JOC The Journal of Organic Chemistry

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Amphidinolide B: Total Synthesis, Structural Investigation, and Biological Evaluation

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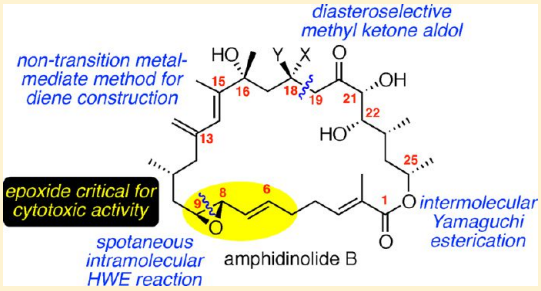
Supporting Information

ABSTRACT: The total syntheses of amphidinolide B_1 and the proposed structure of amphidinolide B_2 have been accomplished. Key aspects of this work include the development of a practical, non-transition-metal-mediated method for the construction of the C_{13}–C_{15} diene, the identification of α-chelation and dipole minimization models for diastereoselective methyl ketone aldol reactions, the discovery of a spontaneous Horner–Wadsworth–Emmons macrocyclization strategy, and the development of a novel late stage method for construction of an allylic epoxide moiety. The originally proposed structure for amphidinolide B_2 and diastereomers thereof display potent antitumor activities with IC_{50} values ranging from 3.3 to 94.5 nM against human solid and blood tumor cells. Of the different stereoisomers, the proposed structure of amphidinolide B_2 is over 12-fold more potent than the $C_{8,9}$-epimer and C_{18}-epimer in human DU145 prostate cancer cells. These data suggest that the epoxide stereochemistry is a significant factor for anticancer activity.



INTRODUCTION

First reported in 1986, the amphidinolide family of natural products has long captured the attention of the scientific community.[1] To date, over 30 members of this family have been isolated.[2] Given their fascinating structures and diverse biological activity, these targets have attracted considerable attention in both the synthetic[3−5] and biological communities.[6]

From this diverse collection of compounds, the amphidinolide B subfamily possesses some of the most intriguing structural features and biological activity. Kobayashi and co-workers reported the isolation of the 26-membered macrolide (amphidinolide B) from the dinoflagellate *Amphidinium* sp. in small amounts (Figure 1).[2b] The planar original structure was proposed as compound **1**. Subsequent reisolation by Shimizu and co-workers as well as structure determination through X-ray crystallographic analysis by Clardy and co-workers provided the relative stereochemistry of amphidinolide B (which was renamed amphidinolide B_1) as compound **2**.[2c] In addition, the location of the methyl moiety of the dienyl system was reassigned to the C_{15} position. Absolute configuration of **2** was later established via degradation.[2d] Shimizu and co-workers also reported the isolation of two related members of this family, amphidinolide B_2 (**3**) and B_3 (**4**), and proposed their structures based on analogy to **2** and comparison of the NMR spectra. More recently, Kobayashi and co-workers reported the isolation of additional members of this subfamily, amphidinolide B_4 and B_5 (**5** and **6**)[2e] as well as amphidinolides B_6 and B_7 (not shown).[2f] Structurally related amphidinolides G and H [e.g., amphidinolide H_1 (**7**) and amphidinolide G_1 (**8**)] have also been reported.[2p−r] In particular, amphidinolide B_1 (**2**) has proven to be the most cytotoxic member of the amphidinolide family, demonstrating impressive potency in early cancer screening [IC_{50} levels: L1210 murine leukemia cell line (0.14 ng/mL),[2b] human colon tumor HCT 116 cell line (0.12 μg/mL),[2c] and KB cancer cell line (4.2 ng/mL)].[1f]

In addition to the intriguing biological activity, macrolide **2** has a compelling architecture with nine stereogenic centers embedded within a 26-membered macrocycle including a reactive allylic epoxide moiety at C_6–C_9 and a highly substituted diene moiety at C_{13}–C_{15}. Consequently, this target **2** has attracted considerable synthetic attention from numerous laboratories[7] including our own.[8−10] In 2008, we reported the first total syntheses of amphidinolide B_1 (**2**) as well as the proposed structure of amphidinolide B_2 (**3**) which we established to be incorrect.[4] Subsequent to our efforts, Fürstner and co-workers published their synthesis of **2** in 2009[5] and more recently Nishiyama and co-workers completed their total synthesis in 2012.[11] It should be noted that Fürstner reported the first syntheses of related amphidinolides G and H in 2007.[3aa] Herein, we disclose a full account of our work and the biological evaluation of synthesized analogues of amphidinolide B.

RESULTS AND DISCUSSION

Our initial retrosynthetic strategy is shown in Scheme 1. We intended to install the fragile allylic epoxide moiety at a late stage from the corresponding C_7–C_9 enone motif. Macrolactonization of the corresponding seco acid **9** under Mitsunobu conditions[12] could form the key 26-membered ring system. The C_8–C_9 bond

Received: December 5, 2012
Published: February 13, 2013

   dx.doi.org/10.1021/jo3026077 | J. Org. Chem. 2013, 78, 2213−2247

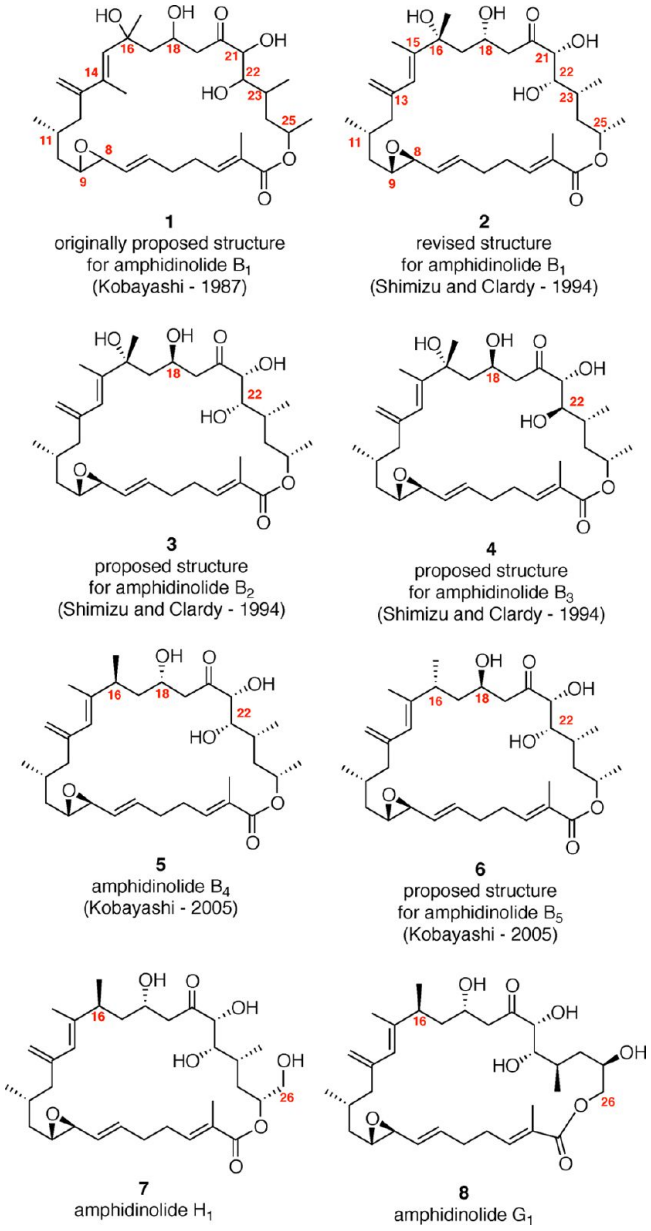
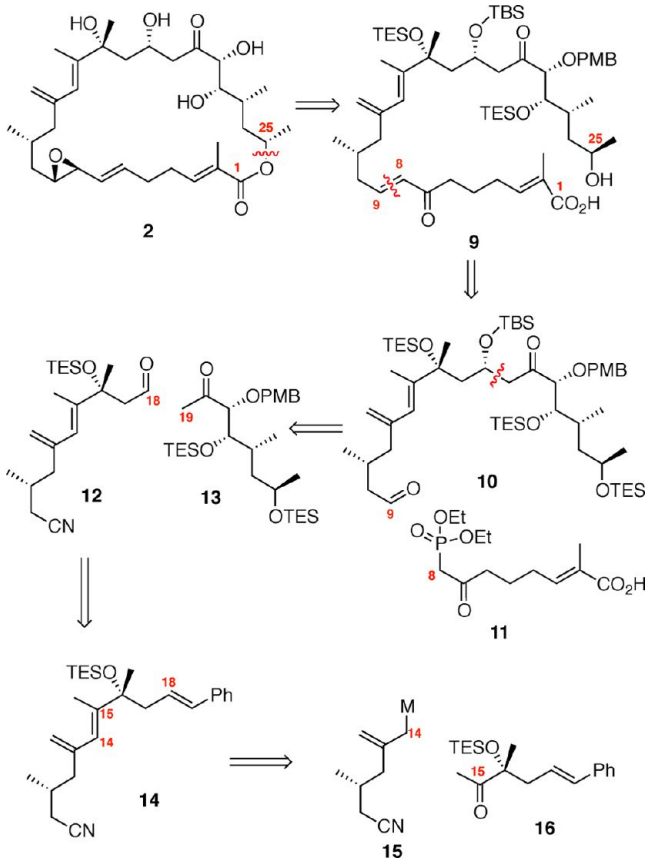


Figure 1. Amphidinolides B, G, and H.

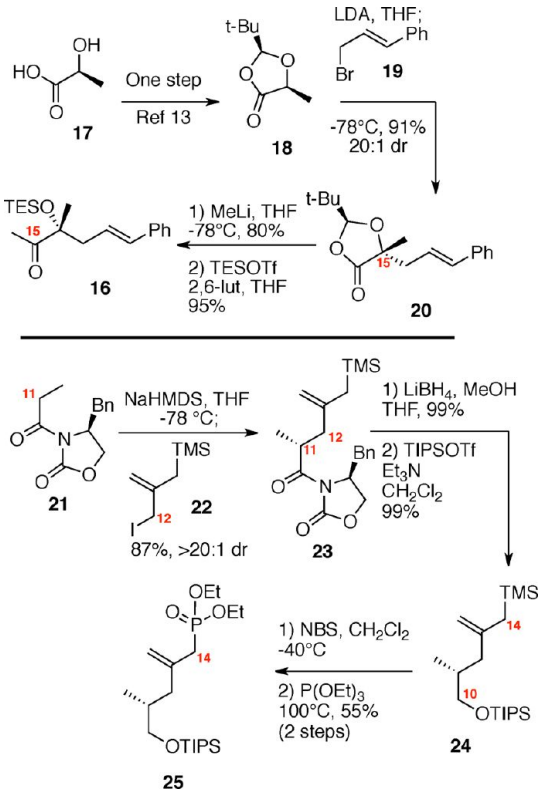
would be accessible from a HWE olefination with the keto phosphonate **11** and aldehyde **10**. The C_{18} stereogenic center could be constructed by a chelation-controlled aldol condensation between aldehyde **12** and α-benzyloxy ketone **13**. The aldehyde **12** would be derived from the styrenyl compound **14** through a regioselective oxidative cleavage. The diene could be accessed from the coupling of an allylic metallo species such as **15** and the methyl ketone **16**.

Synthesis of the nucleophilic components **24** and **25** and styrenyl compound **16** are shown in Scheme 2. The methyl ketone **16** could be prepared in four steps from L-lactic acid (**17**). Using Seebach chemistry,[13] stereochemistry originally contained in the hydroxyl acid **17** was transferred cleanly to the lactone **20** with high levels of diastereoselecitivity. Treatment of the lactone with MeLi yielded the α-hydroxy methyl ketone which was protected as its TES ether **16**. For the nucelophilic component **15**, we envisioned multiple options including phosphonate **25** and Peterson-type approaches (e.g., **24**). Starting from the

Scheme 1. Initial Retrosynthetic Analysis of Amphidinolide B_1



Scheme 2. Synthesis of Diene Precursors



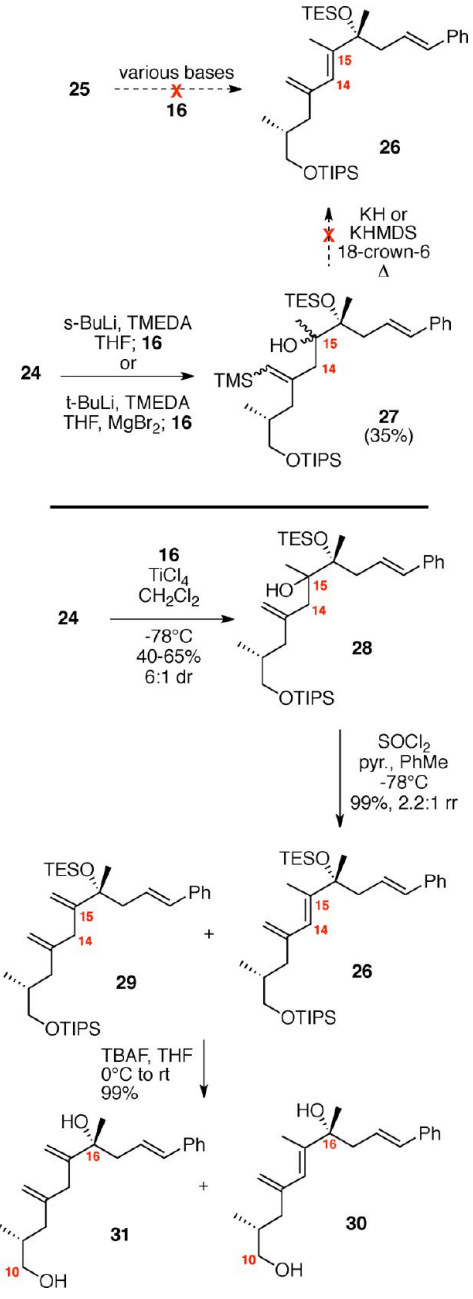
commercially available oxazolidinone **21** and known iodide **22**,[14] Evans alkylation followed by reduction and protection generated

dx.doi.org/10.1021/jo3026077 | J. Org. Chem. 2013, 78, 2213−2247

the allyl silane **24**. Bromination at C_{14} using NBS followed by Arbuzov reaction generated the allyl phosphonate **25** in 55% yield over two steps.

With the coupling partners in hand, we envisioned multiple options for their combination (Scheme 3). One of the initial approaches we explored was a phosphonate olefination strategy. Unfortunately, using a range of bases (e.g., *n*-BuLi, *t*-BuLi, *s*-BuLi, KHMDS) we were unable to facilitate the olefination. An alternative strategy involving a Peterson olefination could arrive at the same target **26**. Anions derived from allyl trimethylsilanes can attack a carbonyl electrophile through either α-position or γ-position.[15] Using conditions developed by Magnus and co-workers,[16] we observed exclusive formation of the vinylsilane product **27** derived from reactivity in the γ position. A modified procedure using $MgBr_2$[17] failed to override this preference.

Scheme 3. Synthesis of Diene



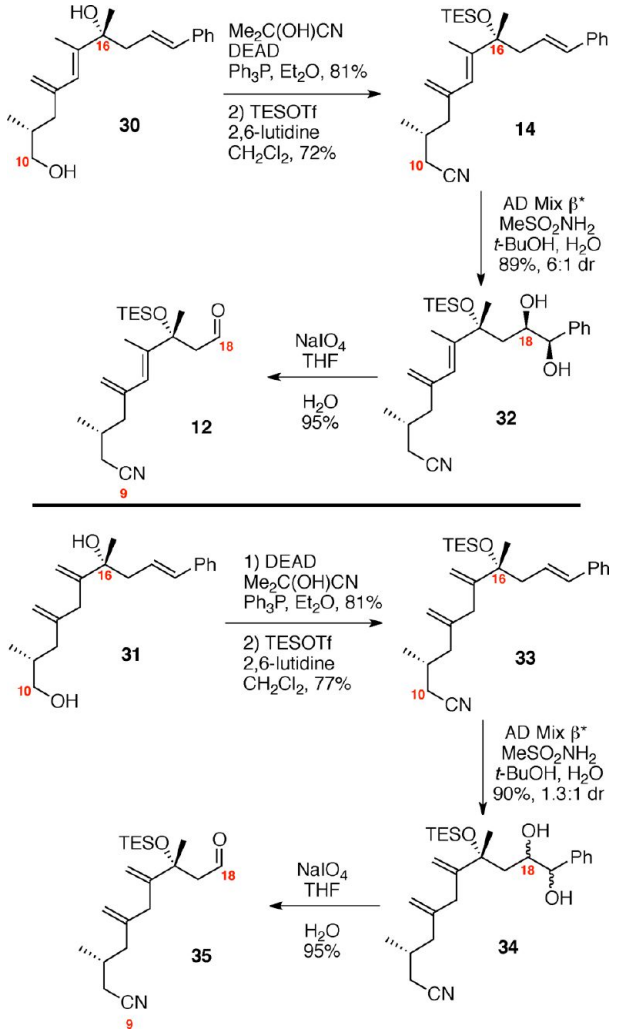
While the vinyl silane product **27** is in theory still a viable intermediate in the synthesis of the diene **26**, we were unable to facilitate the subsequent conversion to the target diene.[18] We also explored a Sakurai-type approach[19] to C−C bond formation using allyl silane **24**. Treatment of **24** and **16** under a range of Lewis acidic conditions (e.g., TMSOTf, $BF_3{\cdot}Et_2O$, Me_2AlCl, $AlMe_3$, $SnCl_4$) did not provide any of the desired coupled material **28**. Fortunately, treatment with freshly distilled $TiCl_4$ did facilitate the $C_{14}-C_{15}$ bond construction in up to 65% yield and 6:1 dr (stereochemistry at C_{15} undetermined). While effective, this reaction did prove to be scale dependent (typically providing 50−65% yield at 0.65 mmol scale, but 20−30% yield at 2.0 mmol scale). Despite considerable effort to ascertain the nature of the scale dependence, we were unable to fully address this shortcoming. Consequently, this transformation was often run in parallel batches to bring through sufficient amounts of material. Subsequent elimination of the tertiary alcohol **28** was best facilitated using $SOCl_2$ and pyridine in toluene at −78 °C to yield the desired diene in near-quantitative yield as a 2.2:1 ratio of diene regioisomers (rr) (**26**:**29**). The diene rr was not impacted by use of a single C_{15} stereoisomer of alcohol **28**. Use of alternate conditions (e.g., MsCl, $POCl_3$, Tf_2O, Burgess reagent, Martin's sulfurane) led to no product formation or inferior levels of regioselectivity. While these diene regioisomers **26** and **29** were not readily separable by column chromatography, removal of the silyl protecting group provided the corresponding regioisomeric diols **30** and **31** that were separable.

The functionalization of the polyene is shown in Scheme 4. Mitsunobu-type conversion of the C_{10} alcohol into the corresponding nitrile followed by silyl protection yielded **14**. Next, we required the selective functionalization of the $C_{18}-C_{19}$ alkene in the presence of the less sterically hindered 1,1-disubstituted alkene at C_{13} and the more electron rich alkene at $C_{14}-C_{15}$. We had hoped that regioselective dihydroxylation at $C_{18}-C_{19}$ could be possible by exploiting a π-stacking interaction between the phenyl ring and aromatic systems present in Sharpless ligands. While this sort of phenomenon has been used previously to explain enhanced enantioselectivity[20] and even diastereoselectivity[21] in Sharpless asymmetric dihydroxylation, we were unaware of prior examples to exploit purely a regioselective directing effect. To our delight, the AD Mix β* [the * denotion represents higher percentages of $K_2OsO_4{\cdot}2H_2O$ and $(DHQD)_2PHAL$ as compared to the commercial amounts] provided excellent regioselectivity for the desired location. As hypothesized, use of standard OsO_4/NMO conditions provided a complex mixture of products. Interestingly, AD Mix α* also proved to be a poor reagent of this transformation. While we can rationalize the poor outcome of the ligandless system, a rational for the reactivity differences between the pseudoenantiomeric ligand systems is less obvious. One possible explanation may be that the C_{16} stereocenter exerts a pronounced influence on the conformation of the neighboring alkenes, resulting in a mismatched interaction between the $(DHQ)_2PHAL$ ligand in AD mix α and the desired alkene. It is also clear that a conformational change occurs between the unconjugated system **33** and the conjugated system **14**, dihydroxylation of polyene **33** results in a regioselective oxidation at $C_{18}-C_{19}$; however, the reaction does not show any diastereoselectivity. Periodate cleavage under standard conditions yielded the aldehydes **12** and **35**.

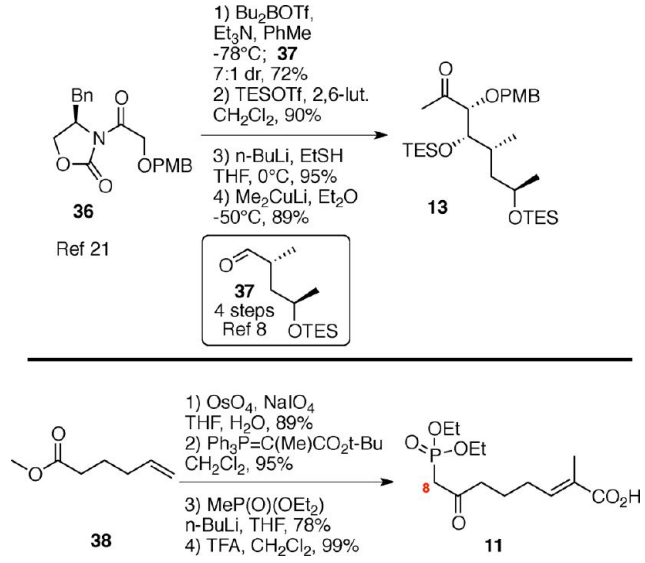
Synthesis of the eastern subunit[4] and southern fragment are shown in Scheme 5. Evans *syn* glycolate reaction between oxazolidinone **36**[22] and readily available aldehyde **37**[8] provided the desired product in reasonable diastereoselectivity (7:1 dr)

dx.doi.org/10.1021/jo3026077 | J. Org. Chem. 2013, 78, 2213−2247

Scheme 4. Synthesis of Western Subunit



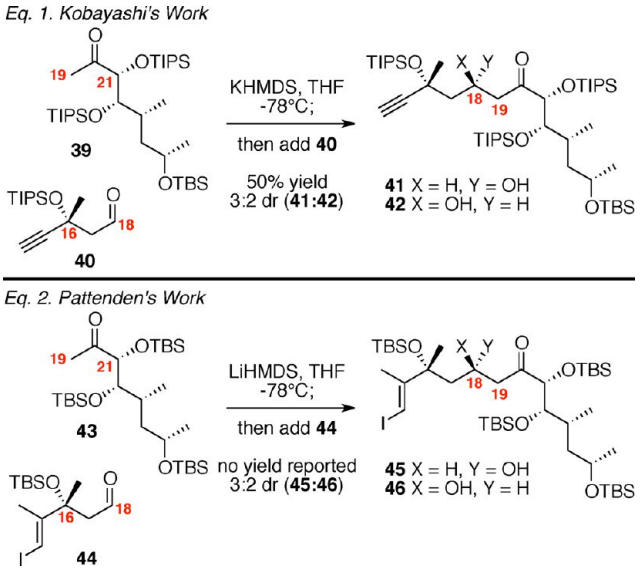
Scheme 5. Synthesis of Eastern and Southern Subunits



and good yield. After TES silylation, subsequent conversion to the thioester with lithium thiolate followed by cuprate addition yielded the methyl ketone **13**. This strategy for synthesis of the C_{19}–C_{26} subunit has been subsequently exploited by Fürstner and co-workers.[3aa,5] The carboxylic acid **11** was available in four straightforward steps from the commercially available ester **38.**

With the subunits now constructed, our efforts shifted toward their combination. We were particularly focused on addressing the diastereoselectivity in the methyl ketone aldol reaction between **12** and **13**. Prior to our entry into the field, Pattenden[7e] and Kobayashi[7k] had independently explored related coupling strategies with limited success (Scheme 6). In both cases, poor

Scheme 6. Precedent for C_{18}–C_{19} Aldol Reaction



diastereoselectivity was observed (3:2 dr) as well as low chemical yield (50% in Kobayashi's case, no chemical yield reported in Pattenden's example). Stereocontrolling models for *β*-silyloxy aldehydes such as **40** and **44** have been proposed;[23] however, it is unclear if the tertiary nature of the C_{16} silyl ether is compatible with that analysis. In addition, models have been developed for exploiting the stereochemical controlling nature of *α*-chiral ketones (albeit primarily on ethyl ketone substrates). We had hypothesized the poor stereocontrol in these pioneering examples by Pattenden and Kobayashi could be attributed to the absence of a chelating protecting group at C_{21}, which rigidifies the facial selectivity of the enolate in the aldol transition state. Compelling evidence of the potential for this strategy can be found in Chakraborty's related work toward amphidinolides G and H (which lack the C_{16} hydroxyl functionality).[24] Pioneering precedent for the stereocontrolling ability of *α*-oxy enolates had been reported by Paterson,[25] Heathcock,[26] and Masamune;[27] however, the majority of the examples were on ethyl ketones. Aldol reactions using methyl ketones have been reported to proceed through both chair and boat transition states, which could lead to an erosion in stereoinduction.[28] White,[29] Trost,[30] and Evans[31] reported some of the earliest successful examples in this area. Other laboratories have subsequently explored this transformation with varying degrees of stereocontrol.[32]

Our exploration into the diastereoselective aldol reaction is detailed in Scheme 7. We initially employed the unconjugated diene **35** as a model for the actual system. To our considerable disappointment, this substrate **35** performed poorly in the transformation, providing low diastereoselectivity (2:1 dr) in modest chemical yield (60%) (eq 1). Similar results were observed with the achiral aldehyde 3,3-dimethylbutanal (2–3:1 dr) (eq 2).

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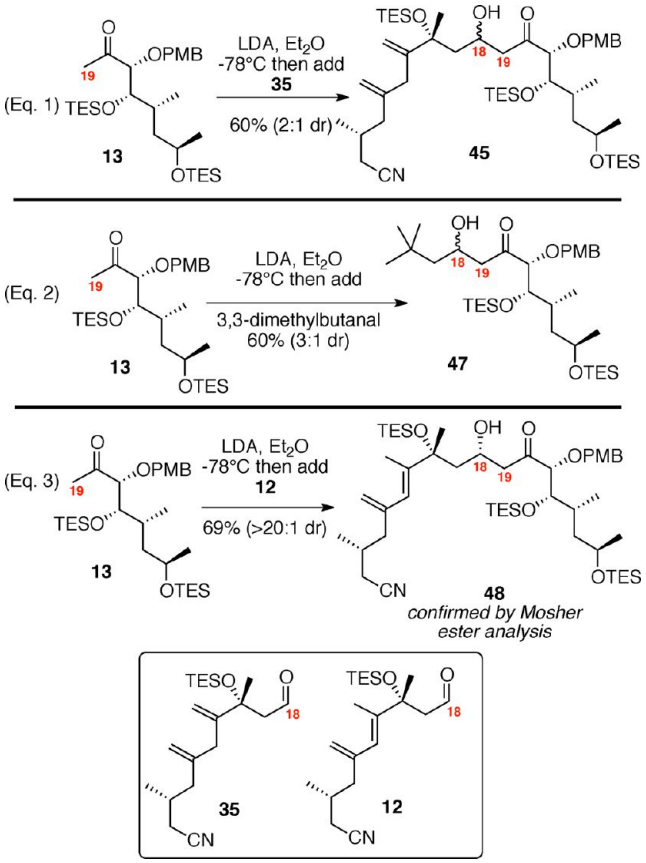
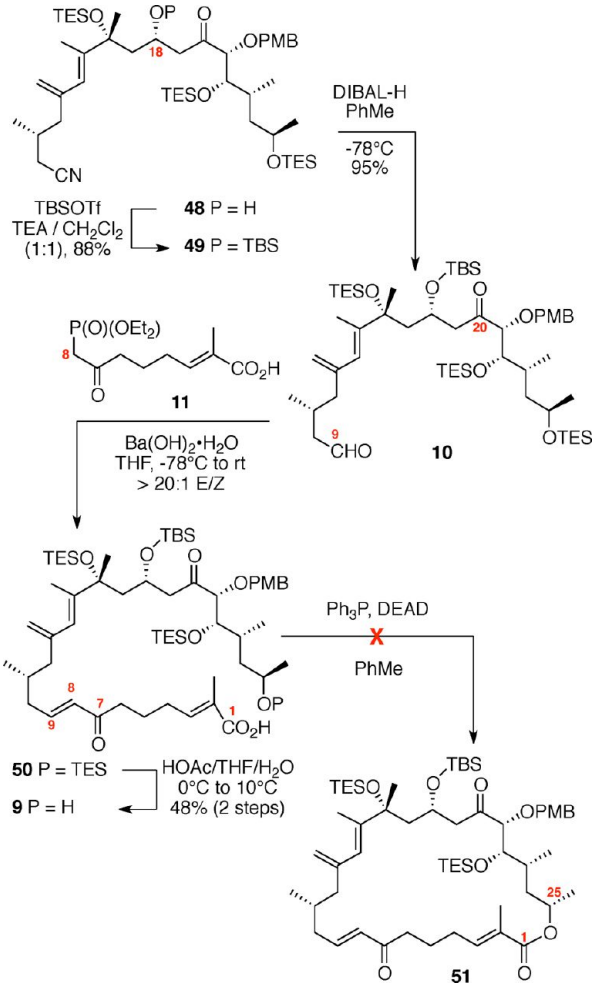
Scheme 7. Methyl Ketone Aldol Reaction



Undeterred by these discouraging model studies, we next studied the conjugated diene system **12** (eq 3). We were delighted to see that this transformation proceeded with high levels of stereocontrol; we only observed a single diastereomer in 69% yield. The configuration of the newly established stereocenter was confirmed by advanced Mosher ester method.[33] The subtle nature of the controlling influences of this aldol reaction warrants further comment. We are hesitant to put forth a model for the controlling influences of this transformation; however, it is important to note that both the trisubstituted alkene at C_{14}–C_{15} and the chelating protecting group at C_{21} appear to work in concert to influence the stereochemical outcome of the aldol reaction. The C_{16} silyl ether does not appear to exert considerable influence as this chelation strategy has subsequently proven useful in amphidinolide G/H series by both Fürstner[3aa,5] and Zhao[34] which does not contain the C_{16} alcohol moiety.

The construction of the macrocyclization precursor is shown in Scheme 8. Silylation of the C_{18} alcohol proceeded smoothly with TBSOTf and a large excess of triethylamine.[35] Interestingly, use of near stoichiometric amounts of an amine base [e.g., 2,6-lutidine (1.2 equiv)] led to elimination (~20%) and alkene isomerization (~10%). Regioselective reduction of the C_9 nitrile was accomplished with DIBAL-H. Horner-Wadsworth-Emmons olefination of the resultant aldehyde using $Ba(OH)_2$[36] yielded the desired α,β-unsaturated ketone in good yield and excellent *E*/*Z* selectivity. Alternate conditions on related systems (DBU, LiCl or KHMDS, THF) were less effective for this olefination.[37] Subsequent selective cleavage of the C_{25} TES ether produced the key Mitsunobu macrolactonization[12] precursor. Unfortunately, this substrate was resistant to all efforts to facilitate the macrocycle formation under these sterochemically invertive conditions.

Scheme 8. Unsuccessful Macrocyclization Strategy



Based on our frustrations with facilitating a successful Mitsunobu macrolactonization, we decided a reorganization of our strategy for macrocyclic formation was needed. Specifically, we turned to inverting the C_{25} stereocenter prior to coupling, forming the C_1 ester bond in an intermolecular fashion and constructing the C_8–C_9 alkene through an intramolecular pathway. Toward this end, synthesis of a modified methyl ketone **54** was necessary (Scheme 9). Selective TES removal could be accomplished under aqueous acidic conditions in excellent yield. Martin's modified Mitsunobu conditions proceeded smoothly to give the inverted C_{25} ester. Finally, saponification of the PNB moiety with $Ba(OH)_2{\cdot}8H_2O$ and methanol followed by TMS protection revealed the coupling partner **54**.

Synthesis of the modified aldehyde coupling partner is illustrated in Scheme 10. Conversion of the C_9 nitrile to its corresponding acetate was accomplished via DIBAL-H reduction to the aldehyde followed by $NaBH_4$ reduction to the alcohol and acylation. Regioselective functionalization at C_{18} was again accomplished using Sharpless AD conditions followed by periodate cleavage to reveal the C_{18} aldehyde.

While the original route to the aldehydes **12** and **57** was effective, it suffered from logistical impracticalities; notably, the titanium-mediated coupling of the allyl silane proved to be a scale-dependent reaction and the thionyl chloride elimination step gave a mixture of olefin products. Consequently, we sought to develop a more scalable approach to this subunit (Scheme 11).

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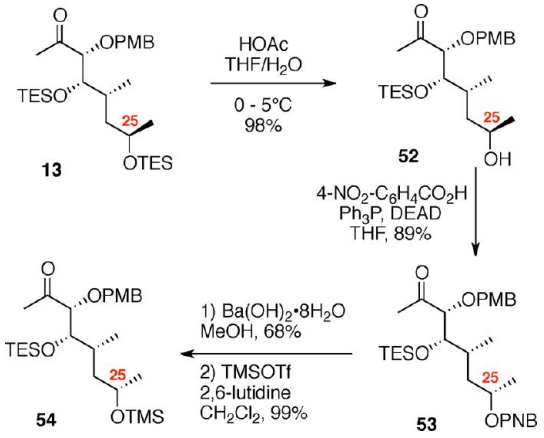
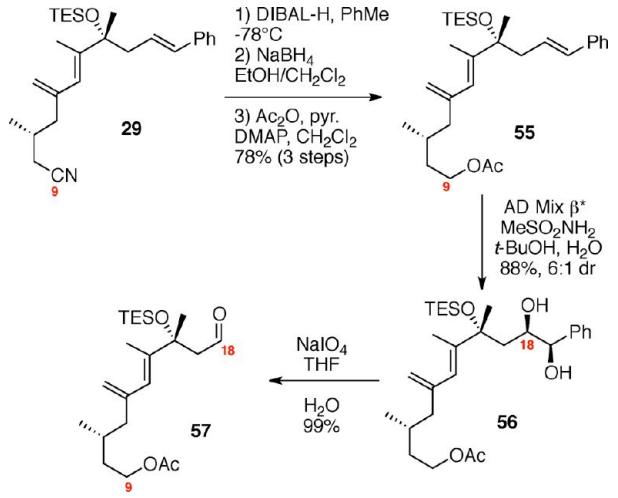
Scheme 9. Second-Generation Synthesis of Eastern Subunit



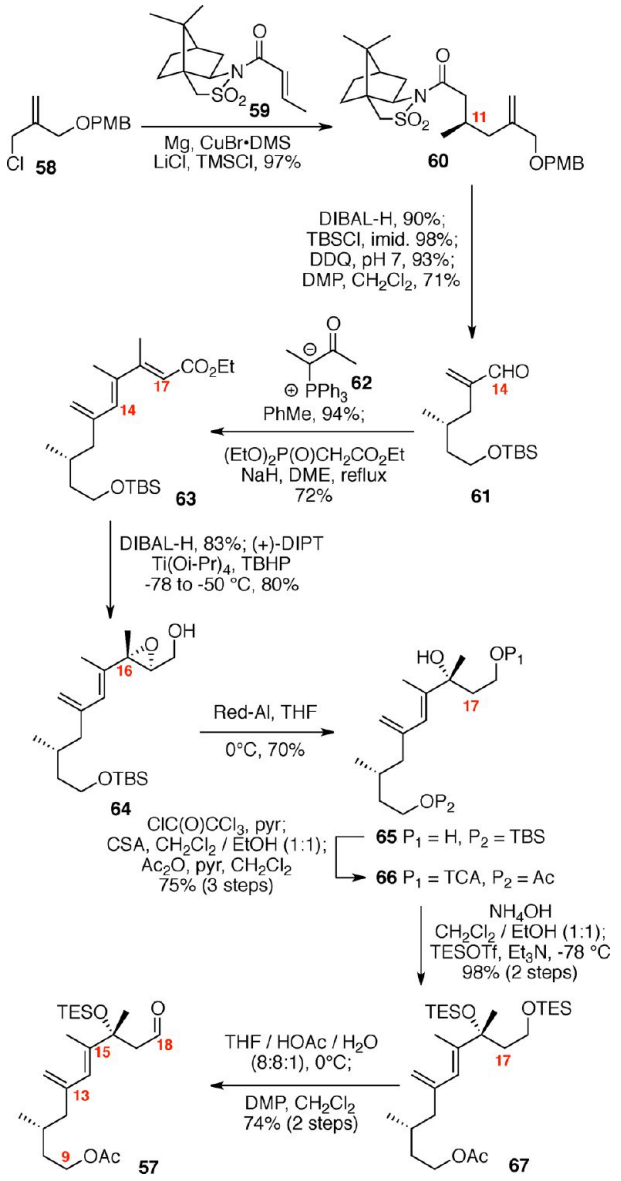
Scheme 10. Modification of the Western Subunit



Starting from the commercially available Oppolzer sultam derivative **59**, cuprate addition in accord with conditions developed by Paquette[38] cleanly generated the key C_{11} stereocenter in compound **60**. After functional group manipulation to provide aldehyde **61**, we were gratified to find that key sequential Wittig/Horner–Wadsworth–Emmons (HWE) reactions cleanly introduced the triene **63** as a single stereoisomer. After DIBAL-H reduction, the resulting trienyl alcohol proved remarkably reactive to Sharpless asymmetric epoxidation conditions (proceeding at −78 °C to −50 °C) to provide epoxide **64**. In fact, if this reaction was performed at higher temperatures (e.g., −20 °C), another product was observed that appeared to be the result of a 1,2-alkyl shift to produce an aldehyde.[39] Subsequent Red-Al reduction provided the diol **65**. Finally, protecting group exchange followed by 1° TES deprotection and oxidation provided the C_9–C_{18} subunit **57**. The high efficiency of this route (11.5% overall yield) provided us with access to gram quantities of aldehyde **57**.

With these modified coupling partners in hand, we revisited our aldol coupling strategy (Scheme 12). We were pleased to observe that similar levels of diastereoselectivity continued to be observed using the LDA conditions (62% yield, >20:1 dr). Silylation of the C_{18} alcohol proved significantly more complicated than expected. Use of TBSOTf led to significant exchange of the C_{25} TMS ether to the corresponding TBS ether. Use of TESOTf minimized this problem, providing a 95% yield of a 5:1 ratio of the C_{25} TMS to C_{25} TES. Both of these

Scheme 11. Second Generation Approach to the C_9–C_{18} Western Fragment of Amphidinolide B_1



compounds were productive intermediates and could be converted to the corresponding C_{25} alcohol using HOAc/THF/H_2O conditions. Intermolecular Yamaguchi esterification provided the phosphonate **71**. Next, removal of the C_9 acetate was cleanly accomplished using $Ba(OH)_2$•$8H_2O$. Subsequent oxidation using TPAP provided the aldehyde cyclization precursor **73**. Interestingly, this compound proved to be surprisingly reactive—leading to spontaneous macrocyclization under the TPAP conditions. $Ba(OH)_2$·$8H_2O$ was added to drive this transformation to completion with an 85% overall yield from the alcohol **72**.

