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A Second-Generation Total Synthesis of (+)-Phorboxazole A

Amos B. Smith, III,* Thomas M. Razler, Jeffrey P. Ciavarri, Tomoyasu Hirose, Tomoyasu Ishikawa, and Regina M. Meis

Department of Chemistry, The Penn Center for Molecular Discovery, and Monell Chemical Senses Center, University of Pennsylvania, Philadelphia, Pennsylvania 19104

smithab@sas.upenn.edu

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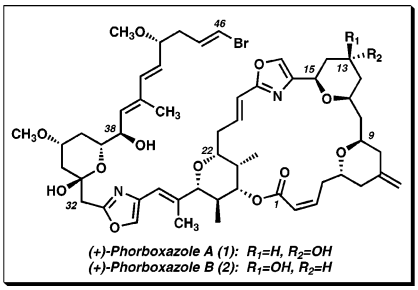
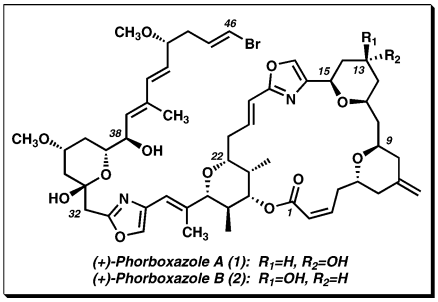


A highly convergent second-generation synthesis of (+)-phorboxazole A has been achieved. Highlights of the synthetic approach include improved Petasis−Ferrier union/rearrangement conditions on a scale to assemble multigram quantities of the C(11−15) and C(22−26) *cis*-tetrahydropyrans inscribed with the phorboxazole architecture, a convenient method to prepare *E*- and *Z*-vinyl bromides from TMS-protected alkynes utilizing radical isomerization of *Z*-vinylsilanes, and a convergent late-stage Stille union to couple a fully elaborated C(1−28) macrocyclic iodide with a C(29−46) oxazole stannane side chain to establish the complete phorboxazole skeleton. The synthesis, achieved with a longest linear sequence of 24 steps, proceeded in 4.6% overall yield.

The oceans of the world have provided a rich source of interesting and important natural products. In addition to their magnificent architecture, many marine-derived products have exceedingly potent biological properties. For example, discodermolide,[1a] the halichondrins,[1b] and the spongistatins[1c] display impressive nanomolar and in some cases subnanomolar cell growth inhibitory activities when evaluated against a number of human cancer cell lines. Given their important biological activities, in conjunction with their often extreme scarcity, total synthesis comprises the only viable resource to access these potentially medicinally important compounds.

In 1995, Searle and Molinski isolated (+)-phorboxazoles A and B (**1** and **2**) from an extract of the sponge *Phorbas* sp., endemic to the Indian Ocean near the western coast of Australia.[2] Through a series of NMR, degradation, and synthetic correlation experiments, the relative and absolute configurations of both **1** and **2** were determined to possess a novel macrocyclic architecture.[3] In addition to 15 stereogenic centers, (+)-phorboxazole A and B [epimeric at C(13)] possess seven olefins, a 21-membered C(1−26) macrolactone ring, with four embedded rings, including a C(16−18) oxazole, and one *trans*- and two *cis*-2,6-tetrahydropyran units. In addition, the C(27−46) side chain display a diverse array of functional motifs, including two rings, represented by a C(29−31) oxazole and a C(33−37) tetrahydropyranyl hemiacetal accompanied by four olefins, terminating in a C(45−46) *E*-vinyl bromide.



In addition to their impressive architectural features, **1** and **2** have been shown to possess both antifungal and antibiotic

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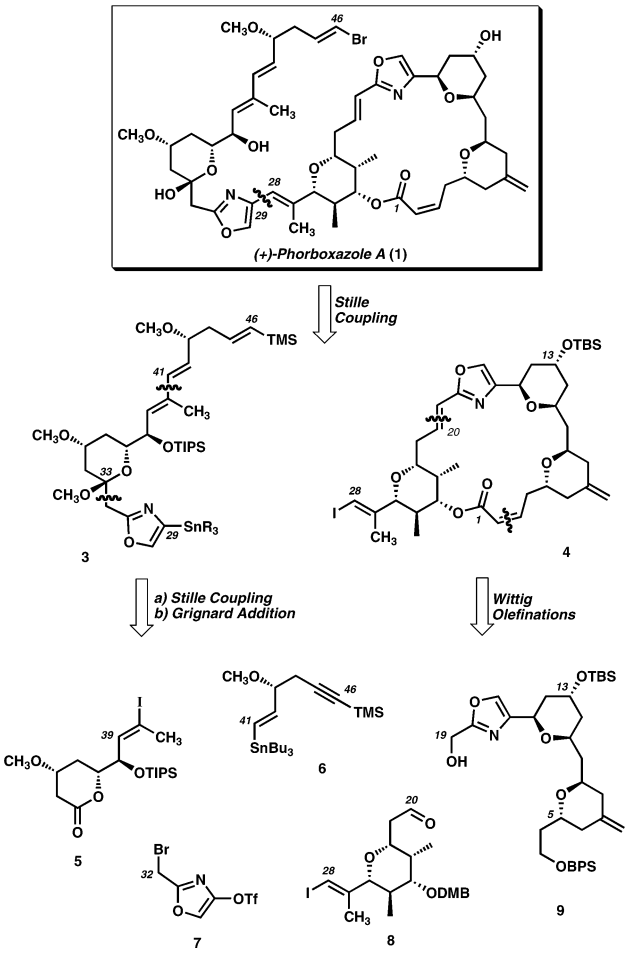
activity when evaluated against *Candida albicans* and *Saccharomyces carlsberensis*, respectively. It is their extreme cytotoxicity, however, that has attracted the greatest interest from the scientific community. When evaluated against the National Cancer Institute's (NCI) panel of human cancer cell lines, both phorboxazole A and B displayed extraordinarily potent activity; a mean GI_{50} value of 1.58×10^{-9} was observed across the entire NCI panel. More specifically, when screened against the HCT-116 (colon tumor) and MCF7 (breast) cancer cell lines, activities of 4.36×10^{-10} and 5.62×10^{-10} were observed, respectively. These data place the phorboxazoles in the category of the halichondrins and spongistatins as some of the most selective cytotoxic agents known.

