetylenic monomeric precursor **39** secured, preparations for its dimerization began in earnest. Thus, **39** was reacted with catecholborane in THF in the presence of catalytic amounts of dicyclohexylborane at ambient temperature for 30 min, and the mixture so obtained was treated with water (excess) and further stirred for 1 h at the same temperature. Without isolation, the resulting boronic acid (**4**) was then reacted with catalytic amounts of $Pd(PPh_3)_4$ in the presence of TlOEt (4.0 equiv) in THF/H_2O (4:1)[23] (0.01 M concentration) at room temperature with the expectation of observing, at least partially, its dimerization to marinomycin-type structures. Much to our disappointment, however, and somewhat surprisingly, only the monomeric macrolactone **52** was obtained in this reaction, even after further experimentation involving different concentrations (1.0−0.005 M). These results suggested that once the palladium is inserted into the substrate the resulting species encounters very little resistance, if any, to ring closure (intramolecular reaction), as opposed to reaction with another monomeric unit

(23) Frank, S. A.; Chen, H.; Kunz, R. K.; Schnaderbeck, M. J.; Roush, W. R. *Org. Lett.* **2000**, *2*, 2691.

Scheme 5. Attempted Mitsunobu Reaction between **37** and **45** and Model Studies[a]



[a] Reagents and conditions: (a) DEAD, PPh_3, Et_2O, 20 h, no reaction; (b) DEAD, PPh_3, THF; **49a**, 24 h, trace product; **49b**, 3 h, 65%; **49c**, 1 h, 72%; (c) DEAD, PPh_3, THF, 1 h, 81%.

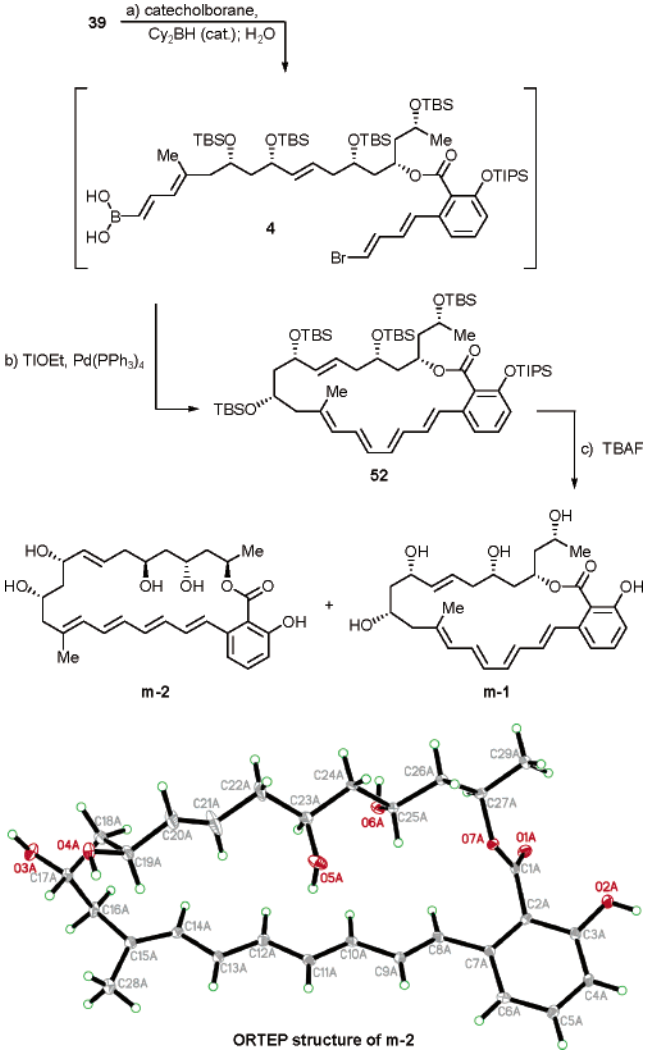
(intermolecular reaction). The sought-after dimeric product **57** (see Scheme 7 for structure) was, nevertheless, generated by the use of a large excess (300 equiv) of TlOEt, albeit in only 2% yield after global desilylation, in addition to monomer **52**, which was formed in 72% yield. Global desilylation of monomeric product **52** by the action of tetrabutylammonium fluoride (TBAF) in THF at room temperature, furnished not only the expected all-*trans* 22-membered ring **m-1**, coined monomarinomycin A,[8] but also the expanded, all-*trans* 24-membered lactone **m-2**, coined *iso*-monomarinomycin A,[8] as a separable 1:1 mixture in 85% total yield (Scheme 6). The two isomeric monomarinomycins A (**m-1** and **m-2**) were purified, first by preparative plate chromatography (silica gel, CH_2Cl_2/MeOH, 93:7, two elutions) and then by HPLC (C18-Dynamax column, 60 Å, 10 mm × 250 mm, 45% MeCN in H_2O).

