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Synthesis of the Monomeric Counterpart of Marinomycin A

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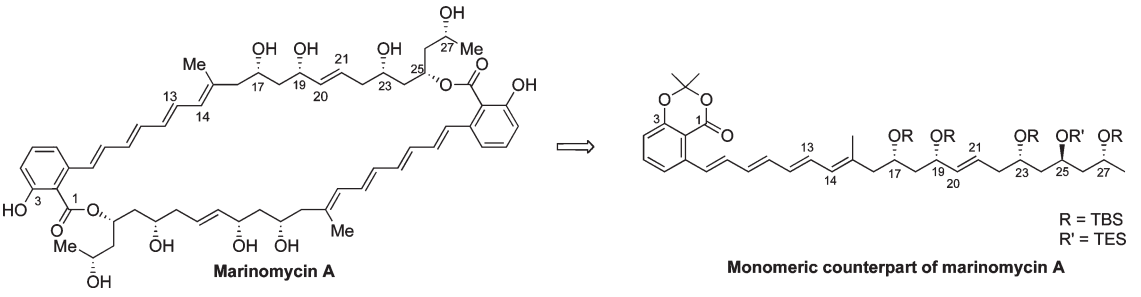

An efficient and highly convergent synthesis of the monomeric counterpart of the antitumor-antibiotic marine natural product marinomycin A was achieved by using optically active titanium complexes to control the configuration of the stereogenic centers, a highly stereo- and regioselective cross-metathesis to generate the (*E*)-configured C20−C21 double bond, and a Horner−Wadsworth−Emmons olefination followed by a Pd-catalyzed Stille cross-coupling to construct the tetraene moiety.

Introduction

Oceans provide an extraordinary source of biologically active natural products. Marinomycins A−C are three polyenic macrodiolides isolated in 2006 by Fenical et al. from the saline culture of a new group of marine actinomycetes, *Marinispora* strain CNQ-140, cultured from a sediment collected from the bottom of the ocean offshore of La Jolla, CA (USA).[1] These natural products display significant antibiotic activities, with MIC values of 0.1−0.6 μM, against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*. Further studies also revealed that marinomycins A−C demonstrated impressive and selective cancer cell cytotoxicities against six of the eight melanoma cell lines in the National Cancer Institute's 60 cell line panel (IC_{50} = 0.2−2.7 μM). Interestingly, only marinomycin A, C_2-symmetric, showed antifungal activity against *Candida albicans* (MIC_{90} = 10 μM). The molecular architecture of these three 44-membered dimeric macrolides is characterized by the presence of a tetraene conjugated with an aromatic unit derived from 2-hydroxybenzoic acid and connected to a pentahydroxylated polyketide chain. Fenical et al. have also shown that marinomycin A, the most abundant and most active of all, was photochemically convertible into an equilibrium mixture of marinomycins A (**1**), B (**2**), and C (**3**) upon exposure to ambient light (Scheme 1).[1] Consequently, the total synthesis of marinomycin A would constitute a total synthesis of the two others. Due to its complex molecular architecture and its exceptional biological properties, marinomycin A constitutes an ideal target for total synthesis. To the best of our knowledge, only one total synthesis has been reported to date from Nicolaou's group.[2] Herein, we wish to report the full account of our efforts that culminated in a concise and highly convergent synthesis of the monomeric counterpart of marinomycin A, and our attempts at dimerization.[3]

Results and Discussion

In our initial endeavor to synthesize marinomycin A (**1**), we opted for a dimerization strategy as depicted in Scheme 2, and we therefore concentrated our efforts toward the synthesis of

(1) (a) Kwon, H. C.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *J. Am. Chem. Soc.* **2006**, *128*, 1622–1632. (b) Erratum: Kwon, H. C.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *J. Am. Chem. Soc.* **2006**, *128*, 16410.

(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.

(3) For a preliminary communication, see: Amans, D.; Bellosta, V.; Cossy, J. *Org. Lett.* **2007**, *9*, 1453–1456.

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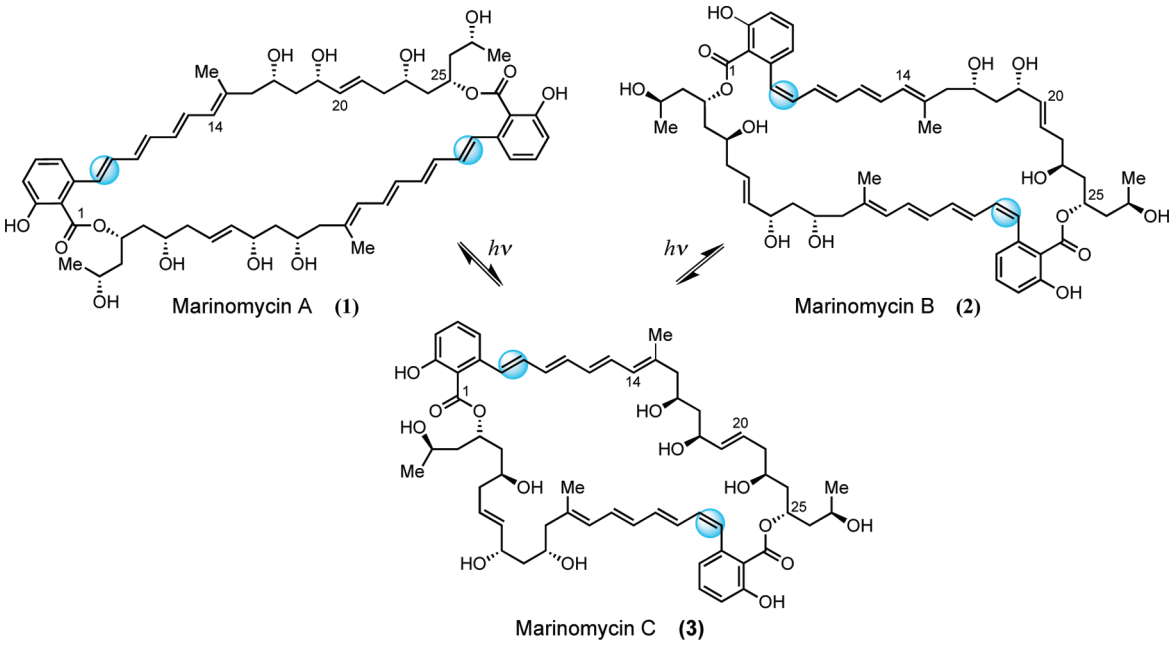
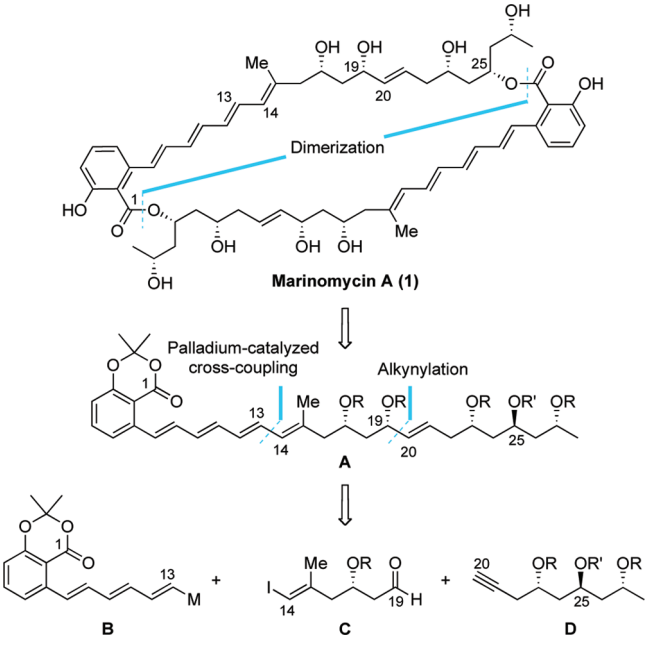
SCHEME 1



SCHEME 2

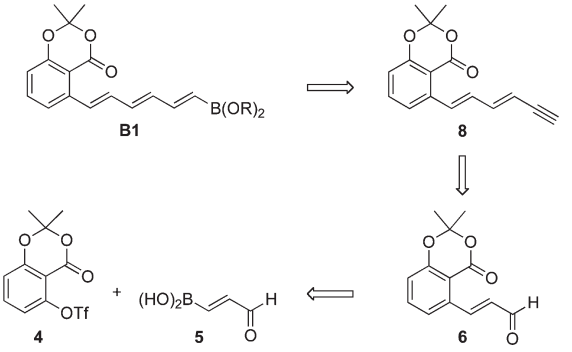


its monomeric counterpart **A**, which contains all the structural and stereochemical features of the natural product.