With the macrocycle in hand, the remaining challenges to be addressed were the successful incorporation of the C_6–C_9 allylic epoxide and global deprotection (Scheme 13). CBS reduction[40] proceeded smoothly to provide the desired allylic alcohol **75** in excellent diastereoselectivity. Subsequent Sharpless asymmetric epoxidation[41] provided the desired epoxide **76** in 10:1 dr. Incorporation of the alkene could be best accomplished by inversion at C_7 to provide the selenide **78**[42] followed by TPAP

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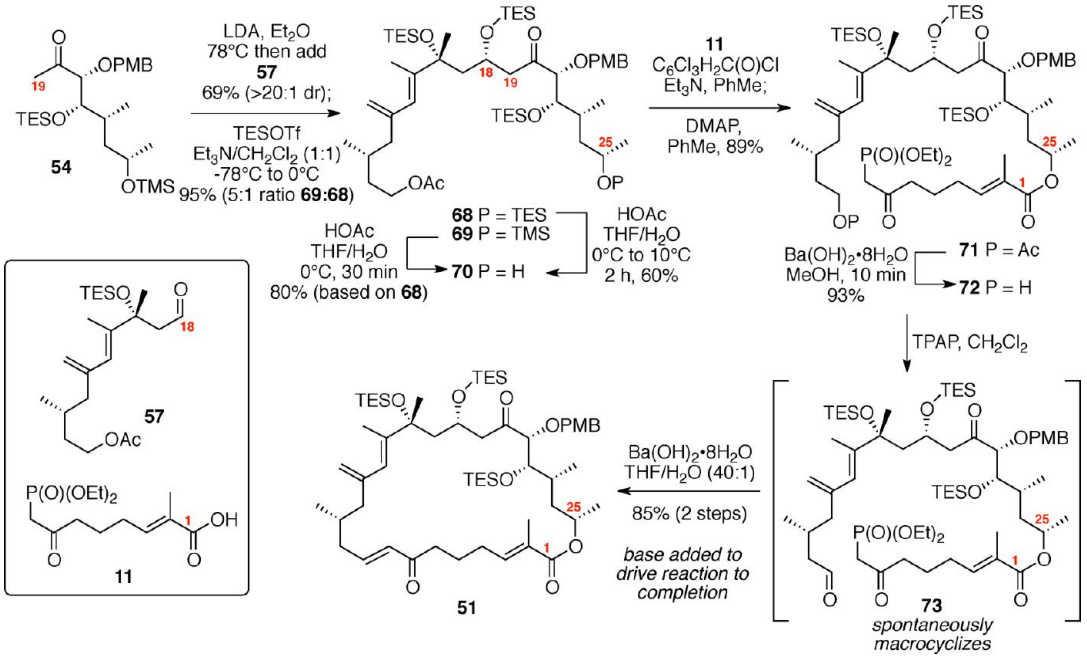
Scheme 12. Spontaneous Macrocyclization Strategy

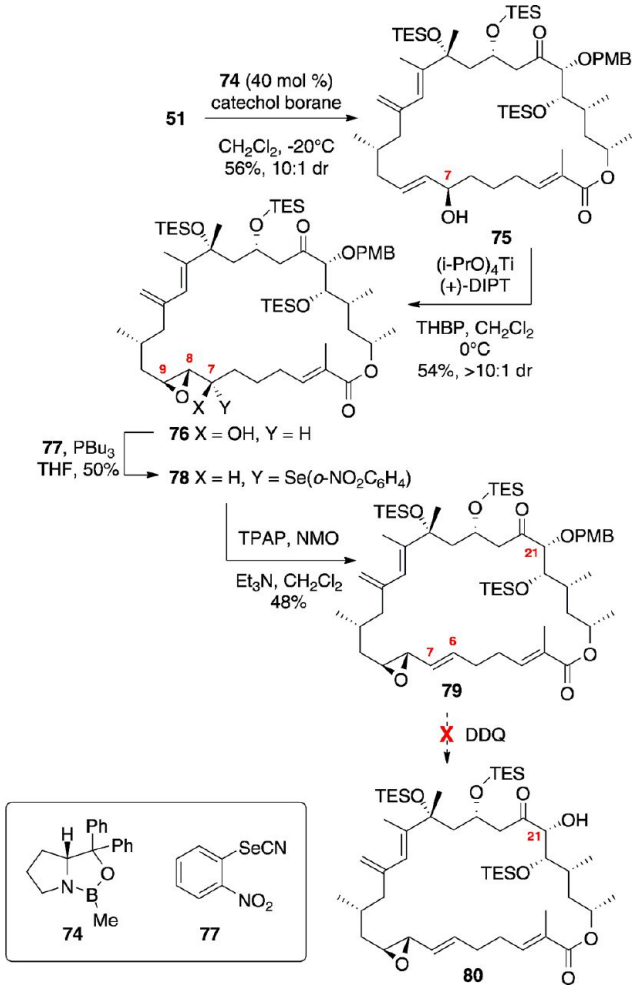


mediated oxidation[43] to the selenoxide and syn elimination to yield the allylic epoxide as a single olefin geometry. Despite compelling precedent from Nicolaou and co-workers for a related deprotection in the synthesis of amphidinolide N,[2v] we were unable to effect PMB removal using DDQ under buffered aqueous or anhydrous conditions. Based on this unfortunate result, it became clear that an alternate C_{21} protecting group strategy was necessary to complete the total synthesis of amphidinolide B_1.

We initially considered a 3,4-dimethoxybenzyl (DMB) protecting group as a viable alternative to the C_{21} PMB group as DMB groups are more readily oxidized by DDQ (Scheme 14). We synthesized the necessary C_{19}–C_{26} subunit via an analogous route as described previously. Interestingly, aldol reaction with the C_{18} aldehyde **82** proceeded smoothly but in significantly lower diastereoselectivity (4:1 dr). We are unsure as to the cause of this difference between the PMB and DMB series. Next, we explored the possibility of deprotecting the C_{21} DMB group using DDQ. Interestingly, treatment of **83** with DDQ under buffer aqueous conditions led to formation of the acetal **86** in modest yield, but as a single diastereomer. This product is likely the result of initial oxidation to the oxonium ion followed by nucleophilic attack by the C_{22} OTES ether. Subsequent silyl migration to the C_{18} position would produce the observed product **86**. Despite this encouraging early result, we were unable to increase the chemical yield of this transformation through variation of oxidant or reaction conditions. Consequently, this approach was abandoned.

Given our setbacks with benzyl-derived protection at C_{21}, we revisited our central strategy for stereocontrol at C_{18} through the C_{21} chelation model described previously (Scheme 15). Traditionally, silyl protecting groups are not viewed as moieties that participate in chelation;[44] however, it is important to acknowledge work by Heathcock,[45] Eliel and Frye,[46] Willard[47] and Evans[48] which showed that silyl chelation is feasible under certain conditions. We were particularly drawn to Heathcock's work in the area in which TMEDA was a key additive in their chelation-controlled aldol reaction (eq 1). Alternatively, a dipole

Scheme 13. Incorporation of the Allylic Epoxide Moiety



minimization stereocontrol model produced the alternate facial attack on the aldehyde (eq 2). Silyl protection at C_{21} would

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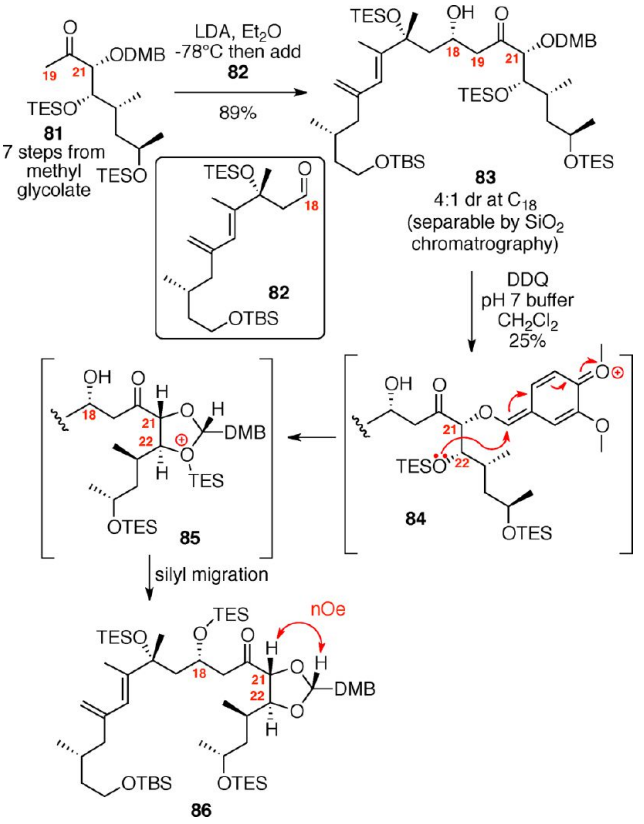
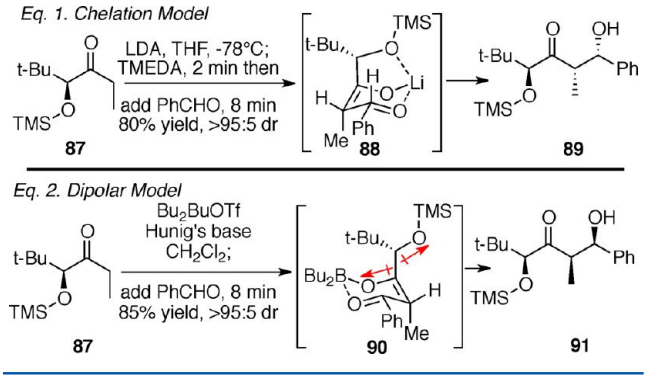
Scheme 14. C_{21} Dimethoxybenzyl Protection Series



Scheme 15. Heathcock's Pioneering Stereoselective Aldol Work

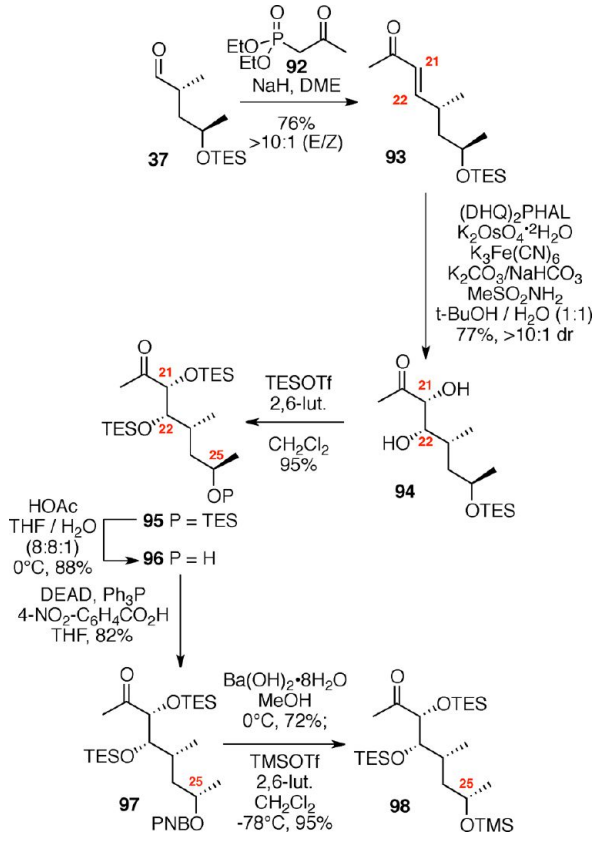


simplify the endgame deprotection sequence and circumvent the problematic DDQ deprotection strategy.

The synthesis of the C_{21} silyl methyl ketone **98** is shown in Scheme 16. One attractive advantage to this strategy is that it greatly simplifies the synthesis of the methyl ketone as differential protection at C_{21} and C_{22} is no longer needed. Olefination of aldehyde **37** provided the α,β-unsaturated enone **93**. Sharpless dihydroxylation under buffered conditions yielded the diol in good diastereoselectivity. Bis-silyl protection using TESOTf cleanly provided the tris-TES methyl ketone **95**. The C_{25} TES ether could be cleanly removed using HOAc/THF/H_2O conditions followed by inversion and protection as its C_{25} TMS ether.

Exploration of the key aldol reaction on the C_{21} silyl series generated intriguing results (Scheme 17 and Table 1). Initial studies with the C_{25} epimer **95** exhibited poor diastereoselectivity, but good reactivity under the Heathcock's TMEDA conditions (entry 1). It should be noted that the replacement of THF with

Scheme 16. Tris-silyl Methyl Ketone Synthesis



Scheme 17. Exploration into Aldol Stereoselectivity

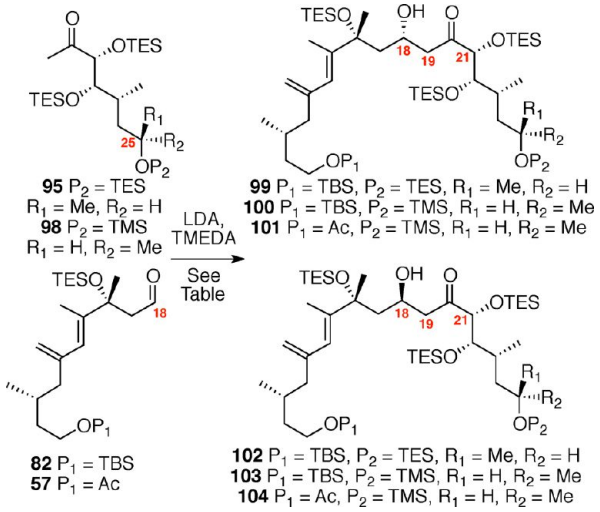


Table 1. Exploration into Aldol Stereoselectivity

entry	substrates	conditions	yield (%) [dr]
1	**95, 82**	THF, −78 °C	64 [1.1:1 (**99:102**)]
2	**95, 82**	Et_2O, −78 °C	<10 [1.5:1 (**99:102**)]
3	**98, 82**	THF, −78 °C	67 [1:5 (**100:103**)]
4	**98, 82**	THF, −40 °C	68 [1.8:1 (**100:103**)]
5	**98, 57**	THF, −100 °C	65 [1:8 (**101:104**)]
6	**98, 57**	THF, −40 °C	66 [1.2:1 (**101:104**)]

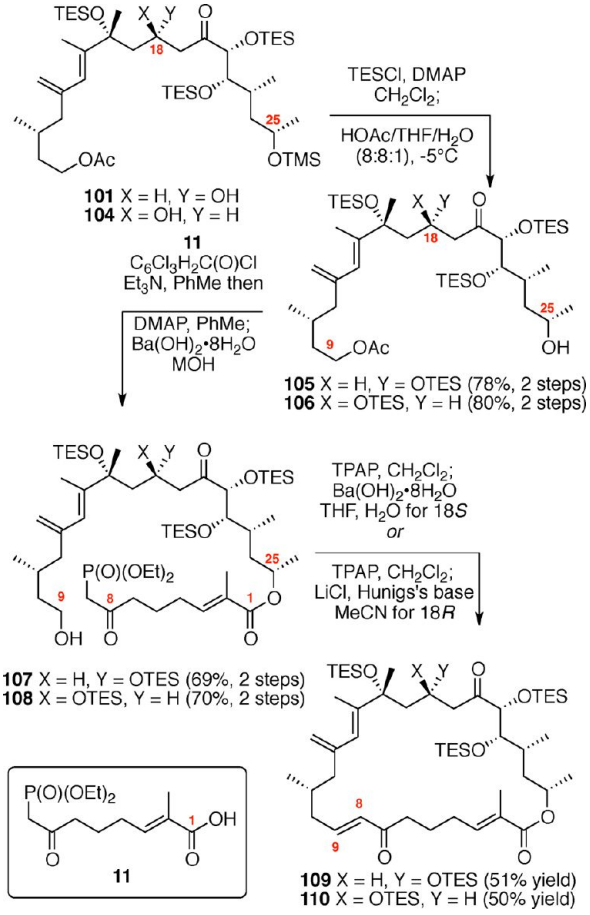
Et_2O led to a dramatic decrease in chemical yield (entry 2). Interestingly, use of the required C_{25} stereochemistry for amphidinolide B led to a more stereoselective aldol process

dx.doi.org/10.1021/jo3026077 | J. Org. Chem. 2013, 78, 2213−2247

(entries 3–6). If the reaction was conducted at −78 °C, the transformation appeared to proceed through a dipole minimization model to yield the 18*R* stereochemistry as the major product (5:1 **103**:**100**). If the otherwise identical transformation was conducted at −40 °C, the stereoselectivity for the transformation reversed to now favor the 18*S* stereochemistry. This divergent stereocontrol model could be attributed to reversible nature of aldol reactions.[49] A similar phenomenon was observed with the aldehyde **57** (entries 5 and 6). While unexpected, these results opened the door for the synthesis of both amphidinolide B_1 and B_2.

Synthesis of the macrocycle using the aldol products was accomplished based on close analogy to our C_{21} PMB series (Scheme 18). TES protection at C_{18} using TESCl/DMAP

Scheme 18. Second-Generation Macrocycle Formation



conditions followed by C_{25} desilylation revealed the C_{25} alcohol. Yamaguchi esterification followed by saponification of the acetate protecting group produced the C_9 alcohol. As employed in our previous macrocyclization, TPAP oxidation produced the reactive aldehyde, which appeared to undergo spontaneous macrocyclization. The cyclization could be driven to completion by addition of $Ba(OH)_2 \cdot 8H_2O$ for 18*S* series and LiCl/Hunig's base for the 18*R* series for optimal yields. While the yields for these macrocyclizations were not as high as the C_{21} PMB series, the ability to successfully close the macrocycle was gratifying. Fortuitously, macrocycle **109** produced crystals suitable for X-ray crystallographic analysis, thereby confirming the stereochemical assignment (Figure 2).

With the macrocycle in hand and the stereochemistry firmly established, the remaining hurdles for completing the synthesis

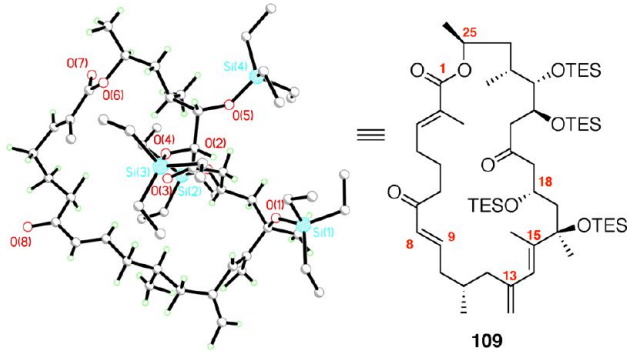


Figure 2. ORTEP Representation of Macrocycle **109**.

were incorporation of the allylic epoxide moiety and global deprotection. We first advanced the 18*S* stereoisomer, which would lead to the synthesis of amphidinolide B_2 (Scheme 19). CBS reduction produced the allylic alcohol in good diastereoselectivity. Although epoxidation under tartrate-mediated Sharpless conditions as used previously proved ineffective, titanium-mediated epoxidation (in the absence of tartrate ligand) produced the epoxide alcohols in modest diastereoselectivity (2:1 dr, 74% yield). Given the increased steric demands of the Ti–tartate complex, we attribute the reactivity difference between the C_{20} OPMB series and the C_{20} OTES series to a conformational change to the macrocycle, which increases the steric hindrance surrounding the allylic alcohol moiety. While we cannot rigorously assign the stereochemistry of the newly created stereocenters, they were assigned based on literature precedent.[40,50] Incorporation of the selenide followed by TPAP-mediated oxidation and *syn* elimination provided the allyl epoxide **116**. Unfortunately, we were again unable to effect global desilylation under a range of conditions (e.g., TAS-F or HF·pyr). Fortunately, the ordering of the final events could be altered (global deprotection followed by *syn* elimination using TMSOOTMS for selenide oxidation) to reveal the proposed structure for amphidinolide B_2 (**3**). It should be noted that the use of TMSOOTMS has not been previously reported for selenide oxidation/elimination. H_2O_2 was ineffective in this transformation, likely due to unwanted Baeyer–Villiger-type oxidation of the C_{20} ketone. To our surprise, the spectral data did not match the literature values for amphidinolide B_2. We had presumed that the incorrect epoxide had been utilized. Consequently, we repeated the analogous endgame, but this product **114** also did not match the natural product. It became clear that the assignment of amphidinolide B_2 was incorrect. Comparison of the synthesized material with the literature data revealed a large chemical shift difference for H_{14} [isolation data: 5.93 (bs), synthetic **3**: 6.06 (bs), synthetic **114**: 6.08 (bs)] and $H_{19a,b}$ [isolation data: 3.09 (dd, J = 2.3, 8.8 Hz, 1H) and 2.69 (dd, J = 8.6, 17.7 Hz, 1H), synthetic **3**: 3.05 (m) and 2.48 (dd, J = 8.0, 17.0 Hz), synthetic **114**: 2.90 (dd, J = 9.9, 17.1 Hz) and 2.45 (m)]. Careful inspection of the structure elucidation paper[2c] revealed that while amphidinolide B_1 was assigned by crystallographic analysis, amphidinolide B_2 was assigned based on analogy and comparison of the NMR spectra. We hypothesize that the actual structure of amphidinolide B_2 likely contains the opposite stereochemistry at C_{16} (e.g., **117**), thereby maintaining a *syn* relationship between the two alcohols at C_{16} and C_{18}.

The successful completion of amphidinolide B_1 is shown in Scheme 20. Starting from the macrocycle **109**, CBS reduction provided the allylic alcohol **118** in 74% yield (3.5:1 dr). Titanium-mediated epoxidation of the alkene was high yielding,

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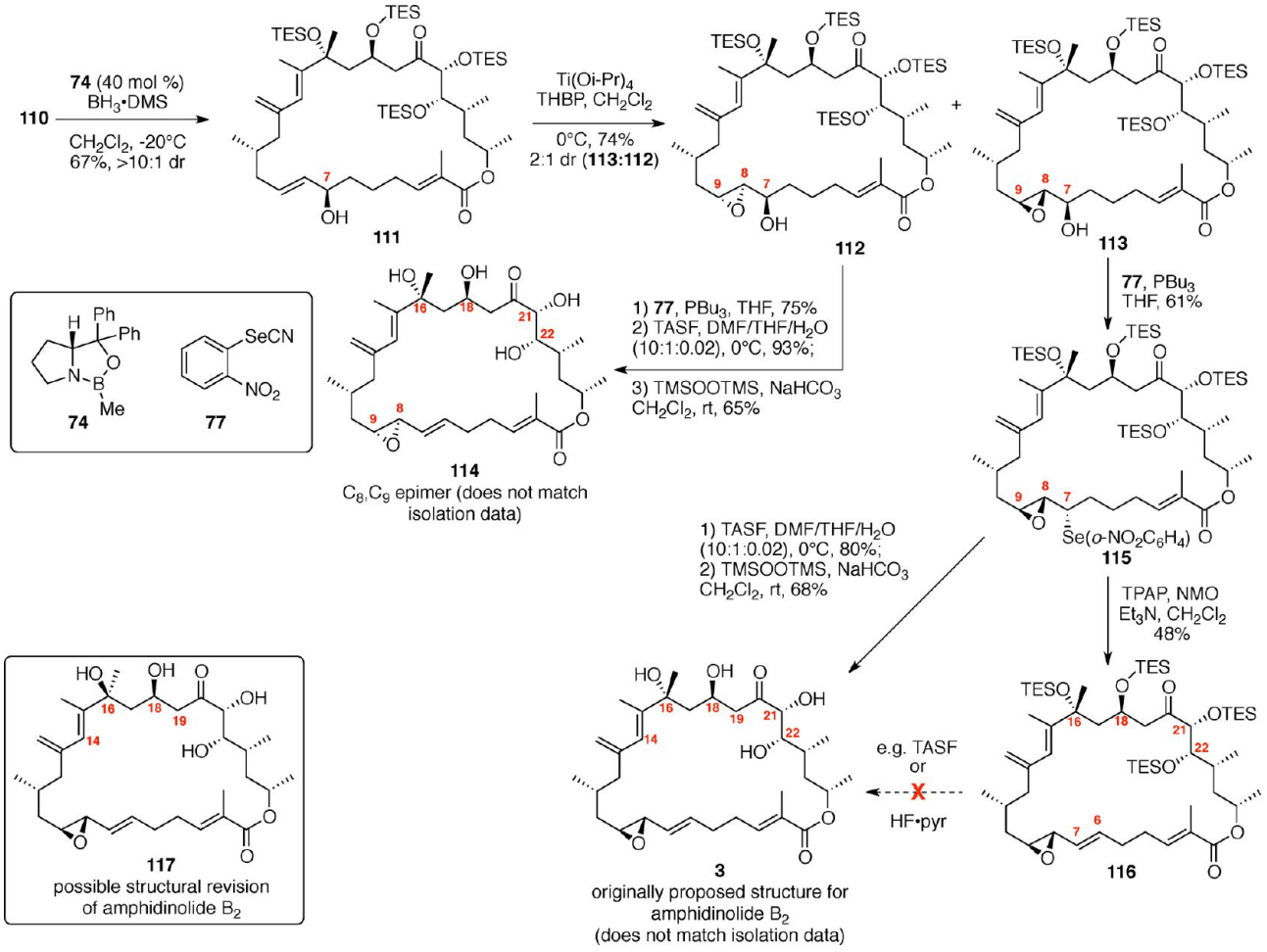
Scheme 19. Synthesis of Proposed Structure for Amphidinolide B_2



but unselective (1:1.5 dr). Incorporation of the aryl selenide using previously described conditions followed by global deprotection and selenide oxidation/*syn* elimination yielded amphidinolide B_1 (**2**). Comparison of the synthetic material with literature values showed excellent agreement (^{1}H NMR, ^{13}C NMR, $[\alpha]_D$). For analogue studies, we also carried the epimeric epoxide series onto 8,9-*epi*-amphidinolide B_1 (**121**).

To assess the cytotoxic effects of the proposed structure of amphidinolide B_2 on human solid and blood cancer cells, cell viability assays were conducted using a nine cancer cell line panel.[58] Compound **3** differentially reduced cell viabilities at 0.1 μM in human DU145 prostate cancer, MDA-MB-435 breast cancer, OCI-LY3 lymphoma, K562 CML, MOLT-4 ALL, Reh ALL, U266 myeloma, KG1a AML and HL60 AML cells (Table 2). To further understand these antitumor activities of amphidinolide B_2, we determined IC_{50} values = 36.4 ± 2.9 nM, 94.5 ± 8.0 nM, 3.3 ± 0.9 nM and 7.4 ± 0.6 nM against DU145, MDA-MB-435, KG1a and HL60 AML cancer cells, respectively (Table 3). Next, compared the potency of compound **3** to $C_{8,9}$ epimer **114** and C_{18} epimer **121** in DU145 prostate cancer cells, compound **3** exhibited over 12-fold increase in biological activity (Figure 3). These findings suggest that the stereochemistry of the epoxide plays an important role in eliciting potent anticancer effects.

Cell viability assays were carried out as described in the Experimental Section. Human DU145 prostate cancer, MDA-MB-435 breast cancer, OCI-LY3 lymphoma, K562 CML, MOLT-4 ALL, Reh ALL, U266 myeloma, KG1a AML and HL60 AML cells were seeded in 96-well plates (5000/well for DU145 and MDA-MB-435, 10000/well for OCI-LY3, K562, MOLT-4, Reh, U266, KG1a and HL60), incubated overnight at 37 °C in 5% (v/v) CO_2 and exposed to 0.1 μM of compound **3** for 72 h. Absorbance was measured at 490 nm using an automated ELISA plate reader. Each experiment was performed in quadruplicate. Data are mean ± SD.

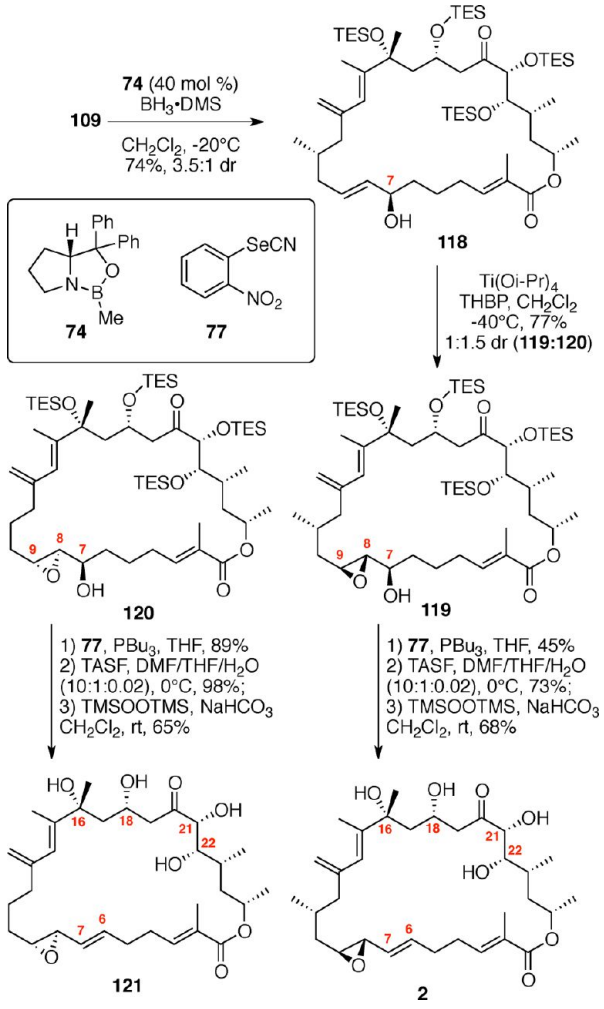
IC_{50} values of compound **3** were determined in human DU145 prostate cancer, MDA-MB-435 breast cancer, KG1a AML and HL60 AML cells. Cells were seeded in 96-well plates (5000/well for DU145 and MDA-MB-435, 10000/well for KG1a and HL60), incubated overnight at 37 °C in 5% (v/v) CO_2 and exposed to compound **3** in a dose-dependent manner for 72 h. Absorbance was measured at 490 nm using an automated ELISA plate reader. Each experiment was performed in quadruplicate. Data are mean ± SD.

■ CONCLUSION

In summary, the first total synthesis of amphidinolide B_1 and the proposed structure for amphidinolide B_2 has been achieved. In our initial approach to this family, we utilized a chelation-controlled aldol reaction to provide excellent stereoselectivity at C_{18}. Unfortunately, late-stage removal of the PMB group proved not feasible in our hands. Consequently, a revised approach utilizing a dipole-minimized aldol provided access to a stereoselective aldol product. The stereoselectivity in this key aldol

dx.doi.org/10.1021/jo3026077 | J. Org. Chem. 2013, 78, 2213−2247

Scheme 20. Synthesis of Amphidinolide B_1 and 8,9-*epi*-Amphidinolide B_1



process could be controlled by variation of the temperature. Other highlights of the synthetic route include two non-metal-catalyzed methods to construct the C_{13}–C_{15} diene, a spontaneous HWE macrocyclization strategy, and a novel late-stage epoxidation/elimination strategy to incorporate the sensitive C_6–C_9 allylic epoxide moiety.

The proposed structure for amphidinolide B_2 displays potent and stereoselective antitumor activities against human solid and blood tumor cells at low nanomolar concentrations that include highly aggressive and metastatic prostate and breast cancer cells. In contrast, $C_{8,9}$-epimer and C_{18} epimer exhibit an over 12-fold decrease in antitumor activity in comparison. The stereochemistry of the epoxide plays a key role in the anticancer effects.

EXPERIMENTAL SECTION

General Methods. Infrared spectra were recorded neat unless otherwise indicated and are reported in cm^{-1}. ^1H NMR spectra were recorded in deuterated solvents and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. ^{13}C NMR spectra were recorded in deuterated solvents and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. HRMS data was collected using a TOF mass spectrometer.

Routine monitoring of reactions was performed using EM Science DC-Alufolien silica gel, aluminum-backed TLC plates. Flash chromatography was performed with the indicated eluents on EM Science Gedurian 230–400 mesh silica gel.

Air- and/or moisture-sensitive reactions were performed under usual inert atmosphere conditions. Reactions requiring anhydrous conditions were performed under a blanket of argon, in glassware dried in an oven at 120 °C or by flame, then cooled under argon. Dry THF and DCM were obtained via a solvent purification system. All other solvents and commercially available reagents were either purified via literature procedures or used without further purification.

Table 3. Determination of IC_{50} Values of Compound 3 against Human Cancer Cells (nM)

DU145	HL60	KG1a	MDA-MB-435
36.4 ± 2.9	7.4 ± 0.6	3.3 ± 0.9	94.5 ± 8.0

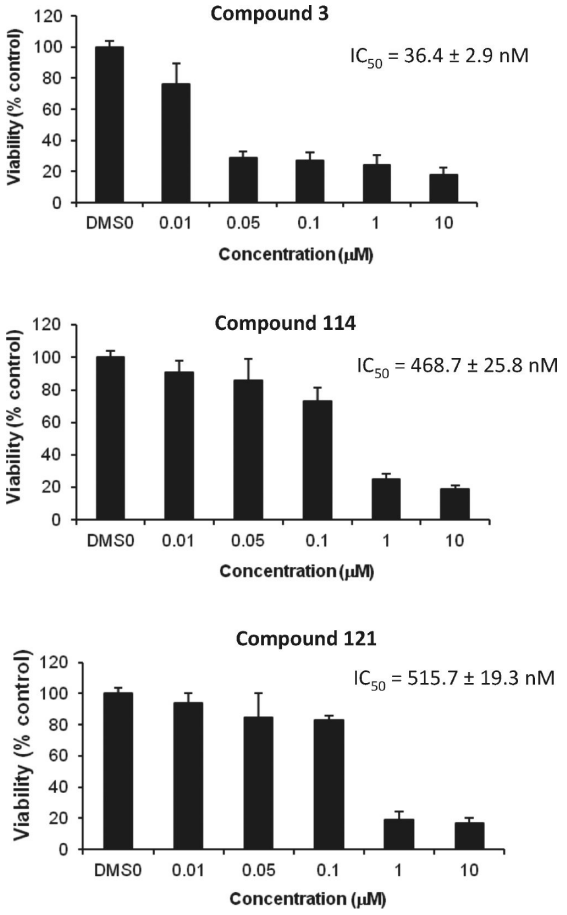
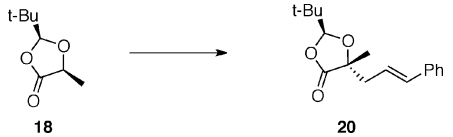


Figure 3. Comparison of Synthetic Analogues for Biological Activity.



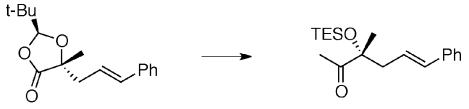
Lactone 20. To a solution of diisopropylamine (1.67 g, 2.3 mL, 16.5 mmol) in THF (7.6 mL) at −78 °C was added *n*-BuLi (6.6 mL,

Table 2. Effects of Compound 3 on Viabilities of Human Cancer Cells (% control)

DU145	MDA-MB-435	OCI-LY3	K562	MOLT-4	Reh	U266	KG1a	HL60
31 ± 5	54 ± 10	0	67 ± 6	47 ± 4	82 ± 5	76 ± 5	10 ± 2	0

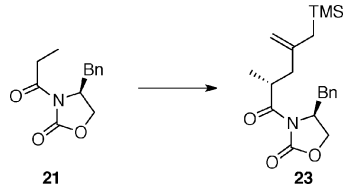
dx.doi.org/10.1021/jo3026077 | J. Org. Chem. 2013, 78, 2213–2247

16.5 mmol, 2.5 M in hexanes) dropwise. After 10 min, the white slurry was warmed to −10 °C for 30 min. Then, the solution was cooled to −78 °C, and another 58 mL of THF was added slowly to the above solution. Next, a solution of Seebach lactone **18**[51] (2.37 g, 15.0 mmol) in THF (15 mL) was added dropwise to the above solution. After 20 min, a solution of cinnamyl bromide **19** (4.43 g, 3.33 mL, 22.5 mmol) in THF (10 mL) was added dropwise. After 30 min, the reaction was warmed slowly to −10 °C over 2 h. After 5 min, the reaction was quenched with satd aq NH_4Cl (30 mL) and warmed to rt. After 10 min, the organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 30 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 2−10% EtOAc/hexanes, to give **20** (3.74 g, 13.7 mmol, 91%) as a white solid: $[\alpha]^{23}_D$ +45.5 (*c* 1.21, $CHCl_3$); IR (thin film) 3027, 2963, 1796, 1484, 1173, 1138, 970, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28−7.42 (m, 5H), 6.58 (d, *J* = 15.6 Hz, 1H), 6.23 (dt, *J* = 15.6, 6.0 Hz, 1H), 5.24 (s, 1H), 2.72 (dd, *J* = 6.0, 10.8 Hz, 1H), 2.62 (dd, *J* = 6.0, 10.8 Hz, 1H), 1.51 (s, 3H), 0.98 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 137.1, 135.3, 128.8, 127.9, 126.5, 122.4, 108.9, 80.2, 40.3, 34.8, 23.5, 23.1; HRMS (FAB+) calcd for $C_{17}H_{23}O_3$ (M + H) 275.1647, found 275.1650.



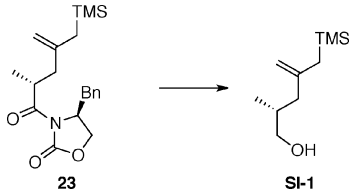
20 **16**

Methyl Ketone 16. To a solution of lactone acetal **20** (1.37 g, 5.0 mmol) in THF (100 mL) at −78 °C was added MeLi (4.64 mL, 5.6 mmol, 1.2 M in Et_2O) via syringe pump. After 15 min, the resulting solution was warmed to rt. After an additional 10 min, the solvent was concentrated in vacuo, diluted with Et_2O (50 mL), filtrated through a plug of Celite, and concentrated again in vacuo. The yellow oil was purified by chromatography over silica gel, eluting with 10−30% EtOAc/hexanes, to give a ketone intermediate (0.78 g, 3.85 mmol, 77%) as a colorless oil. To a solution of the above intermediate (340 mg, 1.66 mmol) in THF (8.3 mL) at −78 °C was added 2,6-lutidine (0.27 g, 0.29 mL, 2.49 mmol). After 5 min, TESOTf (0.53 g, 0.45 mL, 1.99 mmol) was added. After 30 min, the reaction was warmed to rt. After 5 min, the reaction was quenched with satd aq NH_4Cl (10 mL). After 10 min, the organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 15 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 2−6% EtOAc/hexanes, to give **16** (448 mg, 1.41 mmol, 88%) as a colorless oil: $[\alpha]^{23}_D$ +0.7 (*c* 0.70, $CHCl_3$); IR (thin film) 3027, 2955, 2916, 2876, 1718, 1457, 1415, 1350, 1239, 1166, 1131, 1016, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20−7.33 (m, 5H), 6.38 (d, *J* = 15.9 Hz, 1H), 6.09−6.20 (m, 1H), 2.40−2.63 (m, 2H), 2.21 (s, 3H), 1.38 (s, 3H), 1.01 (t, *J* = 7.5 Hz, 9H), 0.68 (q, *J* = 7.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.2, 137.8, 133.6, 128.9, 127.6, 126.5, 125.1, 83.0, 45.2, 26.2, 25.4, 7.6, 7.1; HRMS (FAB+) calcd for $C_{19}H_{31}O_2Si$ (M + H) 319.2093, found 319.2094.



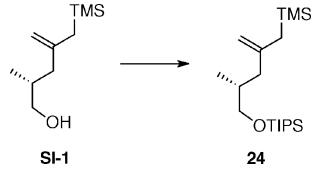
21 **23**

Allylsilane 23. To a solution of NaHMDS (5.6 mL, 5.6 mmol, 1.0 M in THF) at −78 °C was added a solution of imide **21** (1.09 g, 4.67 mmol) in THF (4.6 mL). After 20 min, a solution of allyl iodide **22**[52] (3.6 g, 14 mmol) in THF (3 mL) was added via cannula. After 10 min, the reaction was warmed slowly to 10 °C over 4 h and quenched with satd aq NH_4Cl (25 mL). After 10 min at rt, the organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 4−15% EtOAc/hexanes, to give **23** (1.46 g, 4.06 mmol, 87%) as a colorless oil: $[\alpha]^{23}_D$ +30.6 (*c* 0.66, $CHCl_3$); IR (thin film) 2954, 1780, 1699, 1632, 1454, 1385, 1349, 1246, 1207, 1101, 851, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20−7.35 (m, 5H), 4.66−4.69 (m, 1H), 4.69 (s, 1H), 4.64 (s, 1H), 4.14−4.19 (m, 2H), 4.06 (q, *J* = 6.9 Hz, 1H), 3.26 (dd, *J* = 3.3, 13.2 Hz, 1H), 2.71 (dd, *J* = 3.9, 13.2 Hz, 1H), 2.52 (dd, *J* = 7.5, 14.4 Hz, 1H), 2.04 (dd, *J* = 7.5, 14.4 Hz, 1H), 1.59 (d, *J* = 3.6 Hz, 2H), 1.17 (d, *J* = 6.9 Hz), 0.04 (s. 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4, 153.5, 145.1, 135.8, 129.9, 129.3, 127.7, 109.7, 66.3, 55.7, 42.6, 38.4, 36.2, 26.8, 17.4, −1.0; HRMS (FAB+) calcd for $C_{20}H_{30}NO_3Si$ (M + H) 360.1995, found 360.1989.