Suitable crystals for X-ray crystallographic analysis were obtained [mp 213 °C (dec) from $CDCl_3$/MeOH-d_4] for *iso*-monomarinomycin A (**m-2**, see ORTEP representation in Scheme 6),[24] which confirmed its assigned structure and those of its predecessor compounds, including monomarinomycin A (**m-1**).

As a matter of interest, the TBAF-induced formation of monomarinomycins A (**m-1** and **m-2**) from the pentasilylated product **52** as a function of time was studied and the results are tabulated in Table 2. The reaction was carried out with 50 equiv

(24) CCDC-607141 (**m-2**) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Scheme 6. Formation of Monomarinomycins **m-1** and **m-2** and ORTEP Structure of **m-2**[a]

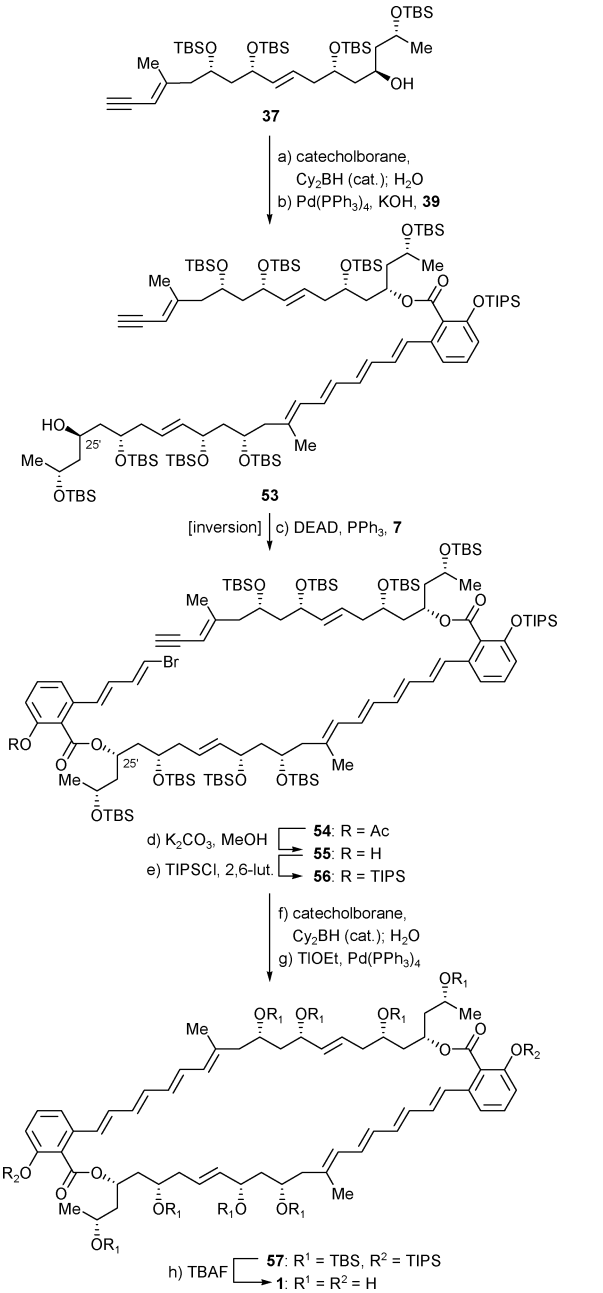


[a] Reagents and conditions: (a) catecholborane (1.0 M in THF, 3.0 equiv), Cy_2BH (0.1 M in THF, 0.2 equiv), THF, 25 °C, 30 min; H_2O (excess), 25 °C, 1 h; (b) TlOEt (4.0 equiv), $Pd(PPh_3)_4$ (0.1 equiv), THF/H_2O (4:1, 0.01 M), 25 °C, 1 h, 72% over two steps; the use of 300 equiv of TlOEt in this reaction gave, in addition to **52** (72%), the dimeric product **57** (2%); (c) TBAF (30 equiv), THF, 18 h, 25 °C, 85%. Abbreviation: TBAF, tetra-*N*-butylammonium fluoride.