The monomer **A** could be accessed by performing a palladium-catalyzed cross-coupling between the trienic vinylmetal of type **B** and vinyl iodide **C** to create the C13−C14 bond, while the addition of the lithium acetylide of alkyne **D** onto *β*-hydroxyaldehyde **C** would allow the formation of the C19−C20 bond.

Synthesis of the Boronic Ester B1 [M = B(OR)$_2$]. The synthesis of boronic ester **B1** was envisioned via the hydroboration of enyne **8**. The latter would be obtained from the olefination of aldehyde **6**, which in turn would result from

SCHEME 3



a palladium-catalyzed Suzuki cross-coupling between aryl triflate **4** and vinylboronic acid **5** (Scheme 3).

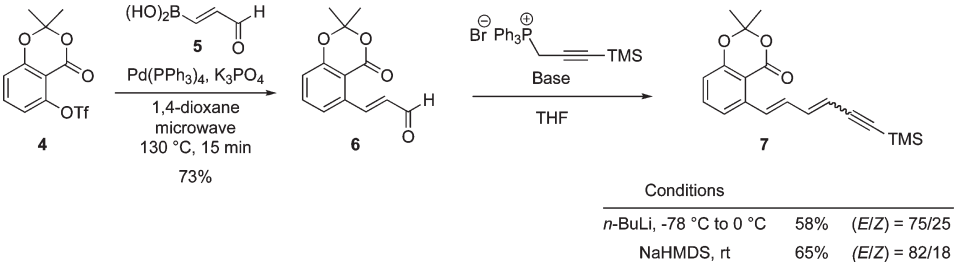
The coupling between aryl triflate **4**[4] and vinyl boronic acid **5**[5] turned out to be not as trivial as it seemed, partly due to significant decomposition of the α,*β*-unsaturated aldehyde generated in the course of the reaction. Nevertheless, scrupulous optimization of the reaction conditions allowed us to perform the envisaged Suzuki coupling using K_3PO_4 as a base in 1,4-dioxane, in the presence of $Pd(PPh_3)_4$, under microwave irradiation (130 °C, 15 min) to give the required aldehyde **6** in 73% yield.

Treatment of aldehyde **6** by the phosphonium ylide generated in situ upon treatment of commercially available (3-trimethylsilyl-2-propynyl)triphenylphosphonium bromide with

(4) Arylic triflate **4** was synthesized in two steps from commercially available 2,6-dihydroxybenzoic acid according to the following: (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.

(5) Boronic acid **5** was prepared in two steps via hydroboration of commercially available propiolaldehyde dimethylacetal according to the following: Touré, B. B.; Hoveyda, H. R.; Tailor, J.; Ulaczyk-Lesanko, A.; Hall, D. G. *Chem. Eur. J.* **2003**, *9*, 466–474.

SCHEME 4



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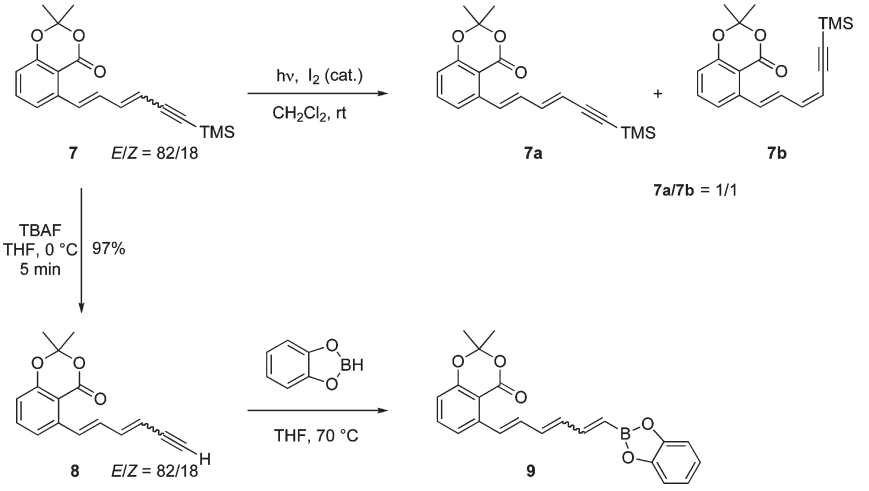


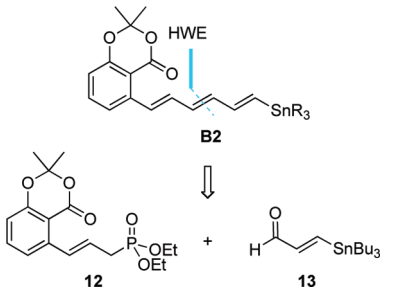
n-BuLi resulted in the formation of enyne **7** as a 75/25 inseparable mixture of *E*/*Z* geometric isomers, in 58% yield. Replacing *n*-BuLi by sodium bis(trimethylsilyl)amide (NaHMDS) slightly improved the *E*/*Z* ratio to 82/18 in favor of the desired *E*-isomer and the reaction proceeded in similar yield (Scheme 4).

At this stage, we believed that the *E*/*Z* ratio could be improved by irradiation of compound **7** with visible light. Against all expectations, exposure of enyne **7** to day light in the presence of a catalytic amount of iodine led to an increase of the proportion of the *Z*-isomer (*E*/*Z* ratio = 1:1). Being aware of the fact that the isomerization of the polyenic moiety could in principle be conducted at a later stage of the synthesis, we pursued the preparation of the targeted trienic vinyl boronic ester **9** with the mixture of *E*/*Z*-isomers of enyne **7**. After treatment of the latter with tetra-*n*-butylammonium fluoride (TBAF) at 0 °C in THF, the resulting terminal alkyne **8** underwent a chemo- and stereoselective hydroboration with catecholborane in THF to furnish vinylboronic ester **9** as a mixture of *E*/*Z*-isomers (Scheme 5). Unfortunately, numerous attempts to purify this unstable boronic ester both by flash chromatography on silica gel and by filtration over Florisil led to the degradation of the product.

Having experienced difficulties to obtain the required vinylboronic ester **9** of type **B1** in a satisfactory pure form, we decided to explore another route toward the synthesis of fragment **B**, using a vinyl stannane.