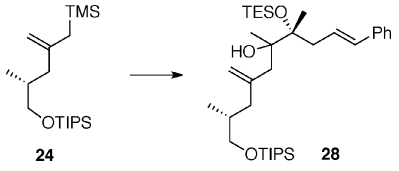
23 **SI-1**

Allylsilane 24. To a solution of **23** (1.88 g, 5.23 mmol) in THF (35 mL) at 0 °C were added sequentially MeOH (0.20 g, 0.25 mL, 6.28 mmol) followed by $LiBH_4$ (3.14 mL, 6.28 mmol, 2.0 M in THF). After 2 h at 0 °C, the reaction was warmed to rt. After 2 h, the reaction was quenched with satd aq sodium tartrate (25 mL). After stirring for 20 min, the organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 25 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 15−25% Et_2O/pentane, to give free alcohol **SI-1** (0.96 g, 5.18 mmol, 99%) as a colorless oil: $[\alpha]^{23}_D$ (+) 9.4 (*c* 0.84, $CHCl_3$); IR (thin film) 3337 (br), 3072, 2954, 2916, 1631, 1455, 1419, 1248, 1036, 849 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5,60 (d, *J* = 15.6 Hz, 2H), 3.44−3.52 (m, 2H), 2.03−2.10 (m, 1H), 1.77−1.89 (m, 2H), 1.54 (s, 2H), 1.41 (t, OH), 0.91 (d, *J* = 6.3 Hz, 3H), 0.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.6, 109.2, 68.7, 43.1, 34.2, 26.7, 17.2, −0.9; HRMS (FAB+) calcd for $C_{10}H_{22}OSi$ (M) 186.1440, found 186.1447.



SI-1 **24**

TIPS Ether 24. To a solution of alcohol intermediate **SI-1** (308 mg, 1.65 mmol) in CH_2Cl_2 at −78 °C were added sequentially Et_3N (0.25 g, 0.34 mL, 2.48 mmol) and TIPSOTf (607 mg, 0.53 mL, 1.98 mmol). After 20 min, the reaction was warmed to rt. After 5 min, the reaction was quenched with satd aq NH_4Cl (25 mL). After 5 min, the organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 1% EtOAc/hexanes, to give **24** (560 mg, 1.64 mmol, 99%) as a colorless oil: $[\alpha]^{23}_D$ −4.9 (*c* 0.98, $CHCl_3$); IR (thin film) 3072, 2944, 2866, 1631, 1463, 1387, 1248, 1103, 1068, 878, 849, 796, 681 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.57−4.58 (m, 1H), 4.54 (s, 1H), 3.47−3.51 (m, 2H), 2.18 (dd, *J* = 5.4, 13.8, 1H), 1.78−1.82 (m, 1H), 1.63−1.71 (m, 1H), 1.51 (s, 2H), 1.04−1.08 (m, 21H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.20 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.6, 108.8, 68.9, 42.7, 34.6, 26.7, 18.5, 17.0, 12.4, −0.9; HRMS (FAB+) calcd for $C_{19}H_{42}OSi_2$ (M^+) 342.2774, found 342.2772.

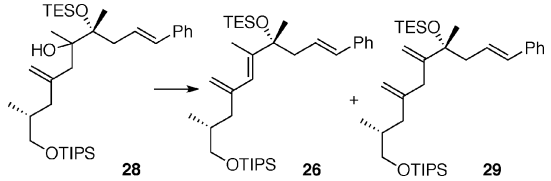


24 **28**

Tertiary Alcohol 28. To a solution of allylsilane **24** (214 mg, 0.62 mmol) and ketone **16** (96 mg, 0.3 mmol) in CH_2Cl_2 (3.0 mL) at −78 °C was added freshly distilled $TiCl_4$ (117.6 mg, 70 μL, 0.62 mmol) via microsyringe dropwise. After 15 min, the dark red solution was quenched with satd aq K_2CO_3 (5 mL) and warmed to rt immediately. After 20 min, the organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting carefully with 0.5−2% EtOAc/hexanes, to give **28** (382 mg,

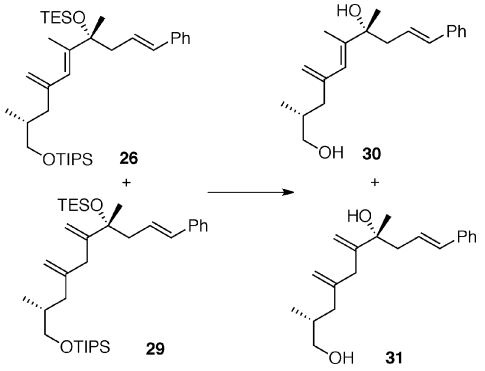
dx.doi.org/10.1021/jo3026077 | J. Org. Chem. 2013, 78, 2213−2247

0.19 mmol, 65%) as a colorless oil of a mixture of isomers (dr = 6:1). Major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24−7.39 (m, 5H), 6.35−6.44 (m, 2H), 4.93 (s, 1H), 4.84 (s, 1H), 3.57−3.61 (m, 1H), 3.43−3.48 (m, 1H), 2.55−2.60 (m, 2H), 2.35−2.40 (m, 1H), 2.31 (dd, J = 5.7, 10.8, 1H), 2.16 (d, J = 9.9 Hz, 1H), 2.03 (dd, J = 5.7, 10.8 Hz, 1H), 1.85−1.88 (m, 1H), 1.33 (s, 3H), 1.20 (s, 3H), 1.08−1.10 (m, 21H), 0.99 (t, J = 6.0 Hz, 9H), 0.94 (d, J = 5.1 Hz, 3 H), 0.70 (q, J = 6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.1, 138.0, 132.5, 128.9, 127.9, 127.4, 126.4, 115.4, 81.9, 77.7, 68.6, 43.3, 42.2, 42.1, 34.8, 23.1, 21.3, 18.5, 17.5, 12.4, 7.7, 7.4; HRMS (FAB+) calcd for $C_{35}H_{64}O_3Si_2$ (M^+) 588.4394, found 588.4382.



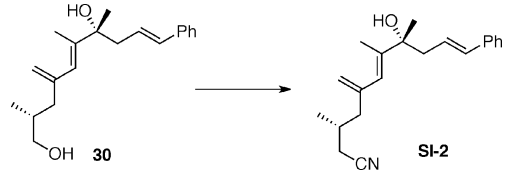
Dienes 26 and 29. To a solution of **28** (118 mg, 0.20 mmol) in PhMe (5.0 mL) at −78 °C were added sequentially pyridine (79.0 mg, 0.08 mL, 1.0 mmol) and $SOCl_2$ (71.4 mg, 44 μL, 0.60 mmol) via microsyringe. After 30 min, the reaction was quenched with satd aq $NaHCO_3$ (10 mL) and warmed to rt. After 20 min, the organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting carefully with 0.5−1% EtOAc/hexanes, to give a mixture of **26** and **29** (114 mg, 0.20 mmol, 99%, 2.2:1 ratio) separable by HPLC as a colorless oil. Conjugate diene **26**: $[\alpha]^{23}_D$ −43.2 (c 0.1, $CHCl_3$); IR (thin film) 2954, 2866, 1640, 1459, 1156, 1119, 1013, 882, 741 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20−7.34 (m, 5H), 6.35 (d, J = 12.0 Hz, 1H), 6.18 (dt, J = 12.0, 5.4 Hz, 1H), 5.89 (s, 1H), 5.01 (s, 1H), 4.82 (s, 1H), 3.44 (d, J = 4.2 Hz, 2H), 2.48−2.50 (m, 2H), 2.35 (dd, J = 3.6, 9.9 Hz, 1H), 1.84 (d, J = 0.9 Hz, 3H), 1.82 (dd, J = 3.6, 9.9 Hz, 1H), 1.66−1.72 (m, 1H), 1.46 (s, 3H), 1.07−1.09 (m, 21H), 1.00 (t, J = 5.7 Hz, 9H), 0.78 (d, J = 5.6 Hz, 3H), 0.64 (q, J = 5.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.7, 142.8, 138.3, 131.9, 128.8, 127.4, 127.2, 126.3, 125.5, 114.5, 78.7, 68.6, 46.3, 42.6, 34.9, 27.2, 18.5, 16.7, 15.0, 12.4, 7.6, 7.2; HRMS (FAB+) calcd for $C_{35}H_{62}O_2Si_2$ (M^+) 570.4288, found 570.4277.

Unconjugated diene 29: $[\alpha]^{23}_D$ −1.3 (c 1.74, $CHCl_3$); IR (thin film) 3026, 2942, 2865, 1643, 1495, 1462, 1381, 1241, 1097, 1012, 882 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22−7.36 (m, 5H), 6.38 (d, J = 12.0 Hz, 1H), 6.16−6.20 (m, 1H), 5.16 (s, 1H), 4.92 (s, 1H), 4.89 (s, 1H), 4.88 (s, 1H), 3.55−3.59 (m, 1H), 3.44−3.47 (m, 1H), 2.84 (s, 2H), 2.47−2.50 (m, 2H), 2.25 (dd, J = 3.6, 9.9 Hz, 1H), 1.74−1.85 (m, 2H), 1.43 (s, 3H), 1.08−1.10 (m, 21H), 1.00 (t, J = 6.0 Hz, 9H), 0.92 (d, J = 4.8 Hz, 3H), 0.64 (q, J = 6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0, 146.7, 138.3, 132.2, 128.9, 127.5, 127.2, 126.4, 113.9, 111.1, 78.3, 68.8, 46.4, 39.8, 38.8, 34.6, 27.5, 18.5, 17.2, 12.4, 7.6, 7.3.

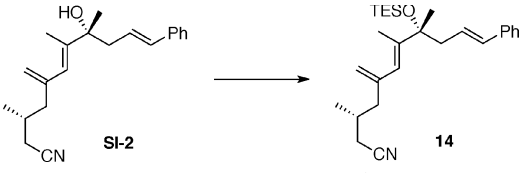


Diols 30 and 31. To a mixture of **26** and **29** (75 mg, 0.13 mmol) in THF (0.1 mL) at 0 °C was added TBAF (0.6 mL, 1.0 M in THF). After 10 min, the reaction was warmed to rt. After 1 h, the reaction was quenched with satd aq NH_4Cl (3 mL). After 10 min, the mixture was extracted with Et_2O (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20% EtOAc/hexanes, to give diol **30** (20 mg, 0.069 mmol, 61%) as a white foam: $[\alpha]^{23}_D$ −4.9 (c 0.98, $CHCl_3$); IR (thin film) 3373 (br), 3026, 2955, 2925, 2870, 1722, 1627, 1448, 1373, 1032, 966, 897, 741, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.38 (m, 5H), 6.46 (d, J = 15.6 Hz, 1H), 6.12−6.20 (m, 1H), 5.97 (s, 1H), 5.07 (s, 1H), 4.86 (s, 1H), 3.28−3.40 (m, 2H), 2.66 (dd, J = 7.2, 14.0 Hz, 1H), 2.46 (dd, J = 8.0, 14.0 Hz, 1H), 2.26 (dd, J = 5.6, 13.6 Hz, 1H), 1.89 (s, 3H), 1.84−1.88 (m, 1H), 1.61−1.66 (m, 1H), 1.42 (s, 3H), 0.85 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 142.9, 137.7, 133.8, 129.0, 127.8, 126.5, 125.9, 125.1, 115.2, 76.0, 68.5, 44.4, 42.5, 34.9, 28.1, 16.6, 15.4; HRMS (ES+) calcd for $C_{20}H_{28}O_2Na$ (M + Na) 323.1987, found 323.1996.

Diol 31: colorless oil; $[\alpha]^{23}_D$ +7.6 (c 1.21, $CHCl_3$); IR (thin film) 3373, 3081, 3026, 2957, 2926, 2870, 1724, 1644, 1496, 1449, 1373, 1112, 1034, 967, 900, 739, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.39 (m, 5H), 6.49 (d, J = 15.6 Hz, 1H), 6.16−6.23 (m, 1H), 5.23 (s, 1H), 4.96 (s, 3H), 3.48−3.52 (m, 2H), 2.85−2.96 (m, 2H), 2.62−2.66 (m, 1H), 2.48−2.52 (m, 1H), 2.18−2.24 (m, 1H), 1.86−1.93 (m, 2H), 1.40 (s, 3H), 0.94 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 146.9, 137.7, 134.3, 128.9, 127.7, 126.6, 125.7, 114.3, 111.8, 75.7, 68.6, 45.0, 40.1, 39.2, 34.3, 28.2, 17.1; HRMS (ES+) calcd for $C_{20}H_{28}O_2Na$ (M + Na) 323.1987, found 323.1989.



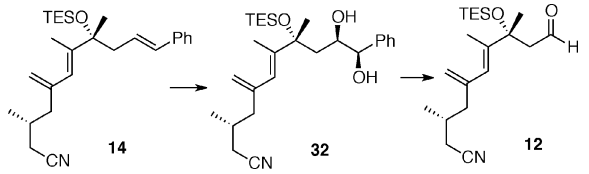
Nitrile 14. To a solution of **30** (98 mg, 0.33 mmol) in Et_2O (1.6 mL) at 0 °C were added sequentially PPh_3 (342 mg, 1.3 mmol) and DEAD (0.24 mL, 1.3 mmol, 40% w/w in PhMe). After 15 min, acetone cyanohydrin (70.0 mg, 74.5 μL, 0.82 mmol) was added dropwise. After 5 min, the reaction was warmed to rt. After 6 h, the reaction was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10% EtOAc/hexanes, to give a corresponding nitrile intermediate (80 mg, 0.26 mmol, 81%) as a colorless oil: $[\alpha]^{23}_D$ +7.8 (c 0.99, $CHCl_3$); IR (neat) 3479 (br), 2962, 2927, 2246, 1733, 1496, 1456, 1420, 1381, 1105, 968, 902, 743, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.37 (m, 5H), 6.47 (d, J = 16.0 Hz, 1H), 6.12−6.18 (m, 1H), 5.95 (s, 1H), 5.12 (s, 1H), 4.92 (s, 1H), 2.66 (dd, J = 7.2, 14.0 Hz, 1H), 2.48 (dd, J = 7.2, 14.0 Hz, 1H), 2.05−2.20 (m, 4H), 1.88 (s, 3H), 1.76−1.88 (m, 1H), 1.75 (br, 1H), 1.43 (s, 3H), 0.97 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 143.5, 137.5, 134.0, 129.0, 127.9, 126.5, 125.5, 124.3, 119.1, 116.4, 76.0, 44.8, 44.5, 29.3, 28.1, 24.2, 19.5, 15.5; HRMS (FAB+) calcd for $C_{21}H_{28}NO$ (M + 1) 310.2171, found 310.2144.



To a solution of the above intermediate (80 mg, 0.26 mmol) in CH_2Cl_2 (1.0 mL) at −78 °C was added 2,6-lutidine (111.0 mg, 0.12 mL, 1.04 mmol) followed by TESOTf (136.9 mg, 0.12 mL, 0.52 mmol). After 30 min, the reaction was warmed to rt and quenched with satd aq NH_4Cl (3 mL). After 5 min, the mixture was extracted with Et_2O (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 1% EtOAc/hexanes, to give nitrile **14** (80 mg, 0.19 mmol, 72%) as a colorless oil: $[\alpha]^{23}_D$ −37.6 (c 0.98, $CHCl_3$); IR (neat) 2957, 2933, 2876, 2240, 1733, 1496, 1457, 1420, 1381, 1160, 1122, 1016, 967, 902, 742, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21−7.33 (m, 5H), 6.33 (d, J = 11.7 Hz, 1H), 6.15−6.19 (m, 1H), 5.87 (s, 1H), 5.07 (s, 1H), 4.87 (s, 1H), 2.50 (d, J = 5.4 Hz, 2H), 2.15 (dd, J = 5.4, 9.9 Hz, 1H), 2.00−2.06 (m, 3H), 1.81 (s, 3H), 1.72−1.79 (m, 1H), 1.47 (s, 3H), 1.02 (t, J = 5.7 Hz, 9H), 0.85 (d, J = 5.1 Hz, 3H), 0.67 (q, J = 5.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 143.7, 138.1, 131.9, 129.0, 127.4, 127.3, 126.3, 124.6, 119.0, 116.0, 78.8, 46.0, 44.9, 29.3,

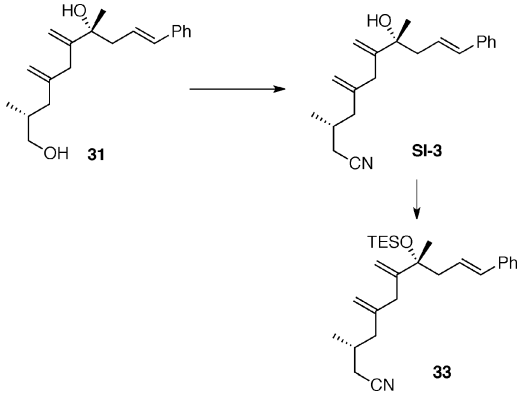
dx.doi.org/10.1021/jo3026077 | J. Org. Chem. 2013, 78, 2213−2247

27.6, 24.1, 19.4, 15.1, 7.64, 7.26; HRMS (FAB+) calcd for $C_{27}H_{42}OSiN$ (M + 1) 424.3036, found 424.3044.



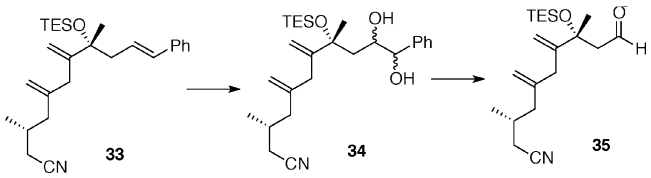
Aldehyde 12. To a solution of **14** (75 mg, 0.18 mmol) in *t*-BuOH/H_2O (3 mL, 1:1) were added $MeSO_2NH_2$ (25.6 mg, 0.27 mmol) and AD mix β*[53] (250 mg). After 16 h, the reaction was quenched with satd aq $Na_2S_2O_3$ (3 mL). After 20 min, the mixture was extracted with EtOAc (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20% EtOAc/hexanes, to give a mixture of diol isomers (73 mg, dr = 6:1, 0.16 mmol, 89%) as a colorless oil. The diol substrate was applied to the next step without further purification.

A solution of the mixture described above in THF/Et_2O (2.8 mL, 1:1) was added $NaIO_4$ (304 mg, 1.42 mmol) and H_2O (1.4 mL). After 2 h, the reaction was quenched with satd aq NaCl (3 mL), and the mixture was extracted with Et_2O (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo to give aldehyde **12** (54 mg, 0.15 mmol, 96%) as a colorless oil: $[\alpha]^{23}_D$ −12.6 (*c* 1.22, $CHCl_3$); IR (neat) 3081, 2957, 2917, 2876, 2246, 1722, 1628, 1457, 1417, 1381, 1240, 1163, 1126, 1046, 1017, 904, 802, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.66 (t, *J* = 3.2 Hz, 1H), 5.99 (s, 1H), 5.10 (s, 1H), 4.89 (s, 1H), 2.61 (dd, *J* = 3.2, 14.8 Hz, 1H), 2.47 (dd, *J* = 2.8, 14.8 Hz, 1H), 2.32 (dd, *J* = 5.2, 16.8 Hz, 1H), 2.15−2.25 (m, 2H), 2.08 (dd, *J* = 7.2, 13.6 Hz, 1H), 1.83−1.92 (m, 1H), 1.80 (s, 3H), 1.47 (s, 3H), 1.04 (d, *J* = 6.4 Hz, 3H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.63 (q, *J* = 8.0 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.2, 143.2, 142.7, 125.2, 118.9, 116.8, 54.5, 44.8, 30.1, 29.6, 28.3, 24.3, 19.8, 15.2, 7.5, 7.2; HRMS (FAB+) calcd for $C_{20}H_{36}O_2SiN$ (M + 1) 350.2515, found 350.2508.



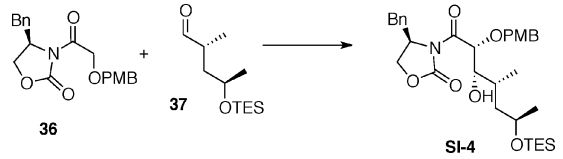
Nitrile 33. To a solution of **31** (30 mg, 0.10 mmol) in Et_2O (0.5 mL, 0.2 M) at 0 °C were added sequentially PPh_3 (104 mg, 0.4 mmol) and DEAD (72 μL, 0.4 mmol, 40% solution in PhMe). After 15 min, acetone cyanohydrin (21.2 mg, 23.0 μL, 0.25 mmol) was added dropwise. After 5 min, the reaction was warmed to rt. After 6 h, the reaction was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10% EtOAc/hexanes, to give a corresponding nitrile intermediate (25 mg, 0.08 mmol, 81%) as a colorless oil.

To a solution of the above nitrile (25 mg, 0.08 mmol) in CH_2Cl_2 (0.32 mL, 0.25 M) at −78 °C were added sequentially 2,6-lutidine (34.3 mg, 37 μL, 0.32 mmol) and TESOTf (42.1 mg, 36 μL, 0.16 mmol). After 30 min, the reaction was warmed to rt and quenched with satd aq NH_4Cl (3 mL). After 5 min, the mixture was extracted with Et_2O (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 1% EtOAc/hexanes, to give **33** (26 mg, 62 μmol, 77%) as a colorless oil: $[\alpha]^{23}_D$ −13.6 (*c* 0.28, $CHCl_3$); IR (neat) 2957, 2933, 2911, 2875, 2247, 1238, 1157, 1123, 1063, 1005, 967, 905, 742, 693 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.17−7.26 (m, 5H), 6.35 (d, *J* = 15.9 Hz, 1H), 6.08−6.19 (m, 1H), 5.14 (s, 1H), 4.93 (s, 2H), 4.71 (s, 1H), 2.75−2.85 (m, 2H), 2.46 (dd, *J* = 0.6, 6.9 Hz, 2H), 2.24−2.32 (m, 1H), 1.97−2.17 (m, 4H), 1.38 (s, 3H), 0.95−1.04 (m, 12H), 0.58−0.68 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.7, 144.9, 138.1, 132.3, 128.9, 127.4, 127.1, 126.4, 119.2, 115.8, 111.1, 78.2, 46.4, 42.3, 38.2, 28.9, 27.7, 24.3, 20.0, 7.6, 7.3.



Aldehyde 35. To a solution of **33** (26 mg, 62 μmol) in *t*-BuOH/H_2O (1 mL, 1:1) were added $MeSO_2NH_2$ (8.8 mg, 93 μmol) and AD mix β*[53] (87 mg). After 16 h, the reaction was quenched with satd aq $Na_2S_2O_3$ (3 mL). After 20 min, the mixture was extracted with EtOAc (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20% EtOAc/hexanes, to give a mixture of the diol isomers (25.5 mg, dr = 1.3:1, 56 μmol, 90%) as a colorless oil. The diol substrate was applied to the next step without further purification.

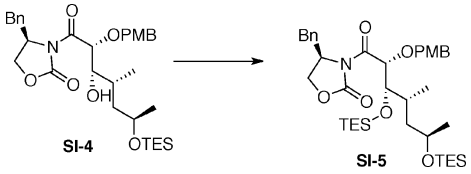
A solution of the mixture described above in THF/Et_2O (1.24 mL, 1:1) was added $NaIO_4$ (120 mg, 0.56 mmol) and H_2O (0.62 mL). After 2 h, the reaction was quenched with satd aq NaCl (3 mL) and the mixture was extracted with Et_2O (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo to give aldehyde **35** (18.5 mg, 0.053 mmol, 95%) as a colorless oil: $[\alpha]^{23}_D$ −11.4 (*c* 1.57, $CHCl_3$); IR (neat) 2958, 2915, 2876, 2737, 2246, 1722, 1645, 1457, 1417, 1375, 1239, 1165, 1123, 1045, 1005, 909, 743, 726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.66 (t, *J* = 3.0 Hz, 1H), 5.28 (s, 1H), 4.95 (s, 1H), 4.94 (s, 1H), 4.90 (s, 1H), 2.76 (s, 2H), 2.20−2.62 (m, 5H), 2.02−2.06 (m, 2H), 1.46 (s, 3H), 1.08 (d, *J* = 6.3 Hz, 3H), 0.96 (t, *J* = 7.8 Hz, 9H), 0.63 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.3, 150.5, 144.3, 119.0, 116.2, 112.6, 54.5, 42.1, 38.4, 28.9, 28.5, 24.3, 24.0, 19.9, 7.5, 7.2.



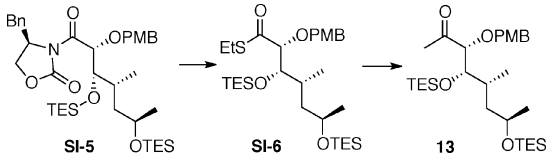
Methyl Ketone 13. To a solution of imide **36**[22] (107 mg, 0.3 mmol) in PhMe (0.7 mL) at −50 °C were added sequentially Et_3N (34.4 mg, 48.2 μL, 0.34 mmol) and Bu_2BOTf (86.0 mg, 80.0 μL, 0.32 mmol). After 1.5 h, a solution of aldehyde **37**[8] (46 mg, 0.20 mmol) in PhMe (0.25 mL) was transferred dropwise into the reaction via cannula. After 40 min, the reaction was warmed to −30 °C within 30 min. After 1 h, the reaction was quenched with aq phosphate buffer solution (0.5 mL, pH 7), MeOH (0.5 mL), and THF (0.5 mL). Next, the mixture was warmed up to rt. A solution of H_2O_2 (0.5 mL, 30% H_2O_2 in H_2O) in MeOH (0.5 mL) was added dropwise. After 1 h, the reaction mixture was extracted with EtOAc (3 × 15 mL) and the combined organic extract was diluted with an aqueous phosphate buffer solution (20 mL, pH 7). The mixture was concentrated in vacuo and extracted again with Et_2O (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 15−20% EtOAc/hexanes, to give an aldol adduct **SI-4** (83 mg, 0.14 mmol, 72%) as a colorless oil: $[\alpha]^{23}_D$ −3.9 (*c* 0.83, $CHCl_3$); IR (thin film) 3490 (br), 2956, 2875, 1781, 1708, 1612, 1514, 1389, 1248, 1211, 1051, 1012, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25−7.39 (m, 7H), 6.92 (d, *J* = 8.8 Hz, 2H), 5.36 (d, *J* = 2.0 Hz, 1H), 4.64−4.72 (m, 1H), 4.64 (d, *J* = 10.8 Hz, 1H), 4.49 (d, *J* = 10.8 Hz, 1H), 4.20−4.29 (m, 2H), 3.84−3.90 (m, 1H), 3.82 (s, 3H), 3.61−3.64 (m, 1H), 3.34 (dd, *J* = 2.8, 13.2 Hz, 1H), 2.78 (dd, *J* = 3.6, 13.5 Hz, 1 H), 2.31 (d, *J* = 10.0 Hz, 1H), 1.74−1.81 (m, 1H), 1.56−1.62 (m, 1H), 1.40−1.48 (m, 1H), 1.15 (d, *J* = 5.6 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.99 (t, *J* = 7.6 Hz, 9H), 0.62 (q, *J* = 7.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 160.0, 153.6, 135.6, 130.7, 129.8, 129.6, 129.4, 127.8, 114.3, 78.4, 76.6, 73.0, 67.4, 67.3, 56.2,

dx.doi.org/10.1021/jo3026077 | J. Org. Chem. 2013, 78, 2213−2247

55.7, 43.1, 38.2, 34.6, 23.6, 16.2, 7.3, 5.3; HRMS (FAB+) calcd for $C_{32}H_{48}NO_7Si$ (M + 1) 586.3200, found 586.3202.

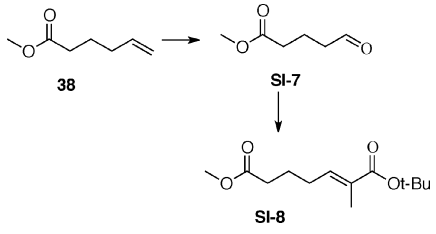


TES Ether SI-5. To a solution of the aldol adduct **SI-4** (78 mg, 0.13 mmol) in CH_2Cl_2 (0.3 mL) at 0 °C were added sequentially 2,6-lutidine (27.8 mg, 29.8 μL, 0.26 mmol) and TESOTf (68.5 mg, 60.1 μL, 0.26 mmol). After 1 h, the reaction was warmed to rt and quenched with satd aq NH_4Cl (3 mL). After 5 min, the mixture was extracted with Et_2O (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 4–6% EtOAc/hexanes, to give the corresponding protected alcohol **SI-5** (84 mg, 0.12 mmol, 90%) as a colorless oil: $[\alpha]^{23}_D$ −33.8 (*c* 1.9, $CHCl_3$); IR (thin film) 2956, 2911, 2875, 1785. 1704, 1612, 1513, 1456, 1381, 1248, 1082, 1011, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.26 (m, 7H), 6.84 (d, *J* = 8.4 Hz, 2H), 5.25 (d, *J* = 6.0 Hz, 1H), 4.64 (d, *J* = 11.7 Hz, 1H), 4.52 (d, *J* = 11.7 Hz, 1H), 4.46–4.49 (m, 1H), 4.03–4.12 (m, 3H), 3.73–3.98 (m, 1H), 3.79–3.81 (m, 1H), 3.74 (s, 3H), 3.11 (dd, *J* = 3.0, 13.2 Hz, 1H), 2.40 (dd, *J* = 3.0, 13.5 Hz, 1H), 1.47–1.55 (m, 2H), 1.09 (d, *J* = 6.0 Hz, 3H), 0.87–0.97 (m, 21H), 0.53–0.63 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 159.9, 153.3, 135.8, 130.6, 130.3, 129.7, 129.4, 127.8, 114.0, 79.6, 77.8, 73.4, 67.6, 66.8, 56.4, 55.6, 44.7, 37.8, 33.9, 24.1, 15.2, 7.5, 7.4, 5.8, 5.4; HRMS (FAB+) calcd for $C_{38}H_{60}NO_7Si_2$ (M − 1) 698.3908, found 698.3890.



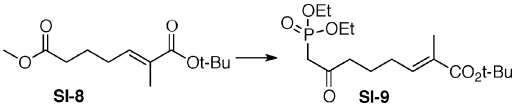
Methyl Ketone 13. To a solution of EtSH (75 mg, 90.2 μL, 1.21 mmol) in THF (9.0 mL) at 0 °C was added *n*-BuLi (0.43 mL, 1.07 mmol, 2.5 M in hexane). After 20 min, a solution of the above intermediate (500 mg, 0.714 mmol) in THF (3.0 mL) was transferred via cannula dropwise. After 20 min, the reaction was quenched with satd aq NH_4Cl (10 mL). After 5 min, the mixture was extracted with Et_2O (3 × 20 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by a plug of silica gel, eluting with 10% EtOAc/hexanes, to give the corresponding thioester intermediate (375 mg, 0.68 mmol, 95%) as a colorless oil.

To a suspension of CuI (796 mg, 4.18 mmol) in Et_2O (9.0 mL) at 0 °C was added MeLi (5.2 mL, 8.36 mmol, 1.6 M in Et_2O). After 15 min, the colorless solution was cooled to −50 °C, and a solution of the above thioester intermediate (375 mg, 0.68 mmol) in Et_2O (2.4 mL) was transferred into the reaction dropwise via cannula. After 2 h, the reaction was quenched with satd aq NH_4Cl (10 mL) at −50 °C, warmed to rt, and extracted with Et_2O (3 × 20 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 2–4% EtOAc/hexanes, to give methyl ketone **13** (326 mg, 0.60 mmol, 89%) as a colorless oil: $[\alpha]^{23}_D$ +31.0 (*c* 0.80, $CHCl_3$); IR 2956, 2912, 2876, 1716, 1613, 1514, 1457, 1416, 1249, 1172, 1082, 1037, 1007, 820, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.40 (d, *J* = 11.4 Hz, 1H), 4.38 (d, *J* = 11.4 Hz, 1H), 3.81 (s, 3H), 3.69–3.81 (m, 3H), 2.11 (s, 3H), 1.45–1.48 (m, 3H), 1.09 (d, *J* = 6.0 Hz, 3H), 0.85–0.97 (m, 21H), 0.53–0.61 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.5, 159.8, 130.1, 129.9, 114.1, 88.9, 73.1, 67.4, 55.7, 44.9, 33.5, 27.4, 23.9, 14.3, 7.4, 7.3, 5.7, 5.4; HRMS (FAB+) calcd for $C_{29}H_{55}O_5Si_2$ (M + 1) 539.3588, found 539.3559.

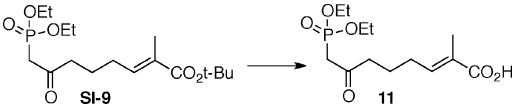


Carboxylic Acid 11. To a solution of **38** (320 mg, 0.35 mL, 2.50 mmol) in THF/H_2O (35 mL, 1:1) at rt were added $K_2OsO_4·H_2O$ (14 mg, 15 μmol) and $NaIO_4$ (2.4 g, 11.25 mmol). After 3 h, the reaction was quenched with satd aq $Na_2S_2O_3$ (5 mL). After 20 min, the mixture was extracted with Et_2O (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo to give an aldehyde intermediate (247 mg, 1.90 mmol, 76%) as a colorless oil. The aldehyde intermediate **SI-7** was used directly in the next step without further purification.

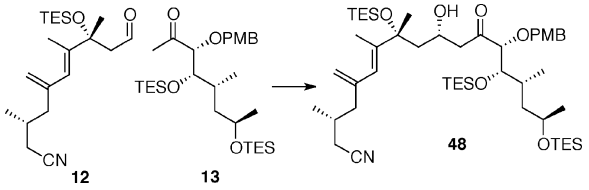
To a solution of the above aldehyde intermediate **SI-7** (247 mg, 1.90 mmol) in CH_2Cl_2 (5.4 mL) at rt was added Wittig reagent $Ph_3P{=}C(Me)CO_2t$-Bu (725 mg, 2.0 mmol). After 30 min, the reaction was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5% EtOAc/hexanes, to give Wittig product **SI-8** (377 mg, 1.56 mmol, 82%) as a colorless oil: IR (neat) 2977, 1739, 1704, 1652, 1456, 1436, 1367, 1289, 1252, 1159, 1121, 1083, 852, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.59 (dt, *J* = 1.2, 7.5 Hz, 1H), 3.65 (s, 3H), 2.32 (t, *J* = 7.5 Hz, 2H), 2.17 (q, *J* = 7.5 Hz, 2H), 1.71–1.83 (m, 5H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 167.8, 139.9, 130.5, 80.5, 51.9, 33.9, 28.5, 28.3, 24.2, 12.8; HRMS (FAB+) calcd for $C_{13}H_{23}O_4$ (M + 1) 243.1596, found 243.1598.



Phosphonate SI-9. To a solution of methyl diethylphosphonate (318 mg, 0.3 mL, 2.09 mmol) in THF (10 mL) at −78 °C was added *n*-BuLi (0.83 mL, 2.09 mmol, 2.5 M in hexane). After 20 min, this resulted solution was transferred dropwise into a solution of the above Wittig product **SI-8** (202 mg, 0.83 mmol) in THF (4 mL) at −78 °C via cannula. After 30 min, the reaction was quenched with satd aq NH_4Cl (3 mL). The mixture was extracted with EtOAc (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 80% EtOAc/hexanes, to give phosphonate intermediate **SI-9** (254 mg, 0.65 mmol, 78%) as a colorless oil: IR (neat) 2978, 2932, 1701, 1652, 1392, 1366, 1254, 1162, 1024, 965, 794 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.58 (dt, *J* = 1.2, 7.5 Hz, 1H), 4.07–4.17 (m, 4H), 3.09 (s, 1H), 3.01 (s, 1H), 2.63 (t, *J* = 7.2 Hz, 2H), 2.13 (q, *J* = 7.5 Hz, 2H), 1.75 (s, 3H), 1.67–1.75 (m, 2H), 1.46 (s, 9H), 1.31 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 167.8, 140.2, 130.4, 80.5, 63.0, 43.7, 42.0, 28.5, 28.1, 22.7, 16.7, 12.8; HRMS (FAB+) calcd for $C_{17}H_{32}O_6P$ (M + 1) 363.1937, found 363.1942.



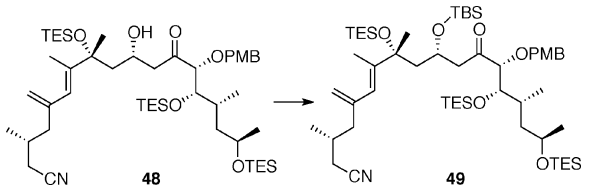
Acid 11. To a solution of the above phosphonate **SI-9** (102 mg, 0.28 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C was added TFA (1.15 g, 0.75 mL, 9.7 mmol). After 5 min, the reaction was warmed to rt. After 2 h, the reaction was concentrated in vacuo and purified by chromatography over silica gel, eluting with 4% MeOH/CH_2Cl_2, to give **11** (84.8 mg, 0.28 mmol, 99%) as a colorless oil: IR (neat) 3418, 2986, 2934, 1772, 1715, 1395, 1209, 1163, 1023, 973, 799, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.86 (t, *J* = 7.5 Hz, 1H), 6.07 (br, 1H), 4.12–4.23 (m, 4H), 3.18 (s, 1H), 3.10 (s, 1H), 2.64 (t, *J* = 7.2 Hz, 2H), 2.22 (q, *J* = 7.5 Hz, 2H), 1.82 (s, 3H), 1.71–1.80 (m, 2H), 1.30 (t, *J* = 7.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 170.5, 143.5, 128.5, 63.2, 43.6, 41.9, 28.2, 22.5, 16.7, 12.5; HRMS (FAB+) calcd for $C_{13}H_{24}O_6P$ (M + 1) 307.1311, found 307.1322.