of TBAF in THF at 25 °C, and the formation of the products was monitored by HPLC. Under these conditions, only monomarinomycin A (**m-1**) was present after 1 h. After 2 h, however, the acyl migration-based ring expansion began to set in, as revealed by the appearance of *iso*-monomarinomycin A (**m-2**) (**m-1**/**m-2** ca. 7:1), the latter compound being the most abundant after 24 h. Interestingly, monomarinomycin A (**m-1**) could no longer be detected after 72 h, although a number of other decomposition products were present, indicating that essentially all the material can be converted to *iso*-monomarinomycin A (**m-2**) through a base-induced acyl migration, a process that presumably relieves strain from the originally formed 22-membered ring.

Stepwise Approach toward the Marinomycins. Faced with the disappointingly low yield of the direct dimerization strategy and our inability to improve the situation, we opted for a stepwise approach to the total synthesis of the marinomycins. This modified sequence would require the same key building

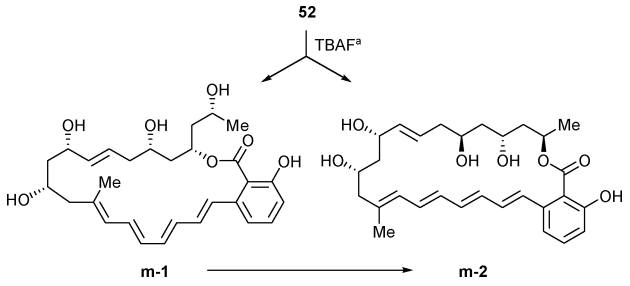
Scheme 7. Completion of the Total Synthesis of Marinomycin A (**1**)[a]



[a] Reagents and conditions: (a) catecholborane (1.0 M in THF, 3.0 equiv), Cy_2BH (0.2 equiv), THF, 25 °C, 30 min; (b) KOH (10 equiv), $Pd(PPh_3)_4$ (0.1 equiv), THF/H_2O (4:1), 25 °C, 1 h, 63% based on **39**; (c) DEAD (6.0 equiv), PPh_3 (6.0 equiv), **7** (6.0 equiv), THF, 25 °C, 1 h; (d) K_2CO_3 (0.05 equiv), THF/MeOH (1:1), 25 °C, 15 min; (e) TIPSOTf (30 equiv), 2,6-lut. (60 equiv), CH_2Cl_2, 25 °C, 18 h, 78% over three steps; (f) catecholborane (1.0 M in THF, 3.0 equiv), Cy_2BH (0.2 equiv), THF, 25 °C, 30 min; (g) TlOEt (300 equiv), $Pd(PPh_3)_4$ (1.0 equiv), THF/H_2O (10:1), 25 °C, 4 h; (h) TBAF (50 equiv), THF, 25 °C, 18 h (23% over three steps).

blocks as before, namely **7** (Scheme 3), **37** (Scheme 4), and **39** (Scheme 4), and was carried out as shown in Scheme 7. Thus, hydroxy enyne **37** was converted to its boronic acid by reaction with catecholborane in THF and in the presence of catalytic amounts of dicyclohexylborane at ambient temperature, followed by hydrolysis with H_2O, which was, without isolation, coupled with dienyl bromide **39** (0.67 equiv) under the influence of KOH and catalytic amounts of $Pd(PPh_3)_4$ in THF/H_2O (4:1) at ambient temperature to afford hydroxy polyene **53** in 63% overall yield

Table 2. TBAF-Induced Formation of Monomarinomycins A (**m-1** and **m-2**) from **52** as a Function of Time



entry	time (h)	ratio (**m-1**/**m-2**)[b]
1	1	1:0
2	2	7:1
3	3	4:1
4	5	2.5:1
5	7	2:1
6	24	1:2

[a] TBAF (50 equiv), THF, 25 °C. [b] Ratio determined by HPLC (C18-Sunfire 5μ column, 10mm × 250 mm, 100 Å, 10−100% MeCN in H_2O over 20 min, 5 mL/min).