Synthesis of the Vinyl Stannane B2 [M = $SnBu_3$]. We believed that trienic vinyl stannane **B2** could result from a Horner−Wadsworth−Emmons olefination between

SCHEME 6



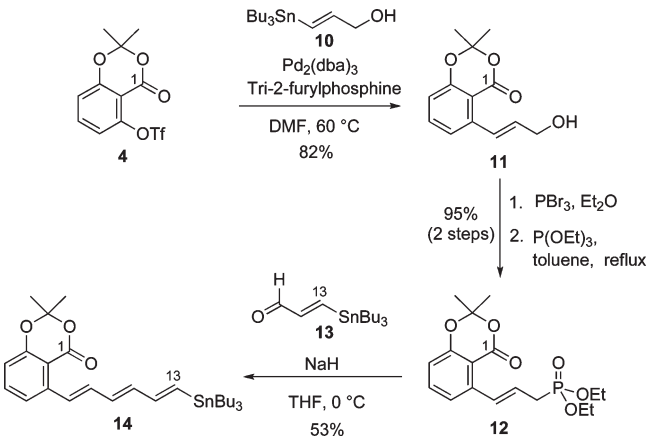
allylphosphonate **12** and the α,β-unsaturated aldehyde **13** (Scheme 6).

The preparation of phosphonate **12** was achieved by performing a palladium-catalyzed Stille cross-coupling between (*E*)-3-(tributylstannyl)prop-2-en-1-ol **10**[6] and aryl triflate **4** [$PdCl_2(PPh_3)_2$, tri-2-furylphosphine, DMF, 60 °C], which furnished allylic alcohol **11** in 82% yield.[7] Subsequent bromination of the latter by PBr_3, followed by exposure of the resulting allylic bromide to Arbuzov conditions [$P(OEt)_3$, toluene] provided the required diethyl allylphosphonate **12** in excellent yield. Olefination between

(6) (*E*)-3-(Tributylstannyl)prop-2-en-1-ol **10** was synthesized by performing a stereo- and regioselective stannylcupration of commercially available prop-2-yn-1-ol, using the mixed higher order cuprate [$(Bu_3Sn)BuCu(CN)Li_2$] generated in situ according to the following: Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Reuter, D. C. *Tetrahedron Lett.* **1989**, *30*, 2065–2068.

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

SCHEME 7



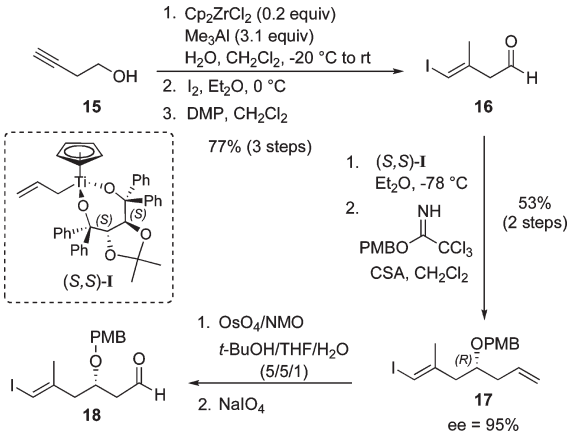
the previously obtained allylic phosphonate **12** and α,β-unsaturated aldehyde **13** was attempted. Addition of aldehyde **13**[8] to a solution of the sodium salt of allylic phosphonate **12** led to the desired trienic vinyl stannane **14** in 53% yield (Scheme 7).[9]

Having now efficiently obtained the required trienic stannane **14** (of type **B2**), we turned our attention toward the synthesis of vinyl iodide **C**.

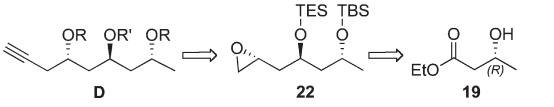
Synthesis of Vinyl Iodide C. The synthesis of vinyl iodide **C** commenced from the regio- and stereoselective carboalumination of homopropargyl alcohol **15** catalyzed by zirconium (Cp_2ZrCl_2, Me_3Al, H_2O)[10,11] followed by a metal−halogen exchange with iodine to give, after oxidation with Dess−Martin periodinane (DMP), the *E*-configured trisubstituted vinyl iodide **16** (77% yield over three steps). Aldehyde **16** was subsequently treated by the highly face-selective Hafner−Duthaler complex[12] (*S*,*S*)-**I** to provide, after protection of the resulting secondary alcohol as a PMB-ether under acidic conditions, the homoallylic alcohol **17** with high enantio selectivity (95% ee).[13] Regioselective oxidative cleavage of the terminal double bond (OsO_4, NMO then $NaIO_4$) ultimately furnished the desired aldehyde **18**, which was not purified but directly used in the subsequent alkynylation step (vide infra) (Scheme 8).

The last fragment, alkyne **D**, needed to be synthesized. Its preparation was first planned via opening of the optically active terminal epoxide **22**, which in turn could derive from the commercially available (*R*)-(−)-3-hydroxybutyrate **19** (Scheme 9).

SCHEME 8



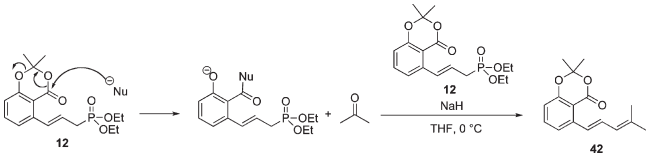
SCHEME 9



The (*R*)-3-hydroxybutyrate **19** was first protected as a TBS-ether and subsequently reduced to provide the corresponding aldehyde,[14] which was directly submitted to enantioselective allyltitanation by using the (*S*,*S*)-**I** allyltitanium complex to furnish, after protection as a TES-ether (TESCl, Et_3N, DMAP, CH_2Cl_2), the optically active homoallylic alcohol **20** with excellent diastereomeric purity (dr > 95/5) and in good overall yield (67% over four steps). Sharpless asymmetric dihydroxylation[15] of alkene **20** with AD-mix-β proceeded uneventfully to furnish the 1,2-diol **21** in 56% yield as a 75/25 mixture of inseparable diastereomers in favor of the desired diastereoisomer **21**. Subsequent treatment of this mixture of 1,2-diols by NaH and tosylimidazole successfully provided the optically active epoxide **22** in 83% yield as an inseparable 75/25 mixture of diastereoisomers. Oxirane **22** was then exposed to the lithium salt of trimethylsilylacetylene in the presence of $BF_3 \cdot Et_2O$ in THF, yielding the expected homopropargylic alcohol **23** (77% yield). Protection of the latter as a TBS-ether followed by

(8) β-Stannylacrolein **13** was synthesized by performing a regio- and stereoselective stannylcupration of commercially available propiolaldehyde diethylacetal followed by acetal hydrolysis according to the following: (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. (c) Beaudet, I.; Parrain, J.-L.; Quintard, J.-P. *Tetrahedron Lett.* **1991**, *32*, 6333–6336.

(9) It should be noted that aldehyde **13** needs to be added right away after the deprotonation of phosphonate **12** by NaH, to prevent the competitive formation of the *gem*-dimethylated olefin **42**, hardly separable from the desired trienic vinylstannane **14** by flash chromatography on silica gel. The diene **42** is the result of the condensation between the sodium salt of phosphonate **12** with acetone, presumably generated from the attack of an unidentified nucleophile in the reaction mixture (maybe the sodium salt of phosphonate **12** itself), on the carbonyl group of the aryl ester **12**.



(10) (a) Van Horn, D. E.; Negishi, E. *J. Am. Chem. Soc.* **1978**, *100*, 2252–2254. (b) Negishi, E.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639–6647.

(11) (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.