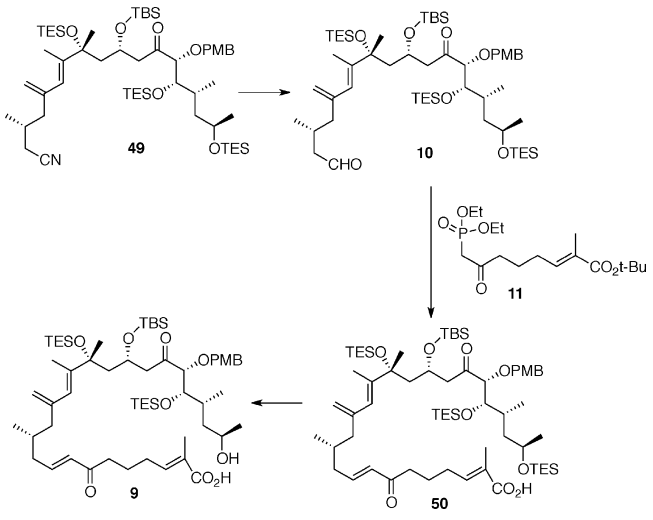
Alcohol 48. To a solution of **13** (73 mg, 0.14 mmol) in Et_2O (0.7 mL) at −78 °C was added LDA[54] (0.15 mL, 1.0 M in THF). After 20 min, a precooled (−78 °C) solution of aldehyde **12** (31.5 mg,

dx.doi.org/10.1021/jo3026077 | J. Org. Chem. 2013, 78, 2213–2247

0.09 mmol) in Et_2O (0.4 mL) was transferred in one portion via cannula at −78 °C. After 20 min, the reaction was quenched with satd aq NH_4Cl (3 mL), and the mixture was extracted with Et_2O (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5% EtOAc/hexanes, to give **48** (55 mg, 0.06 mmol, 69%) as a colorless oil: $[\alpha]^{23}_D$ +21.3 (*c* 0.60, $CHCl_3$); IR (neat) 3496, 2955, 2911, 2876, 1715, 1614, 1515, 1457, 1418, 1379, 1249, 1086, 1036, 1008, 903, 807, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.87 (s, 1H), 5.09 (s, 1H), 4.89 (s, 1H), 4.47 (d, *J* = 10.8 Hz, 1H), 4.33−4.36 (m, 2H), 3.80 (s, 3H), 3.76−3.80 (m, 3H), 3.61 (s, 1H), 2.95 (dd, *J* = 7.2, 18.0 Hz, 1H), 2.05−2.40 (m, 6H), 1.88−1.95 (m, 1H), 1.81 (s, 3H), 1.52 (s, 3H), 1.37−1.52 (m, 5H), 1.07 (d, *J* = 6.9 Hz, 3H), 1.05 (d, *J* = 6.0 Hz, 3H), 0.83−0.98 (m, 30H), 0.51−0.67 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.1, 159.7, 144.8, 143.2, 130.1, 124.3, 118.9, 116.7, 114.1, 88.5, 79.7, 72.9, 67.3, 65.1, 55.7, 48.4, 47.2, 45.1, 44.9, 33.5, 29.6, 26.7, 24.3, 23.6, 19.8, 15.2, 13.9, 7.5, 7.4, 7.3, 7.0, 5.7, 5.4; HRMS (FAB+) calcd for $C_{49}H_{90}O_7Si_3N$ (M + 1) 888.6025, found 888.6052.



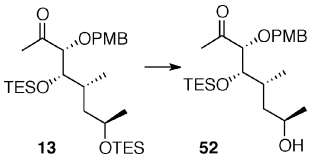
Silyl Ether 49. To a solution of **48** (55 mg, 60 μmol) in CH_2Cl_2 (0.15 mL) at rt was added Et_3N (0.15 mL). The solution was then cooled to −78 °C. After 5 min, TBSOTf (65.8 mg, 60.4 μL, 0.25 mmol) was added dropwise. After 5 min, the reaction was warmed to rt. After 20 min, the reaction was quenched with satd aq NH_4Cl (3 mL), and the mixture was extracted with Et_2O (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 3% EtOAc/hexanes, to give **49** (53 mg, 53 μmol, 88%) as a colorless oil: $[\alpha]^{23}_D$ +35.1 (*c* 0.50, $CHCl_3$); IR (neat) 2954, 2928, 2876, 1714, 1615, 1515, 1458, 1381, 1250, 1167, 1125, 1065, 1006, 987, 835, 776, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.80 (s, 1H), 5.07 (s, 1H), 4.89 (s, 1H), 4.51 (d, *J* = 10.5 Hz, 1H), 4.21−4.25 (m, 2H), 3.81 (s, 3H), 3.64−3.81 (m, 3H), 3.17 (dd, *J* = 9.3, 18.0 Hz, 1H), 2.58 (dd, *J* = 2.7, 17.7 Hz, 1H), 2.38 (dd, *J* = 4.5, 16.8 Hz, 1H), 2.19 (dd, *J* = 6.9, 16.8 Hz, 1H), 2.05−2.10 (m, 2H), 1.86−1.94 (m, 2H), 1.79 (s, 3H), 1.66−1.79 (m, 1H), 1.58−1.62 (m, 1H), 1.40 (s, 3H), 1.28−1.35 (m, 2H), 1.07 (d, *J* = 6.3 Hz, 3H), 1.05 (d, *J* = 5.4 Hz, 3H), 0.86−0.97 (m, 30H), 0.78 (s, 9H), 0.50−0.65 (m, 18H), 0.05 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.2, 159.5, 143.6, 143.1, 130.3, 129.9, 124.9, 119.0, 116.6, 113.9, 89.1, 77.3, 72.3, 67.2, 66.1, 55.6, 49.7, 46.4, 45.5, 44.7, 33.7, 29.4, 29.0, 26.3, 24.3, 23.5, 19.7, 18.4, 15.4, 12.9, 7.7, 7.4, 7.3, 5.7, 5.3, −3.7, −4.2; HRMS (FAB+) calcd for $C_{55}H_{104}O_7Si_4N$ (M + 1) 1002.6890, found 1002.6923.



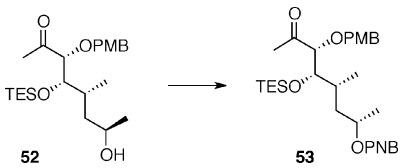
Acid 9. To a solution of **49** (11 mg, 11 μmol) in PhMe (0.25 mL) at −78 °C was added DIBAL-H (13.2 μL, 13.2 μmol, 1.0 M in PhMe) dropwise. After 10 min, another portion of DIBAL-H (6.0 μL, 6.0 μmol, 1.0 M in PhMe) was added. The reaction was quenched sequentially with MeOH (0.5 mL), satd aq tartaric acid (0.1 mL), and H_2O (2 mL). Next, the mixture was warmed to rt. After 1 h, the mixture was extracted with Et_2O (3 × 10 mL), and the dried ($MgSO_4$) extract was concentrated in vacuo to give the unstable aldehyde **10** as a colorless oil. The aldehyde was applied immediately to the next step without further purification.

To a solution of **11** (4.0 mg, 0.012 mmol) in THF/H_2O (0.2 mL, 40:1) at rt was added $Ba(OH)_2{\cdot}8H_2O$ (7.6 mg, 0.024 mmol). After 30 min, a solution of the above aldehyde intermediate **10** in THF (0.15 mL) was added dropwise via cannula. After 16 h, the reaction was quenched with satd aq NH_4Cl (2 mL) and the mixture was extracted with Et_2O (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo was applied immediately to the next step without further purification.

To a flask containing crude **50** at 0 °C was added a premixed solution of HOAc/THF/H_2O (4.0 mL, 8:4:1) dropwise. After 2 h, the solution was allowed to warm to 10 °C. After 6 h, the reaction was warmed to rt. After 6 h, the reaction was concentrated in vacuo. Benzene was added to further dry the product **9** (11.3 mg): ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.8 Hz, 2H), 6.84−6.98 (m, 4H), 6.10 (d, *J* = 15.9 Hz, 2H), 5.83 (s, 1H), 4.99 (s, 1H), 4.83 (s, 1H), 4.52 (d, *J* = 10.5 Hz, 1H), 4.12−4.27 (m, 2H), 3.81 (s, 3H), 3.68−3.80 (m, 3H), 3.16 (m, 1H), 2.59−2.68 (m, 3H), 2.28−2.38 (m, 1H), 2.21−2.25 (m, 2H), 1.91−2.11 (m, 4H), 1.82 (s, 3H), 1.75 (s, 3H), 1.71−1.82 (m, 4H), 1.64−1.69 (m, 1H), 1.43 (s, 3H), 1.25−1.35 (m, 4H), 1.09 (d, *J* = 4.0 Hz, 3H), 0.88−1.01 (m, 31H), 0.81 (s, 9H), 0.55−0.68 (m, 18H), 0.09 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.5, 201.2, 168.6, 159.6, 147.0, 145.0, 144.0, 142.1, 132.1, 130.1, 129.9, 128.9, 125.7, 115.5, 113.9, 88.5, 77.3, 72.2, 67.2, 66.1, 55.6, 49.6, 47.0, 46.0, 43.9, 40.3, 39.3, 33.3, 32.3, 31.5, 29.1, 28.6, 26.3, 23.3, 23.5, 23.0, 19.6, 18.3, 14.7, 14.5, 12.5, 7.7, 7.4, 7.3, 7.0, 6.2, 5.6, −3.8, −4.1.



Alcohol 52. To a flask containing **13** (120 mg, 0.22 mmol) at 0 °C was added a premixed solution of HOAc/THF/H_2O (4.0 mL, 8:8:1) dropwise. After 10 min, the solution was allowed to warm to 5 °C. After 2 h, the reaction was quenched with satd aq $NaHCO_3$ (10 mL) dropwise. Next, the mixture was extracted with Et_2O (3 × 10 mL), and the dried ($MgSO_4$) extract was concentrated in vacuo to give product **52** (90 mg, 0.21 mmol, 95%) as a colorless oil: $[\alpha]^{23}_D$ (+) 17.7 (*c* 0.34, $CHCl_3$); IR (thin film) 3413, 2958, 2910, 2875, 1712, 1613, 1514, 1457, 1354, 1302, 1249, 1172, 1076, 1055, 1009, 820, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.4 Hz, 2H) 6.86 (d, *J* = 8.4 Hz, 2H), 4.43 (d, *J* = 11.4 Hz, 1H), 4.38 (d, *J* = 11.4 Hz, 1H), 3.81−3.91 (m, 2H), 3.80 (s, 3H), 3.74 (d, *J* = 6.3 Hz, 1H), 2.40 (br, 1H), 2.14 (s, 3H), 1.49−1.65 (m, 2H), 1.32−1.40 (m, 1H), 1.14 (d, *J* = 6.0 Hz, 3H), 0.85−0.99 (m, 12H), 0.58 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 210.8, 159.8, 130.2, 129.7, 114.2, 88.4, 75.3, 72.9, 66.2, 55.7, 43.5, 33.5, 27.5, 24.2, 15.1, 7.4, 5.6; HRMS (FAB+) calcd for $C_{23}H_{41}O_5Si$ (M + 1) 425.2723, found 425.2730.



Ester 53. To a solution of **52** (237 mg, 0.56 mmol), *p*-NO_2-benzonic acid (374 mg, 2.24 mmmol), and PPh_3 (587 mg, 2.24 mmol) in THF (3.7 mL) at 0 °C was added DEAD (1.0 mL, 1.04 g, 2.24 mmol, 40% w/w in PhMe) dropwise. After 10 min, the reaction was warmed to rt. After 2 h, the reaction was concentrated in vacuo and purified by

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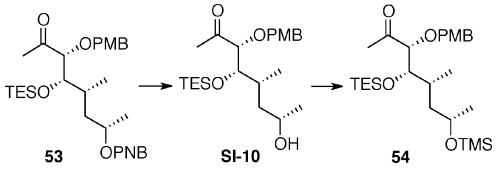
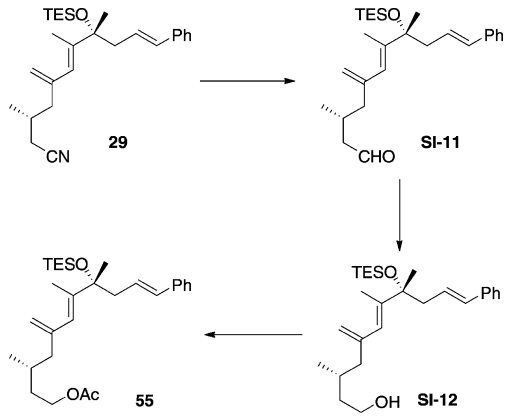
chromatography over silica gel, eluting with 10−15% EtOAc/hexanes, to give **53** (46 mg, 0.084 mmol, 80%) as a colorless oil: $[\alpha]^{23}_{D}$ (+) 38.1 (*c* 0.48, $CHCl_3$); IR (thin film) 2954, 2875, 1719, 1610, 1528, 1514, 1457, 1349, 1275, 1102, 1036, 1013, 823, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.8 Hz, 2H), 8.19 (d, *J* = 8.8 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 5.24−5.29 (m, 1H), 4.53 (d, *J* = 11.2 Hz, 1H), 4.38 (d, *J* = 11.2 Hz, 1H), 3.80−3.83 (m, 3H), 2.16 (s, 3H), 2.01−2.08 (m, 1H), 1.67−1.69 (m, 1H), 1.55−1.61 (m, 1H), 1.39 (d, *J* = 6.0 Hz, 3H), 0.93 (t, *J* = 8.0 Hz, 9H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.59 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 211.3, 164.8, 159.9, 150.8, 136.5, 131.0, 130.3, 129.6, 123.9, 114.2, 87.6, 77.4, 73.1, 71.3, 55.7, 39.9, 33.7, 28.0, 21.4, 14.7, 7.4, 5.5.



Silyl Ether 54. To a solution of **53** (125 mg, 0.23 mmol) in MeOH (4.7 mL) was added $Ba(OH)_2.8H_2O$ (36.1 mg, 0.12 mmol). After 1 h, the reaction was quenched with satd aq NH_4Cl (5 mL). The mixture was extracted with Et_2O (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10−15% EtOAc/hexanes, to give an alcohol intermediate **SI-10** (63 mg, 0.15 mmol, 65%) as a colorless oil: $[\alpha]^{23}_{D}$ (+) 38.4 (*c* 1.87, $CHCl_3$); IR (thin film) 3439, 2958, 2933, 2875, 1713, 1613, 1514, 1458, 1376, 1302, 1249, 1079, 1035, 820, 786, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.44 (d, *J* = 11.4 Hz, 1H), 4.38 (d, J= 11.4 Hz, 1H), 3.75−3.80 (m, 6H), 2.14 (s, 3H), 1.70 (br, 1H), 1.50−1.59 (m, 1H), 1.27−1.35 (m, 2H), 1.16 (d, *J* = 6.0 Hz, 3H), 0.92 (t, *J* = 7.8 Hz, 9H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.58 (q, *J* = 6.9 Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 211.5, 159.8, 130.2, 129.7, 114.2, 88.3, 73.0, 66.4, 55.7, 43.9, 33.8, 27.7, 24.9, 14.7, 7.4, 5.6; HRMS (FAB+) calcd for $C_{23}H_{40}O_5SiNa$ (M + Na) 447.2543, found 447.2561.

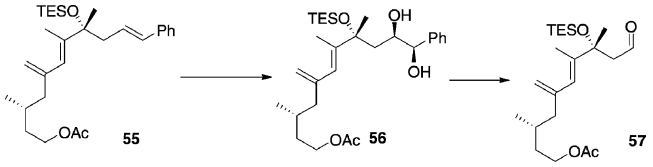
To a solution of the alcohol intermediate **SI-10** (77 mg, 0.18 mmol) in CH_2Cl_2 (0.9 mL) at −78 °C were added 2,6-lutidine (78 mg, 84.8 μL, 0.73 mmol) and TMSOTf (80 mg, 65.2 μL, 0.36 mmol). After 20 min, the reaction was quenched with satd aq NH_4Cl (5 mL) and extracted with Et_2O (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo to give product **54** (80 mg, 0.16 mmol, 90%) as a colorless oil: $[\alpha]^{23}_{D}$ (+) 31.8 (*c* 2.80, $CHCl_3$); IR (thin film) 2955, 2911, 2876, 1715, 1613, 1514, 1458, 1414, 1372, 1352, 1249, 1124, 1088, 1038, 1006, 820, 787, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23(d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 4.42 (d, *J* = 11.4 Hz, 1H), 4.36 (d, *J* = 11.4 Hz, 1H), 3.74−3.85 (m, 5H), 3.68 (d, *J* = 6.9 Hz, 1H), 2.09 (s, 3H), 1.55−1.61 (m, 1H), 1.41−1.50 (m, 1H), 1.25−1.35 (m, 1H), 1.12 (d, *J* = 6.0 Hz, 3H), 0.92 (t, *J* = 7.8 Hz, 9H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.58 (q, *J* = 7.8 Hz, 6H), 0.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.0, 159.7, 130.2, 129.7, 114.1, 89.3, 73.1, 66.2, 55.6, 45.2, 32.4, 26.9, 25.3, 12.9, 7.4, 5.7, 0.7; HRMS (ES+) calcd for $C_{26}H_{48}O_5NaSi_2$ (M + Na) 519.2938, found 519.2914.



Acetate 55. To a solution of **33** (45 mg, 0.11 mmol) in PhMe (0.53 mL) at −78 °C was added DIBAL-H (0.15 mL, 0.15 mmol, 1.0 M in PhMe). After 10 min, the reaction was quenched sequentially with MeOH (0.2 mL), satd aq tartaric acid (0.2 mL) and H_2O (2.0 mL). After stirring 12 h at rt, the mixture was extracted with Et_2O (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo to give the corresponding crude aldehyde (0.11 mmol).

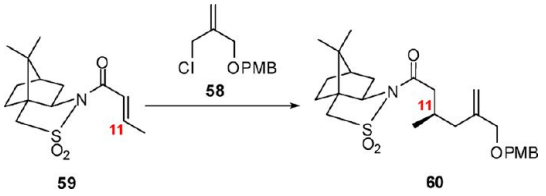
To a mixed solution of the above aldehyde (0.11 mmol) in CH_2Cl_2 (0.5 mL) and EtOH (0.5 mL) at 0 °C was added $NaBH_4$ (8.4 mg, 0.22 mmol). After 15 min, the reaction was quenched with a brine solution (5 mL) and extracted with Et_2O (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 6% EtOAc/hexanes, to give the corresponding alcohol intermediate (38 mg, 0.09 mmol, 85%) as a colorless oil.

To a solution of the above alcohol intermediate (29 mg, 0.07 mmol) in CH_2Cl_2 at 0 °C were added sequentially pyridine (21.4 mg, 22.1 μL, 0.27 mmol), DMAP (8.3 mg, 0.07 mmol), and Ac_2O (13.9 mg, 12.8 μL, 0.14 mmol). After 15 min, the reaction was quenched with satd aq NH_4Cl (5 mL) and extracted with Et_2O (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo to give product **55** (31 mg, 64 μmol, 94%) as a colorless oil: $[\alpha]^{23}_{D}$ (−) 39.3 (*c* 0.40, $CHCl_3$); IR (thin film) 3026, 2955, 2913, 2875, 1741, 1496, 1457, 1367, 1236, 1158, 1121, 1053, 1016, 966, 898, 793, 741, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.15−7.28 (m, 5H), 6.32 (d, *J* = 15.9 Hz, 1H), 6.07−6.17 (m, 1H), 5.85 (s, 1H), 4.96 (s, 1H), 4.79 (s, 1H), 3.98−4.07 (m, 2H), 2.41−2.52 (m, 2H), 2.10 (dd, *J* = 5.7, 13.5 Hz, 1H), 2.00 (s, 3H), 1.85 (dd, *J* = 7.8, 13.2 Hz, 1H), 1.79 (s, 3H), 1.58−1.67 (m, 2H), 1.43 (s, 3H), 1.28−1.36 (m, 1H), 0.97 (t, *J* = 7.5 Hz, 9H), 0.75(d, *J* = 6.6 Hz, 3H), 0.61 (q, *J* = 7.5 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 145.3, 143.0, 138.3, 132.0, 128.9, 127.4, 127.3, 126.3, 125.3, 114.9, 78.7, 63.3, 46.4, 46.2, 35.6, 29.0, 27.4, 21.4, 19.6, 15.0, 7.6, 7.2; HRMS (FAB+) calcd for $C_{29}H_{46}O_3SiNa$ (M + Na) 493.3114, found 493.3130.



Aldehyde 57. To a solution of **55** (31 mg, 66 μmol) in *t*-BuOH (0.55 mL) and H_2O (0.55 mL) at rt was added AD mix β*[53] (92 mg) and $CH_3SO_2NH_2$ (9.5 mg, 0.10 mmol). After 16 h, the reaction was quenched with 10% aq $Na_2S_2O_3$ (2 mL). After 30 min, the mixture was extracted with EtOAc (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20% EtOAc/hexanes, to give the corresponding diol (29 mg, 58 μmol, 88%, 6:1 dr).

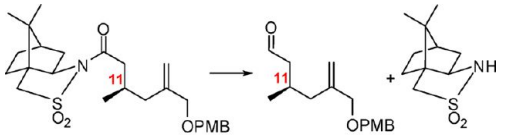
To a solution of the above diol (26 mg, 52 μmol) in THF/Et_2O/H_2O (1.7 mL, 1:1:1) at rt was added $NaIO_4$ (110 mg, 0.52 mmol). After 2 h, the reaction was quenched with a brine solution (2 mL) and extracted with Et_2O (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo to give the aldehyde **57** (20.4 mg, 52 μmol, 99%) as a colorless oil. The aldehyde intermediate was applied to the next step without further purification: $[\alpha]^{23}_{D}$ = −11.6 (*c* 1.83, $CHCl_3$); IR (neat) 2957, 2877, 1741, 1724, 1458, 1368, 1239, 1050, 1017, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.66 (t, *J* = 3.0 Hz, 1H), 6.02 (s, 1H), 5.03 (s, 1H), 4.83 (s, 1H), 4.14−4.04 (m, 2H), 2.65 (dd, *J* = 15.1, 2.9 Hz, 1H), 2.46 (dd, *J* = 15.1, 3.1 Hz, 1H), 2.14 (dd, *J* = 13.6, 5.8 Hz, 1H), 2.04 (s, 3H), 1.92 (dd, *J* = 13.5, 7.8 Hz, 1H), 1.82 (s, 3H), 1.70 −1.60 (m, 2H), 1.48 (s, 3H), 1.45−1.39 (m, 1H), 1.00−0.94 (m, 9H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.68−0.56 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 171.2, 144.3, 141.2, 125.7, 115.1, 62.8, 54.0, 45.8, 35.3, 28.7, 27.9, 20.9, 19.2, 14.7, 7.1, 6.7, 6.6, 5.8; HRMS (EI^+) calcd for $C_{22}H_{40}O_4Si$ (M^+) 396.2696, found 396.2678.



dx.doi.org/10.1021/jo3026077 | J. Org. Chem. 2013, 78, 2213−2247

Sultam 60. Following the similar procedure described by Paquette,[38a] Mg (36.0 g, 1.5 mol) was stirred vigorously at rt in a dry flask under Ar. After 120 h, when a black coating formed inside the flask, THF (200 mL) and 1,2-dibromoethane (2.60 g, 1.2 mL, 13.9 mmol) were added sequentially. After 30 min, a solution of allyl chloride **58** (17.0 g, 75.0 mmol) in THF (80 mL) was added slowly to the Mg slurry over 5 h. The resulted mixture was stirred overnight at rt to give 300 mL of Grignard reagent (0.12 M, 47%) as a gray solution. The concentration of the Grignard reagent was determined by the titration using menthol in the presence of 1,10-phenanthroline.[55]

Separately, $CuBr{\cdot}SMe_2$ (7.29 g, 35.5 mmol) and LiCl (1.61 g, 37.9 mmol) were dissolved in THF (80 mL) and added to the solution of Grinard reagent (263 mL, 31.5 mmol) at −78 °C via syringe. TMSCl (3.96 g, 4.5 mL, 36.5 mmol) was then added followed by a solution of known sultam **59**[56] (6.9 g, 24.3 mmol) in THF (60 mL). After another 90 min, the reaction was quenched with NH_4Cl−NH_4OH (9:1, pH 9, 60 mL), warmed to rt. The aqueous layer was extracted with EtOAc (3 × 200 mL). The organic phase was washed with satd aq NaCl (100 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 8−15% EtOAc/hexanes, to give the product **60** (11.2 g, 34.4 mmol, 97%) as a colorless oil: $[\alpha]^{23}_D$ = −68.0 (*c* 0.51, $CHCl_3$); IR (neat) 2959, 2927, 2851, 1693, 1512, 1454, 1328, 1246, 1032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.12 (s, 1H), 4.96 (s, 1H), 4.44 (t, *J* = 11.8 Hz, 2H), 3.94 (t, *J* = 11.8 Hz, 2H), 4.00 (dd, *J* = 14.0 Hz, 2H), 3.88 (t, *J* = 6.2 Hz, 1H), 3.82 (s, 3H), 3.46 (dd, *J* = 23.0, 13.8 Hz, 2H), 2.78 (dd, *J* = 16.1, 5.7 Hz, 1H), 2.51 (dd, *J* = 16.1, 7.6 Hz, 1H), 2.30−2.40 (m, 1H), 2.02−2.15 (m, 4H), 1.82−1.96 (m, 3H), 1.28−1.45 (m, 3H), 1.15 (s, 3H), 0.99 (d, *J* = 6.4 Hz, 3H), 0.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 159.1, 144.1, 130.6, 129.3, 113.7, 113.6, 72.4, 71.7, 65.2, 55.3, 53.0, 48.3, 47.7, 44.7, 42.5, 40.8, 38.6, 32.9, 28.0, 26.5, 20.8, 19.9; HRMS (ES^+) calcd for $C_{26}H_{37}NO_5SNa$ (M + Na) 498.2290, found 498.2271.

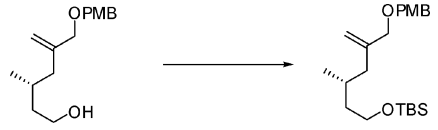


60 **SI-13** **SI-14**

Aldehyde SI-13. To a stirred solution of sultam **60** (11.0 g, 23.1 mmol) in CH_2Cl_2 (115 mL) at −78 °C was added DIBAL-H (50.8 mL, 50.8 mmol, 1.0 M in CH_2Cl_2). After 2 h, the reaction was carefully quenched with methanol (2.0 mL) and poured into aq sodium potassium tartrate (250 mL, 10% aq) at rt. The reaction flask was rinsed with an additional portion of CH_2Cl_2 (150 mL). After 3 h, the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10% EtOAc/hexanes, to give the aldehyde **SI-13** (5.9 g, 22.6 mmol, 98%) as a colorless oil. Further elution with 5% MeOH/EtOAc gave recovered auxiliary **SI-14** (4.9 g, 22.4 mmol, 97%). **SI-13**: $[\alpha]^{23}_D$ = +5.93 (*c* 0.91, $CHCl_3$); IR (neat) 2956, 2929, 2837, 1723, 1612, 1513, 1247, 1077, 1034 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (t, *J* = 1.5 Hz, 1H), 7.29 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 5.14 (d, *J* = 1.2 Hz, 1H), 4.95 (s, 1H), 4.44 (s, 2H), 3.93 (s, 2H), 3.83 (s, 3H), 2.47 (ddd, *J* = 14.0, 4.0, and 1.3 Hz, 1H), 2.17−2.34 (m, 2H), 2.01−2.11 (m, 2H), 0.98 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 159.2, 143.9, 130.3, 129.3, 114.1, 113.8, 72.4, 71.7, 55.3, 50.6, 41.0, 26.3, 20.1; HRMS (ES^+) calcd for $C_{16}H_{22}O_3Na$ (M + Na) 285.1467, found 285.1494.

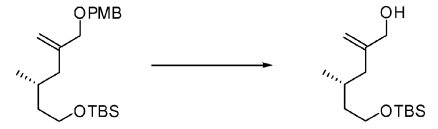
SI-13 **SI-15**

Aldohol SI-15. To a stirred solution of aldehyde **SI-13** (5.6 g, 21.4 mmol) in CH_2Cl_2 (110 mL) at −78 °C was added DIBAL-H (28.3 mL, 28.3 mmol, 1.0 M in CH_2Cl_2). After 1 h, the reaction was carefully quenched with methanol (2.0 mL) and poured into aq sodium potassium tartrate (250 mL, 10% aq) at rt. The reaction flask was rinsed with an additional portion of CH_2Cl_2 (150 mL). After 3 h, the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The dried extract ($MgSO_4$) was concentrated in vacuo to give the alcohol **SI-15** (5.6 g, 20.8 mmol, 97%) as a colorless oil: $[\alpha]^{23}_D$ = −2.94 (*c* 0.51, $CHCl_3$); IR (neat) 3407, 2926, 2868, 1612, 1513, 1461, 1248, 1059, 1036 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 5.10 (s, 1H), 4.94 (s, 1H), 4.44 (t, *J* = 12.2 Hz, 2H), 3.91 (t, *J* = 13.4 Hz, 2H), 3.82 (s, 3H), 3.61−3.78 (m, 2H), 2.15 (dd, *J* = 13.8, 6.0 Hz, 1H), 1.89−1.96 (m, 1H), 1.89−1.96 (m, 1H), 1.72−1.86 (m, 1H), 1.57−1.69 (m, 1H), 1.23−1.45 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 144.6, 130.4, 129.3, 113.8, 113.4, 72.6, 71.6, 61.0, 55.3, 41.3, 39.7, 27.5, 19.7, 18.8; HRMS (ES^+) calcd for $C_{16}H_{24}O_3Na$ (M + Na) 287.1623, found 287.1649.



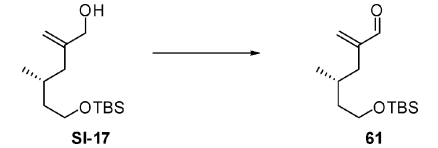
SI-15 **SI-16**

TBS Ether SI-16. To a stirred solution of alcohol **SI-15** (5.5 g, 20.8 mmol) in DMF (50 mL) at rt were sequentially added imidazole (3.4 g, 50.0 mmol) and TBSCl (3.8 g, 25.2 mmol). After 1 h, the reaction was quenched with satd aq NH_4Cl (50 mL) and extracted with Et_2O (3 × 150 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5% EtOAc/hexanes, to give TBS ether **SI-16** (7.7 g, 20.3 mmol, 97%) as a colorless oil: $[\alpha]^{23}_D$ = −3.27 (*c* 1.31, $CHCl_3$); IR (neat) 2954, 2928, 2856, 1513, 1249, 1094, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 5.11 (s, 1H), 4.93 (s, 1H), 4.44 (s, 2H), 3.92 (s, 2H), 3.83 (s, 3H), 3.63−3.70 (m, 2H), 2.13 (dd, *J* = 13.8, 6.3 Hz, 1H), 1.88−1.96 (m, 1H), 1.76−1.86 (m, 1H), 1.57−1.69 (m, 1H), 1.28−1.35 (m, 1H), 0.91 (s, 9H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 144.7, 130.6, 129.3, 113.8, 112.8, 72.6, 71.6, 61.3, 55.3, 41.4, 39.8, 27.5, 26.0, 19.6, 18.3, −5.3; HRMS (ES^+) calcd for $C_{22}H_{38}O_3NaSi$ (M + Na) 401.2488, found 401.2489.



SI-16 **SI-17**

Alcohol SI-17. To a stirred solution of TBS ether **SI-16** (3.85 g, 10.2 mmol) in CH_2Cl_2/pH 7 buffer (10: 1, 110 mL) was added DDQ (2.77 g, 12.2 mmol) at rt. After 1 h, the reaction was quenched with satd aq $NaHCO_3$ (50 mL) and extracted with Et_2O (3 × 100 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 8% EtOAc/hexanes, to give a mixture of product **SI-17** and 4-methoxybenzaldehyde (3.90 g, 1:1 mol/mol, 9.9 mmol, 97%) as a colorless oil. An analytically pure sample was prepared by chromatography over silica gel, eluting with 3−5% EtOAc/hexanes, for characterization, but the product mixture was used in the subsequent step without complete removal of 4-methoxybenzaldehyde. **SI-17**: $[\alpha]^{23}_D$ = −6.09 (*c* 1.21, $CHCl_3$); IR (neat) 3338, 2955, 2929, 2858, 1471, 1463, 1255, 1098, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.09 (d, *J* = 1.5 Hz, 1H), 4.89 (s, 1H), 4.07 (d, *J* = 6.3 Hz, 2H), 3.61−3.75 (m, 2H), 2.13 (dd, *J* = 13.5, 6.0 Hz, 1H), 1.75−1.95 (m, 2H), 1.55−1.66 (m, 1H), 1.41−1.50 (m, 1H), 1.27−1.38 (m, 1H), 0.91 (s, 9H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 110.7, 65.8, 61.2, 41.2, 39.6, 27.6, 26.0, 19.7, 18.3, −5.3; HRMS (EI^+) calcd for $C_{14}H_{31}O_2Si$ (M + H) 259.2093, found 259.2091.

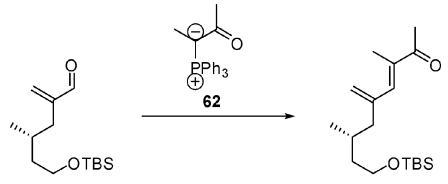


SI-17 **61**

Aldehyde 61. To a stirred solution of alcohol **SI-17** and 4-methoxybenzaldehyde (7.8 g, 1:1 mol/mol, 19.7 mmol) in CH_2Cl_2 (200 mL) were sequentially added $NaHCO_3$ (3.0 g, 35.7 mmol) and DMP (10.0 g, 23.7 mmol) at rt. After 1 h, the reaction was quenched with satd aq $NaHCO_3$ (50 mL) and extracted with Et_2O (3 × 150 mL).

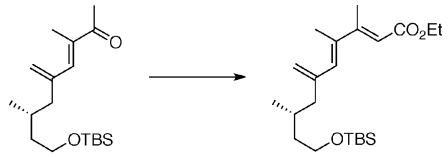
dx.doi.org/10.1021/jo3026077 | J. Org. Chem. 2013, 78, 2213−2247

The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 3% EtOAc/hexanes, to give aldehyde **61** (4.6 g, 17.7 mmol, 90%) as a colorless oil: $[\alpha]^{23}_D = -8.20$ (*c* 1.21, $CHCl_3$); IR (neat) 2956, 2929, 2857, 1698, 1255, 1099, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H), 6.28 (s, 1H), 6.07 (s, 1H), 3.60−3.73 (m, 2H), 2.28 (dd, *J* = 14.1, 6.9 Hz, 1H), 2.12 (dd, *J* = 13.8, 8.1 Hz, 1H),1.77−1.86 (m, 1H), 1.53−1.64 (m, 1H), 1.29−1.39 (m, 1H), 0.91 (s, 9H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.7, 149.0, 135.2, 61.1, 39.5, 35.2, 28.4, 25.9, 25.5, 19.4, −5.4; HRMS (EI^+) calcd for $C_{14}H_{28}O_2Si$ (M) 256.1859, found 256.1861.



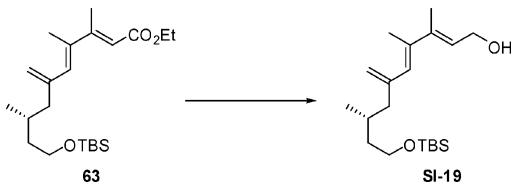
61 SI-18

Methyl Ketone SI-18. A solution of aldehyde **61** (4.5 g, 17.5 mmol) and ylide **62**[57] (10.2 g, 30.7 mmol) in toluene (60 mL) was refluxed in a sealed tube (oil bath 112 °C). After 16 h, the reaction mixture was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5% EtOAc/hexanes (1% Et_3N added), to give diene **SI-18** (5.0 g, 16.1 mmol, 92%) as a slightly yellow oil: $[\alpha]^{23}_D = -41.1$ (*c* 0.53, $CHCl_3$); IR (neat) 2955, 2928, 2857, 1671, 1255, 1100, 836, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.90 (s, 1H), 5.29 (s, 1H), 5.14 (s, 1H), 3.62−3.73 (m, 2H), 2.37 (s, 3H), 2.30 (dd, *J* = 10.2, 4.8 Hz, 1H), 2.05 (dd, *J* = 10.5, 6.3 Hz, 1H), 1.97 (d, *J* = 10.2 Hz, 3H), 1.71−1.78 (m, 1H), 1.59−1.64 (m, 1H), 1.34−1.38 (m, 1H), 0.91 (s, 9H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 143.7, 140.9, 137.8, 118.9, 61.0, 45.1, 39.6, 28.4, 25.9, 25.7, 19.3, 18.3, 13.1, −5.3; HRMS (FAB^+) calcd for $C_{18}H_{35}O_2Si$ (M + H) 311.2406, found 311.2400.



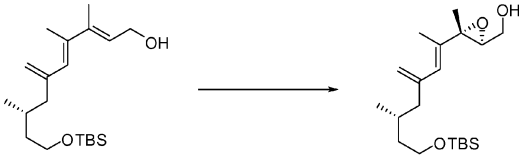
SI-18 63

Triene Ester 63. To a stirred slurry of NaH (1.29 g, 32.2 mmol) in DME (50 mL) was added ethyl 2-(diethoxyphosphoryl)acetate (6.48 g, 5.74 mL, 28.9 mmol) at rt. After 1 h, a solution of methyl ketone **SI-18** (5.00 g, 16.1 mmol) in DME (25 mL) was added. The resulted solution was refluxed for 3 h and then quenched with H_2O (15 mL) and extracted with Et_2O (3 × 150 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 2% EtOAc/hexanes (1% Et_3N added), to give triene ester **63** (4.42 g, 11.6 mmol, 70%) as a colorless oil: $[\alpha]^{23}_D = -34.7$ (*c* 1.66, $CHCl_3$); IR (neat) 2955, 2928, 2857, 1716, 1610, 1255, 1163, 1098, 836, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.24 (s, 1H), 5.92 (s, 1H), 5.13 (s, 1H), 4.93 (s, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.61−3.68 (m, 2H), 2.36 (s, 3H), 2.20 (dd, *J* = 13.3, 5.9 Hz, 1H), 1.93−2.00 (m, 4H), 1.53−1.71 (m, 2H), 1.31 (t, *J* = 7.2 Hz, 3H), 0.89 (s, 9H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 156.4, 144.7, 137.8, 132.4, 116.4, 115.9, 61.2, 59.7, 45.7, 39.7, 28.3, 25.9, 19.5, 18.3, 15.8, 15.5, 14.4, −5.3; HRMS (EI^+) calcd for $C_{22}H_{40}O_3Si$ (M + H) 380.2747, found 380.2732.



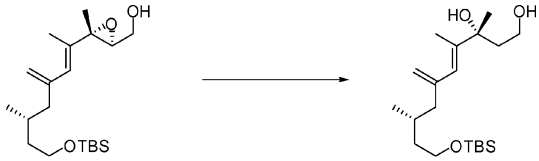
63 SI-19

Allyl Alcohol SI-19. To a stirred solution of triene ester **63** (8.61 g, 22.6 mmol) in THF (200 mL) was added DIBAL-H (46 mL, 46.0 mmol, 1 M in toluene) at −78 °C. After 1.5 h, the reaction was quenched with MeOH (1.0 mL) and poured into aq sodium potassium tartrate (350 mL, 10% aq) at rt. The reaction flask was rinsed with an additional portion of Et_2O (50 mL). After 3 h, the aqueous layer was extracted with Et_2O (3 × 200 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 8% EtOAc/hexanes, to give allyl alcohol **SI-19** (6.20 g, 18.3 mmol, 81%) as a colorless oil: $[\alpha]^{23}_D = -36.6$ (*c* 1.66, $CHCl_3$); IR (neat) 3327, 2954, 2928, 2857, 1471, 1462, 1376, 1255, 1098, 1006, 835, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.97 (s, 1H), 5.80 (t, *J* = 6.3 Hz, 1H), 5.08 (s, 1H), 4.87 (s, 1H), 4.34 (d, *J* = 6.4 Hz, 2H), 3.46−3.72 (m, 2H), 2.18 (dd, *J* = 13.6, 6.0 Hz, 1H), 1.99 (d, *J* = 0.8 Hz, 3H), 1.93 (dd, *J* = 13.5, 5.2 Hz, 1H), 1.86 (s, 3H), 1.54−1.73 (m, 2H), 1.28−1.37 (m, 1H), 0.90 (s, 9H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 139.3, 137.6, 128.1, 125.9, 115.4, 61.3, 60.1, 46.0, 39.7, 28.3, 25.9, 19.5, 18.3, 15.6, 14.2, −5.3; HRMS (EI^+) calcd for $C_{20}H_{38}O_2Si$ (M) 338.2641, found 338.2612.