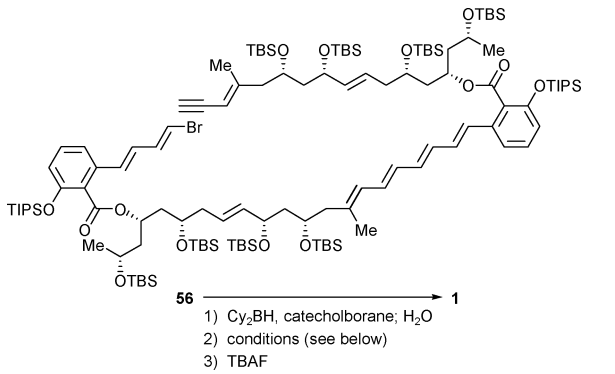
based on **39**. Subsequent Mitsunobu reaction between hydroxy polyene **53** and carboxylic acid **7** (excess) (DEAD, PPh_3, THF, 25 °C) proceeded smoothly to yield the expected ester (with inversion of configuration), whose lone acetyl moiety was exchanged for a TIPS group (K_2CO_3, MeOH; TIPSOTf, 2,6-lut., 25 °C), furnishing, in 78% overall yield for the three steps, enyne ester **56** via the intermediacy of phenolic compound **55**.

Reaction of enyne ester **56** with catecholborane and dicyclohexylborane (catalytic) in THF at ambient temperature, followed by aqueous quench, afforded the corresponding boronic acid, which was, without isolation, subjected to the Suzuki coupling conditions [$Pd(PPh_3)_4$, TlOEt, THF, 25 °C] to provide the expected macrodiolide **57** as shown in Scheme 7. Continuing the sequence without purification, TBAF (50 equiv, THF, 25 °C) was employed as a desilylating agent to cause the desired global deprotection, furnishing, after HPLC purification (C8-Luna 5μ column, 100 Å, 10 mm × 250 mm, 60% MeCN in H_2O), marinomycin A (**1**) in 23% overall yield for the three steps from **56**. Synthetic marinomycin A (**1**) exhibited identical properties (R_f, t_R, UV, $[\alpha]_D^{25}$, ^1H and ^{13}C NMR, and HRMS) to those reported for the naturally occurring substance.[6] This stepwise approach was not only higher yielding than the direct dimerization approach (11 vs 2% overall yield from **39**), but also led to a cleaner final mixture, from which the desired product could conveniently be isolated by HPLC.

Several attempts (see Table 3) to improve the overall yield of the final product for the last three steps for the synthesis of marinomycin A (**1**) failed to uncover a superior procedure than the one described above (entry 1, Table 3). It was, however, interesting to observe that, while the conditions involving Ag_2O and K_2CO_3 in DME resulted in nearly the same yield (20% overall for the last three steps, entry 11, Table 3) as the best conditions (TlOEt in THF/H_2O, 23% overall yield), the conditions of KOH in THF/H_2O so successfully employed in the preparation of **53** from **37** and **39** (as described above, Scheme 7) resulted in only trace amounts of the desired product (entry 4, Table 3).

Following the report of Fenical et al.,[6] we subjected marinomycin A (**1**) to photoinduced (ambient light) isomerization

Table 3. Attempts To Improve the Yield of Marinomycin A (**1**) for the Last Three Steps of the Synthesis



entry[a]	additive(s)	solvent(s)	yield (%)[b]
1	TlOEt	THF/H_2O (10:1)	23
2	Cs_2CO_3	THF/H_2O (2:1)	trace[c]
3	Me_3SnOH	THF/H_2O (2:1)	trace[c]
4	KOH	THF/H_2O (2:1)	trace[c]
5	KOAc	toluene	NR[d]
6	K_3PO_4	DME	5
7	*t*-BuOK	DME/*t*-BuOH (20:1)	17
8	Ag_2O, *t*-BuOK	DME/*t*-BuOH (20:1)	15
9	Ag_2O	THF	4
10	Ag_2O	DME	9
11	Ag_2O, K_2CO_3	DME	20

[a] All reactions were carried out on 1.0 mmol scale and under $Pd(PPh_3)_4$ catalysis, except for entry 6, in which $Pd_2(dba)_3$ was used instead. [b] Yields of **1** are over three steps, from **56**. [c] Trace product was observed by TLC analysis. [d] No reaction.