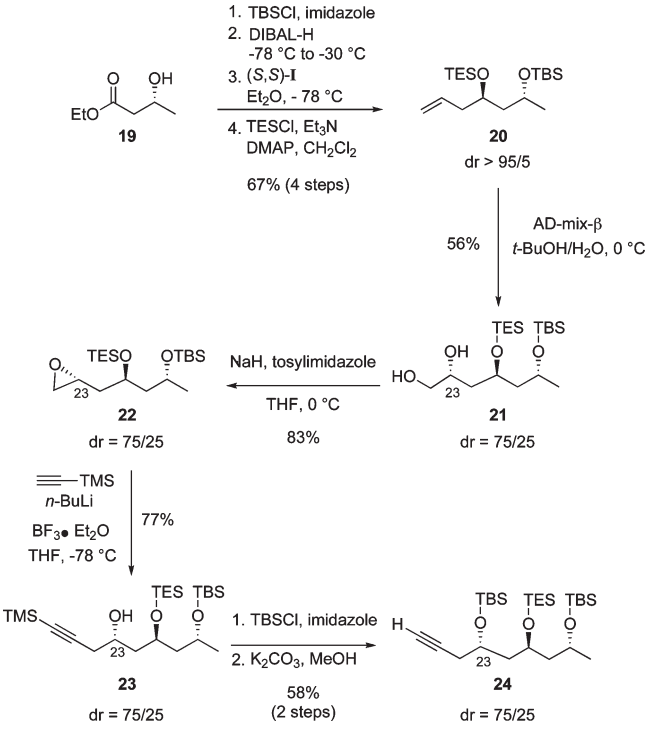
(12) (a) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, J.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321–2336. (b) Duthaler, R. O.; Hafner, A. *Chem. Rev.* **1992**, *92*, 807–832. (c) Cossy, J.; BouzBouz, S.; Pradaux, F.; Willis, C.; Bellosta, V. *Synlett* **2002**, 1595–1606.

(13) The (*R*) absolute configuration of **17** was confirmed by examination of the ^1H NMR spectra of the two corresponding mandelates, following the procedure described by the following: Seco, J. M.; Quiñoa, E.; Riguera, R. *Tetrahedron: Asymmetry* **2001**, *12*, 2915–2925.

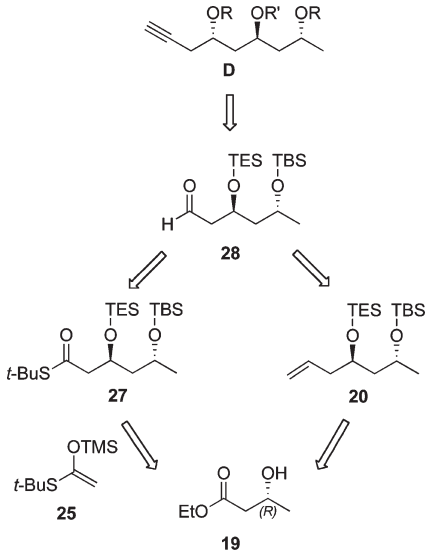
(14) Wattanasereekul, S.; Maier, M. E. *Adv. Synth. Catal.* **2004**, *346*, 855–861.

(15) For a review on Sharpless catalytic asymmetric dihydroxylation, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, 2483–2547.

SCHEME 10



SCHEME 11

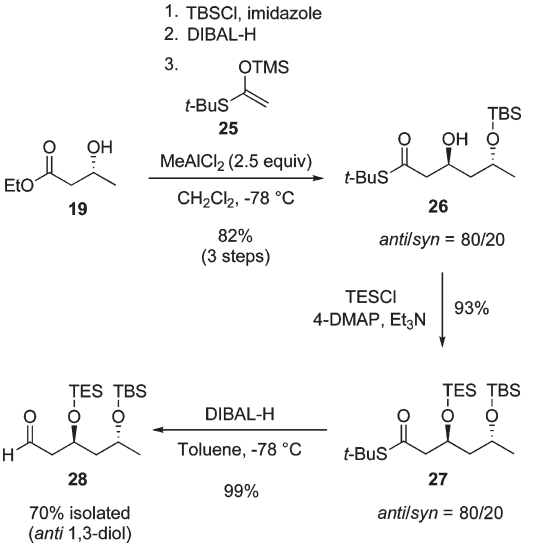


selective desilylation of the alkyne upon treatment with potassium carbonate in MeOH ultimately furnished the desired alkyne **24** (74% yield), unfortunately contaminated with 25% of its epimer at C23 (Scheme 10).

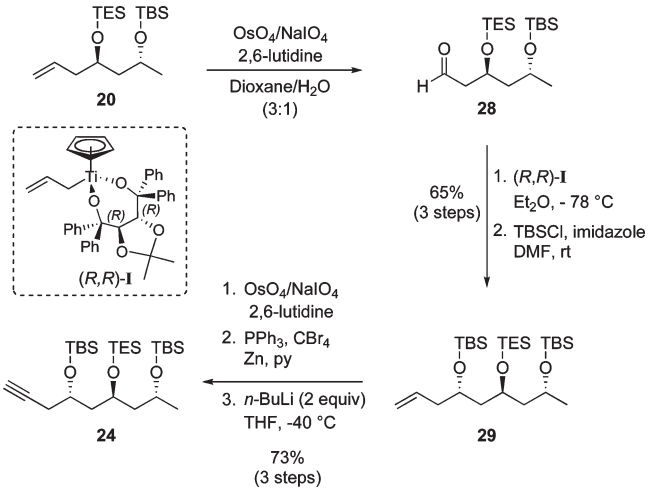
As we were not able to separate the mixture of epimers at C23 of alkyne **24**, another synthetic route was investigated for the diastereoselective preparation of the required 1,3,5-triol of type **D**.

Alkyne **D** could alternatively be accessed from aldehyde **28**, which could be obtained via two distinct synthetic pathways. A first possibility would involve a diastereoselective Mukaiyama-type aldol reaction between silylketene

SCHEME 12



SCHEME 13

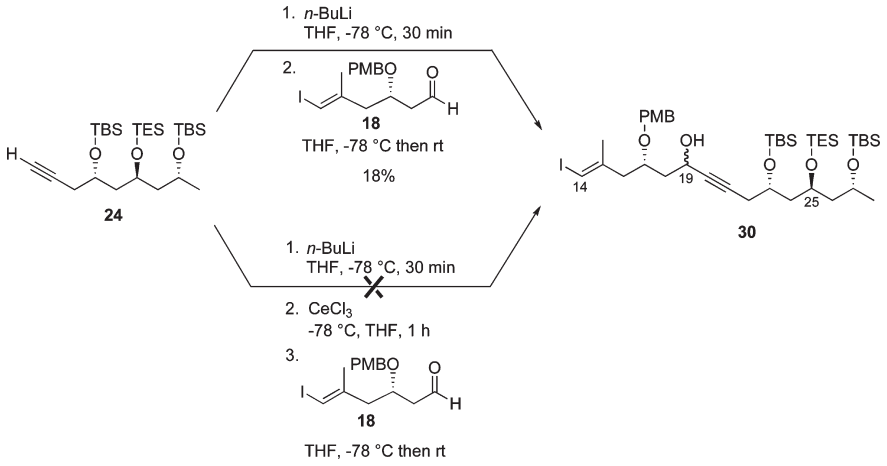


acetal **25** and the β-hydroxyaldehyde derived from ester **19**, while a diasteroselective allyltitanation of the latter followed by oxidative cleavage of the resulting homoallylic alcohol **20** would also provide the required aldehyde **28** (Scheme 11).