SI-19 64

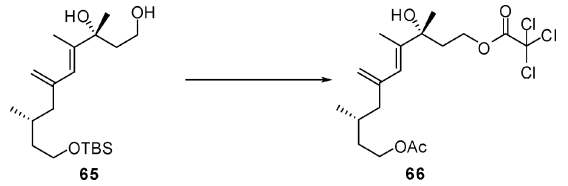
Epoxide 64. To a stirred solution of (+)-DIPT (41.5 mg, 0.18 mmol) and 4 Å molecular sieves (about 200 mg) in CH_2Cl_2 (4.0 mL) were sequentially added Ti(O-*i*-Pr)$_4$ (34 mg, 34.6 μL, 0.12 mmol) and TBHP (236 μL, 1.30 mmol, 5.0−6.0 M in decane) at −20 °C. After 20 min, the reaction mixture was cooled to −78 °C, and a precooled solution (−78 °C) of allyl alcohol **SI-19** (200 mg, 0.59 mmol) in CH_2Cl_2 (4.0 mL) was added via cannula. The resulted solution was warmed to −50 °C. After another 60 min, the reaction was quenched with pH 7 phosphate buffer (0.5 mL), filtered over Celite, and extracted with Et_2O (3 × 20 mL). The dried organic layers ($MgSO_4$) were concentrated in vacuo and purified by chromatography over silica gel, eluting with 10% EtOAc/hexanes, to give epoxide **64** (167 mg, 0.47 mmol, 80%) as a colorless oil: $[\alpha]^{23}_D = -17.3$ (*c* 1.66, $CHCl_3$); IR (neat) 3430, 2954, 2927, 2856, 1471, 1463, 1378, 1255, 1097, 836, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.89 (s, 1H), 5.03 (s, 1H), 4.86 (s, 1H), 3.86−3.92 (m, 1H), 3.73−3.81 (m, 1H), 3.62−3.71 (m, 2H), 3.02 (dd, *J* = 10.5, 6.3 Hz, 1H), 2.14 (dd, *J* = 13.5, 5.6 Hz, 1H), 1.91 (dd, *J* = 13.5, 8.4 Hz, 1H), 1.84 (d, *J* = 1.1 Hz, 3H), 1.54−1.66 (m, 2H), 1.45 (s, 3H), 1.27−1.34 (m, 1H), 0.91 (s, 9H), 0.83 (d, *J* = 6.4 Hz, 3H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 137.5, 126.2, 115.2, 63.7, 61.3, 45.6, 39.8, 28.2, 26.0, 19.3, 18.3, 16.7, 14.8, −5.3; HRMS (CI^+) calcd for $C_{20}H_{39}O_3Si$ (M + H) 355.2669, found 355.2666.



64 65

Diol 65. To a stirred solution of epoxide **64** (1.5 g, 4.23 mmol) in THF (30 mL) was added Red-Al (1.5 mL, 9.91 mmol, 65% w/v in toluene) at 0 °C. After 1 h, another portion of Red-Al (1.5 mL, 9.91 mmol, 65% w/v in toluene) was added. After another 1.5 h, the reaction was quenched with H_2O (0.10 mL), and extracted with CH_2Cl_2 (3 × 150 mL). The dried organic layers ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 6−12% EtOAc/hexanes (1% Et_3N added), to give diol **65** (1.05 g, 2.96 mmol, 70%) as a colorless oil: $[\alpha]^{23}_D = -29.4$ (*c* 0.81, $CHCl_3$); IR (neat) 3389, 2955, 2928, 2858, 1471, 1462, 1382, 1255, 1097, 836, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.10 (s, 1H), 5.04 (d, *J* = 0.9 Hz, 1H), 4.84 (s, 1H), 3.62−3.77 (m, 4H), 3.04 (s, br, 1H), 2.60 (s, br, 1H), 2.16 (dd, *J* = 13.2, 5.1 Hz, 1H), 1.88−1.96 (m, 3H), 1.79 (d, *J* = 0.9 Hz, 3H), 1.55−1.70 (m, 2H), 1.37 (s, 1H), 1.27−1.34 (m, 1H), 0.91 (s, 9H), 0.86 (d, *J* = 6.5 Hz, 3H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 141.7, 125.1, 114.4, 77.1, 61.6, 60.4, 46.1, 40.1, 39.7, 28.6, 28.2, 26.0, 19.6, 18.4, 15.1, −5.2; HRMS (ES^+) calcd for $C_{20}H_{40}O_3SiNa$ (M + Na) 379.2644, found 379.2643.

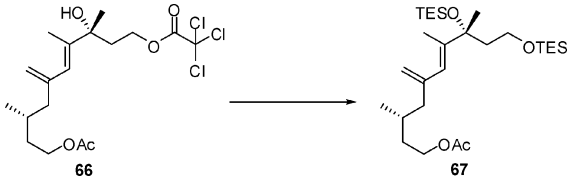
dx.doi.org/10.1021/jo3026077 | J. Org. Chem. 2013, 78, 2213−2247



Ester 66. To a stirred solution of diol **65** (2.10 g, 5.89 mmol) in CH_2Cl_2 (50 mL) were sequentially added pyridine (1.37 g, 1.40 mL, 17.7 mmol) and trichloroacetyl chloride (1.29 g, 0.79 mL, 7.09 mmol). After 3 h, the reaction was quenched with satd aq NH_4Cl (10 mL) and extracted with ether (3 × 30 mL). The dried extract ($MgSO_4$) was concentrated in vacuo to give crude ester (3.30 g) as a colorless oil, which was used in the next step without further purification.

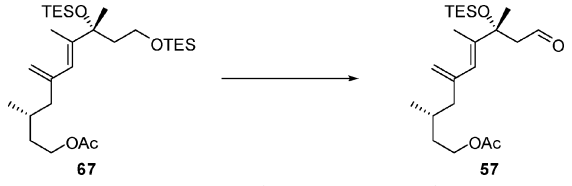
To a stirred solution of crude ester (3.30 g) in CH_2Cl_2/EtOH (1:1, 50 mL) was added CSA (2.31 g, 9.88 mmol) at 0 °C. After 1.5 h, the reaction was quenched with satd aq $NaHCO_3$ (10 mL) and extracted with ether (3 × 40 mL). The dried extract ($MgSO_4$) was concentrated in vacuo to give crude diol (2.02 g), which was used in the next step without further purification.

To a stirred solution of crude diol (2.02 g) in CH_2Cl_2 (50 mL) were added sequentially pyridine (1.53 g, 1.57 mL, 19.5 mmol) and Ac_2O (0.99 g, 0.92 mL, 9.73 mmol). After 1.5 h, the reaction was quenched with satd aq NH_4Cl (10 mL) and extracted with ether (3 × 40 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10% EtOAc/hexanes, to give **66** (1.90 g, 4.42 mmol, 75% over 3 steps) as a colorless oil: $[\alpha]^{23}_D$ = −14.1 (*c* 1.16, $CHCl_3$); IR (neat) 3481, 2962, 2928, 1766, 1739, 1720, 1458, 1368, 1247, 828, 682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.01 (s, 1H), 5.04 (s, 1H), 4.85 (s, 1H), 4.47−4.36 (m, 2H), 4.15−4.06 (m, 2H), 2.12−2.02 (m, 3H), 2.03 (s, 3H), 1.97−1.89 (m, 3H), 1.83 (s, 3H), 1.70−1.60 (m, 2H), 1.50−1.38 (m, 1H), 1.41 (s, 3H), 0.89 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 161.9, 144.1, 141.4, 124.9, 115.3, 74.6, 66.5, 62.3, 45.6, 37.8, 35.2, 28.7, 28.3, 21.0, 19.4, 14.9; HRMS (EI$^+$) calcd for $C_{18}H_{27}O_5Cl_3$ (M^+) 428.0924, found 428.0932.



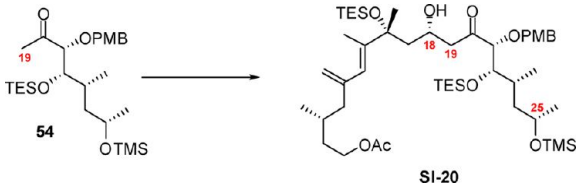
TES Ether 67. To a stirred solution of alcohol **66** (1.90 g, 4.4 mmol) in CH_2Cl_2/EtOH (1:1, 50 mL) was added $NH_3{\cdot}H_2O$ (15 mL) at rt. After 1 h, the reaction was quenched with satd aq NH_4Cl (15 mL) and extracted with ether (3 × 40 mL). The dried extract ($MgSO_4$) was concentrated in vacuo to afford crude diol (1.55 g), which which was used in the next step without further purification.

To a stirred solution of crude diol (1.55 g) in CH_2Cl_2/Et_3N (1:1, 30 mL) was added freshly distilled TESOTf (3.52 g, 3.01 mL, 13.1 mmol) at −78 °C. After 20 min, the reaction was quenched with satd aq $NaHCO_3$ (10 mL) and extracted with ether (3 × 40 mL). The dried extract ($MgSO_4$) was concentrated in vacuo andpurified by chromatography over silica gel, eluting with 2% EtOAc/hexanes, to give TES ether **67** (2.12 g, 4.09 mmol, 93% over two steps) as a colorless oil: $[\alpha]^{23}_D$ = −18.4 (*c* 1.11, $CHCl_3$); IR (neat) 29554, 2912, 2876, 1748, 1458, 1238, 1086, 1016, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.89 (s, 1H), 5.00 (d, *J* = 1.2 Hz, 1H), 4.81 (d, *J* = 1.2 Hz, 1H), 4.18−4.05 (m, 2H), 3.72−3.63 (m, 1H), 3.54−3.41 (m, 1H), 2.15 (dd, *J* = 13.5, 5.4 Hz, 1H), 2.05 (s, 3H), 1.95−1.89 (m, 2H), 1.87−1.78 (m, 1H), 1.77 (d, *J* = 1.2 Hz, 3H), 1.71−1.58 (m, 2H), 1.49−1.39 (m, 1H), 1.42 (s, 3H), 1.12−0.91 (m, 18H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.74−0.50 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 144.8, 142.3, 124.3, 114.4, 77.2, 62.3, 59.5, 46.0, 44.4, 35.3, 28.8, 27.8, 21.0, 19.3, 14.6, 7.2, 6.9, 6.8, 6.4, 5.8, 4.4; HRMS (EI$^+$) calcd for $C_{28}H_{56}O_4Si_2Na$ (M + Na) 535.3615, found 535.3637.

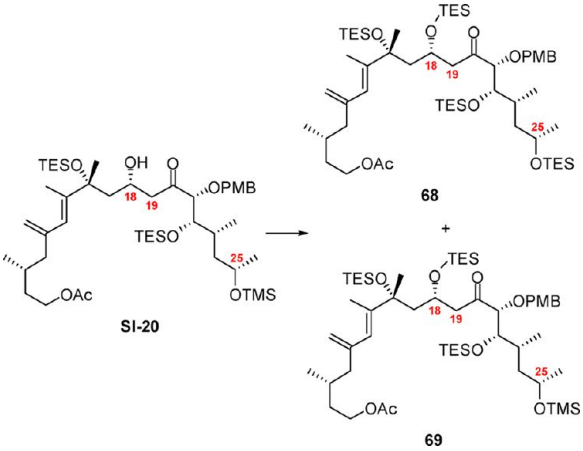


Aldehyde 57. TES ether **67** (2.1 mg, 4.09 mmol) was dissolved in a stirred solution of HOAc/THF/H_2O (34 mL, 8:8:1) at 0 °C. After 1.5 h, the reaction was then quenched with solid $NaHCO_3$ and extracted with ether (4 × 50 mL). The dried extract ($MgSO_4$) was concentrated in vacuo to afford crude alcohol (2.0 g), which was used in the next step without further purification.

To a stirred solution of crude alcohol (2.0 g) in CH_2Cl_2 (20 mL) were added sequentially solid $NaHCO_3$ (1.0 g, 11.9 mmol) and DMP (2.16 g, 5.09 mmol) at rt. After 1 h, the reaction was quenched with satd aq $NaHCO_3$ (15 mL) and extracted with ether (3 × 40 mL). The dried extract ($MgSO_4$) was concentrated in vacuo andpurified by chromatography over silica gel, eluting with 5% EtOAc/hexanes, to give aldehyde **57** (1.36 g, 3.43 mmol, 74% over two steps) as a colorless oil.



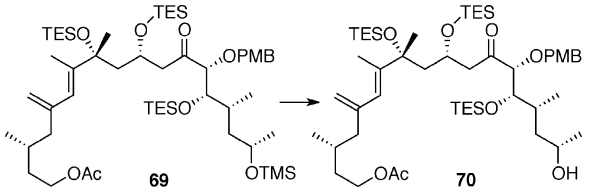
Aldol Product SI-20. To a solution of methyl ketone **54** (38 mg, 76 μmol) in Et_2O (0.4 mL) at −78 °C was added LDA[54] (85.0 μL, 1.0 M in THF). After 20 min, a precooled (−78 °C) solution of aldehyde intermediate (20 mg, 50 μmol) in Et_2O (0.25 mL) was transferred in one portion via cannula at −78 °C. After 20 min, the reaction was quenched with satd aq NH_4Cl (3 mL) and extracted with Et_2O (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5% EtOAc/hexanes, to give the alcohol intermediate **SI-20** (28 mg, 31 μmol, 62%) as a colorless oil: $[\alpha]^{23}_D$ (+) 15.7 (*c* 1.55, $CHCl_3$); IR (neat) 3515, 2955, 2912, 2876, 1741, 1717, 1615, 1515, 1417, 1368, 1247, 1117, 1037, 1008, 899, 806, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 9.0 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.87 (s, 1H), 5.01 (s, 1H), 4.83 (s, 1H), 4.50 (d, *J* = 11.1 Hz, 1H), 4.34−4.51 (m, 1H), 4.33 (d, *J* = 11.1 Hz, 1H), 4.04−4.14 (m, 2H), 3.80 (s, 3H), 3.71−3.78 (m, 3H), 3.03 (dd, *J* = 7.5, 17.4 Hz, 1H), 2.29 (dd, *J* = 4.5, 17.4 Hz, 1H), 2.12 (dd, *J* = 5.7, 8.7 Hz, 1H), 2.03 (s, 3H), 1.83−1.96 (m, 2H), 1.82 (s, 3H), 1.59−1.73 (m, 3H), 1.52 (s, 3H), 1.42−1.49 (m, 4H), 1.11 (d, *J* = 6.0 Hz, 3H), 0.86−0.98 (m, 21H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.51−0.67 (m, 12H), 0.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.7, 171.6, 159.6, 144.6, 143.8, 130.3, 130.1, 125.2, 115.6, 114.0, 88.4, 79.8, 77.6, 72.8, 66.2, 65.1, 63.3, 55.6, 48.5, 46.7, 46.2, 44.8, 35.7, 32.5, 29.1, 26.5, 25.2, 21.4, 19.7, 15.1, 13.3, 7.5, 7.4, 7.0, 5.7, 0.7; HRMS (ES+) calcd for $C_{48}H_{88}O_9Si_3Na$ (M + Na) 915.5634, found 915.5564.



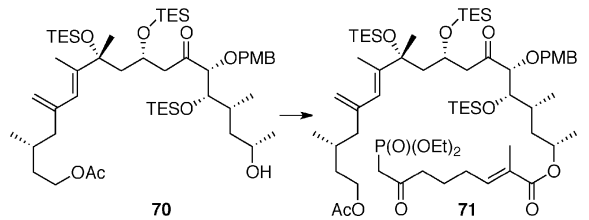
TES Ethers 68 and 69. To a solution of the above alcohol intermediate (40 mg, 45 μmol) in CH_2Cl_2 (0.15 mL) and Et_3N (0.15 mL) at −78 °C was added TESOTf (32.0 mg, 28.3 μL, 0.12 mmol). After

dx.doi.org/10.1021/jo3026077 | J. Org. Chem. 2013, 78, 2213−2247

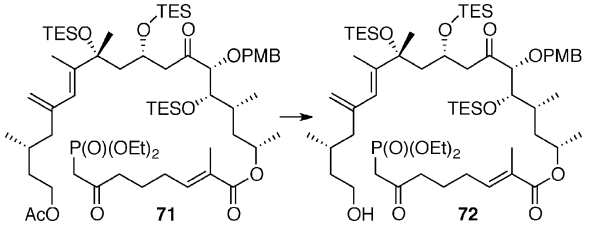
20 min, the reaction was quenched with satd aq NH_4Cl (3 mL). The mixture was extracted with Et_2O (3 × 10 mL), and the dried ($MgSO_4$) extract was concentrated in vacuo to give **69** (36 mg, 36 μmol, 82%) as a colorless oil: $[\alpha]^{23}_D$ (+) 18.6 (*c* 1.58, $CHCl_3$); IR (neat) 2955, 2926, 2876, 2855, 1742, 1716, 1615, 1515, 1458, 1366, 1249, 1127, 1084, 1006, 899, 835, 776, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.84 (s, 1H), 5.04 (s, 1H), 4.89 (s, 1H), 4.59 (d, *J* = 10.8 Hz, 1H), 4.29–4.35 (m, 1H), 4.27 (d, *J* = 10.8 Hz, 1H), 4.10–4.17 (m, 2H), 3.84 (s, 4H), 3.76–3.78 (m, 1H), 3.71 (d, *J* = 7.2 Hz, 1H), 3.19 (dd, *J* = 8.4, 17.6 Hz, 1H), 2.54 (dd, *J* = 3.3, 17.6 Hz, 1H), 2.11–2.15 (m, 1H), 2.06 (s, 3H), 1.86–1.98 (m, 2H), 1.85 (s, 3H), 1.63–1.77 (m, 4H), 1.52–1.56 (m, 1H), 1.45 (s, 3H), 1.30–1.38 (m, 2H), 1.13 (d, *J* = 6.4 Hz, 3H), 0.83–0.98 (m, 30H), 0.86 (d, *J* = 6.4 Hz, 3H), 0.52–0.64 (m, 18H), 0.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.3, 171.2, 159.1, 144.4, 142.6, 130.1, 129.7, 125.1, 115.0, 113.5, 88.2, 77.4, 76.4, 72.0, 65.9, 63.0, 55.3, 50.0, 46.5, 46.0, 44.0, 35.3, 32.3, 29.7, 28.7, 28.0, 24.7, 21.0, 19.3, 14.9, 13.3, 7.3, 7.1, 7.0, 6.8, 6.6, 6.4, 5.3, 5.1, 0.4; HRMS (ES+) calcd for $C_{54}H_{102}O_9Si_4Na$ (M + Na) 1029.6499, found 1029.6470.



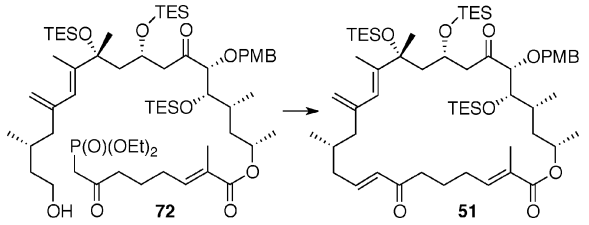
Alcohol 70. To a flask with **69** (180 mg, 0.18 mmol) at 0 °C was added a freshly prepared stock solution of HOAc/THF/H_2O (3.0 mL, 8:8:1) dropwise. After 40 min, the reaction was quenched with satd aq $NaHCO_3$ (20 mL) carefully and extracted with Et_2O (3 × 10 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5% EtOAc/hexanes, to give **70** (102 mg, 0.11 mmol, 61%) as a colorless oil: $[\alpha]^{23}_D$ (+) 23.7 (*c* 0.60, $CHCl_3$); IR (neat) 3546, 2955, 2926, 2876, 2855, 1742, 1716, 1615, 1515, 1458, 1366, 1249, 1127, 1084, 1006, 899, 835, 776, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 5.87 (s, 1H), 5.02 (s, 1H), 4.86 (s, 1H), 4.55 (d, *J* = 10.8 Hz, 1H), 4.23–4.29 (m, 1H), 4.23 (d, *J* = 10.8 Hz, 1H), 4.12–4.17 (m, 2H), 3.85 (s, 4H), 3.75–3.85 (m, 3H), 3.18 (dd, *J* = 9.2, 17.6 Hz, 1H), 2.54 (dd, *J* = 2.8, 17.6 Hz, 1H), 2.13 (dd, *J* = 5.6, 13.6 Hz, 1H), 2.06 (s, 3H), 1.86–1.94 (m, 2H), 1.83 (s, 3H), 1.63–1.80 (m, 4H), 1.52–1.56 (m, 1H), 1.45 (s, 3H), 1.38–1.45 (m, 2H), 1.19 (d, *J* = 6.0 Hz, 3H), 0.88–1.01 (m, 33H), 0.55–0.68 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.3, 171.2, 159.1, 144.9, 141.7, 130.0, 129.8, 125.5, 114.9, 113.5, 88.5, 77.4, 77.2, 76.4, 71.8, 65.8, 63.2, 55.3, 49.5, 46.2, 45.8, 44.1, 35.4, 33.2, 29.7, 28.7, 28.5, 24.5, 21.0, 19.3, 14.9, 13.6, 7.3, 7.0, 6.95, 6.87, 5.2, 5.1; HRMS (ES+) calcd for $C_{51}H_{94}O_9Si_3Na$ (M + Na) 957.6103, found 957.6157.



Ketophosphonate 71. To a solution of phosphonate acid **11** (74 mg, 0.24 mmol) in PhMe (0.5 mL) at rt was added triethylamine (26.2 mg, 36.0 μL, 0.24 mmol) and 2,4,6-trichlorobenzoyl chloride (56 mg, 36.0 μL, 0,24 mmol). After 6 h, solvent of the reaction was removed in vacuo. A solution of the alcohol **70** (60 mg, 64 μmol) in PhMe (0.5 mL) was transferred into the above flask via cannula and DMAP (29.6 mg, 0.24 mmol) were added sequentially. After 16 h, the reaction was purified by chromatography over silica gel, eluting with 70% EtOAc/hexanes, to give **71** (50 mg, 41 μmol, 64%) as a colorless oil: $[\alpha]^{23}_D$ (+) 25.3 (*c* 1.50, $CHCl_3$); IR (neat) 2954, 2933, 2876, 1739, 1712, 1613, 1515, 1461, 1366, 1251, 1165, 1124, 1026, 968, 901, 835, 770, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.69 (t, *J* = 7.2 Hz, 1H), 5.85 (s, 1H), 5.03 (br, 2H), 4.88 (s, 1H), 4.62 (d, *J* = 10.8 Hz, 1H), 4.25–4.31 (m, 1H), 4.25 (d, *J* = 10.8 Hz, 1H), 4.05–4.21 (m, 6H), 3.84 (s, 3H), 3.81–3.83 (m, 1H), 3.72 (d, *J* = 6.0 Hz, 1H), 3.16 (dd, *J* = 8.8, 17.6 Hz, 1H), 3.12 (s, 1H), 3.07 (s, 1H), 2.67 (t, *J* = 7.2 Hz, 2H), 2.60 (dd, *J* = 2.8, 17.6 Hz, 1H), 2.16 (dd, *J* = 7.6, 14.8 Hz, 2H), 2.08–2.12 (m, 1H), 2.06 (s, 3H), 1.83–1.94 (m, 4H), 1.83 (s, 3H), 1.81 (s, 3H), 1.61–1.77 (m, 5H), 1.52–1.55 (m, 1H), 1.43 (s, 3H), 1.40–1.43 (m, 1H), 1.36 (t, *J* = 6.8 Hz, 6H), 1.22 (d, *J* = 6.0 Hz, 3H), 0.90–1.00 (m, 30H), 0.86 (d, *J* = 6.4 Hz, 3H), 0.54–0.66 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.7, 201.5, 201.4, 171.2, 167.7, 159.2, 144.5, 142.3, 140.6, 129.9, 129.7, 129.0, 125.2, 115.0, 113.6, 87.4, 76.0, 72.0, 68.9, 66.0, 63.1, 62.6, 62.5, 55.3, 49.9, 46.8, 45.9, 43.4, 43.1, 41.8, 39.3, 35.3, 33.0, 28.7, 28.2, 27.7, 22.3, 21.0, 20.8, 19.3, 16.4, 16.3, 14.9, 14.1, 12.5, 7.3, 7.0, 6.9, 6.8, 5.2, 5.1; HRMS (ES+) calcd for $C_{64}H_{115}O_{14}PSi_3Na$ (M + Na) 1245.7230, found 1245.7181.



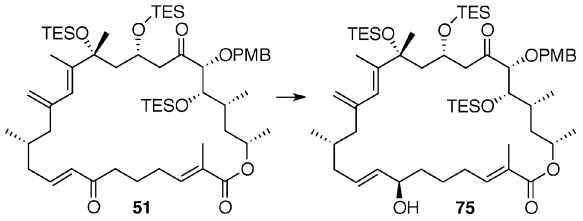
Alcohol 72. To a flask containing **71** (50.0 mg, 41 μmol) at rt was added a premixed solution of $Ba(OH)_2{\cdot}8H_2O$ (1.5 mL, 0.1 M in MeOH). After 10 min, the mixture was purified by chromatography over silica gel, eluting with 50% EtOAc/hexanes, to give **72** (42 mg, 36 μmol, 88%) as a colorless oil: $[\alpha]^{23}_D$ (+) 19.8 (*c* 0.78, $CHCl_3$); IR (neat) 3444, 2954, 2929, 2876, 1713, 1614, 1515, 1458, 1379, 1251, 1165, 1125, 1059, 1024, 970, 900, 835, 809, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.69 (t, *J* = 7.6 Hz, 1H), 5.85 (s, 1H), 5.03–5.06 (m, 2H), 4.85 (s, 1H), 4.62 (d, *J* = 10.4 Hz, 1H), 4.12–4.27 (m, 7H), 3.84 (s, 3H), 3.81 (dd, *J* = 3.2, 6.8 Hz, 1H) 3.70–3.76 (m, 3H), 3.19 (dd, *J* = 9.2, 17.2 Hz, 1H), 3.13 (s, 1H), 3.07 (s, 1H), 2.68 (t, *J* = 7.2 Hz, 2H), 2.60 (dd, *J* = 2.8, 17.6 Hz, 1H), 2.18 (q, *J* = 7.6 Hz, 2H), 2.10 (dd, *J* = 5.2, 18.4 Hz, 1H), 1.83–1.91 (m, 3H), 1.83 (s, 3H), 1.81 (s, 3H), 1.51–1.81 (m, 7H), 1.43 (s, 3H), 1.38–1.43 (m, 1H), 1.36 (t, *J* = 7.2 Hz, 6H), 1.23 (d, *J* = 6.0 Hz, 3H), 0.87–1.00 (m, 33H), 0.54–0.66 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.3, 201.5, 201.4, 167.7, 159.2, 144.9, 141.7, 140.7, 130.0, 129.7, 129.0, 125.6, 114.9, 113.5, 87.6, 77.5, 75.9, 72.0, 68.9, 66.2, 62.6, 62.5, 61.0, 55.3, 49.5, 46.6, 46.2, 43.4, 43.1, 41.8, 40.1, 39.5, 32.9, 29.7, 28.4, 28.3, 27.7, 22.3, 20.8, 19.2, 16.4, 16.3, 15.1, 14.1, 13.9, 12.5, 7.3, 7.0, 6.9, 6.8, 5.2, 5.1; HRMS (ES+) calcd for $C_{62}H_{113}O_{13}PSi_3Na$ (M + Na) 1203.7124, found 1203.7054.



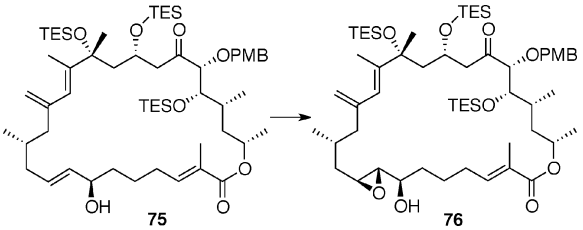
Macrolactone 51. To a solution of **72** (42 mg, 36 μmol) in CH_2Cl_2 (1.2 mL) at rt. was added TPAP (15 mg, 43 μmol). After 1 h, THF (3.3 mL), H_2O (82.8 μL) and $Ba(OH)_2{\cdot}8H_2O$ (43 mg, 0.13 mmol) were sequentially added to the reaction. After 3 h, the reaction was directly purified by chromatography over silica gel, eluting with 5% EtOAc/hexanes, to give **51** (30.6 mg, 30 μmol, 85%) as a colorless oil: $[\alpha]^{23}_D$ (+) 1.6 (*c* 0.45, $CHCl_3$); IR (neat) 2954, 2925, 2875, 2854, 1710, 1673, 1614, 1515, 1461, 1377, 1251, 1171, 1120, 1068, 1018, 985, 835, 808, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.6 Hz, 2H), 6.94–7.01 (m, 1H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.71 (t, *J* = 7.6 Hz, 1H), 6.09 (d, *J* = 16.0 Hz, 1H), 5.77 (s, 1H), 5.05 (s, 1H), 4.96–5.04 (m, 1H), 4.87 (s, 1H), 4.53 (d, *J* = 10.8 Hz, 1H), 4.21–4.27 (m, 1H), 4.21 (d, *J* = 10.8 Hz, 1H), 3.84 (s, 3H), 3.67–3.74 (m, 2H), 3.15 (dd, *J* = 9.2, 17.6 Hz, 1H), 2.56–2.67 (m, 3H), 2.08–2.27 (m, 3H), 1.90 (s, 3H), 1.78 (s, 3H), 1.47–1.78 (m, 9H), 1.43 (s, 3H), 1.26–1.42 (m, 2H), 1.25 (d, *J* = 6.0 Hz, 3H), 0.90–1.00 (m, 30H), 0.83 (d, *J* = 6.4 Hz, 3H), 0.54–0.66 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.8, 200.8, 167.6, 159.2, 147.0, 144.5, 142.7, 140.8, 132.3, 130.0, 129.5, 129.2, 125.3, 115.5, 113.6,

dx.doi.org/10.1021/jo3026077 | J. Org. Chem. 2013, 78, 2213–2247

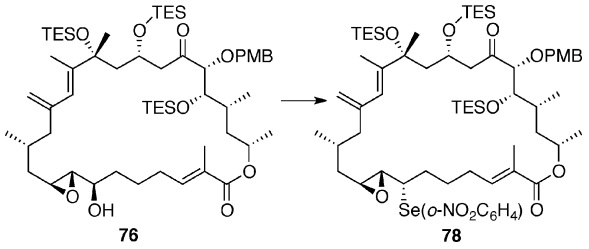
87.9, 71.7, 68.9, 65.4, 55.3, 49.2, 47.1, 45.8, 41.8, 40.6, 37.4, 32.0, 31.5, 31.4, 27.4, 22.9, 21.0, 19.5, 15.2, 14.2, 12.5, 7.3, 7.0, 6.9, 6.8, 5.2, 5.1; HRMS (ES+) calcd for $C_{58}H_{100}O_9Si_3Na$ (M + Na) 1047.6573, found 1047.6494.



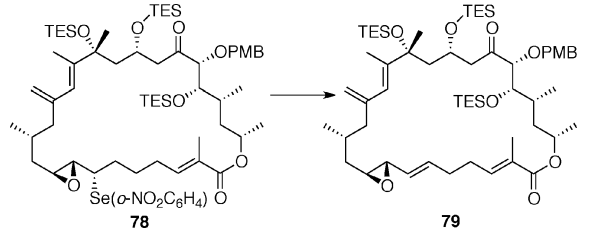
Allylic Alcohol 75. To a solution of (*S*)-2-methyl-CBS-oxazaborolidine (10.1 μL, 10 μmol, 1.0 M in PhMe) in CH_2Cl_2 (0.3 mL) at rt was added catechol borane (0.20 mL, 0.20 mmol, 1.0 M CH_2Cl_2). After 10 min, the resulted solution was cooled to −20 °C. A solution of macrolactone **51** (26 mg, 25 μmol) in CH_2Cl_2 (0.65 mL) was added into the above solution dropwise via cannula. After 2 h, the reaction was quenched with MeOH (2.0 mL) and concentrated in vacuo. The resultant mixture was purified by preparative TLC, eluting with 25% EtOAc/hexane, to give **75** (14 mg, 14 μmol, 56%) as a colorless oil: $[\alpha]^{23}_D$ (+) 7.6 (*c* 0.88, $CHCl_3$); IR (neat) 3459, 2954, 2917, 2875, 2849, 1709, 1614, 1515, 1461, 1377, 1251, 1173, 1125, 1070, 1018, 835, 776, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.72 (t, *J* = 7.6 Hz, 1H), 5.79 (s, 1H), 5.68−5.72 (m, 1H), 5.49 (dd, *J* = 6.8, 15.2 Hz, 1H), 5.05 (s, 1H), 4.97−5.04 (m, 1H), 4.87 (s, 1H), 4.57 (d, *J* = 10.8 Hz, 1H), 4.28−4.32 (m, 1H), 4.22 (d, *J* = 10.8 Hz, 1H), 4.13−4.17 (m, 1H), 3.85 (s, 3H), 3.65−3.73 (m, 2H), 3.16 (dd, *J* = 9.2, 18.0 Hz, 1H), 2.53 (dd, *J* = 3.2, 18.0 Hz, 1H), 2.21−2.24 (m, 4H), 1.98−2.04 (m, 4H), 1.88 (s, 3H), 1.82 (s, 3H), 1.75−1.84 (m, 2H), 1.53−1.70 (m, 7H), 1.44 (s, 3H), 1.30−1.36 (m, 1H), 1.24 (d, *J* = 5.6 Hz, 3H), 0.89−1.00 (m, 30H), 0.82 (d, *J* = 6.0 Hz, 3H), 0.54−0.66 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.6, 167.8, 159.2, 145.1, 142.6, 141.7, 134.5, 130.4, 129.9, 129.8, 128.5, 125.6, 115.1, 113.5, 88.1, 77.2, 76.6, 72.4, 71.7, 68.6, 65.5, 55.3, 53.5, 49.5, 46.4, 44.9, 41.1, 39.4, 36.6, 32.2, 31.4, 28.6, 27.5, 23.7, 21.1, 19.8, 15.0, 12.6, 11.9, 7.3, 7.0, 6.9, 6.8, 5.2, 5.1; HRMS (ES+) calcd for $C_{58}H_{102}O_9Si_3Na$ (M + Na) 1049.6729, found 1049.6678.



Hydroxyl Epoxide 76. To a solution of (+)-DIPT (0.11 mL, 89 μmol, 0.8 M in CH_2Cl_2) were added CH_2Cl_2 (0.30 mL) and 4 Å MS (30 mg). The resulting mixture was cooled to −20 °C, and Ti(O-*i*-Pr)$_4$ (21.6 mg, 20.0 μL, 76 μmol) was added. After 30 min, TBHP (14.2 μL, 76 μmol, 5.5 M in decane) was added dropwise. After another 30 min, a solution of alcohol **75** (13 mg, 13 μmol) in CH_2Cl_2 (0.30 mL) was added dropwise via cannula, and the reaction was allowed to warm to 0 °C. After 16 h, the reaction was cooled back to −20 °C, and a brine solution of NaOH (0.5 mL, 1.0 M) was added. After 5 min, the reaction was diluted with brine (0.5 mL) and CH_2Cl_2 (0.5 mL) and warmed to rt. Next, the mixture was extracted with CH_2Cl_2 (3 × 15 mL) and the dried ($MgSO_4$) extract concentrated in vacuo. The crude mixture was purified by preparative TLC, eluting with 25% EtOAc/hexane, to give vinyl epoxide **76** (7.0 mg, 7.0 μmol, 54%) as a colorless oil: $[\alpha]^{23}_D$ (+) 12.2 (*c* 0.36, $CHCl_3$); IR (neat) 3467, 3017, 2954, 2917, 2875, 2849, 2107, 1709, 1515, 1462, 1378, 1251, 1173, 1125, 1070, 1018, 835, 756, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.77 (t, *J* = 7.6 Hz, 1H), 5.80 (s, 1H), 5.06 (s, 1H), 4.95−5.00 (m, 1H), 4.87 (s, 1H), 4.60 (d, *J* = 10.8 Hz, 1H), 4.22−4.30 (m, 1H), 4.21 (d, *J* = 10.8 Hz, 1H), 3.85 (s, 3H), 3.75−3.84 (m, 1H), 3.67−3.74 (m, 2H), 3.22 (dd, *J* = 9.2, 18.0 Hz, 1H), 3.05−3.10 (m, 1H), 2.78−2.81 (m, 1H), 2.54 (dd, *J* = 3.2, 18.0 Hz, 1H), 2.38 (br, 1H), 2.21−2.30 (m, 4H), 1.89−1.92 (m, 1H), 1.89 (s, 3H), 1.84 (s, 3H), 1.75−1.86 (m, 3H), 1.53−1.70 (m, 7H), 1.45 (s, 3H), 1.30−1.36 (m, 1H), 1.26 (d, *J* = 5.6 Hz, 3H), 0.91−1.01 (m, 30H), 0.56−0.67 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.8, 167.8, 159.2, 144.7, 142.4, 141.2, 129.9, 129.8, 128.9, 125.6, 115.4, 113.6, 88.1, 77.1, 71.8, 68.7, 68.2, 65.4, 61.3, 55.3, 54.2, 49.8, 46.5, 45.4, 41.8, 39.5, 33.3, 31.1, 30.8, 28.5, 27.7, 24.1, 21.1, 20.1, 15.1, 12.5, 11.8, 7.3, 7.0, 6.9, 5.3, 5.1; HRMS (ES+) calcd for $C_{58}H_{102}O_{10}Si_3Na$ (M + Na) 1065.6679, found 1065.6774.



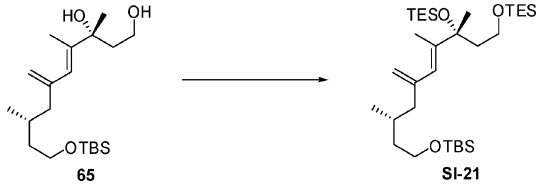
Selenide 78. To a solution of vinyl epoxide **76** (5.0 mg, 5 μmol) in THF (0.15 mL) at rt were added **77** (33 mg, 0.15 mmol) and PBu_3 (29 mg, 36.2 μL, 0.15 mmol). After 1 h, the reaction mixture was directly purified by preparative TLC, eluting with 25% EtOAc/hexane, to give selenide **78** (3.0 mg, 2.5 μmol, 50%) as a colorless oil: $[\alpha]^{23}_D$ (−) 9.9 (*c* 0.22, $CHCl_3$); IR (neat) 2956, 2932, 2874, 1701, 1515, 1457, 1250, 1074, 1007, 806, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, *J* = 6.9 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.48−7.54 (m, 1H), 7.48−7.55 (m, 3H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.69 (t, *J* = 7.6 Hz, 1H), 5.84 (s, 1H), 5.05 (s, 1H), 4.96−5.00 (m, 1H), 4.87 (s, 1H), 4.56 (d, *J* = 10.5 Hz, 1H), 4.25−4.30 (m, 1H), 4.21 (d, *J* = 10.5 Hz, 1H), 3.84 (s, 3H), 3.70 (s, 2H), 3.26 (dd, *J* = 9.6, 17.4 Hz, 1H), 3.20 (d, *J* = 8.1, 14.4 Hz, 1H), 2.99−3.04 (m, 1H), 2.96 (dd, *J* = 8.1, 15.0 Hz, 1H), 2.57 (dd, *J* = 2.8, 17.4 Hz, 1H), 2.21−2.30 (m, 4H), 1.89−1.92 (m, 1H), 1.84 (s, 3H), 1.79 (s, 3H), 1.45−1.78 (m, 10H), 1.42 (s, 3H), 1.30−1.36 (m, 1H), 1.25 (d, *J* = 5.6 Hz, 3H), 0.91−1.01 (m, 30H), 0.56−0.67 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.9, 167.5, 159.1, 147.7, 144.5, 142.4, 140.3, 133.4, 131.3, 129.9, 129.7, 129.2, 126.1, 126.0, 125.5, 115.4, 113.5, 88.5, 77.2, 71.7, 68.9, 65.6, 62.1, 59.6, 55.3, 49.6, 45.9, 45.7, 44.8, 41.1, 39.6, 31.7, 31.6, 30.9, 28.3, 26.2, 21.0, 19.9, 15.2, 12.6, 12.1, 7.3, 7.0, 6.9, 5.3, 5.1; HRMS (ES+) calcd for $C_{64}H_{106}NO_{11}Si_3Se$ (M + 1) 1228.6239, found 1228.6216.