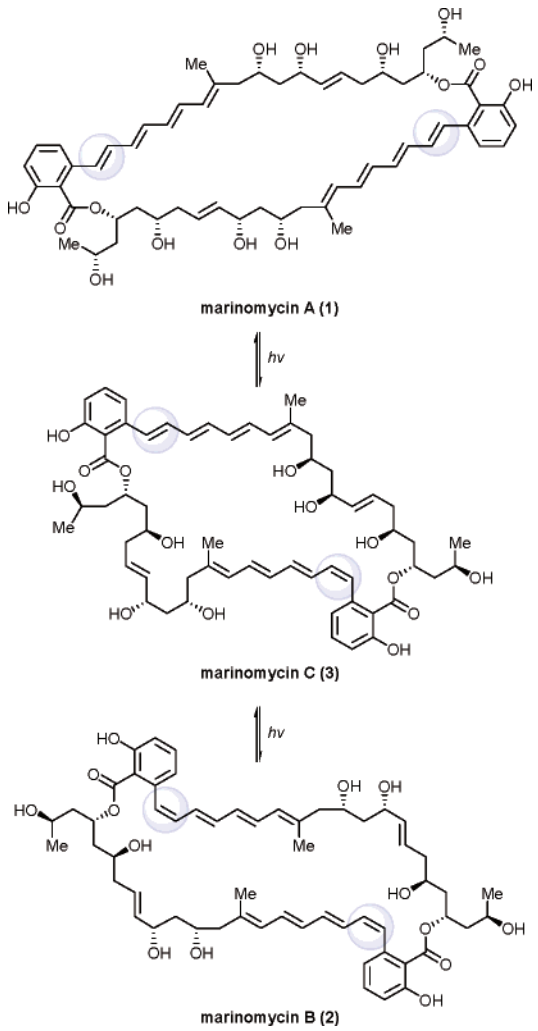
in methanol in an open vial for 2 h, monitoring the reaction every 30 min by HPLC. As seen from Table 4, the isomerization progressed to a mixture of marinomycins A (**1**), B (**2**), and C (**3**) in a ratio that was close to that reported (**1**/**2**/**3** ca. 16:2:9).[6] This ratio changed in favor of marinomycin C (**3**), reaching a value of ca. 1.1:1:1.5 (**1**/**2**/**3**) after 2 h, with the retention times (t_R) and the UV spectra of all three marinomycins matching those reported for the natural products.[6]

Attempted Double Stille Dimerization To Form the Marinomycin A Skeleton. Prompted by our previous success in establishing macrocyclic systems[25] through a double Stille stitching cyclization employing a dienyl halide and *trans*-1,2-bis-(tri-*n*-butylstannyl)ethylene (**60**),[26] we prepared dienyl bromide **59** ($ZrCp_2HCl$; NBS) and attempted its stitching dimerization with distannane **60** in the presence of $Pd(MeCN)_2Cl_2$ as a catalyst (THF, 25 °C). As seen in Scheme 8, the only products obtained from this reaction were the terminal olefin stannane **61** (25% yield from **58**), the vinyl bromide stannane **62** (30% overall yield from **58**), and the monomarinomycin A pentasilylated derivative **52** (13% overall yield from **58**). It was presumed that **62** served as the precursor to **52** in this reaction, and, therefore, this bromostannane could, in principle, yield further amounts of the monomarinomycin A (**52**). However, it was clear that the Suzuki approach provided a superior entry into these systems, and thus no further experimentation was pursued along this Stille coupling-based strategy.