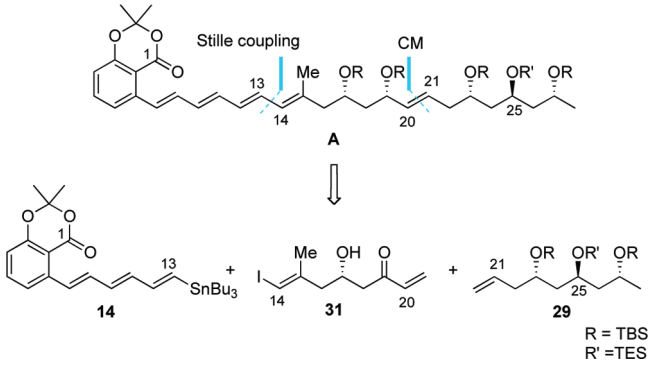
The Mukaiyama-aldol strategy was first explored. Thus, after protection and reduction of commercially available β-hydroxyester **19** of (*R*)-configuration with DIBAL-H, the resulting β-hydroxyaldehyde was subjected to the addition of the silylketene acetal derived from *tert*-butyl thioacetate **25**, in the presence of 2.5 equiv of $MeAlCl_2$ (−78 °C in CH_2Cl_2), which gave rise to 1,3-diol **26** as a 80/20 mixture of inseparable diastereoisomers in favor of the desired *anti* 1,3-diol (82% yield).[16] Subsequent protection of the secondary alcohol as a TES-ether followed by reduction of the *tert*-butyl thioester upon treatment with DIBAL-H in toluene led to aldehyde **28** in 99% yield (*anti*/*syn* = 80/20). At this stage, the two epimers could be easily separated

(16) Evans, D. A.; Allison, B. D.; Yang, M. G.; Masse, C. E. *J. Am. Chem. Soc.* **2001**, *123*, 10840–10852.

SCHEME 14



SCHEME 15



by flash chromatography on silica gel and the desired optically pure *anti* 1,3-diol **28** was isolated in 70% yield (Scheme 12).

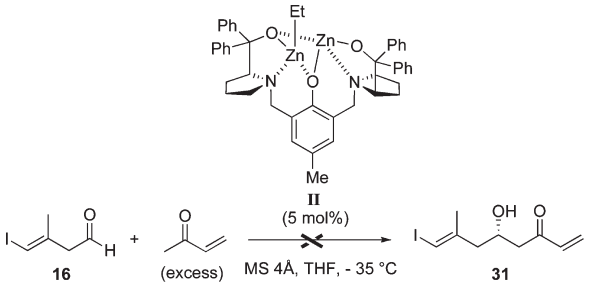
The second approach, which turned out to be equally efficient in providing the *anti* 1,3-diol **28**, involved an oxidative cleavage of the terminal double bond of the previously obtained diol **20** to give the desired aldehyde **28**. The latter was directly treated with allyltitanium complex (*R*,*R*)-**I** to furnish, after protection of the resulting homoallylic alcohol as a TBS-ether (TBSCl, imidazole, DMF),[17] the protected 1,3,5-triol **29** (65% yield over three steps). Oxidative cleavage of the terminal double bond (OsO_4, $NaIO_4$, 2,6-lutidine)[18] provided the corresponding aldehyde, which was subsequently transformed into the corresponding *gem*-dibromo olefin under Corey−Fuchs conditions (PPh_3, CBr_4, Zn, py). Subjection of the obtained *gem*-dibromoalkene to 2 equiv of *n*-BuLi allowed for the Fritsch−Buttemberg−Wiechell rearrangement to proceed and ultimately provided the desired alkyne **24** in 87% yield (Scheme 13).

With the three fragments **14** (of type **B**), **18** (of type **C**), and **24** (of type **D**) in hand, the coupling reactions could be implemented to complete the synthesis of the monomeric counterpart of marinomycin A. Alkyne **24** was deprotonated

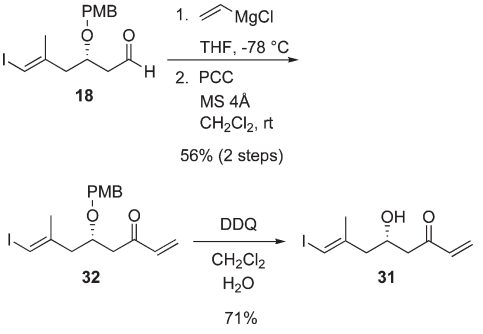
(17) It should be noted that the utilization of TBSOTf and 2,6-lutidine led to migrations of the silyl groups from one oxygen to another.

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

SCHEME 16



SCHEME 17

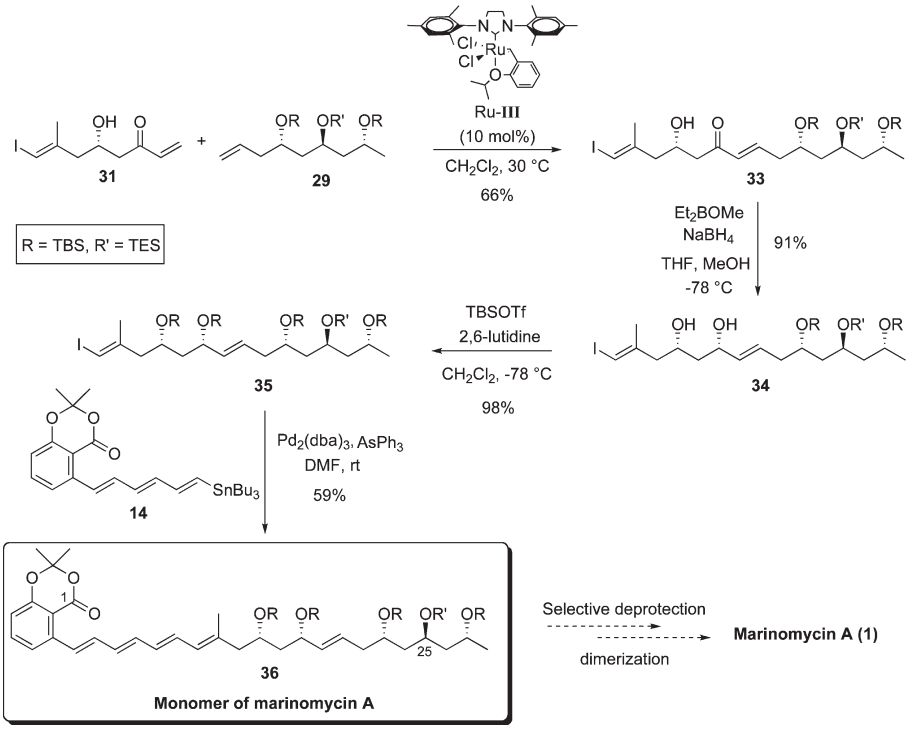


by *n*-BuLi and the resulting lithium acetylide was then condensed onto aldehyde **18**, in THF at −78 °C, to give propargylic alcohol **30** as a mixture of two epimers at C19 in 18% yield. Several experiments were performed with the aim of improving the yield, to no avail.[19]

To lower the basicity of the lithium acetylide while at the same time increasing its reactivity, the alkynyl lithium species generated in situ was transmetalated to the corresponding organocerium reagent upon exposure to cerium trichloride. Unfortunately, subsequent addition of aldehyde **18** (−78 °C, THF) failed to provide the desired propargylic alcohol **30** (Scheme 14).

(19) This coupling was also attempted by replacing aldehyde **18** by the corresponding Weinreb amide, but under these conditions no trace of the desired acetylenic ketone could be detected.

SCHEME 18

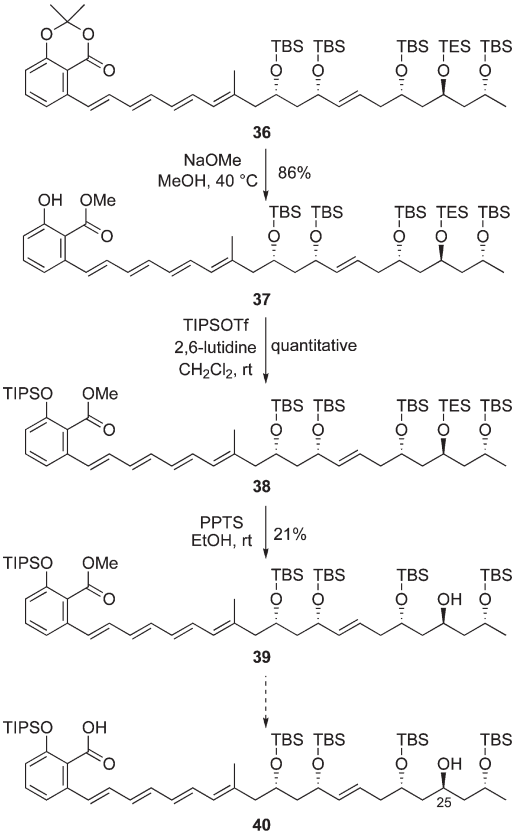


The lack of success associated with this strategy led us to investigate a revised approach for the synthesis of the monomeric counterpart of marinomycin A.