Allyl Epoxide 79. To a solution of selenide **78** (5.7 mg, 5.0 μmol) in CH_2Cl_2 (0.25 mL) at rt were added sequentially triethylamine (19 mg, 26.0 μL, 0.18 mmol), TPAP (16 mg, 45 μmol), and NMO (35 mg, 0.3 mmol). After 30 min, the reaction mixture was purified directly by preparative TLC, eluting with 25% EtOAc/hexanes, to give vinyl epoxide **79** (2.5 mg, 2.4 μmol, 48%) as a colorless oil: $[\alpha]^{23}_D$ −1.3 (*c* 0.15, $CHCl_3$); IR (neat) 3467, 3017, 2954, 2917, 2875, 2849, 2107, 1709, 1515, 1462, 1378, 1251, 1173, 1125, 1070, 1018, 835, 756, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.73 (t, *J* = 7.6 Hz, 1H), 5.85−5.92 (m, 1H), 5.78 (s, 1H), 5.27 (dd, *J* = 8.0, 15.2 Hz, 1H), 5.01−5.04 (m, 2H), 4.85 (s, 1H), 4.57 (d, *J* = 10.4 Hz, 1H), 4.28−4.32 (m, 1H), 4.21 (d, *J* = 10.4 Hz, 1H), 3.85 (s, 3H), 3.70−3.74 (m, 2H), 3.25 (dd, *J* = 9.6, 17.2 Hz, 1H), 3.09 (dd, *J* = 2.0, 6.4 Hz, 1H), 2.90−2.94 (m, 1H), 2.54 (dd, *J* = 2.8, 17.2 Hz, 1H), 2.06−2.28 (m, 4H), 1.94 (d, *J* = 2.4, 10.8 Hz, 1H), 1.86 (s, 3H), 1.80−1.86 (m, 3H), 1.79 (s, 3H), 1.53−1.70 (m, 7H), 1.46 (s, 3H), 1.30−1.36 (m, 1H), 1.25 (d, *J* = 6.0 Hz, 3H), 0.90−1.01 (m, 27H), 0.86 (d, *J* = 6.0 Hz, 3H), 0.54−0.68 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.0, 167.6, 159.1, 144.6, 142.4, 140.5, 134.3, 130.1, 129.8, 129.5, 128.7, 125.2, 115.3, 113.5, 88.4, 76.4, 71.7, 68.9, 65.7, 59.6, 58.5, 55.3, 49.4, 46.1, 45.6, 40.6, 40.2, 32.1, 30.9, 30.5, 29.7, 28.0, 27.8, 20.4, 19.8,

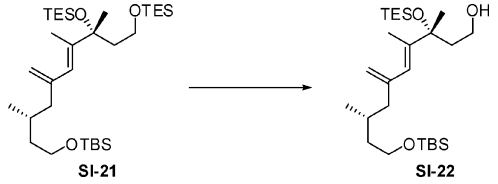
dx.doi.org/10.1021/jo3026077 | J. Org. Chem. 2013, 78, 2213−2247

15.2, 13.0, 12.5, 7.3, 7.0, 6.9, 6.8, 5.2, 5.1; HRMS (ES+) calcd for $C_{58}H_{100}O_9Si_3Na$ (M + Na) 1047.6573, found 1047.6664.



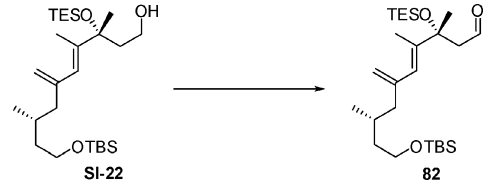
65 SI-21

TES Ether SI-21. To a stirred solution of diol **65** (470 mg, 1.32 mmol) in DCM/TEA (6 mL, 1:1) was added freshly distilled TESOTf (1.05 g, 0.89 mL, 3.96 mmol) at −78 °C. After 30 min, the reaction was quenched with satd aq $NaHCO_3$ (1 mL) and extracted with ether (3 × 20 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 2−5% EtOAc/hexanes, to give **SI-21** (732 mg, 1.25 mmol, 95%) as a colorless oil: $[\alpha]^{23}_D$ = −21.3° (*c* 1.37, $CHCl_3$); IR (neat) 2954, 2929, 2876, 1460, 1254, 1093, 1007, 835, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.88 (s, 1H), 4.99 (s, 1H), 4.80 (s, 1H), 3.61−3.71 (m, 3H), 3.47 (dt, *J* = 15.6, 5.4 Hz, 1H), 2.15 (dd, *J* = 13.5, 5.4 Hz, 1H), 1.80−1.99 (m, 5H), 1.77 (d, *J* = 0.9 Hz, 3H), 1.54−1.66 (m, 1H), 0.88−1.00 (m, 27H), 0.84 (d, *J* = 6.3 Hz, 3H), 0.55−0.66 (m, 12H), 0.063 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 142.0, 124.6, 114.1, 77.2, 61.7, 59.3, 46.2, 44.5, 40.0, 28.7, 26, 19.6, 18.4, 14.7, 7.2, 7.0, 6.9, 6.8, 4.4, −5.3; HRMS (EI^+) calcd for $C_{32}H_{68}O_3Si_3$ (M^+) 584.4476, found 584.4500.



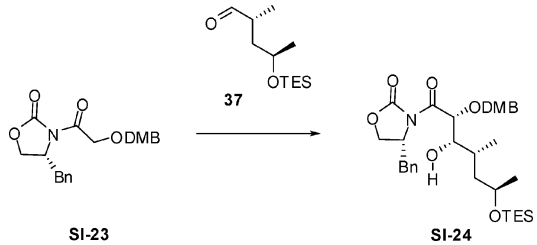
SI-21 SI-22

Alcohol SI-22. TES ether **SI-21** (300 mg, 0.51 mmol) was dissolved in a stirred solution of HOAc/THF/H_2O (8 mL, 8:8:1) at 0 °C. After 1.5 h, the reaction was then quenched with solid $NaHCO_3$ and extracted with ether (3 × 20 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10% EtOAc/hexanes, to give alcohol **SI-22** (241 mg, 0.51 mmol, 99%) as a colorless oil: $[\alpha]^{23}_D$ = −15.5° (*c* 0.64, $CHCl_3$); IR (neat) 3437, 2954, 2928, 2876, 1461, 1254, 1099, 1008, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.02 (s, 1H), 5.04 (s, 1H), 4.85 (s, 1H), 3.63−3.73(m, 4H), 2.79 (t, *J* = 5.6 Hz, 1H), 2.17 (dd, *J* = 13.6, 5.6 Hz, 1H), 1.88−1.97 (m, 3H), 1.74−1.83 (m, 1H), 1.79 (d, *J* = 1.2 Hz, 3H), 1.59−1.68 (m, 1H), 1.47 (s, 3H), 1.28−1.40 (m, 1H), 0.99−1.03 (t, *J* = 7.6 Hz, 9H), 0.92 (s, 9H), 0.88 (d, *J* = 6.4 Hz, 3H), 0.69 (q, *J* = 7.2 Hz, 6H), 0.078 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 141.4, 125.6, 114.6, 80.0, 61.6, 60.1, 46.1, 42.8, 39.9, 29.7, 28.6, 27.6, 26.0, 19.5, 18.4, 14.9, 7.2, 6.9, 6.8, −5.3; HRMS (EI^+) calcd for $C_{26}H_{54}O_3Si_2$ (M^+) 470.3611, found 470.3604.



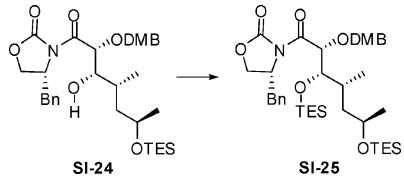
SI-22 82

Aldehyde 82. To a stirred solution of alcohol **SI-22** (1.29 g, 2.73 mmol) in DCM (40 mL, 1:1) were added sequentially DMP (2.17 g, 5.12 mmol) and $NaHCO_3$ (1.68 g, 20.0 mmol) at rt. After 30 min, the reaction was quenched with satd aq $NaHCO_3$ (10 mL) and extracted with ether (3 × 40 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5% EtOAc/hexanes, to give aldehyde **82** (1.17 g, 2.49 mmol, 91%) as a colorless oil: $[\alpha]^{23}_D$ = −12.5 (*c* 0.56, $CHCl_3$); IR (neat) 2955, 2929, 2877, 1725, 1255, 1099, 1007, 836, 726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.69 (t, *J* = 3.3 Hz, 1H), 6.03 (s, 1H), 5.03 (s, 1H), 4.83 (s, 1H), 3.61−3.68(m, 2H), 2.64 (dd, *J* = 15.0, 3.0 Hz, 1H), 2.45 (dd, *J* = 15.0, 3.0 Hz, 1H), 2.15 (dd, *J* = 13.5, 6.0 Hz, 1H), 1.85−1.92 (m, 1H), 1.83 (d, *J* = 1.2 Hz, 3H), 1.54−1.64 (m, 1H), 1.49 (s, 3H), 1.25−1.35 (m, 2H), 0.95−1.00 (t, *J* = 7.7 Hz, 9H), 0.91 (s, 9H), 0.85 (d, *J* = 6.5 Hz, 3H), 0.65 (q, *J* = 7.8 Hz, 6H), 0.061 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 144.7, 141.0, 126.0, 114.9, 76.9, 61.5, 54.2, 46.0, 39.9, 28.5, 27.8, 26.0, 19.5, 18.3, 14.7, 7.1, 6.7, −5.3; HRMS (EI^+) calcd for $C_{26}H_{52}O_3Si_2$ (M^+) 468.3455, found 468.3448.



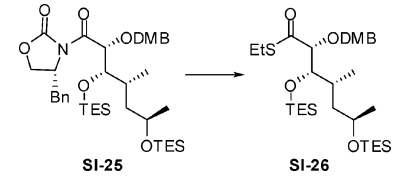
SI-23 SI-24

Aldol Adduct SI-24. To a stirred solution of **SI-23** (1.60 g, 0.15 mmol) in CH_2Cl_2 (11.2 mL) at −60 °C were added sequentially Et_3N (0.44 g, 0.60 mL, 4.33 mmol) and Bu_2BOTf (1.19 g, 1.08 mL, 4.33 mmol). After 3 h, the resulted solution was warmed to 0 °C for 30 min and then cooled back to −60 °C. A solution of aldehyde **37**[8] (1.12 g, 4.86 mmol) in DCM (4.8 mL) was transferred to the reaction mixture via cannula. After 2 h, the reaction was allowed to warm to 0 °C. After another 20 min, the reaction was quenched by addition of pH 7 phosphate buffer (20 mL) followed by MeOH (15 mL) and 30% H_2O_2 (4 mL). After 1 h, the reaction mixture was extracted with EtOAc (4 × 35 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 15−20% EtOAc/hexanes, to give **SI-24** (1.58 g, 2.57 mmol, 62%) as a colorless oil: $[\alpha]^{23}_D$ = −9.2 (*c* 0.77, $CHCl_3$); IR (neat) 3493, 2957, 2876, 1781, 1709, 1593, 1517, 1455, 1390, 1265, 1240, 1159, 1052, 1028, 746 cm^{-1}; ^1H NMR (400 MHz) δ 7.23−7.38 (m, 5H), 6.83−7.03 (m, 3H), 5.36 (d, *J* = 2.0 Hz, 1H), 4.63−4.71 (m, 2H), 4.51 (d, *J* = 10.8 Hz, 1H), 4.21−4.29 (m, 2H), 3.93 (s, 3H), 3.84−3.90 (m, 1H), 3.88 (s, 3H), 3.62−3.66 (m, 1H), 3.32 (dd, *J* = 13.6, 3.6 Hz, 1H), 2.77 (dd, *J* = 13.6, 10.0 Hz, 1H), 2.32 (d, *J* = 10.0 Hz, 1H), 1.78−1.80 (m, 1H), 1.58−1.64 (m, 1H), 1.15 (d, *J* = 6.0 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.98 (t, *J* = 8.0 Hz, 9H), 0.62 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 153.2, 149.1, 149.0, 135.2, 129.5, 129.4, 129.0, 127.4, 121.4, 112.1, 110.9, 78.1, 76.1, 66.9, 55.9, 55.7, 42.8, 37.7, 34.1, 23.2, 15.7, 6.9, 4.9; HRMS (ES^+) calcd for $C_{33}H_{49}NO_8SiNa$ (M + Na) 638.3125, found 638.3155.



SI-24 SI-25

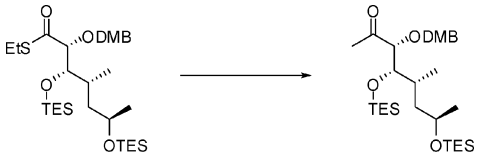
TES Ether SI-25. To a stirred solution of adol adduct **SI-24** (500 mg, 0.81 mmol) in DCM (3.32 mL) at 0 °C were added sequentially 2,6-lutidine (184 mg, 0.20 mL, 1.72 mmol) and TESOTf (287 mg, 0.25 mL, 1.09 mmol). After 1 h, the reaction was quenched with satd aq NH_4Cl (10 mL) and extracted with Et_2O (3 × 30 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 15% EtOAc/hexanes, to give **SI-25** (570 mg, 0.78 mmol, 96%) as a colorless oil: $[\alpha]^{23}_D$ = −40.7 (*c* 0.42, $CHCl_3$); IR (neat) 2955, 2911, 2876, 1784, 1702, 1517, 1456, 1239, 1084, 740 cm^{-1}; ^1H NMR (300 MHz) δ 7.17−7.32 (m,H), 6.80−7.00 (m, 3H), 5.28 (d, *J* = 6.0 Hz, 1H), 4.71 (d, *J* = 11.7 Hz, 1H), 4.54 (d, *J* = 11.7 Hz, 2H), 4.47−4.49 (m, 1H), 4.00−4.12 (m, 3H), 3.90 (s, 3H), 3.84 (s, 3H), 3.78−3.82 (m, 1H), 3.14 (dd, *J* = 3.0, 13.2 Hz, 1H), 2.40 (dd, *J* = 10.5, 13.5 Hz, 1H), 1.42−1.56 (m, 3H), 1.11 (d, *J* = 5.7 Hz, 3H), 0.89−0.97 (m, 21H), 0.55−0.63 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 152.9, 148.7, 148.8, 135.3, 130.3, 129.3, 129.0, 127.3, 121.1, 111.9, 110.7, 73.4, 67.2, 66.4, 56.0, 55.9, 55.8, 44.4, 37.4, 33.5, 23.7, 14.8, 7.1, 6.9, 5.4, 5.3, 5.2, 5.0; HRMS (ES^+) calcd for $C_{39}H_{63}NO_8Si_2Na$ (M + Na) 752.3990, found 752.3992.



SI-25 SI-26

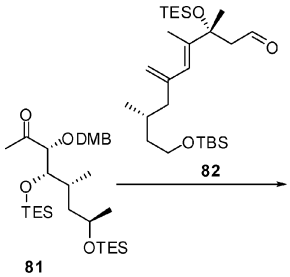
dx.doi.org/10.1021/jo3026077 | J. Org. Chem. 2013, 78, 2213−2247

Thiol Ester SI-26. To a stirred solution of EtSH (90 mg, 0.107 mL, 1.45 mmol) in THF (12.6 mL) at 0 °C was added *n*-BuLi (0.51 mL, 1.27 mmol, 2.5 M in hexanes). After 1 h, a solution of **SI-25** (610 mg, 0.83 mmol) in THF (2.7 mL) was added dropwise via cannula. After another 1 h, the reaction was quenched with satd aq NH_4Cl (10 mL) and extracted with Et_2O (3 × 30 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5−8% EtOAc/hexanes, to give **SI-26** (470 mg, 0.76 mmol, 92%) as a colorless oil: $[\alpha]^{23}_D$ = +42.0 (*c* 0.39, $CHCl_3$); IR (neat) 2955, 2911, 2876, 1683, 1517, 1458, 1419, 1378, 1266, 1240, 1161, 1079, 1032, 811, 740 cm^{-1}; ^1H NMR (400 MHz) δ 7.04 (dd, *J* = 1.6 Hz, 1H), 6.94 (dd, *J* = 1.6, 8.0 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 4.63 (d, *J* = 10.8 Hz, 1H), 4.43 (d, *J* = 10.8 Hz, 1H), 3.94 (s, 3H), 3.92−3.93 (m, 4H), 3.81−3.86 (m, 2H), 2.91 (q, *J* = 7.6 Hz, 2H), 1.45−1.57 (m, 3H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.14 (d, *J* = 6.0 Hz, 3H), 0.90−0.98 (m, 21H), 0.53−0.62 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 148.8, 148.6, 129.9, 120.6, 110.6, 110.7, 88.2, 72.9, 66.9, 55.9, 55.8, 44.9, 32.7, 23.4, 22.5, 14.6, 13.6, 7.0, 6.9, 5.3, 5.2, 5.0; HRMS (ES^+) calcd for $C_{31}H_{58}O_6Si_2SNa$ (M + Na) 637.3390, found 637.3407.

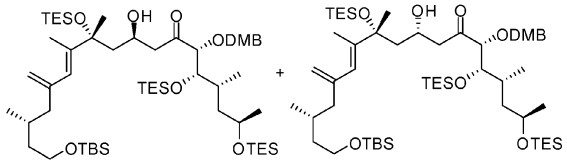


SI-26 81

Methyl Ketone 81. To a stirred slurry of CuI (859 mg, 4.51 mmol) in Et_2O (8.3 mL) at 0 °C was added MeLi (5.6 mL, 9.6 mmol, 1.6 M in Et_2O). After 15 min, the colorless solution was cooled to −50 °C, and a solution of **SI-26** (450 mg, 0.75 mmol) in Et_2O (4.2 mL) was transferred into the reaction mixture dropwise via cannula. After 2 h, the reaction was quenched with satd aq NH_4Cl (10 mL) at −50 °C, warmed to rt, and extracted with Et_2O (3 × 30 mL). The dried ($MgSO_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 2−4% EtOAc/hexanes, to give **81** (296 mg, 0.52 mmol, 71%) as a colorless oil: $[\alpha]^{23}_D$ = +22.6 (*c* 0.23, $CHCl_3$); IR (neat) 2955, 2911, 2876, 1716, 1517, 1457, 1267, 1240, 1082, 1031, 1007, 741 cm^{-1}; ^1H NMR (400 MHz) δ 6.82−6.90 (m, 3H), 4.50 (dd, *J* = 11.4, 15.0 Hz, 2H), 3.90 (s, 6H), 3.80−3.85 (m, 2H), 3.76 (d, *J* = 6.3 Hz, 1H), 2.13 (s, 3H), 1.50−1.52 (m, 3H), 1.13 (d, *J* = 6.0 Hz, 3H), 0.88−1.00 (m, 21H), 0.57−0.64 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.6, 148.8, 129.9, 120.7, 111.4, 110.8, 88.5, 72.9, 67.0, 55.9, 55.8, 44.5, 33.1, 27.0, 23.5, 14.0, 7.0, 6.9, 5.3, 5.0; HRMS (ES^+) calcd for $C_{30}H_{56}O_6Si_2Na$ (M + Na) 591.3513, found 591.3527.

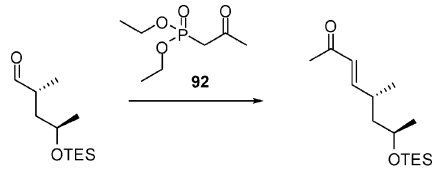


81



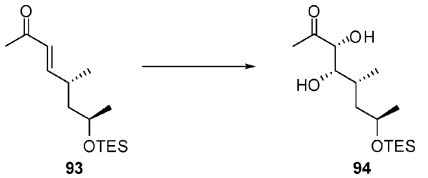
SI-27 83

Aldol Adduct 83. To a stirred solution of methyl ketone **81** (30 mg, 0.0527 mmol) in Et_2O (0.5 mL) at −78 °C was added LDA[54] (64 μL, 0.064 mmol, 1 M in THF). After 15 min, a precooled (−78 °C) solution of aldehyde **82** (50 mg, 0.105 mmol) in THF (0.5 mL) was added via cannula in one portion. After another 0.5 h, the reaction was quenched with satd aq NH_4Cl (2 mL) at −78 °C, warmed to rt, and extracted with ether (3 × 10 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 6−8% EtOAc/hexanes, to sequentially give aldol adduct **SI-27** (10 mg, 0.0096 mmol, 18%) and **83** (39 mg, 0.0375 mmol, 71%) and as colorless oils. **83**: $[\alpha]^{23}_D$ = +9.1 (*c* 0.58, $CHCl_3$); IR (neat) 3503, 2955, 2934, 2876, 1715, 1517, 1463, 1265, 1240, 1095, 1007, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.83−6.97 (m, 3H), 5.90 (s, 1H), 5.05 (s, 1H), 4.85 (s, 1H), 4.53 (d, *J* = 11.2 Hz, 1H), 4.44−4.50 (m, 1H), 4.39(d, *J* = 10.8 Hz, 1H), 3.91 (s, 6H), 3.76−3.83 (m, 3H), 3.66−3.70 (m, 2H), 3.05 (dd, *J* = 17.6, 6.8 Hz, 1H), 2.38 (dd, *J* = 17.6, 5.6 Hz, 1H), 2.19 (dd, *J* = 13.5, 4.8 Hz, 1H), 1.80−1.91 (m, 1H), 1.84 (s, 3H), 1.48−1.68 (m, 4H), 1.57 (s, 3H), 1.20−1.42 (m, 4H), 1.10 (d, *J* = 6.0 Hz, 3H), 0.86−1.00 (m, 42H), 0.57−0.66 (m, 18H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.0, 148.8, 148.6, 144.6, 142.9, 130.1, 125.2, 120.7, 114.9, 111.5, 110.7, 88.3, 79.5, 72.6, 66.9, 64.8, 61.4, 55.9, 55.8, 48.0, 46.7, 46.0, 44.8, 39.9, 33.1, 28.4, 23.3, 19.5, 14.7, 13.5, 7.1, 7.0, 6.9, 6.5, 5.3, 5.0, −5.2; HRMS (ES^+) calcd for $C_{56}H_{107}O_9Si_4$ (M + H) 1035.6992, found 1035.7047.



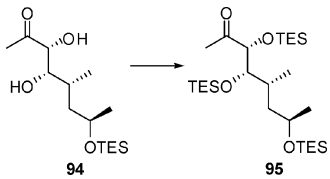
37 93

Enone 93. To a stirred slurry of NaH (36 mg, 0.90 mmol, 60% w/w in mineral oil) in DME (2 mL) was added phosphonate **92** (138 mg, 0.83 mmol) at rt. After 1 h, a solution of aldehyde **37** (160 mg, 0.69 mmol) in DME (2 mL) was added via cannula. After another 6 h, the reaction was quenched with satd aq NH_4Cl (2 mL) and extracted with Et_2O (4 × 10 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5% EtOAc/hexanes, to give enone **93** (142 mg, 0.52 mmol, 76%) as a colorless oil: $[\alpha]^{23}_D$ = −46.0° (*c* 1.47, $CHCl_3$); IR (neat) 2958, 2877, 1700, 1678, 1627, 1458, 1360, 1252, 1139, 1055, 984, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.76 (dd, *J* = 15.9, 7.8 Hz, 1H), 6.09 (d, *J* = 15.9 Hz, 1H), 3.86−3.79 (m, 1H), 2.58−2.53 (m, 1H), 2.26 (s, 3H), 1.41−1.55 (m, 2H), 1.18 (d, *J* = 6.0 Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H), 0.97 (t, *J* = 7.8 Hz, 9H), 0.64 (q, *J* = 7.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 153.5, 129.6, 66.4, 46.3, 33.4, 27.0, 24.3, 20.3, 6.9, 5.2, 5.0; HRMS (EI^+) calcd for $C_{15}H_{30}O_2Si$ (M^+) 270.2015, found 270.2008.



93 94

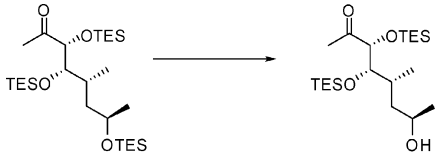
Diol 94. To a stirred solution of enone **93** (142 mg, 0.52 mmol) in *t*-BuOH/H_2O (5 mL, 1:1) at 0 °C were added sequentially AD-mix-α (0.735 g), $NaHCO_3$ (132 mg, 1.57 mmol), $MeSO_2NH_2$ (50.6 mg, 0.53 mmol), and $K_2OsO_2(OH)_4$ (1.9 mg, 0.005 mmol). After 8 h, the reaction was quenched with satd aq Na_2SO_3 (8 mL) and extracted with EtOAc (4 × 10 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 15−40% EtOAc/hexanes, to give diol **94** (122 mg, 0.40 mmol, 77%) as a colorless oil: $[\alpha]^{23}_D$ = −29.2 (*c* 1.5, $CHCl_3$); IR (neat) 3456, 2957, 2877, 1717, 1380, 1238, 1132, 1048, 1011, 744 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.28 (d, *J* = 3.6 Hz, 1H), 4.04−3.99 (m, 1H), 3.72−3.78 (m, 1H and OH), 2.41 (d, *J* = 10.4 Hz, 1H), 2.30 (s, 3H), 1.89−1.96 (m, 1H), 1.71−1.77 (m, 1H), 1.40−1.47 (m, 1H), 1.22 (d, *J* = 6.0 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 1.00 (t, *J* = 7.8 Hz, 9H), 0.68 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.9, 77.7, 75.2, 66.9, 42.8, 34.0, 25.3, 23.1, 16.4, 6.9, 4.9; HRMS (ES^+) calcd for $C_{15}H_{32}O_4SiNa$ (M + Na) 327.1968, found 327.1950.



94 95

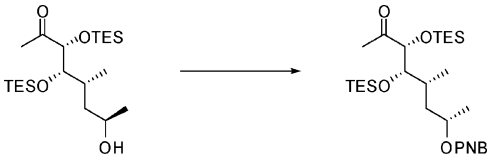
dx.doi.org/10.1021/jo3026077 | J. Org. Chem. 2013, 78, 2213−2247

TES Ether 95. To a stirred solution of diol **94** (800 mg, 2.63 mmol) in CH_2Cl_2 (10 mL) at −78 °C were added sequentially 2,6-lutidine (1.41 g, 1.53 mL, 13.1 mmol) and TESOTf (1.74 g, 1.49 mL, 6.58 mmol). After 30 min, the reaction was quenched with satd aq NH_4Cl (10 mL) and extracted with Et_2O (4 × 25 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10% EtOAc/hexanes, to give TES ether **95** (1.29 g, 2.42 mmol, 92%) as a colorless oil: $[\alpha]^{23}_D$ = −0.83° (*c* 1.2, $CHCl_3$); IR (neat) 2957, 2878, 1716, 1458, 1238, 1005 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.07 (d, *J* = 6.0 Hz, 1H), 3.78−3.85 (m, 1H), 3.70 (dd, *J* = 5.9, 2.6 Hz, 1H), 2.20 (s, 3H), 1.60−1.64 (m, 1H), 1.45−1.51 (m, 2H), 1.13 (d, *J* = 6.0 Hz, 3H), 0.94−1.00 (m, 27H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.55−0.70 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.0, 81.5, 78.6, 67.1, 45.4, 32.2, 27.3, 23.1, 14.0, 7.0, 6.84, 6.79, 5.2, 4.9, 4.8; HRMS (ES^+) calcd for $C_{27}H_{60}O_4Si_3Na$ (M + Na) 555.3697, found 555.3683.



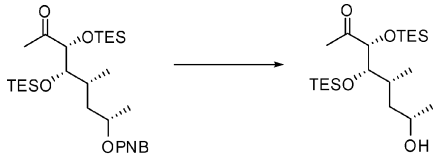
95 **96**

Alcohol 96. TES ether **95** (5.60 g, 10.5 mmol) was dissolved in a stirred solution of HOAc/THF/H_2O (107 mL, 8:8:1) at 0 °C. After 12 h, the reaction was quenched with solid $NaHCO_3$, filtered over Celite, and extracted with ether (4 × 100 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10% EtOAc/hexanes, to give alcohol **96** (3.90 g, 9.31 mmol, 89%) as a colorless oil: $[\alpha]^{23}_D$ = −30.5 (*c* 1.45, $CHCl_3$); IR (neat) 3446, 2958, 2878, 1716, 1458, 1239, 1005, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.18 (d, *J* = 5.6 Hz, 1H), 3.86−3.88 (m, 2H), 2.24 (s, 3H), 1.80−1.90 (m, 1H), 1.41−1.55 (m, 2H), 1.20 (d, *J* = 6.0 Hz, 3H), 0.97−1.05 (m, 18H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.61−0.73 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.3, 81.4, 76.4, 65.6, 43.7, 31.6, 27.8, 23.6, 15.4, 7.0, 6.8, 5.2, 4.8, 4.7; HRMS (ES^+) calcd for $C_{21}H_{46}O_4Si_2Na$ (M + Na) 441.2832, found 441.2836.



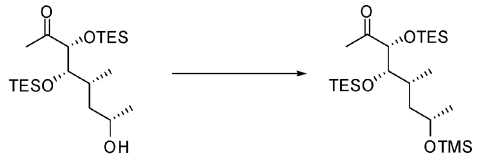
96 **97**

PNB Ester 97. To a stirred solution of alcohol **96** (600 mg, 1.43 mmol) in THF (15 mL) at 0 °C were added sequentially PPh_3 (1.50 g, 5.72 mmol), 4-nitrobenzoic acid (0.96 g, 5.74 mmol), and DEAD (0.99 g, 0.90 mL, 5.70 mmol). After 1 h, the reaction mixture was concentrated in vacuo and purified by chromatography over silica gel, eluting with 1−3% EtOAc/hexanes, to give ester **97** (670 mg, 1.18 mmol, 82%) as a colorless oil: $[\alpha]^{23}_D$ = +13.6 (*c* 1.08, $CHCl_3$); IR (neat) 2956, 2878, 1723, 1530, 1319, 1275, 1014, 721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.31 (d, *J* = 9.0 Hz, 2H), 8.23 (d, *J* = 9.0 Hz, 2H), 5.26 (m, 1H), 4.17 (d, *J* = 4.8 Hz, 1H), 3.69 (t, *J* = 4.8 Hz, 1H), 2.18 (s, 3H), 2.02−2.12 (m, 1H), 1.76 (m, 1H), 1.45−1.49 (m, 1H), 1.38 (d, *J* = 6.1 Hz, 3H), 0.93−1.02 (m, 18H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.56−0.70 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3, 164.3, 150.4, 136.1, 130.7, 123.4, 81.5, 78.2, 70.8, 40.2, 32.4, 27.9, 20.9, 14.8, 7.0, 6.8, 5.1, 4.8; HRMS (ES^+) calcd for $C_{28}H_{49}NO_7Si_2Na$ (M + Na) 590.2945, found 590.2926.



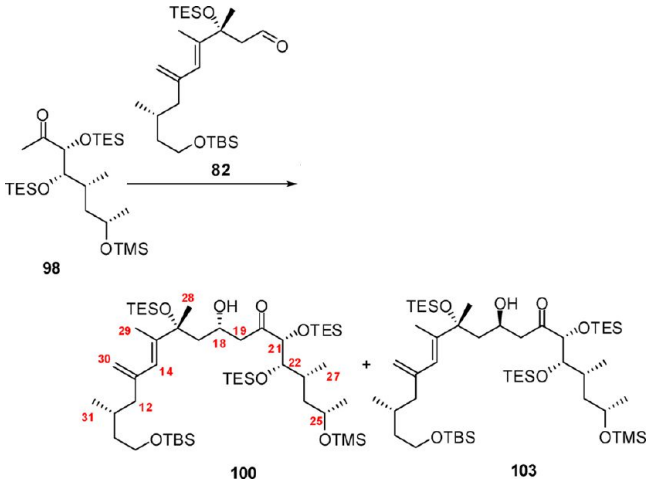
97 **SI-28**

Alcohol SI-28. To a stirred solution of ester **97** (700 mg, 1.23 mmol) in MeOH (20 mL) at 0 °C was added $Ba(OH)_2{\cdot}8H_2O$ (390 mg, 1.24 mmol). After 4 h, the reaction was quenched with satd aq NH_4Cl (10 mL) and extracted with EtOAc (4 × 20 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 15% EtOAc/hexanes, to give alcohol **SI-28** (369 mg, 0.88 mmol, 72%) as a colorless oil: $[\alpha]^{23}_D$ = −7.6 (*c* 1.2, $CHCl_3$); IR (neat) 3434, 2957, 2878, 1716, 1459, 1415, 1239, 1005, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.17 (d, *J* = 5.4 Hz, 1H), 3.81 (m, 1H), 3.69 (dd, *J* = 5.4, 3.9 Hz, 1H), 2.22 (s, 3H), 1.83 (m, 1H), 1.61−1.69 (m, 1H), 1.24−1.30 (m, 1H), 1.20 (d, *J* = 6.0 Hz, 3H), 0.94−1.04 (m, 18H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.58−0.71 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.1, 81.5, 78.1, 66.2, 43.8, 32.9, 27.6, 24.4, 15.2, 7.0, 6.8, 5.2, 4.8; HRMS (ES^+) calcd for $C_{21}H_{47}O_4Si_2$ (M + H) 419.3013, found 419.2993.



SI-28 **98**

TMS Ether 98. To a stirred solution of alcohol **SI-28** (1.90 g, 4.54 mmol) in CH_2Cl_2 (25 mL) at −78 °C were added sequentially 2,6-lutidine (1.45 g, 1.58 mL, 13.5 mmol) and TMSOTf (1.51 g, 1.23 mL, 6.81 mmol). After 30 min, the reaction was quenched with satd aq NH_4Cl (10 mL) and extracted with Et_2O (4 × 20 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10% EtOAc/hexanes, to give TMS ether **98** (2.12 g, 4.32 mmol, 95%) as a colorless oil: $[\alpha]^{23}_D$ = +14.4 (*c* 2.2, $CHCl_3$); IR (neat) 2957, 2878, 1716, 1459, 1415, 1124, 1006, 841, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.03 (d, *J* = 6.3 Hz, 1H), 3.79−3.85 (m, 1H), 3.71 (dd, *J* = 6.3, 2.4 Hz, 1H), 2.19 (s, 3H), 1.73−1.79 (m, 1H), 1.45−1.54 (m, 1H), 1.23−1.32 (m, 1H), 1.16 (d, *J* = 6.0 Hz, 3H), 0.95−1.03 (m, 18H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.58−0.70 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.2, 81.8, 78.6, 65.9, 45.3, 31.3, 26.8, 24.7, 13.2, 7.0, 6.8, 5.3, 4.8, 0.3; HRMS (ES^+) calcd for $C_{24}H_{54}O_4Si_3Na$ (M + Na) 513.3224, found 513.3204.



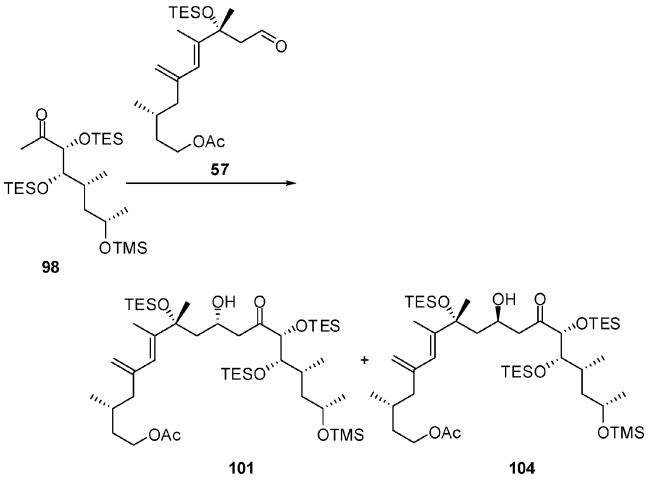
100 **103**

Aldol Adducts 100 and 103. To a stirred solution of methyl ketone **98** (312 mg, 0.64 mmol) in THF (5 mL) at −78 °C was added LDA[2] (0.765 mL, 1 M in THF). After 15 min, TMEDA (133 mg, 0.172 mL, 1.14 mmol) was added. After 5 min, the reaction was warmed up to −40 °C, followed by the addition of a precooled (−40 °C) solution of aldehyde **82** (200 mg, 0.43 mmol) in THF (5 mL) via cannula in one portion. After another 0.5 h, the reaction was quenched with satd aq NH_4Cl (10 mL) −78 °C, warmed to rt, and extracted with ether (4 × 20 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 1−1.5% EtOAc/hexanes, to give aldol adduct **100** (142 mg, 0.15 mmol, 35%) and **103** (114 mg, 0.12 mmol, 28%) as colorless oil. **100**: $[\alpha]^{23}_D$ = −12.0 (*c* 1.3, $CHCl_3$); IR (neat) 3511, 2955, 2929, 2877, 1715, 1460, 1413, 1250, 1092, 1006, 838, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.89 (s, 1H), 5.02 (s, 1H), 4.83 (s, 1H), 4.33 (m, 1H), 4.10 (d, *J* = 5.7 Hz, 1H), 3.82

dx.doi.org/10.1021/jo3026077 | J. Org. Chem. 2013, 78, 2213−2247

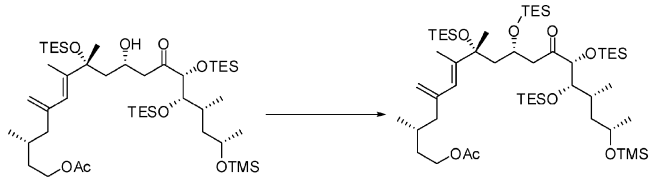
(m, 1H), 3.74 (s, 1H), 3.64−3.72 (m, 3H), 2.96 (dd, J = 17.7, 6.2 Hz, 1H), 2.60 (dd, J = 18.1, 6.4 Hz, 1H), 2.18 (dd, J = 12.8, 4.0 Hz, 1H), 1.81−1.90 (m, 2H), 1.84 (s, 3H), 1.47−1.67 (m, 4H), 1.56 (s, 3H), 1.22−1.38 (m, 3H), 1.15 (d, J = 6.0 Hz, 3H), 0.92−1.03 (m, 36H), 0.87 (d, J = 6.4 Hz, 3H), 0.80 (d, J = 6.7 Hz, 3H), 0.58−0.70 (m, 18H), 0.10 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.7, 144.7, 125.1, 114.7, 81.1, 79.4, 78.4, 65.9, 65.1, 61.5, 48.2, 47.2, 46.0, 45.0, 39.9, 31.1, 28.5,26.2, 26.0, 24.7, 19.5, 18.3, 14.7, 13.8, 7.2, 7.1, 6.9, 6.6, 5.3, 4.9, 0.4, −5.2; HRMS (ES^+) calcd for $C_{50}H_{106}O_7Si_5Na$ (M + Na) 981.6683, found 981.6646.

MTPA Esters. To a solution of **100** (5 mg, 0.005 mmol) in CH_2Cl_2 (0.5 mL) were added sequentially DMAP (6.4 mg, 0.052 mmol) and (*R*)- or (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (6.6 mg, 4.9 μL, 0.026 mmol). After 10 min, the solution was evaporated, and the residue was loaded directly onto silica gel and purified by chromatography, eluting with 2 - 10% EtOAc/hexanes, to give product (***S***)- or (***R***)- **MTPA esters** (52−61%) as colorless oils. ^{1}H NMR difference in ppm [(*S*)-Mosher ester − (*R*)-Mosher ester, $CDCl_3$, $CDCl_3$, 300 MHz NMR] H_{19} = 2.847 − 2.834 = +0.013, H_{21}: 3.996 − 3.961 = +0.035, H_{22}: 3.686 − 3.678 = +0.008, H_{25}: 3.848 − 3.818 = +0.030, H_{31}: 0.881 − 0.876 = +0.005, H_{29}: 1.888 − 1.895 = −0.007, H_{14}: 5.723 − 5.824 = −0.101, H_{28}: 4.905 − 4.925 = −0.020, H_{12}: 2.319 − 2.334 = −0.015, H_{27}: 1.130 − 1.137 = −0.007.