(25) For the first examples of macrocyclization by means of a Stille coupling, see: Stille, J. K.; Tanaka, M.; *J. Am. Chem. Soc.* **1987**, *109*, 3785.

(26) For an example of this "stitching" macrocyclization approach, see: (a) Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419. (b) Nicolaou, K. C.; Piscopio, A. D.; Bertinato, P.; Chakraborty, T. K.; Minowa, N.; Koide, K. *Chem.—Eur. J.* **1995**, *1*, 318.

Table 4. Photoinduced Isomerization of Marinomycins A (**1**), B (**2**), and C (**3**)



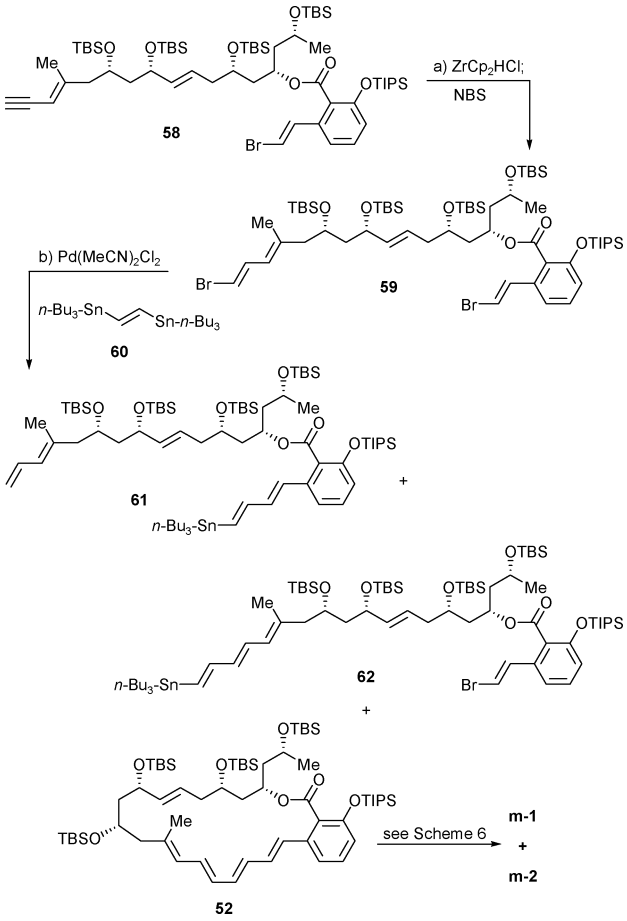
entry	time (min)	Ratio **1/2/3**[a]
1	0	19:0:1
2	30	12.3:1:5.8
3	60	3.6:1:3.0
4	90	1.7:1:2.0
5	120	1.1:1:1.5

[a] Marinomycin A (**1**, 1.0 mg), after an optical rotation, was dissolved in MeOH (2.0 mL) and placed in an open vial under ambient light for 2 h. Small samples were removed every 30 min and analyzed by HPLC using the following conditions: C18-Kromasil 5μ column, 4.6 mm × 150 mm, 100 Å, 10−100% MeCN in H_2O over 20 min, 1.0 mL/min.

Attempted Heck Dimerization To Form the Marinomycin A Skeleton. To explore the possibility of forming the marinomycin A skeleton through a direct, double Heck-type coupling/dimerization reaction,[27] a potential monomeric precursor was sought, as shown in Table 5. To this end, enyne **39** was reacted with $ZrCp_2HCl$ and the resulting zirconium species was quenched with H_2O to afford diene vinyl bromide **63** in 65% overall yield. Various conditions were then explored for achieving the desired reaction as shown in Table 5. Thus, searching for the optimum concentration, it was established that the Heck reaction of **63** with $Pd(OAc)_2$ in DMF at ambient temperature, and in the presence of KOAc and *n*-Bu_4NCl as additives, proceeded best at 2.1 mM (entry 2, Table 5), although the reaction, again, yielded predominantly monomeric product (i.e., 10% yield of monomarinomycin A (**m-1**) and 5% yield of *iso*-monomarinomycin A (**m-2**) overall from **39** after TBAF-induced desilylation]. Further experimentation led to the discovery that switching from KOAc to K_2CO_3 (8.5 equiv) in the above conditions led to a high yield of the monomeric products (60% of **m-1** and 20% of **m-2** from **39** overall after TBAF-induced desilylation) and a trace amount of marinomycin A (**1**) as detected by HPLC. Despite the success of the Heck reaction in this instance, the Suzuki reaction remains the preferred method for the synthesis of the monomarinomycins (**m-1** and **m-2**) and their precursors.