Revised Retrosynthetic Analysis. We believed that the monomeric counterpart of marinomycin A could alternatively be accessed via a stereo- and chemoselective cross-metathesis between β-hydroxy vinyl ketone **31** and olefin **29** to form the *E*-configured C20−C21 double bond. As previously, the vinyl iodide **31** would be connected to vinyl stannane **14** through a Pd-catalyzed Stille cross-coupling (Scheme 15).

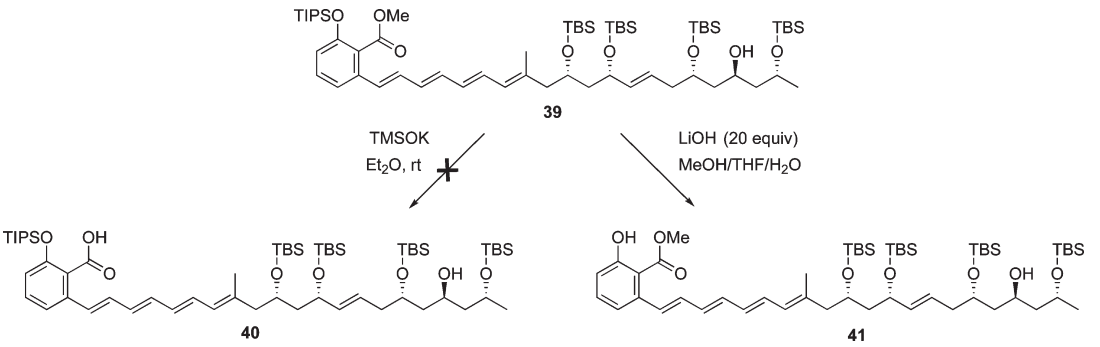
Having previously obtained the trienic vinylstananne **14** as well as 1,3,5-triol **29**, we concentrated our efforts on the enantioselective synthesis of β-hydroxy vinyl ketone **31**. The most direct access to this compound would be to perform an enantioselective addition of methyl vinyl ketone (MVK) enolate to aldehyde **16**. This transformation, although very attractive, is nevertheless extremely challenging due to the base instability of MVK and the aldol product generated throughout the reaction under basic conditions. To the best of our knowledge, only Trost et al. were able to perform such a transformation by using their dinuclear zinc catalyst **II**.[20,21] We consequently decided to attempt this methodology to synthesize the targeted β-hydroxy ketone **31**. Thus, aldehyde **16** was treated with a large excess of MVK (24 equiv), in the presence of dinuclear zinc catalyst **II** of (*S*,*S*)-configuration and molecular sieves 4 Å in THF at −35 °C, which unfortunately resulted in the obtention of a complex mixture of products in which the desired β-hydroxy ketone **31** could not be observed. Presumably, the relatively basic conditions employed led to the formation of elimination products and prevented the isolation of the targeted enone **31** (Scheme 16).

SCHEME 19



(20) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003–12004.
(21) Trost, B. M.; Shin, S.; Sclafani, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8602–8603.

SCHEME 20



We consequently resorted to more classical transformations that involved manipulation of the previously obtained optically active β-hydroxyaldehyde **18** as depicted in Scheme 17. Thus, addition of vinylmagnesium bromide onto aldehyde **18**, followed by oxidation of the resulting epimeric mixture by pyridinium chlorochromate (PCC) allowed the formation of vinyl ketone **32** in 56% yield (over two steps). Exposure of the latter to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) ultimately furnished the desired β-hydroxy ketone **31** in 71% yield (Scheme 17).

Completion of the Synthesis of the Monomeric Counterpart of Marinomycin A. At this stage, we attempted to couple alkenyl ketone **31** with terminal alkene **29** by using a ruthenium-catalyzed cross-metathesis reaction. Gratifyingly, addition of 10 mol % of the Grubbs-Hoveyda second generation catalyst Ru-**III**[22] to an equimolar mixture of vinyl ketone **31** and olefin **29** successfully generated enone **33** in 66% yield and with total *E*-selectivity. Subsequent *syn*-reduction[23] of β-hydroxy ketone **33** occurred uneventfully to produce 1,3-*syn*-diol **34** as a single diastereoisomer (dr > 98/2) in 91% yield. Protection of the two hydroxy groups at C17 and C19 as *tert*-butyldimethylsilyl ethers (TBSOTf, 2,6-lutidine) gave rise to the fully protected penta-alkoxylated alkenyl iodide **35** almost quantitatively. Finally, a Pd-catalyzed Stille cross-coupling[24] between trienic vinyl stannane **14** and alkenyl iodide **35** (Pd_2dba_3, triphenylarsine, DMF) successfully furnished the monomeric counterpart of marinomycin A **36** (of type **A**) in 59% yield (Scheme 18).

To perform the envisaged dimerization reaction, the hydroxy group at C25 protected as a TES-ether needed to be selectively removed.

Due to the intrinsic instability of the acetonide functionality under the acidic conditions required to perform the aforementioned deprotection, compound **36** was subjected to methanolysis by using sodium methanolate in MeOH, to afford the corresponding methyl ester **37** in 86% yield. Subsequent protection of the resulting phenol as a triisopropylsilyl ether (TIPS) furnished compound **38**. To achieve the selective deprotection of the TES-ether at C25 in view of the subsequent dimerization, polyol **38** was treated by pyridinium *p*-toluenesulfonate (PPTS) in EtOH, which ultimately furnished the desired alcohol **39**, albeit in low yield due to significant decomposition (Scheme 19).

Several attempts at saponification of the methyl ester **39** were tested in order to provide the targeted carboxylic acid **40**. The presence of silyl ethers required the utilization of mild basic conditions, to avoid any fortuitous deprotection. Thus, methyl ester **39** was treated with potassium trimethylsilanolate, in ether at rt, which unfortunately failed in giving the desired carboxylic acid **40** (the starting material was recovered). Using an excess of lithium hydroxide (20 equiv) also met with failure, since it led to the deprotection of the phenol, while the methyl ester remained intact (Scheme 20). Unfortunately, despite numerous efforts, we were not able to obtain the targeted hydroxyacid **40**. It may be necessary to change the nature of the protecting groups to achieve the proposed dimerization.

Conclusion

In conclusion, the monomeric counterpart of marinomycin A **36**, which incorporates all the structural and stereochemical features of the natural product, was efficiently synthesized by using a highly convergent approach, in 11 steps from commercially available ethyl (*R*)-3-hydroxybutyrate **19** for the longest linear sequence and in 15% overall yield.

Major highlights of this synthetic endeavor include highly enantioselective allyltitanations to introduce the stereogenic centers at C17, C23, and C25, a stereo- and chemoselective cross-metathesis to form the C20−C21 double bond of *E*-configuration and a Pd-catalyzed Stille cross-coupling to elaborate the very sensitive conjugated tetraenic moiety. A dimerization should in principle lead to the extremely scarce but exceptionally potent natural product marinomycin A.