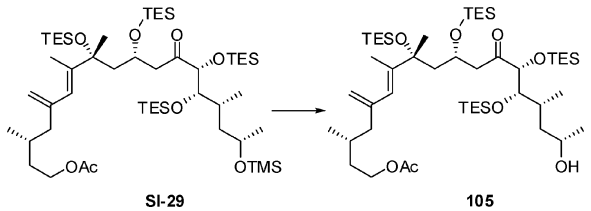


Aldol Adducts 101 and 104. *Method A (−100 °C Conditions).* To a stirred solution of methyl ketone **98** (574 mg, 1.17 mmol) in THF (6 mL) at −78 °C was added LDA[2] (1.38 mL, 1 M in THF). After 15 min, TMEDA (400 mg, 0.310 mL, 3.44 mmol) was added. After 5 min, the reaction was cooled to −100 °C, followed by the addition of a precooled (−100 °C) solution of aldehyde **57** (310 mg, 0.78 mmol) in THF (6 mL) via cannula in one portion. After another 0.5 h, the reaction was quenched with 1 M AcOH in THF (1.5 mL) at −100 °C. The reaction mixture was then warmed up to rt, diluted with satd aq NH_4Cl (10 mL) and extracted with ether (4 × 25 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 50% CH_2Cl_2/hexanes −2% EtOAc/hexanes, to give aldol adduct **104** (405 mg, 0.45 mmol, 58%) and **101** (50 mg, 0.056 mmol, 7%) as colorless oils.

Method B (−40 °C Conditions). To a stirred solution of methyl ketone **98** (37.2 mg, 0.0758 mmol) in THF (0.4 mL) at −78 °C was added LDA[2] (90 μL, 0.09 mmol, 1 M in THF). After 15 min, TMEDA (15.5 mg, 20 μL, 0.133 mmol) was added. After 5 min, the reaction was warmed to −40 °C, followed by the addition of a precooled (−40 °C) solution of aldehyde **57** (20 mg, 0.0504 mmol) in THF (0.4 mL) via cannula in one portion. After another 0.5 h, the reaction was quenched with satd aq NH_4Cl (2 mL) and extracted with ether (4 × 5 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 50% CH_2Cl_2/hexanes −2% EtOAc/hexanes, to give aldol adduct **101** (16.1 mg, 0.0181 mmol, 36%) and **104** (13.4 mg, 0.0151 mmol, 30%) as colorless oils. **101**: $[\alpha]^{23}_D$ = −9.42 (*c* 1.21, $CHCl_3$); IR (neat) 3516, 2956, 2913, 2877, 1743, 1719, 1458, 1414, 1370, 1249, 1116, 1088, 1008, 841, 742 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (s, 1H), 5.02 (s, 1H), 4.83 (s, 1H), 4.38−4.27 (m, 1H), 4.06−4.10 (m, 3H), 3.86−3.75 (m, 1H), 3.72−3.68 (m, 1H), 3.66 (s, 1H, OH), 2.96 (dd, J = 17.9, 6.2 Hz, 1H), 2.59 (dd, J = 18.0, 6.1 Hz, 1H), 2.15 (dd, J = 13.2, 5.7 Hz, 1H), 2.04 (s, 3H), 1.94−1.76 (m, 4H), 1.81 (s, 3H), 1.70−1.63 (m, 2H), 1.54 (s, 3H), 1.48−1.38 (m, 2H), 1.27−1.22 (m, 1H), 1.13 (d, J = 5.9 Hz, 3H), 1.02−0.93 (m, 27H), 0.89 (d, J = 6.3 Hz, 3H), 0.79 (d, J = 6.6 Hz, 3H), 0.59−0.69 (m, 18H), 0.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.8, 171.1, 144.3, 143.3, 124.8, 115.0, 81.0, 79.3, 78.4, 65.9, 65.0, 62.9, 48.2, 47.2, 45.8, 45.0, 35.3, 31.0, 28.7, 26.3, 24.6, 21.0, 19.3, 14.7, 13.8, 7.1, 7.0, 6.8, 6.6, 5.2, 4.9, 0.3; HRMS (ES^+) calcd for $C_{46}H_{94}O_8Si_4Na$ (M + Na) 909.5924, found 909.5895. **104**: $[\alpha]^{23}_D$ = +1.76 (*c* 1.25, $CHCl_3$); IR (neat) 3511, 2956, 2913, 2877, 1743, 1718, 1458, 1369, 1249, 1119, 1088, 1011, 841, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 (s, 1H), 5.03 (s, 1H), 4.88 (s, 1H), 4.17−4.06 (m, 4H), 3.88 (s, 1H, OH), 3.88−3.81 (m, 1H), 3.73−3.69 (m, 1H), 2.66−2.78 (m, 2H), 2.17 (dd, J = 13.5, 6.0 Hz, 1H), 2.05 (s, 3H), 1.97−1.93 (m, 1H), 1.85−1.78 (m, 1H), 1.82(s, 3H), 1.74−1.70 (m, 1H), 1.62−1.14 (m, 4H), 1.44 (s, 3H), 1.28−1.20 (m, 2H), 1.14 (d, J = 5.8 Hz, 3H), 1.02−0.94 (m, 27H), 0.91 (d, J = 6.2 Hz, 3H), 0.78 (d, J = 6.6 Hz, 3H), 0.72−0.57 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.5, 171.1, 144.5, 140.8, 125.4, 114.8, 81.3, 80.7, 78.4, 66.0, 65.7, 63.0, 47.1, 45.9, 45.0, 35.2, 31.0, 29.7, 28.7, 28.2, 24.6, 21.0, 19.4, 14.9, 13.6, 7.1, 7.0, 6.9, 6.8, 6.6, 5.2, 4.8, 0.3; HRMS (ES^+) calcd for $C_{46}H_{94}O_8Si_4Na$ (M + Na) 909.5924, found 909.5948.



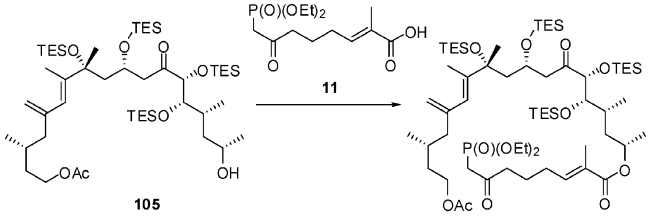
TES Ether SI-29. To a stirred solution of aldol adduct **101** (295 mg, 0.332 mmol) in CH_2Cl_2 (10 mL) at rt were added sequentially DMAP (608 mg, 4.98 mmol) and TESCl (375 mg, 0.418 mL, 2.49 mmol). After 3 h, the reaction mixture was concentrated in vacuo and purified by chromatography over silica gel, eluting with 2% EtOAc/hexanes, to give TES ether **SI-29** (290 mg, 0.289 mmol, 87%) as a colorless oil: $[\alpha]^{23}_D$ = −31.4 (*c* 0.85, $CHCl_3$); IR (neat) 2955, 2913, 2877, 1745, 1718, 1459, 1368, 1249, 1127, 1086, 1007, 841, 742 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (s, 1H), 5.03 (s, 1H), 4.92 (s, 1H), 4.20−4.08 (m, 3H), 4.04 (d, J = 5.7 Hz, 1H), 3.84−3.81 (m, 1H), 3.72−3.68 (m, 1H), 2.86 (dd, J = 18.0, 5.8 Hz, 1H), 2.72 (dd, J = 17.4, 7.2 Hz, 1H), 2.17 (dd, J = 13.8, 6.0 Hz, 1H), 2.05 (s, 3H), 1.93−1.64 (m, 5H), 1.84 (s, 3H), 1.54−1.39 (m, 3H), 1.45 (s, 3H), 1.27−1.21 (m 1H), 1.14 (d, J = 6.0 Hz, 3H), 1.03−0.87 (m, 39H), 0.78 (d, J = 6.7 Hz, 3H), 0.71−0.55 (m, 24H), 0.11 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.6, 171.1, 144.3, 143.0, 125.0, 115.1, 81.0, 78.3, 77.7, 66.1, 65.7, 63.0, 49.8, 48.5, 46.0, 44.9, 35.4, 31.0, 28.6, 27.9, 24.6, 21.0, 19.2, 14.5, 14.2, 7.2, 7.0, 6.9, 6.8, 5.2, 4.9, 0.4; HRMS (ES^+) calcd for $C_{52}H_{108}O_8Si_5Na$ (M + Na) 1023.6788, found 1023.6785.



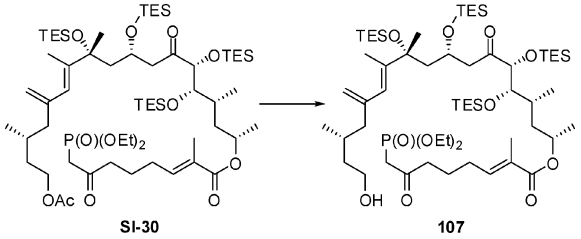
Alcohol 105. To a stirred solution of TMS ether **SI-29** (290 mg, 0.289 mmol) in THF/H_2O (6.52 mL, 8:1) at −20 °C was added HOAc (4 × 1.45 mL) in four portions every 60 min. After 5 h, the reaction was quenched with solid $NaHCO_3$, filtered over Celite, and extracted with ether (4 × 15 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5−10% EtOAc/hexanes, to give alcohol **105** (220 mg, 0.237 mmol, 82%) as a colorless oil: $[\alpha]^{23}_D$ = −31.6 (*c* 1.01, $CHCl_3$); IR (neat) 3510, 2956, 2912, 2877, 1744, 1720, 1458, 1414, 1368, 1239, 1062, 1006, 741

dx.doi.org/10.1021/jo3026077 | J. Org. Chem. 2013, 78, 2213−2247

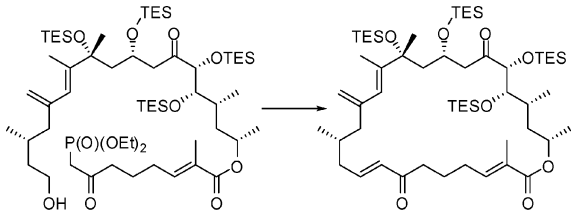
cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.78 (s, 1H), 5.02 (s, 1H), 4.90 (s, 1H), 4.22−4.08 (m, 4H), 3.81−3.77 (m, 1H), 3.69−3.66(m, 1H), 2.94 (dd, J = 18.3, 6.1 Hz, 1H), 2.78 (dd, J = 18.3, 5.7 Hz, 1H), 2.15 (dd, J = 13.1, 5.7 Hz, 1H), 2.04 (s, 3H), 1.93−1.60 (m, 6H), 1.83 (s, 3H), 1.45−1.34 (m, 2H), 1.44 (s, 3H), 1.30−1.20 (m, 1H), 1.17 (d, J = 6.0 Hz, 3H), 1.04−0.87 (m, 39H), 0.82 (d, J = 6.0 Hz, 3H), 0.72−0.56 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.8, 171.2, 144.4, 142.6, 125.2, 115.1, 81.4, 78.1, 77.7, 66.2, 65.4, 63.1, 49.7, 49.0, 45.9, 44.2, 35.3, 32.5, 28.6, 28.0, 24.3, 21.0, 19.2, 15.5, 14.6, 7.2, 7.0, 6.8, 5.3, 5.2, 4.8; HRMS (ES$^+$) calcd for $C_{49}H_{100}O_8Si_4Na$ (M + Na) 951.6393, found 951.6398.



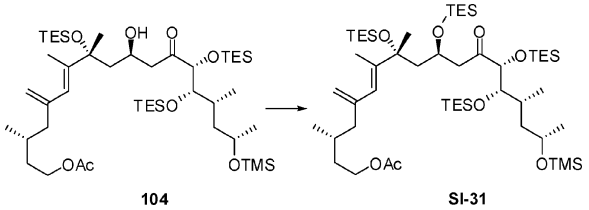
Phosphonate SI-30. To a stirred solution of acid **11** (450 mg, 1.47 mmol) in PhMe (3.2 mL) at rt were added sequentially Et_3N (149 mg, 0.204 mL, 1.47 mmol) and 2,4,6-trichlorobenzoyl chloride (346 mg, 0.222 mL, 1.47 mmol). After 12 h, the resulted solution was concentrated in vacuo. DMAP (180 mg, 1.47 mmol) was added, followed by the addition of a solution of alcohol **105** (240 m mg, 0.258 mmol) in PhMe (5.7 mL). After another 19 h, the reaction was quenched with satd aq NH_4Cl (8 mL) and extracted with EtOAc (4 × 50 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20−60% EtOAc/hexanes, to give phosponate **SI-30** (235 mg, 0.193 mmol, 78%) as a colorless oil: $[\alpha]^{23}_D$ = −23.6 (c 0.83, $CHCl_3$); IR (neat) 2955, 2912, 2877, 1734, 1716, 1458, 1369, 1241, 1056, 1019, 970, 741 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.69 (t, J = 6.3 Hz, 1H), 5.79 (s, 1H), 5.10−5.00 (m, 1H), 5.03 (s, 1H), 4.92 (s, 1H), 4.22−4.08 (m, 8H), 3.72 (dd, J = 5.1, 3.6 Hz, 1H), 3.13 (d, J = 27.8 Hz, 2H), 2.90 (dd, J = 18.0, 5.9 Hz, 1H), 2.77 (dd, J = 17.8, 6.0 Hz, 1H), 2.68 (t, J = 7.2 Hz, 2H), 2.18−2.07 (m, 3H), 2.06 (s, 3H), 1.94−1.68 (m, 9H), 1.842 (s, 3H), 1.82 (s, 3H), 1.46 (s, 3H), 1.43−1.39 (m, 2H), 1.36 (t, J = 7.0 Hz, 6H), 1.25 (d, J = 6.0 Hz, 3H), 1.03−0.92 (m, 36H), 0.90 (d, J = 6.4 Hz, 3H), 0.80 (d, J = 6.7 Hz, 3H), 0.70−0.55 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.4, 201.3, 171.1, 167.6, 144.3, 142.7, 140.5, 127.9, 125.1, 115.1, 80.9, 77.8, 77.6, 68.8, 65.6, 63.0, 62.9, 62.8, 48.7, 49.0, 45.9, 43.4, 41.7, 40.6, 35.3, 31.4, 28.6, 28.0, 27.7, 22.3, 21.0, 20.7, 19.2, 16.3, 16.2, 14.7, 14.5, 12.4, 7.2, 7.0, 6.9, 6.8, 5.3, 5.2, 4.9; HRMS (ES$^+$) calcd for $C_{62}H_{121}O_{13}Si_4PNa$ (M + Na) 1239.7520, found 1239.7458.



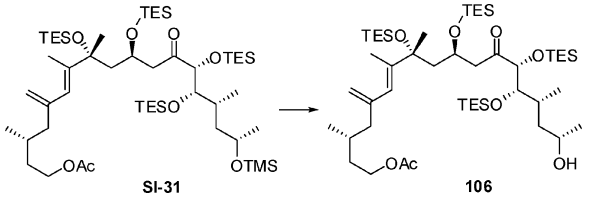
Alcohol 107. To a stirred solution of ester **SI-30** (230 mg, 0.189 mmol) in MeOH (10 mL) at rt was added $Ba(OH)_2{\cdot}8H_2O$ (66.4 mg, 0.189 mmol). After 1 h, the reaction mixture was purified directly by chromatography over silica gel, eluting with 20−60% EtOAc/hexanes, to give alcohol **107** (204 mg, 0.168 mmol, 89%) as a colorless oil: $[\alpha]^{23}_D$ = −27.0 (c 0.80, $CHCl_3$); IR (neat) 3434, 2955, 2877, 1716, 1458, 1376, 1242, 1019, 742 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.68 (t, J = 6.8 Hz, 1H), 5.78 (s, 1H), 5.11−5.00 (m, 1H), 5.00 (s, 1H), 4.86 (s, 1H), 4.19−4.05 (m, 6H), 3.73−3.66 (m, 3H), 3.07 (d, J = 27.8 Hz, 2H), 2.93 (dd, J = 18.0, 6.1 Hz, 1H), 2.78 (dd, J = 18.3, 5.7 Hz, 1H), 2.65 (t, J = 7.1 Hz, 2H), 2.22−2.11 (m, 3H), 1.92−1.59 (m, 8H), 1.81 (s, 6H), 1.43 (s, 3H), 1.42−1.39 (m, 3H), 1.33 (t, J = 7.0 Hz, 6H), 1.23 (d, J = 6.3 Hz, 3H), 1.02−0.85 (m, 39H), 0.78 (d, J = 6.5 Hz, 3H), 0.69−0.52 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.0, 201.4, 167.6, 144.8, 142.3, 140.5, 129.0, 125.5, 114.9, 80.8, 77.8, 77.7, 68.8, 65.6, 62.6, 62.5, 61.0, 49.5, 49.0, 46.2, 43.3, 41.6, 40.6, 40.0, 31.4, 28.3, 28.1, 27.7, 22.3, 20.7, 19.3, 16.3, 16.2, 14.7 (2C), 12.4, 7.2, 7.0, 6.9, 6.8, 5.2, 5.1, 4.9; HRMS (ES$^+$) calcd for $C_{60}H_{119}O_{12}Si_4PNa$(M + Na) 1197.7414, found 1197.7422.



Macrocycle 109. To a stirred solution of alcohol **107** (125 mg, 0.106 mmol) in CH_2Cl_2 (4 mL) at rt was added TPAP (45 mg, 0.127 mmol). After 0.5 h, the reaction mixture was diluted with THF (6.5 mL)/H_2O (16 μL), and $Ba(OH)_2{\cdot}8H_2O$ (3 × 74 mg, 0.636 mmol) was added in three portions every 30 min. After another 2 h, the reaction mixture was purified directly by chromatography over silica gel, eluting with 5% EtOAc/hexanes, to give macrocycle **109** (54 mg, 0.053 mmol, 50% over two steps) as colorless crystals: $[\alpha]^{23}_D$ = −27.0 (c 0.40, $CHCl_3$); IR (neat) 2955, 2925, 2876, 1727, 1708, 1675, 1458, 1417, 1260, 1127, 1064, 1009, 741 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15−7.03 (m, 1H), 6.73 (t, J = 6.9 Hz, 1H), 6.19 (d, J = 16.3 Hz, 1H), 5.78 (s, 1H), 5.00 (s, 1H), 5.05−4.97 (m, 1H), 4.82 (s, 1H), 4.18−4.09 (m, 1H), 4.11 (d, J = 5.1 Hz, 1H), 3.62−3.58 (m, 1H), 3.00−2.93 (m, 2H), 2.85−2.70 (m, 1H), 2.62−2.50 (m, 1H), 2.37−2.21 (m, 3H), 2.15−2.00 (m, 2H), 1.91−1.63 (m, 7H), 1.80 (s, 6H), 1.45−1.35 (m, 2H), 1.41 (s, 3H), 1.25 (d, J = 6.1 Hz, 3H), 1.08−0.83 (m, 39H), 0.75−0.47 (m, 27H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.2, 201.0, 167.6, 147.2, 144.7, 141.8, 140.6, 132.4, 129.2, 125.8, 115.4, 80.5, 79.6, 77.9, 68.3, 64.9, 49.7, 48.6, 46.7, 43.2, 41.1, 37.5, 31.0, 29.2, 28.9, 27.8, 22.6, 21.0, 18.8, 15.6, 13.3, 12.5, 7.3, 7.1, 7.0, 5.2, 4.8; HRMS (ES$^+$) calcd for $C_{56}H_{106}O_8Si_4Na$ (M + Na) 1041.6863, found 1041.6812.



TES Ether SI-31. To a stirred solution of aldol adduct **104** (440 mg, 0.496 mmol) in CH_2Cl_2 (20 mL) at rt were added sequentially DMAP (910 mg, 7.44 mmol) and TESCl (557 mg, 0.620 mL, 3.72 mmol). After 3 h, the reaction mixture was concentrated in vacuo and purified by chromatography over silica gel, eluting with 2% EtOAc/hexanes, to give TES ether **SI-31** (445 mg, 0.444 mmol, 90%) as a colorless oil: $[\alpha]^{23}_D$ = −20.0 (c 0.24, $CHCl_3$); IR (neat) 2955, 2912, 2877, 1744, 1717, 1458, 1249, 1127, 1069, 1008, 840, 742 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81 (s, 1H), 5.00 (s, 1H), 4.85 (s, 1H), 4.43−4.30 (m, 1H), 4.16−4.03 (m, 3H), 3.88−3.78 (m, 1H), 3.69−3.72 (m, 1H), 2.88 (dd, J = 17.4, 4.8 Hz, 1H), 2.73 (dd, J = 17.4, 7.2 Hz, 1H), 2.13 (dd, J = 13.8, 6.0 Hz, 1H), 2.04 (s, 3H), 1.82−1.94 (m, 3H), 1.79 (s, 3H), 1.64−1.75 (m, 3H), 1.46 (s, 3H), 1.39−1.51 (m, 2H), 1.20−1.28 (m, 1H), 1.14 (d, J = 6.0 Hz, 3H), 0.84−1.03 (m, 39H), 0.77 (d, J = 6.6 Hz, 3H), 0.56−0.71 (m, 24H), 0.11 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.4, 171.1, 144.3, 143.8, 124.3, 114.8, 81.1, 78.4, 77.3, 66.1 (2C), 62.9, 50.3, 48.7, 45.9, 45.2, 35.2, 30.7, 28.7, 26.9, 24.7, 21.0, 19.3, 14.8, 13.8, 7.2, 7.0, 6.9, 6.7, 5.4, 5.3, 5.0, 0.3; HRMS (ES$^+$) calcd for $C_{52}H_{108}O_8Si_5Na$ (M + Na) 1023.6788, found 1023.6737.



Alcohol 106. To a stirred solution of TMS ether **SI-31** (432 mg, 0.43 mmol) in THF/H_2O (9 mL, 8:1) at −20 °C was added HOAc

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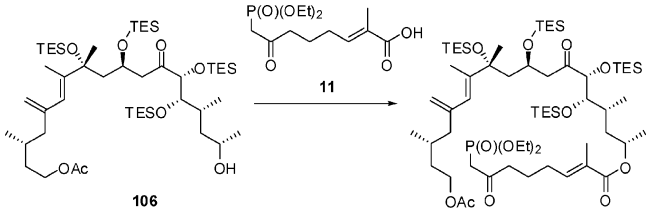
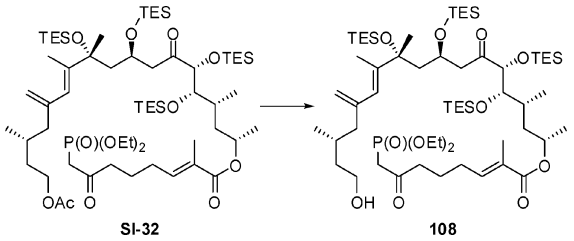
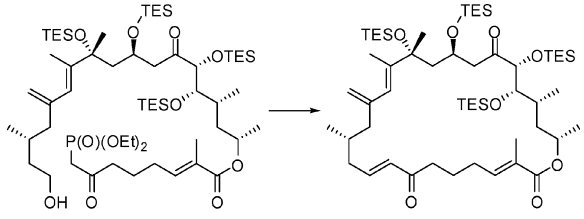
(8 mL). After 5 h, the reaction was quenched with solid $NaHCO_3$, filtered over Celite and extracted with ether (4 × 20 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5−10−20% EtOAc/hexanes, to give alcohol **106** (338 mg, 0.36 mmol, 85%) as a colorless oil: $[\alpha]^{23}_D$ = −20.8 (*c* 1.01, $CHCl_3$); IR (neat) 3503, 2955, 2912, 2877, 1744, 1720, 1458, 1414, 1367, 1239, 1007, 741 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.85 (s, 1H), 5.02 (s, 1H), 4.86 (s, 1H), 4.50−4.40 (m, 1H), 4.18−4.03 (m, 3H), 3.85−3.77 (m, 1H), 3.67 (t, *J* = 5.0 Hz, 1H), 2.74−2.86 (m, 2H), 2.19 (br, OH), 2.14 (dd, *J* = 13.6, 6.3 Hz, 1H), 2.06 (s, 3H), 1.89−1.96 (m, 2H), 1.80 (s, 3H), 1.66−1.85 (m, 5H), 1.45 (s, 3H), 1.39−1.42 (m, 1H), 1.19 (d, *J* = 6.0 Hz, 3H), 1.10−1.22 (m, 1H), 0.95−1.05 (m, 36H), 0.90 (d, *J* = 6.4 Hz, 3H), 0.85 (d, *J* = 6.4 Hz, 3H), 0.59−0.72 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4, 171.2, 144.3, 143.5, 124.4, 115.0, 82.1, 78.5, 77.3, 66.0, 65.9, 63.0, 50.0, 48.0, 45.9, 44.4, 35.2, 32.3, 28.7, 27.3, 24.2, 21.0, 19.3, 15.4, 15.0, 7.3, 7.1, 7.0, 6.9, 6.8, 5.3, 5.2, 4.9; HRMS (ES^+) calcd for $C_{49}H_{100}O_8Si_4Na$ (M + Na) 951.6393, found 951.6418.



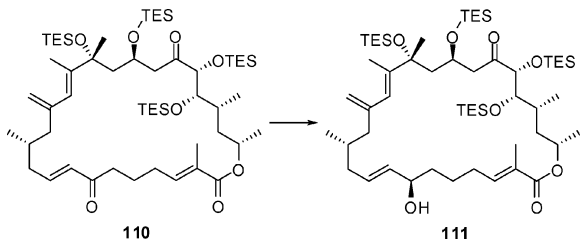
Phosphonate SI-32. To a stirred solution of acid **11** (837 mg, 2.73 mmol) in PhMe (6 mL) at rt were added sequentially Et_3N (276 mg, 0.379 mL, 2.73 mmol) and 2,4,6-trichlorobenzoyl chloride (641 mg, 0.411 mL, 2.73 mmol). After 12 h, the resulted solution was concentrated in vacuo. DMAP (333 mg, 2.73 mmol) was added, followed by the addition of a solution of alcohol **106** (445 mg, 0.479 mmol) in PhMe (10.5 mL). After another 19 h, the reaction was quenched with satd aq NH_4Cl (15 mL) and extracted with EtOAc (4 × 50 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20−60% EtOAc/hexanes, to give phosphonate **SI-32** (450 mg, 0.100 mmol, 77%) as a colorless oil: $[\alpha]^{23}_D$ = −20.3 (*c* 1.23, $CHCl_3$); IR (neat) 2955, 2913, 2877, 1740, 1716, 1458, 1368, 1243, 1056, 1019, 968, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.69 (t, *J* = 6.4 Hz, 1H), 5.82 (s, 1H), 5.10−5.02 (m, 1H), 5.01 (s, 1H), 4.84 (s, 1H), 4.42−4.32 (m, 1H), 4.21−4.02 (m, 7H), 3.76−3.68 (m, 1H), 3.12 (d, *J* = 22.8 Hz, 2H), 2.85 (dd, *J* = 17.4, 4.1 Hz, 1H), 2.65−2.76 (m, 3H), 2.12−2.22 (m, 2H), 2.10−2.04 (m, 1H), 2.05 (s, 3H), 1.58−1.93 (m, 10H), 1.82 (s, 3H), 1.79 (s, 3H), 1.45 (s, 3H), 1.43−1.39 (m, 1H), 1.35 (t, *J* = 7.1 Hz, 6H), 1.24 (d, *J* = 5.9 Hz, 3H), 0.87−1.03 (m, 39H), 0.79 (d, *J* = 6.6 Hz, 3H), 0.55−0.68 (m, 24H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.3, 201.4, 171.1, 167.6, 144.3, 143.7, 140.5, 129.0, 124.4, 114.9, 81.1, 77.9, 77.34, 68.8, 66.2, 62.9, 62.6, 62.5, 50.3, 49.0, 45.9, 43.3, 41.6, 40.8, 35.2, 31.1, 28.7, 27.7, 26.9, 22.3, 21.0, 20.7, 19.3, 16.3, 16.2, 14.8, 14.3, 12.4, 7.2, 7.1, 7.0, 6.9, 6.7, 5.3, 5.2, 5.0; HRMS (ES^+) calcd for $C_{62}H_{121}O_{13}Si_4PNa$ (M + Na) 1239.7520, found 1239.7563.



Alcohol 108. To a stirred solution of ester **SI-32** (170 mg, 0.140 mmol) in MeOH (0.5 mL) at rt was added a saturated solution of $Ba(OH)_2{\cdot}8H_2O$ in MeOH (6.0 mL). After 20 min, the reaction mixture was purified directly by chromatography over silica gel, eluting with 20−60% EtOAc/hexanes, to give alcohol **108** (150 mg, 0.127 mmol, 91%) as a colorless oil: $[\alpha]^{23}_D$ = −20.3 (*c* 0.60, $CHCl_3$); IR (neat) 3440, 2955, 2877, 1716, 1458, 1242, 1019, 969, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.69 (t, *J* = 6.2 Hz, 1H), 5.82 (s, 1H), 5.10−5.03 (m, 1H), 5.00 (s, 1H), 4.83 (s, 1H), 4.42−4.31 (m, 1H), 4.20−4.08 (m, 5H), 3.63−3.74 (m, 3H), 3.12 (d, *J* = 22.8 Hz, 2H), 2.78−2.72 (m, 2H), 2.66 (t, *J* = 7.1 Hz, 2H), 2.04−2.19 (m, 3H), 1.89−1.61 (m, 10H), 1.81 (s, 3H), 1.78 (s, 3H), 1.44 (s, 3H), 1.43−1.38 (m, 1H), 1.35 (t, *J* = 7.1 Hz, 6H), 1.24 (d, *J* = 5.9 Hz, 3H), 1.03−0.92 (m, 36H), 0.87 (d, *J* = 6.4 Hz, 3H), 0.79 (d, *J* = 6.6 Hz, 3H), 0.55−0.71 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.5, 201.5, 167.7, 144.6, 143.5, 140.6, 129.0, 124.7, 114.7, 81.2, 78.0, 68.8, 66.1, 62.6, 62.5, 61.1, 50.3, 49.1, 46.1, 43.5, 43.4, 41.8, 40.9, 39.8, 31.1, 28.5, 27.8, 27.1, 22.3, 20.8, 19.5, 16.4, 16.3, 14.9, 14.2, 12.4, 7.3, 7.1, 7.0, 6.9, 6.8, 5.3, 5.2, 5.0; HRMS (ES^+) calcd for $C_{60}H_{119}O_{12}Si_4PNa$ (M + Na) 1197.7414, found 1197.7423.



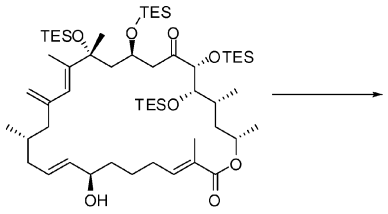
Macrocycle 110. To a stirred solution of alcohol **108** (170 mg, 0.144 mmol) in CH_2Cl_2 (4 mL) at rt was added TPAP (61 mg, 0.173 mmol). After 0.5 h, the reaction mixture was diluted with CH_2Cl_2 (3 mL)/CH_3CN (7 mL) and Hunig's base (297 mg, 0.4 mL, 2.29 mmol) was added, followed by the addition of LiCl (20 mg, 0.476 mmol). After 24 h, the reaction mixture was purified directly by chromatography over silica gel, eluting with 5% EtOAc/hexanes, to give macrocycle **110** (75 mg, 0.073 mmol, 51% over two steps) as a colorless oil: $[\alpha]^{23}_D$ = −10.0 (*c* 0.62, $CHCl_3$); IR (neat) 2955, 2913, 2876, 1708, 1674, 1457, 1417, 1375, 1240, 1124, 1072, 1008, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.88 (dt, *J* = 16.2, 7.4 Hz, 1H), 6.72 (t, *J* = 8.0 Hz, 1H), 6.10 (d, *J* = 16.0 Hz, 1H), 5.82 (s, 1H), 5.08−4.99 (m, 1H), 5.02 (s, 1H), 4.87 (s, 1H), 4.30−4.22 (m, 1H), 4.01 (d, *J* = 6.4 Hz, 1H), 3.58 (dd, *J* = 6.4, 2.7 Hz, 1H), 2.86 (dd, *J* = 17.4, 8.6 Hz, 1H), 2.77 (dd, *J* = 15.4, 6.0 Hz, 1H), 2.62−2.54 (m, 2H), 2.36−2.19 (m, 4H), 2.14 (dd, *J* = 17.4, 8.6 Hz, 1H), 2.05−1.76 (m, 7H), 1.80 (s, 3H), 1.79 (s, 3H), 1.70−1.60 (m, 1H), 1.57−1.51 (m, 1H), 1.41 (s, 3H), 1.25 (d, *J* = 6.2 Hz, 3H), 1.05−0.93 (m, 36H), 0.84 (d, *J* = 6.6 Hz, 3H), 0.76 (d, *J* = 6.6 Hz, 3H), 0.73−0.58 (m, 24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.1. 201.0, 167.6, 147.3, 147.1, 144.0, 142.8, 140.8, 132.4, 129.3, 124.7, 115.1, 80.6, 77.4 (2C), 68.5, 65.1, 50.6, 49.0, 46.1, 41.7, 40.2, 37.2, 31.3, 30.8, 27.8, 27.4, 23.1, 21.0, 19.7, 15.3, 12.8, 12.5, 7.3, 7.1, 7.0, 6.9, 5.3, 5.2, 4.9; HRMS (ES^+) calcd for $C_{56}H_{106}O_8Si_4Na$ (M + Na) 1041.6863, found 1041.6824.



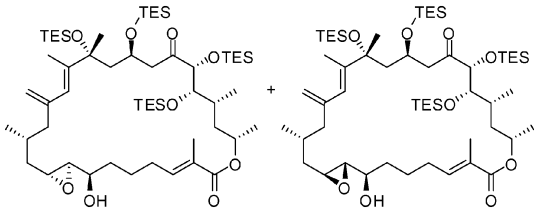
Allylic Alcohol 111. To a stirred solution of macrocycle **110** (107 mg, 0.105 mmol) in CH_2Cl_2 (5.4 mL) at −20 °C were added sequentially (*S*)-CBS (0.42 mL, 0.42 mmol, 1 M in PhMe) and $BH_3{\cdot}DMS$ (0.84 mL, 0.84 mmol, 1 M in THF). After 45 min, the reaction was quenched with MeOH (0.3 mL), diluted with aq $NaHCO_3$ (5 mL), and extracted with Et_2O (3 × 8 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 3−6% EtOAc/hexanes, to give allylic alcohol **111** (72 mg, 0.0704 mmol, 67%) as a colorless oil: $[\alpha]^{23}_D$ = −16.3 (*c* 0.30, $CHCl_3$); IR (neat) 3431, 2954, 2913, 2876, 1708, 1674, 1458, 1414, 1376, 1241, 1128, 1073, 1009, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.80 (t, *J* = 8.0 Hz, 1H), 5.89 (s, 1H), 5.63−5.52 (m, 1H), 5.45 (dd, *J* = 15.4, 7.5 Hz, 1H), 5.10−5.00

dx.doi.org/10.1021/jo3026077 | J. Org. Chem. 2013, 78, 2213−2247

(m, 1H), 4.98 (s, 1H), 4.82 (s, 1H), 4.32–4.20 (m, 1H), 4.19–4.09 (m, 1H), 4.04 (d, J = 6.2 Hz, 1H), 3.57 (dd, J = 6.2, 2.5 Hz, 1H), 2.87 (dd, J = 17.0, 9.0 Hz, 1H), 2.49 (d, J = 16.8 Hz, 1H), 2.28–2.20 (m, 2H), 2.13–1.98 (m, 3H), 1.90–1.61 (m, 9H), 1.86 (s, 3H), 1.75 (s, 3H), 1.55–1.46 (m, 2H), 1.39 (s, 3H), 1.26 (d, J = 6.0 Hz, 3H), 1.06–0.94 (m, 36H), 0.82 (d, J = 6.4 Hz, 3H), 0.73–0.60 (m, 27H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.5, 167.8, 144.6, 142.0, 141.3, 134.6, 130.8, 128.2, 125.4, 114.4, 80.6, 78.0, 72.9, 68.4, 65.2, 50.3, 49.2, 45.4, 41.8, 39.7, 36.8, 31.3, 30.4, 28.8, 28.2, 24.0, 20.9, 19.6, 15.4, 12.5, 12.4, 7.3, 7.1, 7.0, 5.3, 5.2, 4.9; HRMS (ES$^+$) calcd for $C_{56}H_{108}O_8Si_4Na$ (M + Na) 1043.7019, found 1043.7052.

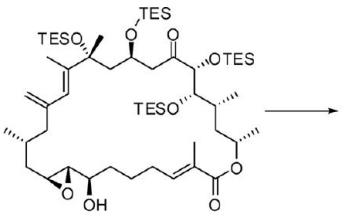


111

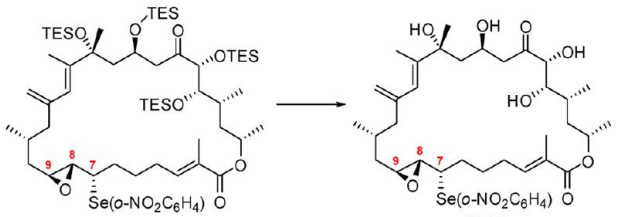


112 113

Epoxide 113 and 112. To a stirred solution of allylic alcohol **111** (70 mg, 0.0685 mmol) in CH_2Cl_2 (6 mL) at −20 °C were added sequentially 4 Å MS (50 mg), TBHP (37 μL, 0.206 mmol, 5.5 M in decane), and Ti(O-*i*-Pr)$_4$ (23.3 mg, 24 μL, 0.082 mmol). After 5 h, the reaction was quenched with aq $NaHCO_3$ (3 mL) and extracted with Et_2O (3 × 7 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 6–10% EtOAc/hexanes, to give epoxide **113** (35 mg, 0.0342 mmol, 50%) and epoxide **112** (17 mg, 0.0166 mmol, 24%) as colorless oils. **113**: $[\alpha]^{23}_D$ = −29.0 (c 0.42, $CHCl_3$); IR (neat) 3431, 2954, 2923, 2876, 1708, 1647, 1458, 1414, 1377, 1242, 1128, 1073, 1009, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (t, J = 8.0 Hz, 1H), 5.88 (s, 1H), 5.05–4.98 (m, 1H), 5.01 (s, 1H), 4.86 (s, 1H), 4.30–4.20 (m, 1H), 4.05 (d, J = 6.1 Hz, 1H), 3.59 (dd, J = 6.1, 2.0 Hz, 1H), 3.52–3.43 (m, 1H), 3.22–3.15 (m, 1H), 2.91 (dd, J = 16.3, 9.1 Hz, 1H), 2.70 (dd, J = 6.0, 2.0 Hz, 1H), 2.44–2.25 (m, 3H), 2.18 (dd, J = 13.0, 5.6 Hz, 1H), 2.10–1.63 (m, 12H), 1.87 (s, 3H), 1.78 (s, 3H), 1.41 (s, 3H), 1.26 (d, J = 6.0 Hz, 3H), 1.15–1.09 (m, 1H), 1.07–0.89 (m, 36H), 0.80 (d, J = 6.4 Hz, 3H), 0.76–0.59 (m, 27H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4, 167.7, 144.0, 142.1, 141.4, 128.6, 125.0, 114.9, 80.8, 78.2, 77.5, 71.8, 68.3, 65.6, 62.8, 56.4, 50.6, 49.1, 46.6, 42.1, 38.9, 33.1, 30.1, 29.4, 28.8, 28.3, 23.7, 21.0, 19.8, 15.5, 12.5, 12.4, 7.3, 7.1, 7.0, 5.3, 5.2, 5.0; HRMS (ES$^+$) calcd for $C_{56}H_{108}O_9Si_4Na$ (M + Na) 1059.6968, found 1059.7009. **112**: $[\alpha]_D$ = −26.2 (c 0.60, $CHCl_3$); IR (neat) 3482, 2954, 2923, 2876, 1708, 1458, 1414, 1377, 1240, 1128, 1008, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (t, J = 7.7 Hz, 1H), 5.87 (s, 1H), 5.05–4.98 (m, 1H), 4.99 (s, 1H), 4.84 (s, 1H), 4.30–4.20 (m, 1H), 4.09 (d, J = 5.9 Hz, 1H), 3.75–3.69 (m, 1H), 3.57 (dd, J = 5.6, 3.2 Hz, 1H), 2.91–2.78 (m, 3H), 2.68–2.60 (m, 2H), 2.38–2.20 (m, 3H), 2.07 (dd, J = 12.9, 6.2 Hz, 1H), 1.93–1.62 (m, 10H), 1.85 (s, 3H), 1.76 (s, 3H), 1.50–1.44 (m, 2H), 1.40 (s, 3H), 1.25 (d, J = 6.0 Hz, 3H), 1.05–0.93 (m, 39H), 0.74–0.59 (m, 27H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.6, 167.8, 144.1, 142.5, 141.5, 128.4, 124.9, 114.9, 81.0, 78.2, 77.4, 69.0, 68.4, 65.5, 60.7, 54.9, 50.3, 49.2, 46.3, 41.7, 38.4, 33.3, 30.7, 30.3, 29.0, 27.9, 23.7, 21.0, 20.0, 15.3, 13.2, 12.4, 7.3, 7.1, 7.0, 6.9, 5.3, 5.2, 4.9; HRMS (ES$^+$) calcd for $C_{56}H_{108}O_9Si_4Na$ (M + Na) 1059.6968, found 1059.7009.