(27) (a) Mitsudo, T.-A.; Fischetti, W.; Heck, R. F. *J. Org. Chem.* **1984**, *49*, 1640. (b) For a recent review of the Heck, reaction, see: Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.

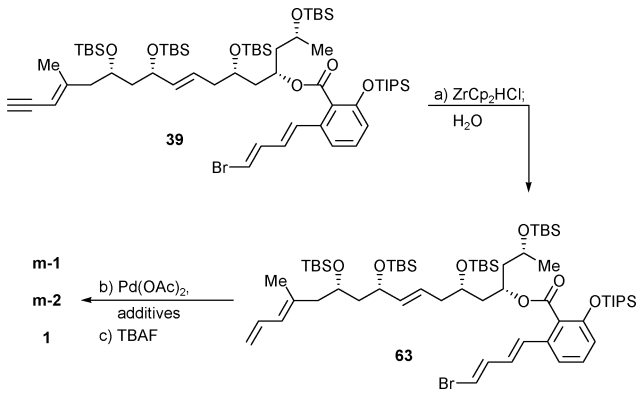
Scheme 8. Attempted Stille Dimerization to Form Marinomycin A (**1**)[a]



[a] Reagents and conditions: (a) $ZrCp_2HCl$ (2.0 equiv), THF, 25 °C, 20 min; then NBS (5.0 equiv), −78 °C, 5 min; (b) **60**, $Pd(MeCN)_2Cl_2$ (0.1 equiv), THF, 25 °C, 3.5 h, **52** (13% overall from **58**), **61** (25% overall from **58**), **62** (30% overall from **58**).

Biological Evaluation of the Synthesized Marinomycins. In view of the biological properties[6] of the naturally occurring marinomycins A−C (**1**−**3**), we were interested in finding out whether the synthesized monomarinomycins A (**m-1** and **m-2**) possess any of the same activities as their naturally occurring parents. These compounds were, therefore, along with marinomycin A (**1**), tested against the drug-resistant bacteria MRSA and VREF, the fungus *Candida albicans*, and the HCT-116 cell line. As shown in Table 6, neither monomarinomycin matched, or even came close to, the potency of marinomycin A (**1**) against these biological species, with monomarinomycin A (**m-1**)

Table 5. Attempted Heck Dimerization To Afford Marinomycin A (**1**)[a]



entry	substrate, additives	concn (mM)	product[b] m-1 (% yield)	m-2 (% yield)	1 (% yield)
1	**63**, KOAc (2.5 equiv), *n*-Bu_4NCl (2.5 equiv)	21	<5	<5	0
2	**63**, KOAc (2.5 equiv), *n*-Bu_4NCl (2.5 equiv)	2.1	10	5	0
3	**63**, KOAc (2.5 equiv), *n*-Bu_4NCl (2.5 equiv)	0.21	trace[c]	trace[c]	0
4	**63**, *n*-Bu_4OAc (2.5 equiv)	2.1	trace[c]	trace[c]	0
5	**63**, K_2CO_3 (8.5 equiv), *n*-Bu_4NCl (2.5 equiv)	2.1	60	20	trace[c]

[a] Reagents and conditions: (a) $ZrCp_2HCl$ (2.0 equiv), THF, 30 min; then H_2O (excess); (b) **63** (2.1 mmol), $Pd(OAc)_2$ (0.05 equiv), DMF, 25 °C, 18 h; (c) TBAF (50 equiv), THF, 25 °C, 12 h. [b] Yields are determined over two steps, from **63**. [c] Traces of product were detected by HPLC (same conditions as Table 2).