Experimental Section

5-[(1*E*,3*E*,5*E*)-6-(Tributylstannyl)hexa-1,3,5-trienyl]-2,2-dimethyl-4*H* benzo[1,3]dioxin-4-one (14). To a stirred suspension of sodium hydride (60% in oil, 46 mg, 1.16 mmol, 4.0 equiv) in anhydrous THF (2 mL) at 0 °C was added a solution of phosphonate **12** (205 mL, 0.58 mmol, 2.0 equiv) in THF (2 mL) dropwise. The resulting deep purple solution was cooled to −20 °C and a solution of aldehyde **6** (100 mg, 0.29 mmol, 1.0 equiv) in THF (1 mL) was added dropwise. The resulting mixture was warmed to 0 °C and stirred for 15 min, and was then allowed to warm to rt. After 30 min of stirring, the resulting black solution was hydrolyzed by adding a saturated aqueous solution of

(22) (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.

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

(24) (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.

$NaHCO_3$ (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc 98/2) afforded the trienic stannane **14** (83 mg, 53%) as a viscous yellow oil that was prone to decomposition upon storage at −20 °C: R_f 0.5 (petroleum ether/EtOAc 98/2); IR (neat) 2920, 2847, 1734, 1593, 1573, 1473, 1316, 1265, 1209, 1043, 1003, 688, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, 1H, J = 15.5 Hz), 7.43 (t_{app}, 1H, J = 8.0 Hz), 7.33 (d, 1H, J = 7.8 Hz), 6.87−6.80 (m, 2H), 6.65 (dd, 1H, J = 18.3, 9.8 Hz), 6.50−6.32 (m, 3H), 1.71 (s, 6H), 1.57−1.47 (m, 6H), 1.35−1.25 (m, 6H), 0.95−0.86 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4 (s), 157.0 (s), 146.8 (d), 141.7 (s), 137.7 (d), 137.2 (d), 135.0 (d), 133.5 (d), 133.0 (d), 130.3 (d), 120.6 (d), 115.9 (d), 110.5 (s), 105.2 (s), 29.1 (3t), 27.3 (3t), 25.6 (2q), 13.7 (3q), 9.7 (3t); HRMS (ESI) calcd for $C_{28}H_{42}NaO_3Sn + Na^+$ 569.2054, found 569.2050.

(*E*)-(*S*)-5-Hydroxy-8-iodo-7-methylocta-1,7-dien-3-one (31). To a stirred solution of vinyl ketone **32** (1.0 g, 2.49 mmol, 1.0 equiv) in a CH_2Cl_2/H_2O mixture (9/1, 35 mL) was added 2,3-dichloro-5,6-dicyanoquinone (680 mg, 2.99 mmol, 1.2 equiv) at rt. After 45 min of stirring, the resulting deep orange heterogeneous solution was quenched by adding a saturated solution of Na_2SO_3 (20 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel (petroleum ether/AcOEt 95/5 to 80/20) provided the desired β-hydroxy vinyl ketone **31** (498 mg, 71%) as a colorless oil: R_f 0.2 (petroleum ether/EtOAc 80/20); $[\alpha]^{20}_D$ +27.8 (c 1.0, $CHCl_3$); IR (neat) 3423, 2909, 1672, 1612, 1401, 1272, 1047, 964, 766, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.29 (dd, 1H, J = 17.7, 10.3 Hz), 6.18 (dd, 1H, J = 17.7, 1.0 Hz), 5.97 (br s, 1H), 5.85 (dd, 1H, J = 10.3, 1.0 Hz), 4.21 (m, 1H), 2.92 (br s, 1H, OH), 2.73−2.58 (m, 2H), 2.40 (dd, 1H, J_{systAB} = 13.5, 7.5 Hz), 3.29 (dd, 1H, J_{systAB} = 13.5, 5.4 Hz), 1.82 (br s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7 (s), 144.5 (s), 136.6 (d), 129.5 (t), 77.7 (d), 65.5 (d), 46.3 (t), 45.1 (t), 24.2 (q); HRMS (ESI) calcd for $C_9H_{13}O_2I + Na^+$ 302.9858, found 302.9852.

(1*E*,7*E*)-(4*S*,10*S*,12*S*,14*R*)-10,14-Bis(*tert*-butyldimethylsilyloxy)-4-hydroxy-1-iodo-2-methyl-12-triethylsilyloxypentadeca-1,7-dien-6-one (33). To a stirred solution of olefin **29** (90 mg, 0.17 mmol, 1.0 equiv) and β-hydroxy vinyl ketone **31** (49 mg, 0.17 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (2 mL) at rt was added Grubbs−Hoveyda catalyst Ru-**III** (11 mg, 0.017 mmol, 0.1 equiv). The resulting reaction mixture was warmed to 30 °C and stirred at this temperature for 15 h. The reaction mixture was cooled to rt and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc 95/5 to 90/10) provided the desired enone **33** (89 mg, 66%) as a colorless oil: R_f 0.5 (petroleum ether/EtOAc 90/10); $[\alpha]^{20}_D$ + 7.1 (c 0.60, $CHCl_3$); IR (neat) 3460, 2952, 2928, 2879, 2856, 1666, 1627, 1471, 1462, 1376, 1361, 1253, 1068, 1005, 834, 773, 739, 725, 669 cm^1; ^1H NMR (400 MHz, $CDCl_3$) δ 6.82 (dt, 1H, J = 16.0, 7.0 Hz), 6.05 (d, 1H, J = 16.0 Hz), 5.96 (br s, 1H), 4.19 (m, 1H), 3.83 (m, 2H), 3.74 ($quint_{app}$, 1H, J = 7.0 Hz), 3.12 (br s, 1H, OH), 2.65 (dd, 1H, J_{systAB} = 17.5, 3.1 Hz), 2.53 (dd, 1H, J_{systAB} = 17.5, 8.6 Hz), 2.41 (m, 2H), 2.26 (m, 2H), 1.82 (br s, 3H), 1.61−1.39 (m, 4H), 1.09 (d, 3H, J = 6.1 Hz), 0.89 (t, 9H, J = 8.0 Hz), 0.82 (s, 18H), 0.53 (q, 6H, J = 8.0 Hz), 0.01, 0.00, −0.01 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1 (s), 145.6 (d), 144.6 (s), 132.5 (d), 77.5 (d), 68.8 (d), 67.5 (d), 65.9 (d), 65.6 (d), 48.4 (t), 46.3 (t), 46.2 (t), 45.0 (t), 40.5 (t), 26.0, 25.8 (6q), 24.4 (q), 24.2 (q), 18.1 (2s), 7.0 (3q), 5.6 (3t), −3.9 (q), −4.3 (2q), −4.5 (4q); HRMS (ESI) calcd for $C_{34}H_{69}IO_5Si_3 + Na^+$ 791.3395, found 791.3386.