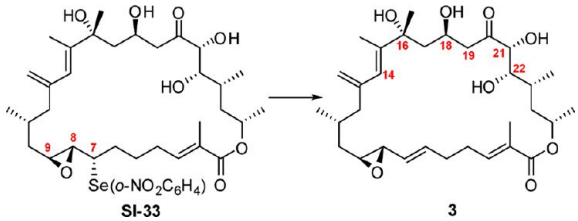
113



115 SI-33

Selenide 115. To a stirred solution of epoxide **113** (42 mg, 0.0405 mmol) in THF (2 mL) at rt were added sequentially *o*-$NO_2C_6H_4SeCN$ (184 mg, 0.809 mmol) and PBu_3 (164 mg, 202 μL, 0.809 mmol). After 5 h, the reaction mixture was concentrated in vacuo purified by chromatography over silica gel, eluting with hexanes then with 4% EtOAc/hexanes, to give crude selenide **115** (30 mg) as a yellow oils which was used directly in next step without further purification.

Polyol SI-33. To a stirred solution of selenide **115** (30 mg) in THF/DMF/H_2O (10:1:0.02, 1.8 mL/180 μL/3.6 μL) at 0 °C was added TAS-F (33.7 mg, 0.123 mmol). The reaction mixture was then warmed to rt. After 2 h, the reaction mixture was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10–65% EtOAc/hexanes, to give polyol **SI-33** (15 mg, 0.0196 mmol, 48% over two steps) as a yellow solid: $[\alpha]^{23}_D$ = −20.1 (c 0.12, $CHCl_3$); IR (neat) 3447, 2925, 2854, 1701, 1520, 1456, 1334, 1273, 759, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 8.3 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.56 (t, J = 8.1 Hz, 1H), 7.38 (t, J = 8.1 Hz, 1H), 6.81 (t, J = 6.4 Hz, 1H), 6.05 (s, 1H), 5.10–5.00 (m, 1H), 5.02 (s, 1H), 4.80 (s, 1H), 4.38 (d, J = 3.6 Hz, 1H), 4.18 (s, 1H), 4.17–4.11 (m, 1H), 4.07 (t, J = 9.6 Hz, 1H), 3.58 (t, J = 8.6 Hz, 1H), 3.18–3.10 (m, 1H), 2.97 (d, J = 8.1 Hz, 1H), 2.79 (dd, J = 12.8, 10.1 Hz, 1H), 2.37–2.28 (m, 1H), 2.40–2.30 (m, 1H), 2.22–2.04 (m, 3H), 1.94–1.76 (m, 7H), 1.83 (s, 3H), 1.79 (s, 3H), 1.72–1.62 (m, 3H), 1.38 (s, 3H), 1.31 (d, J = 6.1 Hz, 3H), 1.25–1.19 (m, 2H), 1.07 (d, J = 6.4 Hz, 3H), 0.83 (d, J = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1, 167.6, 149.6, 144.4, 141.0 (2C), 133.1, 132.5, 128.9, 128.3, 127.0, 126.0, 125.1, 115.0, 78.3, 77.5, 75.3, 68.7, 68.3, 62.3, 59.3, 46.7, 45.7, 45.5, 43.8, 40.4, 40.0, 32.8, 31.6, 29.1, 29.0, 28.1, 26.1, 21.2, 17.7, 16.2, 15.3, 12.5; HRMS (ES$^+$) calcd for $C_{38}H_{55}NO_{10}NaSe$ (M + Na) 788.2889, found 788.2859.

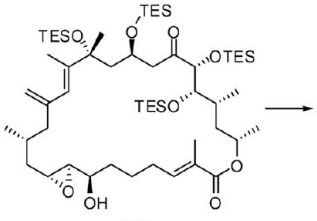


SI-33 3

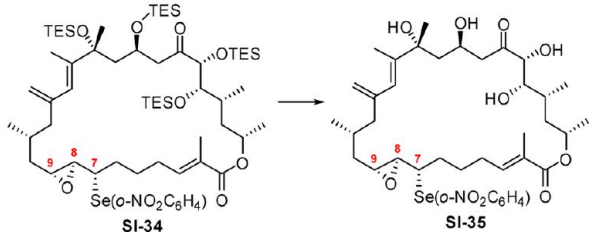
Proposed Structure of Amphidinolide B$_2$ (3). To a stirred solution of selenide **SI-33** (6.0 mg, 0.00784 mmol) in CH_2Cl_2 (1.2 mL) at rt were added sequentially $NaHCO_3$ (60 mg, 0.714 mmol) and TMSOOTMS (41.7 mg, 50 μL, 0.233 mmol). After 1.5 h, the yellow color vanished and the reaction mixture was purified by preparative TLC, eluting with 60% EtOAc/hexanes, to give allylic epoxide **3** (3.0 mg, 0.00533 mmol, 68%): $[\alpha]^{23}_D$ = −52.3 (c 0.21, $CHCl_3$); IR (neat) 3446, 2923, 2853, 1701, 1457, 1273, 1120 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (t, J = 6.4 Hz, 1H), 6.06 (s, 1H), 5.92 (ddd, J = 15.0, 8.9, 4.4 Hz, 1H), 5.20 (dd, J = 15.5, 8.8 Hz, 1H), 5.11–5.07 (m, 1H), 5.07 (s, 1H), 4.86 (s, 1H), 4.28 (d, J = 5.4, 1H), 4.14 (s, OH), 4.14–4.09 (m, 1H), 3.73 (d, J = 5.6 Hz, OH), 3.69 (t, J = 9.5 Hz, 1H), 3.50 (d, J = 6.8 Hz, 1H), 3.23 (dd, J = 8.7, 2.2 Hz, 1H), 3.08–3.03 (m, 2H), 2.95

dx.doi.org/10.1021/jo3026077 | J. Org. Chem. 2013, 78, 2213–2247

(d, J = 9.2 Hz, OH), 2.53−2.45 (m, 1H), 2.45−2.36 (m, 1H), 2.28 (dd, J = 13.2, 1.8 Hz, 1H), 2.17−2.12 (m, 3H), 1.97−1.93 (m, 4H), 1.85 (s, 3H), 1.82−1.79 (m, 1H), 1.80 (s, 3H), 1.78−1.75 (m, 1H), 1.64−1.60 (m, 1H), 1.34 (s, 3H), 1.31 (d, J = 6.1 Hz, 3H), 1.17−1.12 (m, 1H), 1.03 (d, J = 6.7 Hz, 3H), 0.98 (d, J = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.5, 167.7, 144.7, 141.6, 139.5, 136.3, 128.4, 128.3, 124.9, 114.6, 78.1, 75.6, 69.28, 68.23, 61.45, 59.5, 47.1, 46.4, 44.1, 40.0, 39.4, 33.3, 31.0, 29.3, 28.3, 26.7, 21.2, 17.5, 15.9, 15.2, 12.6; HRMS (ES$^+$) calcd for $C_{32}H_{50}O_8Na$ (M + Na) 585.3403, found 585.3390.



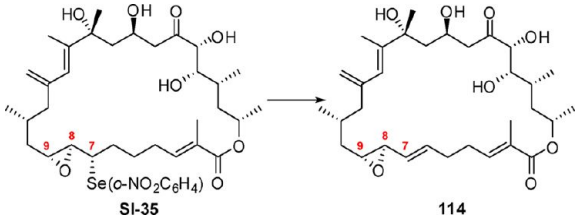
112



SI-34 SI-35

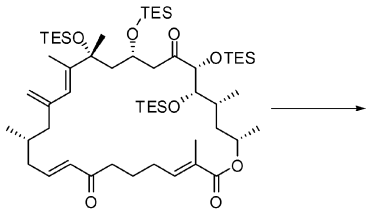
Selenide SI-34. To a stirred solution of epoxide **112** (12 mg, 0.0116 mmol) in THF (0.7 mL) at rt were added sequentially o-$NO_2C_6H_4SeCN$ (53 mg, 0.232 mmol) and PBu_3 (47 mg, 58 μL, 0.232 mmol). After 0.5 h, the reaction mixture was concentrated in vacuo purified by chromatography over silica gel, eluting with Hexanes then with 4% EtOAc/hexanes, to give crude selenide **SI-34** (10.6 mg) as a yellow oil which was used directly in next step without further purification.

Polyol SI-35. To a stirred solution of selenide **SI-34** (10.6 mg) in THF/DMF/H_2O (10:1:0.02, 1.0 mL/100 μL/2.0 μL) at 0 °C was added TAS-F (12 mg, 0.0434 mmol). The reaction mixture was then warmed to rt. After 2 h, the reaction mixture was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10−65% EtOAc/hexanes, to give polyol **SI-35** (6.2 mg, 0.00811 mmol, 70% over two steps) as a yellow oil: $[\alpha]_D$ = −47.0 (c 0.30, $CHCl_3$); IR (neat) 3446, 2925, 2854, 1701, 1515, 1456, 1332, 1271, 757, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.1 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.55 (t, J = 7.4 Hz, 1H), 7.42 (t, J = 7.8 Hz, 1H), 6.85 (t, J = 6.3 Hz, 1H), 6.02 (s, 1H), 5.11−5.05 (m, 1H), 5.04 (s, 1H), 4.81 (s, 1H), 4.38 (d, J = 3.6 Hz, 1H), 4.32−4.25 (m, 1H), 4.17−4.12 (m, 1H), 3.89 (d, J = 4.6 Hz, 1H), 3.72−3.65 (m, 1H), 3.62−3.55 (m, 1H), 3.10−3.05 (m, 2H), 2.84 (dd, J = 14.8, 9.2 Hz, 1H), 2.52 (dd, J = 14.8, 2.5 Hz, 1H), 2.38 (d, J = 9.5 Hz, 1H), 2.40−2.20 (m, 3h), 1.97−1.74 (m, 8H), 1.83 (s, 3H), 1.76 (s, 3H), 1.70−1.60 (m, 3H), 1.36 (s, 3H), 1.33 (d, J = 6.1 Hz, 3H), 1.06 (d, J = 6.7 Hz, 3H), 0.87 (d, J = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.0, 167.7, 147.7, 144.6, 141.3, 140.9, 133.7, 132.3, 130.1, 128.6, 126.5, 126.1, 125.6, 115.1, 78.0, 77.0, 75.5, 69.1, 67.7, 60.6, 58.4, 45.7, 45.6, 43.7, 43.1, 40.4, 39.2, 33.8, 30.3, 29.5, 28.9, 28.0, 27.0, 21.2, 19.7, 16.3, 15.2, 12.5; HRMS (ES$^+$) calcd for $C_{38}H_{55}NO_{10}NaSe$ (M + Na) 788.2889, found 788.2897.

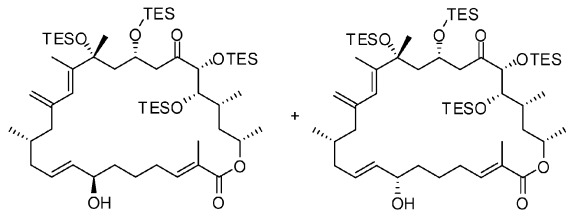


SI-35 114

Allylic Epoxide 114. To a stirred solution of selenide **SI-35** (2.5 mg, 0.00327 mmol) in CH_2Cl_2 (0.5 mL) at rt were added sequentially $NaHCO_3$ (20 mg, 0.238 mmol) and TMSO−OTMS (19.1 mg, 23 μL, 0.107 mmol). After 1.5 h, the yellow color vanished and the reaction mixture was purified by preparative TLC, eluting with 60% EtOAc/hexanes, to give allylic epoxide **114** (1.2 mg, 0.00213 mmol, 65%): $[\alpha]_D$ = −27.5 (c 0.12, $CHCl_3$); IR (neat) 3443, 2924, 2852, 1703, 1457, 1379, 1272, 1118 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.71−6.63 (m, 1H), 6.08 (s, 1H), 5.88−5.78 (m, 1H), 5.26 (dd, J = 15.1, 8.4 Hz, 1H), 5.12−5.05 (m, 1H), 5.05 (s, 1H), 4.84 (s, 1H), 4.29 (dd, J = 5.7, 1.5 Hz, 1H), 4.30−4.20 (m, 1H), 3.71 (t, J = 7.9 Hz, 1H), 3.66 (d, J = 5.7 Hz, 1H), 3.19 (d, J = 9.6 Hz, 1H), 3.12 (dd, J = 8.6, 2.2 Hz, 1H), 3.01−2.87 (m, 2H), 2.46 (dd, J = 14.4, 2.1 Hz, 1H), 2.36−2.20 (m, 5H), 2.00−1.74 (m, 6H), 1.83 (s, 3H), 1.77 (s, 3H), 1.60−1.55 (m, 1H), 1.35 (s, 3H), 1.33−1.28 (m, 1H), 1.30 (d, J = 6.1 Hz, 3H), 1.18−1.11 (m, 1H), 1.03 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.9, 167.5, 144.9, 141.6, 140.3, 136.4, 128.7, 128.6, 125.7, 115.0, 78.2, 76.6, 75.9, 68.5, 68.2, 60.2, 60.0, 45.8, 45.1, 43.8, 39.4, 39.3, 33.6, 31.0, 30.3, 28.5, 27.0, 21.2, 20.0, 15.8, 15.2, 12.7; HRMS (ES$^+$) calcd for $C_{32}H_{50}O_8Na$ (M + Na) 585.3403, found 585.3394.



109



118 SI-36

Allylic Alcohols 118 and 119. To a stirred solution of macrocycle **109** (50 mg, 0.049 mmol) in CH_2Cl_2 (2.3 mL) at −30 °C were added sequentially (*S*)-CBS (0.196 mL, 0.196 mmol, 1 M in PhMe) and BH_3·DMS (0.3934 mL, 0.393 mmol, 1 M in THF). After 45 min, the reaction was quenched with MeOH (0.3 mL), diluted with aq $NaHCO_3$ (3 mL), and extracted with Et_2O (4 × 6 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 3−6% EtOAc/hexanes, to give allylic alcohol **118** (29 mg, 0.028 mmol, 58%) and **SI-36** (8 mg, 0.0078 mmol, 16%) as colorless oils. **118**: $[\alpha]^{23}_D$ = −23.6 (c 0.25, $CHCl_3$); IR (neat) 3503, 2954, 2911, 2876, 1707, 1458, 1376, 1240, 1128, 1007, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (t, J = 6.9 Hz, 1H), 5.76 (s, 1H), 5.70−5.62 (m, 1H), 5.53 (dd, J = 13.2, 6.3 Hz, 1H), 5.00−4.95 (m, 1H), 4.98 (s, 1H), 4.84 (s, 1H), 4.15−4.04 (m, 3H), 3.58 (dd, J = 5.7, 2.4 Hz, 1H), 2.93 (dd, J = 18.4, 6.2 Hz, 1H), 2.78 (dd, J = 18.4, 6.0 Hz, 1H), 2.28−2.22 (m, 2H), 2.18−2.10 (m, 2H), 2.08−1.99 (m, 1H), 1.89−1.57 (m, 9H), 1.84 (s, 3H), 1.81 (s, 3H), 1.48−1.40 (m, 2H), 1.45 (s, 3H), 1.26 (d, J = 6.1 Hz, 3H), 1.07−0.91 (m, 36H), 0.88 (d, J = 6.6 Hz, 3H), 0.74−0.53 (m, 27H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.8, 167.8, 145.5, 142.5 (2C), 134.9, 129.7, 127.9, 125.7, 114.9, 80.6, 79.2, 77.9, 71.9, 68.2, 65.3, 49.6, 49.2, 45.6, 42.2, 39.4, 37.0, 31.8, 29.8, 29.0, 28.1, 23.6, 21.0, 19.9, 14.7, 12.7, 12.4, 7.2, 7.1, 7.0, 6.9, 6.8, 5.3, 5.2, 4.7; HRMS (ES$^+$) calcd for $C_{56}H_{108}O_8Si_4Na$ (M + Na) 1043.7019, found 1043.7072. **SI-36**: $[\alpha]_D$ = −29.1 (c 0.80, $CHCl_3$); IR (neat) 3481, 2954, 2876, 1707, 1458, 1241, 1130, 1008, 742 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (t, J = 7.4 Hz, 1H), 5.77 (s, 1H), 5.75−5.70 (m, 1H), 5.55 (dd, J = 15.5, 7.0 Hz, 1H), 5.00−4.96 (m, 1H), 4.99 (s, 1H), 4.83 (s, 1H), 4.22−4.15 (m, 1H), 4.11−4.06 (m, 1H), 4.07 (d, J = 5.8 Hz, 1H),

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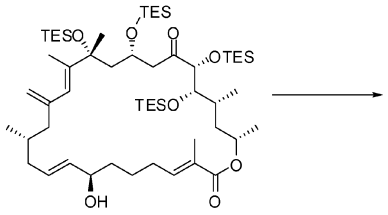
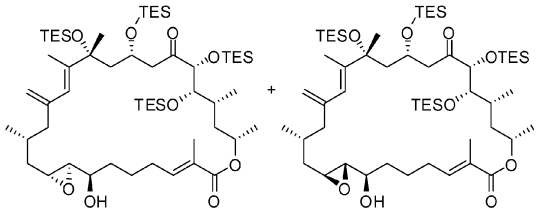
3.57 (dd, J = 5.6, 2.3 Hz, 1H), 2.96 (dd, J = 18.4, 7.4 Hz, 1H), 2.78 (dd, J = 18.3, 4.2 Hz, 1H), 2.23−2.08 (m, 4H), 1.95−1.52 (m, 11H), 1.834 (s, 3H), 1.80 (s, 3H), 1.48−1.40 (m, 1H), 1.43 (s, 3H), 1.25 (d, J = 6.1 Hz, 3H), 1.06−0.87 (m, 39H), 0.73−0.55 (m, 27H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.4, 167.9, 145.3, 142.2, 141.7, 134.2, 130.9, 128.3, 125.9, 114.9, 80.9, 79.0, 77.7, 73.2, 68.4, 65.1, 49.2, 48.8, 45.5, 42.1, 39.8, 36.8, 31.7, 30.1, 28.5, 28.3, 24.5, 21.0, 19.4, 15.0, 13.1, 12.4, 7.3, 7.1, 7.0, 6.9, 6.8, 5.2, 5.1, 4.8; HRMS (ES$^+$) calcd for $C_{56}H_{108}O_8Si_4Na$ (M + Na) 1043.7019, found 1043.6984.

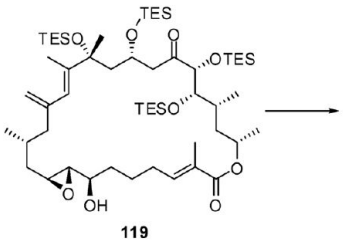


118

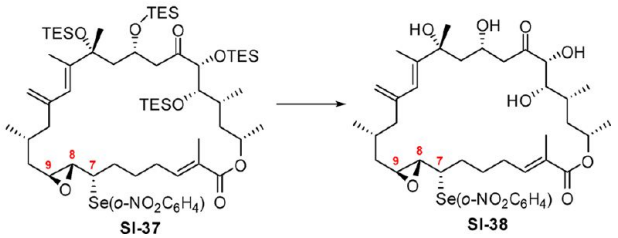


120 119

Epoxides 119 and 120. To a stirred solution of allylic alcohol **118** (29 mg, 0.0284 mmol) in CH_2Cl_2 (2.2 mL) at −40 °C were added sequentially 4 Å MS (20 mg), TBHP (15.5 μL, 0.0852 mmol, 5.5 M in decane), and Ti(O-i-Pr)$_4$ (16.1 mg, 16.6 μL, 0.0567 mmol). After 5 h, the reaction was quenched with aq $NaHCO_3$ (3 mL) and extracted with Et_2O (4 × 4 mL). The dried extract ($MgSO_4$) was concentrated in vacuo and purified by chromatography over silica gel, eluting with 6−10% EtOAc/hexanes, to give epoxide **120** (13.6 mg, 0.0131 mmol, 46%) and epoxide **119** (9.1 mg, 0.00867 mmol, 31%) as colorless oils. **120**: $[\alpha]^{23}_D$ = −32.3 (c 0.73, $CHCl_3$); IR (neat) 3482, 2954, 2911, 2876, 1706, 1458, 1380, 1239, 1131, 1073, 1009, 742 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (t, J = 7.0 Hz, 1H), 5.76 (s, 1H), 5.00−4.92 (m, 1H),4.98 (s, 1H), 4.83 (s, 1H), 4.20−4.10 (m, 1H), 4.10(d, J = 5.5 Hz, 1H), 3.58 (dd, J = 5.4, 1.7 Hz, 1H), 3.60−3.50 (m, 1H), 3.12−3.05 (m, 1H), 2.98−2.92 (m, 2H), 2.90−2.82 (m, 1H), 2.77 (dd, J = 5.0, 2.0 Hz, 1H), 2.40−2.30 (m, 2H), 2.17 (dd, J = 12.7, 4.3 Hz, 1H), 2.12−2.00 (m, 1H), 1.91−1.61 (m, 8H), 1.82 (s, 3H), 1.79 (s, 3H), 1.50−1.40 (m, 3H), 1.42 (s, 3H), 1.30−1.20 (m, 1H), 1.26 (d, J = 6.0 Hz, 3H), 1.08−0.87 (m, 39H), 0.75−0.50 (m, 27H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.1, 167.8, 144.7, 141.8, 141.7, 128.2, 125.9, 115.0, 80.5, 79.4, 77.9, 70.4, 68.2, 65.1, 60.8, 55.8, 49.8, 48.9, 45.9, 42.9, 39.3, 33.6, 30.2, 29.2, 28.6, 28.5 24.0, 21.1, 19.5, 15.1, 12.9, 12.4, 7.3, 7.1, 6.9, 5.2, 4.7; HRMS (ES$^+$) calcd for $C_{56}H_{108}O_9Si_4Na$ (M + Na) 1059.6968, found 1059.7001. **119**: $[\alpha]^{23}_D$ = −25.7 (c 0.42, $CHCl_3$); IR (neat) 3482, 2954, 2876, 1708, 1458, 1378, 1240, 1130, 1008, 742 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 (t, J = 6.1 Hz, 1H), 5.83 (s, 1H), 5.05−4.90 (m, 1H), 5.01 (s, 1H), 4.86 (s, 1H), 4.15−4.10 (m, 1H), 4.08 (d, J = 5.8 Hz, 1H), 3.58 (dd, J = 5.5, 2.6 Hz, 1H), 3.59−3.49 (m, 1H), 3.11−3.03 (m, 1H), 2.95−2.91 (m, 2H), 2.77 (dd, J = 5.5, 2.0 Hz, 1H), 2.35−2.20 (m, 3H), 2.02−1.59 (m, 10H), 1.83 (s, 3H), 1.81 (s, 3H), 1.44 (s, 3H), 1.50−1.40 (m, 3H), 1.25 (d, J = 6.0 Hz, 3H), 1.06−0.89 (m, 39H), 0.74−0.52 (m, 27H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.7, 167.8, 144.8, 142.3, 141.5, 128.4, 125.4, 115.3, 80.8, 78.9, 77.8, 71.5, 68.4, 65.3, 61.8, 55.5, 49.2 (2C), 45.4, 41.7, 38.8, 33.3, 30.4, 29.6, 28.5, 28.3, 23.9, 21.0, 20.0, 15.0, 13.2, 12.5, 7.2, 7.1, 7.0, 6.9, 5.2, 4.8; HRMS (ES$^+$) calcd for $C_{56}H_{108}O_9Si_4Na$ (M + Na) 1059.6968, found 1059.6982.



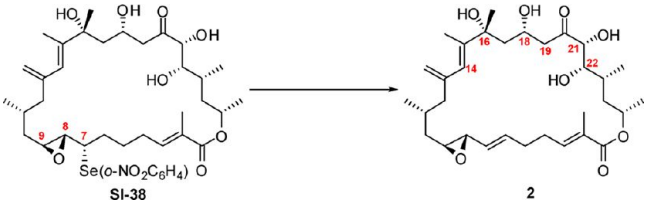
119



SI-37 SI-38

Selenide SI-37. To a stirred solution of epoxide **119** (8.5 mg, 0.00819 mmol) in THF (0.5 mL) at rt were added sequentially o-$NO_2C_6H_4SeCN$ (37 mg, 0.164 mmol) and PBu_3 (33.2 mg, 41 μL, 0.164 mmol). After 5 h, the reaction mixture was concentrated in vacuo purified by chromatography over silica gel, eluting with Hexanes then with 4% EtOAc/hexanes, to give crude selenide **SI-37** (4.5 mg) as a yellow oil which was used directly in next step without further purification.

Polyol SI-38. To a stirred solution of selenide **SI-37** (4.5 mg) in THF/DMF/H_2O (10:1:0.02, 0.50 mL/50 μL/1 μL) at 0 °C was added TAS-F (5 mg, 0.0180 mmol). The reaction mixture was then warmed to rt. After 2 h, the reaction mixture was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10−65% EtOAc/hexanes, to give polyol **SI-38** (2.0 mg, 0.00261 mmol, 32% over two steps) as a yellow oil: $[\alpha]^{23}_D$ = −41.7 (c 0.12, $CHCl_3$); IR (neat) 3446, 2924, 2854, 1701, 1519, 1457, 1378, 1334, 1121, 759, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.55 (t, J = 7.4 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 6.88 (t, J = 6.3 Hz, 1H), 5.87 (s, 1H), 5.15−5.08 (m, 1H), 5.03 (s, 1H), 4.82 (s, 1H), 4.50 (s, 1H), 4.20−4.10 (m, 2H), 3.78−3.69 (m, 1H), 3.20−3.10 (m, 1H), 2.94−2.77 (m, 3H), 2.39−2.33 (m, 1H), 2.30−2.13 (m, 2H), 2.07−1.50 (m, 11H), 1.84 (s, 6H), 1.41 (s, 3H), 1.40−1.28 (m, 5H), 1.07 (d, J = 6.5 Hz, 3H), 0.77 (t, J = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.4, 167.7, 149.7, 144.0, 143.0, 141.1, 133.1, 132.6, 128.8, 128.4, 127.1, 125.9, 123.9, 115.2, 77.6, 76.0, 75.3, 68.3, 66.0, 62.1, 59.0, 46.8, 46.1, 45.3, 44.7, 40.3, 40.2, 32.7, 31.9, 29.2, 28.9, 28.0, 26.3, 21.2, 17.8, 15.9, 15.4, 12.5; HRMS (ES$^+$) calcd for $C_{38}H_{55}NO_{10}NaSe$ (M + Na) 788.2889, found 788.2891.

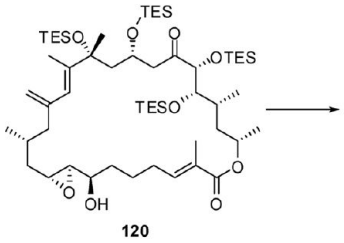


SI-38 2

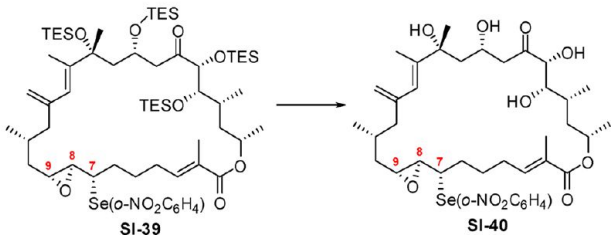
Amphidinolide B$_1$ (2). To a stirred solution of selenide **SI-38** (2.0 mg, 0.00261 mmol) in CH_2Cl_2 (0.4 mL) at rt were added sequentially $NaHCO_3$ (20 mg, 0.238 mmol) and TMSO−OTMS (16.6 mg, 20 μL, 0.0929 mmol). After 1.5 h, the yellow color vanished, and the reaction mixture was purified by preparative TLC, eluting with 60% EtOAc/hexanes, to give amphidinilide B$_1$ (**2**) (1.0 mg, 0.00178 mmol, 68%): $[\alpha]^{23}_D$ = −63.7 (c 0.08, $CHCl_3$) [lit.[2c] $[\alpha]^{23}_D$ = −62.5 (c 0.39, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (t, J = 7.8 Hz, 1H), 5.99 (s, 1H), 5.93 (ddd, J = 15.2, 8.5, 4.8 Hz, 1H), 5.18 (dd, J = 15.8, 8.6 Hz, 1H), 5.06 (m, 1H), 5.05(s, 1H), 4.84 (s, 1H), 4.34 (dd, J = 4.8, 1.4 Hz, 1H), 4.20 (m, 1H), 3.92 (d, J = 3.3 Hz, 1H), 3.88 (d, J = 5.0 Hz, 1H), 3.73 (ddd, J = 10.3, 8.8, 1.5 Hz, 1H), 3.19 (d, J = 10.0 Hz, 1H), 3.16 (dd, J = 8.3, 2.0 Hz, 1H), 2.94 (ddd, J = 8.9, 2.6, 2.2 Hz, 1H), 2.86 (d, J = 7.3 Hz, 1H), 2.80 (dd, J = 15.9, 3.2 Hz, 1H), 2.43 (m, 1H), 2.38 (m, 1H), 2.25 (m, 1H), 2.20 (m, 1H), 2.17 (m, 1H), 2.16 (s, 1H), 1.98−1.91 (m, 4H), 1.80 (s, 6H), 1.76 (dd, J = 14.5, 5.2 Hz, 1H), 1.64 (m, 1H), 1.49 (ddd, J = 13.6, 10.9, 3.0 Hz, 1H), 1.44 (s, 3H), 1.31 (m, 1H), 1.30 (d, J = 6.1 Hz, 3H), 1.26 (m, 1H),

dx.doi.org/10.1021/jo3026077 | J. Org. Chem. 2013, 78, 2213−2247

1.03 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.5, 167.8, 144.5, 143.2, 140.0, 135.5, 128.6, 128.5, 124.4, 114.9, 77.9, 76.1, 75.7, 68.4, 66.7, 60.2, 47.0, 46.0, 45.4, 39.5, 39.4, 33.3, 31.0, 29.4, 28.4, 26.9, 21.1, 18.3, 15.7, 15.2, 12.5; HRMS (ES$^+$) calcd for $C_{32}H_{50}O_8Na$ (M + Na) 585.3403, found 585.3411.



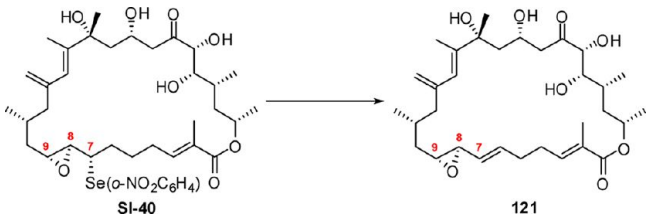
120



SI-39 SI-40

Selenide SI-39. To a stirred solution of epoxide **120** (14.5 mg, 0.0139 mmol) in THF (0.8 mL) at rt were added sequentially o-$NO_2C_6H_4SeCN$ (63 mg, 0.279 mmol) and PBu_3 (56.7 mg, 70 μL, 0.279 mmol). After 1 h, the reaction mixture was concentrated in vacuo purified by chromatography over silica gel, eluting with Hexanes then with 4% EtOAc/hexanes, to give crude selenide **SI-39** (15.2 mg) as a yellow oil which was used directly in next step without further purification.

Polyol SI-40. To a stirred solution of selenide **SI-39** (15.2 mg, 0.0122 mmol) in THF/DMF/H_2O (10:1:0.02, 1.6 mL/0.16 mL/3.2 μL) at 0 °C was added TAS-F (16.8 mg, 0.0610 mmol). The reaction mixture was then warmed up to rt. After 2 h, the reaction mixture was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10−65% EtOAc/hexanes, to give polyol **SI-40** (9.1 mg, 0.0119 mmol, 86% over two steps) as yellow oils: $[\alpha]^{23}_D$ = −51.8 (c 0.44, $CHCl_3$); IR (neat) 3447, 2926, 2855, 1701, 1514, 1456, 1332, 1271, 1037, 902, 756, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 8.3 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.55 (t, J = 7.3 Hz, 1H), 7.36 (t, J = 7.9 Hz, 1H), 6.81 (t, J = 7.0 Hz, 1H), 5.97 (s, 1H), 5.10−5.03 (m, 1H), 5.03 (s, 1H), 4.83 (s, 1H), 4.47 (s, OH), 4.40−4.32 (m, 1H), 4.14 (dd, J = 14.2, 7.2 Hz, 1H), 3.88−3.78 (m, 1H), 3.42−3.35 (m, 1H), 3.05−2.97 (m, 1H and OH), 2.85 (d, J = 4.8 Hz, 2H), 2.50−2.38 (br, 1H), 2.30−2.20 (m, 2H), 2.07 (s, OH), 2.11−2.02 (m, 1H), 1.96−1.65 (m, 11H), 1.83 (s, 6H), 1.44 (s, 3H), 1.40−1.32 (m, 2H), 1.33 (d, J = 5.8 Hz, 3H), 1.08 (d, J = 6.3 Hz, 3H), 0.90 (d, J = 4.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6, 167.9, 147.6, 144.0, 143.5, 141.2, 133.6, 132.3, 130.6, 128.7, 126.4, 126.0, 124.0, 115.5, 78.0, 76.1, 75.0, 69.5, 66.3, 60.7, 58.7, 46.1, 45.8, 44.8, 43.8, 40.5, 39.5, 33.5, 30.4 (2C), 28.2, 27.7, 27.1, 20.8, 19.6, 16.5, 15.2, 12.5; HRMS (ES$^+$) calcd for $C_{38}H_{55}NO_{10}NaSe$ (M + Na) 788.2889, found 788.2934.



SI-40 121

Allylic Epoxide 121. To a stirred solution of selenide **SI-40** (2.7 mg, 0.00353 mmol) in CH_2Cl_2 (0.5 mL) at rt were added sequentially $NaHCO_3$ (30 mg, 0.357 mmol) and TMSO−OTMS (22.5 mg, 27 μL, 0.126 mmol). After 1.5 h, the yellow color vanished and the reaction mixture was purified by preparative TLC, eluting with 60% EtOAc/hexanes, to give allylic epoxide **121** (1.3 mg, 0.00231 mmol, 65%): $[\alpha]^{23}_D$ = +10.0 (c 0.13, $CHCl_3$); IR (neat) 3422, 2923, 2853, 1701, 1457, 1377, 1261, 1103; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (t, J = 4.9 Hz, 1H), 6.04 (s, 1H), 5.88−5.80 (m, 1H), 5.28 (dd, J = 15.4, 8.4 Hz, 1H), 5.10−5.05 (m, 1H), 5.06 (s, 1H), 4.84 (s, 1H), 4.35 (dd, J = 4.2, 1.5 Hz, 1H), 4.30−4.20 (m, 1H), 4.13 (s, 1H), 3.79 (t, J = 9.8 Hz, 1H), 3.77 (d, J = 4.6 Hz, 1H), 3.40 (d, J = 10.2 Hz, 1H), 3.09 (dd, J = 8.5, 2.1 Hz, 1H), 2.98−2.93 (m, 2H), 2.76 (dd, J = 15.4, 2.4 Hz, 1H), 2.38−2.23 (m, 5H), 2.35 (s, 1H), 1.98 (m, 1H), 1.95 (m, 1H), 1.88 (m, 1H), 1.85 (m, 1H), 1.84 (s, 6H), 1.78 (dd, J = 14.6, 4.7 Hz, 1H), 1.70 (m, 1H), 1.64 (m, 1H), 1.32 (m, 1H), 1.30 (d, J = 6.1 Hz, 3H), 1.13 (m, 1H), 1.03 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.4 Hz, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.6, 167.5, 144.6, 143.2, 140.8, 135.9, 128.9, 128.7, 124.3, 114.9, 78.3, 76.1, 75.5, 68.3, 66.8, 60.3, 59.2, 46.5, 46.1, 45.6, 39.6, 33.3, 31.2, 30.5, 29.7, 28.6, 27.1, 21.0, 19.9, 15.7, 15.4, 12.7; HRMS (ES$^+$) calcd for $C_{32}H_{50}O_8Na$ (M + Na) 585.3403, found 585.3409.

Cell Viability Assays. MTS assays were conducted for cell viability as described by the supplier (Promega).[58] Human DU145 prostate cancer, OCI-LY3 lymphoma, K562 CML, MOLT-4 ALL, Reh ALL, U266 myeloma, KG1a AML, HL60 AML, and MDA-MB-435 breast cancer cells were seeded in 96-well plates, incubated overnight at 37 °C in 5% (v/v) CO_2, and exposed to **3**, **114**, or **121** at 0.1 μM or in a dose-dependent manner for 72 h. DMSO was used as the vehicle control. Cell viability was determined by tetrazolium conversion to its formazan dye and absorbance was measured at 490 nm using an automated ELISA plate reader.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C spectra for all new compounds. X-ray crystallographic data (CIF) for compound **109**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support was provided by the National Institutes of Health (NIH) (GM63723) and Oregon State University. We are grateful to Professor Claudia Maier and Jeff Morré (OSU) for mass spectral data and Dr. Lev Zakharov (OSU) for X-ray crystallographic analysis of **109**. Finally, we thank Dr. Roger Hanselmann (Rib-X Pharmaceuticals) for his helpful discussions.

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(52) The iodide was prepared from commercially available 2-(chloromethyl)allyltrimethylsiliane [NaI (2.5 equiv), acetone (0.5 M), 16 h, flask covered in aluminum foil, rt, 99%]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.16 (s, 1H), 4.70 (s, 1H), 3.88 (s, 2H), 1.72 (s, 2H), 0.04 (s, 9H).
(53) AD Mix β* = $(DHQD)_2PHAL$ (15.2 mg), $K_2OsO_4{\cdot}2H_2O$ (2.55 mg), K_2CO_3 (293.6 mg), $K_3Fe(CN)_6$ (699.6 mg). Commercially available AD mix β proved to be slow and inefficient.
(54) Preparation of LDA solution: To a solution of diisopropylamine (101.9 mg, 0.14 mL, 1.0 mmol) in THF (0.46 mL) at −78 °C was added *n*-BuLi (0.4 mL, 1.0 mmol, 2.5 M in THF). After 5 min, the white slurry was warmed to −10 °C and stirred for an additional 15 min.
(55) Titration of Grignard reagent: To a stirred solution of menthol (15.6 mg, 0.1 mmol) and 1,10-phenanthroline (2 mg) in THF (0.5 mL) was added prepared Grignard reagent solution until a burgundy color persisted. The concentration was calculated using the formula: [RMgX] = 0.1 mmol/volume of added RMgX in mL. For the references, see: (a) Lin, H, -S; Paquette, L. A. *Synth. Commun.* **1994**, *24*, 2503. (b) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.
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dx.doi.org/10.1021/jo3026077 | *J. Org. Chem.* 2013, 78, 2213−2247