Table 6. Biological Evaluation of Monomarinomycins A (**m-1** and **m-2**)

compd	*Staphylococcus aureus* methicillin-resistant (MRSA) MIC_{90} (μM)[a]	*Enterococcus faecium* vancomycin-resistant (VREF) MIC_{90} (μM)[a]	wild type *Candida albicans* MIC_{90} (μM)[b]	human colon carcinoma (HCT-116) IC_{50} (μg/mL)[c]
1	0.13	0.13	10	0.18
m-1	50	NSA[d]	NSA[d]	NSA[d]
m-2	NSA[d]	NSA[d]	NSA[d]	NSA[d]

[a] The optical density (OD) was measured at 600 nm using a Molecular Devices Emax microplate reader, and the MIC_{90} was determined by the analysis program SOFTmax PRO. The MIC_{90} of vancomycin is 0.195−0.391 mg/mL, and that of penicillin G is 6.25−12.5 mg/mL in this test. [b] Alamar blue was used as an indicator to measure cell proliferation. The dye yields a colorimetric change that enables the MIC to be confidently estimated by visual means; the MIC of amphotericin B in this test is 1.56−0.78 mg/mL. [c] The OD was measured at 492 nm using a Molecular Devices Emax microplate reader, and the IC_{50} was determined in a MTS colormetric assay; the IC_{50} of etoposide is 1−2 μg/mL in this test. [d] NSA = not significantly active (MIC_{90} values above 50.0 mM or IC_{50} values above 50 μg/mL).

registering weak activity (50 μM) against MRSA. It was clear that the receptor for marinomycin A does not recognize the smaller monomeric species.

Conclusion

With their novel molecular architectures and potent biological properties, the marinomycins (A−C, **1**−**3**) presented an interesting challenge to the synthetic chemist, but also an opportunity to test the scope and applicability of a number of important carbon−carbon bond forming reactions in complex situations. The polyunsaturated nature of these molecules rendered them particularly sensitive to both chemical and light activation, while their, more or less, symmetrical structures made a dimerization strategy an attractive proposition as a means to assemble them from a single monomeric unit. Our flexible approach to these structures allowed us, with slight modifications, to test synthetic strategies based on the Suzuki, Stille, and Heck coupling reactions as well as to probe olefin metathesis as a potential tool for their construction. The results of these investigations were somewhat surprising in that all three palladium-based dimerization/cyclization approaches led to monomeric macrocyclic products, rather than dimeric, the latter being formed in ≤2% yield, even at low dilutions, in certain instances. From the three, the Suzuki reaction proved to be the most expedient, although both the Stille and the Heck approaches delivered the monomeric marinomycins A (**m**-**1** and **m**-**2**). Early results precluded olefin metathesis as a potential means to construct such polyunsaturated systems as the ones present in these target molecules. The propensity of the precursors involved in these dimerization/cyclization reactions to form the monomeric macrocycles clearly reflects the favorable conformational effects and entropic factors for the initial coupling options to form the 22-membered ring of monomarinomycin A (**m**-**1**), and through ring expansion, 24-membered ring of *iso*-monomarinomycin A (**m**-**2**). On the other hand, the inability of the two monomarinomycins A (**m**-**1** and **m**-**2**) to exhibit comparable biological action to the naturally occurring marinomycins underscores the importance of the strict topological requirements of the biological targets to these bioactive molecules. Nevertheless, the exercise unearthed interesting chemistry and produced new chemical entities, the potential uses of which remain to be explored. These results may also serve as a guide in future endeavors directed toward the construction of similar structures to the ones described here.

Acknowledgment. We thank Professor William Fenical for helpful discussions and Dr. Hak Cheol Kwon for assistance in the HPLC purification of synthetic marinomycins A−C and for biological evalutation of the monomarinomycins A. The assistance of Drs. D. H. Huang and R. Chadha with NMR spectroscopic and X-ray crystallographic analyses, respectively, is also acknowledged. Financial support for this work was provided by a grant from the National Institutes of Health and the Skaggs Institute of Chemical Biology. Financial support was also provided by the Pfeiffer Foundation (predoctoral fellowship to A.L.N.), the Kurt Fordan Foundation (Germany) (fellowship to C.S.S), and the National Institutes of Health (postdoctoral fellowship to K.P.C).

Supporting Information Available: Complete citations for footnote 3a,b, experimental procedures and compound characterization (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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