(1*E*,7*E*)-(4*S*,6*S*,10*S*,12*S*,14*R*)-10,14-Bis(*tert*-butyldimethylsilyloxy)-1-iodo-2-methyl-12-triethylsiloxypentadeca-1,7-dien-4,6-diol (34). To a stirred solution of β-hydroxy ketone **33** (75 mg, 0.10 mmol, 1.0 equiv) in a THF/MeOH mixture (4/1, 2 mL) at −78 °C under argon was added dropwise methoxydiethylborane (1 M in THF, 111 μL, 0.11 mmol, 1.1 equiv) and the resulting mixture was stirred for 15 min. Sodium borohydride (5 mg, 0.11 mmol, 1.1 equiv) was added in one portion, and the mixture was stirred for 6 h at −78 °C. The reaction was quenched by adding acetic acid (1 mL), diluted with ethyl acetate (10 mL), and the resulting mixture was successively washed with a saturated aqueous Na_2CO_3 solution (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness under reduced pressure. The residue thus obtained was azeotroped 5 times with methanol until the hydrolysis of the boronate was complete, and then purified by flash chromatography on silica gel (petroleum ether/EtOAc 95/5 to 90/10), which provided the desired *syn*-1,3-diol **34** (69 mg, 91%) as a colorless oil: R_f 0.2 (petroleum ether/EtOAc 90/10); $[\alpha]^{20}_D$ − 4.5 (c 1.1, $CHCl_3$); IR (neat) 3352, 2952, 2928, 2856, 1616, 1462, 1377, 1252, 1067, 1004, 833, 772, 725, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.94 (s, 1H), 5.63 (dt, 1H, J = 15.5, 7.0 Hz), 5.45 (dd, 1H, J = 15.5, 6.9 Hz), 4.27 (q_{app}, 1H, J = 6.9 Hz), 3.95 ($quint_{app}$, 1H, J = 7.0 Hz), 3.83 ($sext_{app}$, 1H, J = 6.0 Hz), 3.78−3.68 (m, 2H), 2.35 (dd, 1H, J_{systAB} = 13.5, 7.4 Hz), 2.26 (dd, 1H, J_{systAB} = 13.5, 5.0 Hz), 2.21−2.07 (m, 2H), 1.82 (br s, 3H), 1.59−1.48 (m, 5H), 1.43 (m, 1H), 1.08 (d, 3H, J = 6.1 Hz), 0.89 (t, 9H, J = 8.0 Hz), 0.82 (s, 9H), 0.81 (s, 9H), 0.53 (q, 6H, J = 8.0 Hz), 0.00 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6 (s), 134.7 (d), 128.3 (d), 77.5 (d), 73.6 (d), 69.5 (2d), 67.6 (d), 66.0 (d), 48.4 (t), 47.8 (t), 45.9 (t), 42.7 (t), 40.3 (t), 25.9 (6q), 24.4 (q), 24.2 (q), 18.1 (2s), 7.1 (3q), 5.7 (3t), −3.9, −4.1, −4.3, −4.5 (4q); HRMS (ESI) calcd for $C_{34}H_{71}IO_5Si_3 + Na^+$ 793.3552, found 793.3546.

(1*E*,7*E*)-(4*S*,6*S*,10*S*,12*S*,14*R*)-4,6,10,14-Tetrakis(*tert*-butyldimethylsilyloxy)-1-iodo-2-methyl-12-triethylsiloxypentadeca-1,7-diene (35). To a stirred solution of **34** (153 mg, 0.20 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) at −78 °C were added 2,6-lutidine (180 μL, 0.79 mmol, 4 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (115 μL, 0.99 mmol, 5 equiv). After 30 min of stirring at −78 °C, a saturated aqueous solution of NH_4Cl (3 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel (petroleum ether/EtOAc 99/1) provided the desired fully protected polyol **35** (193 mg, 98%) as a viscous colorless oil: R_f 0.9 (petroleum ether/EtOAc 95/5); $[\alpha]^{20}_D$ − 8.3 (c 0.72, $CHCl_3$); IR (neat) 2953, 2928, 2885, 2856, 1471, 1462, 1377, 1361, 1252, 1068, 1004, 833, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.84 (s, 1H), 5.50 (m, 1H), 5.35 (dd, 1H, J = 15.5, 6.9 Hz), 4.07 (m, 1H), 3.86−3.76 (m, 4H), 2.35 (dd, 1H, J = 13.4, 4.2 Hz), 2.24 (m, 1H), 2.13 (m, 2H), 1.77 (s, 3H), 1.69−1.41 (m, 6H), 1.08 (d, 3H, J = 6.1 Hz), 0.90 (t, 9H, J = 8.0 Hz), 0.84−0.79 (m, 36H), 0.54 (q, 6H, J = 8.0 Hz), 0.01−0.05 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0 (s), 135.8 (d), 126.6 (d), 77.5 (d), 70.9 (d), 69.4 (d), 67.7 (d), 67.4 (d), 66.0 (d), 48.6 (t), 47.2 (t), 46.5 (t), 45.6 (t), 40.6 (t), 26.1−25.7 (12q), 24.5 (q), 24.1 (q), 18.1 (4s), 7.1 (3q), 5.7 (3t), −2.9 to −4.4 (8q); HRMS (ESI) calcd for $C_{46}H_{99}IO_5Si_5 + Na^+$ 1021.5281, found 1021.5287.

2,2-Dimethyl-5-[(1*E*,3*E*,5*E*,7*E*,13*E*)-(10*S*,12*S*,16*S*,18*S*,20*R*)-10,12,16,20-tetrakis(*tert*-butyldimethylsilyloxy)-8-methyl-18-triethylsilyloxyhenicosa-1,3,5,7,13-pentaenyl]-1,3-benzodixin-4-one (36). To a stirred solution of vinyl iodide **35** (57 mg, 57 μmol, 1.0 equiv) and trienic stannane **14** in anhydrous and degassed DMF (2 mL) were successively added triphenylarsine (2 mg, 6 μmol, 0.1 equiv) and $Pd_2(dba)_3$ (4 mg, 3 μmol, 0.05 equiv) at rt. After 15 h of stirring in the dark at rt, the reaction mixture was diluted in Et_2O (5 mL) and poured in a saturated aqueous NH_4Cl

solution (5 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. Purification of the residue by chromatography on a preparative TLC plate (hexanes/EtOAc 95/5) provided the desired protected monomer **36** (38 mg, 59%) as a yellow oil. R_f 0.5 (petroleum ether/EtOAc 90/10); $[\alpha]^{20}_D$ −12.0 (*c* 0.68, $CHCl_3$); IR (neat) 2954, 2929, 2857, 1739, 1576, 1473, 1253, 1079, 1046, 1005, 836, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, 1H, J = 15.4 Hz), 7.37 (t, 1H, J = 8.0 Hz), 7.27 (d, 1H, J = 7.3 Hz), 6.81 (dd, 1H, J = 15.4, 10.0 Hz), 6.74 (dd, 1H, J = 8.0, 1.0 Hz), 6.47−6.37 (m, 3H), 6.17 (dd, 1H, J = 14.7, 10.0 Hz), 6.88 (d, 1H, J = 14.7 Hz), 5.50 (dt, 1H, J = 15.4, 6.8 Hz), 5.36 (dd, 1H, J = 15.4, 6.8 Hz), 4.10 (br q, 1H, J = 6.5 Hz), 3.86−3.74 (m, 4H), 2.23 (dd, 1H, J = 13.3, 4.8 Hz), 2.14 (m, 3H), 1.74 (s, 3H), 1.65 (s, 6H), 1.62−1.43 (m, 6H), 1.07 (d, 3H, J = 6.1 Hz), 0.90 (t, 9H, J = 8.0 Hz), 0.84−0.79 (m, 36H), 0.54 (q, 6H, J = 13.3 Hz), 0.00 to −0.06 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5 (s), 157.0 (s), 141.9 (s), 137.9 (s), 136.0 (d), 135.9 (d), 134.9 (d), 133.7 (d), 132.2 (d), 130.9 (d), 130.8 (d), 129.1 (d), 128.3 (d), 126.4 (d), 120.5 (d), 115.7 (d), 110.5 (s), 105.1 (s), 70.9 (d), 69.4 (d), 68.2 (d), 67.7 (d), 66.0 (d), 48.6 (t), 48.1 (t), 46.6 (t), 45.6 (t), 40.6 (t), 25.9 (12q), 25.6 (2q), 24.1 (q), 18.1 (4s), 17.8 (q), 7.1 (3q), 5.7 (3t), −3.8 to −4.7 (8q); HRMS (ESI) calcd for $C_{62}H_{114}O_8Si_5 + Na^+$ 1149.7258, found 1149.7248.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **6**, **8**, **11**, **12**, **14**, **17**, **20**, **22**−**24**, **26**−**29**, and **31**−**38**. This material is available free of charge via the Internet at http://pubs.acs.org.