Due to the architectural complexity and extraordinary biological activity, (+)-phorboxazoles A and B (**1** and **2**) have attracted a great deal of attention from the synthetic community. To date, six total syntheses of (+)-phorboxazole A (**1**),[4] four total syntheses of (+)-phorboxazole B (**2**),[5] and a number of related synthetic studies have been reported.[6] Determination of the mechanism of action responsible for the exceedingly potent cancer cell line growth inhibitory activity of **1** and **2**, however, has only recently been investigated.[7]

Given that only milligram quantities of **1** and **2** were procured through isolation and total synthesis, we initiated a synthetic campaign to produce quantities (ca. hundreds of milligrams) of (+)-phorboxazole A and phorboxazole congeners amenable to more extensive biological evaluation. In particular, we envisioned a more convergent and efficient synthesis based upon our successful 2001 first-generation total synthesis of (+)-phorboxazole A.[4b,c] Improvements would clearly be necessary to facilitate throughput of multigram scale quantities of the highly complex intermediates. Herein we disclose a full account of a now highly convergent, second-generation total synthesis of (+)-phorboxazole A. In the accompanying paper,[31] we will provide a full account of the design, synthesis, and evaluation of a series of side chain and simplified macrocycle analogues, which provide additional understanding of the functionality required to retain potent human tumor cell growth inhibitory activity. Importantly, we have discovered a new, highly potent subnanomolar analogue, (+)-C(46)-chlorophorboxazole A, which has proven to be more readily available synthetically than the parent (+)-phorboxazole A (**1**).

To construct meaningful quantities of (+)-phorboxazole A, we required a highly convergent synthesis wherein fully elaborated side chain **3** and macrocyclic **4** fragments would be coupled at a late stage (Scheme 1). To avoid unwanted side

SCHEME 1



reactions, we envisioned protection of the C(45−46) *E*-vinyl bromide as the corresponding *E*-vinylsilane. After side chain−macrocycle union, two steps would be required to complete the synthesis: installation of the C(46) bromide via exposure to an electrophilic source of bromine and final global deprotection.

Construction of the side chain was projected to arise via a route similar to our 2001 synthesis. Specifically, Stille union of vinyl iodide **5** with vinylstannane **6** would furnish a dienyl lactone intermediate which upon treatment with the Grignard reagent derived from oxazole **7** would provide the complete side-chain carbon framework (Scheme 1). However, unlike the first-generation synthesis, introduction of the C(45−46) *E*-

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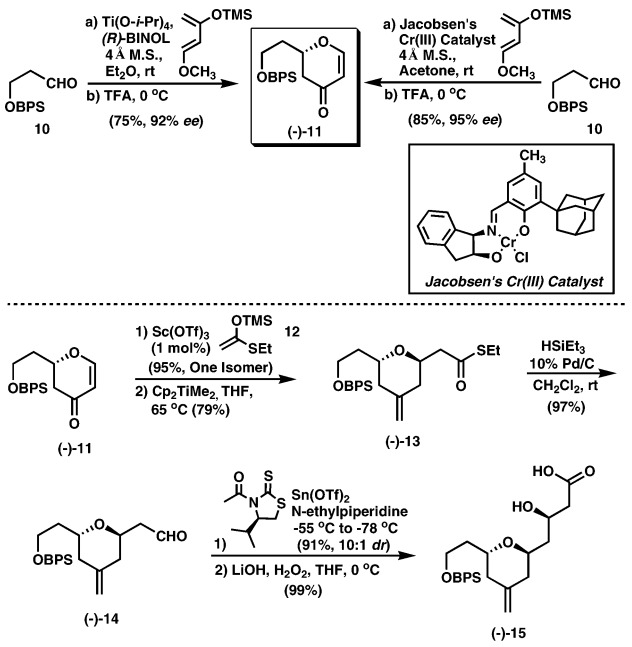
vinylsilane was then projected to arise via a transition-metal-mediated hydrometalation event involving the free alkyne or *syn*-reduction of the TMS-alkyne, followed by isomerization to the thermodynamically favored *E*-silane. The synthetic flexibility of this strategy would thereby permit evaluation of both Stille and Suzuki coupling tactics with macrocycle **4**. That is, simple palladium-mediated stannylation or boronation of the bidirectional oxazole triflate developed in our laboratory[8] would permit the opportunity to explore both synthetic tactics.

To construct macrocycle **4**, we envisioned utilizing the *Z*-selective Still−Gennari modified Horner−Emmons olefination to fashion the C(2−3) *Z*-enoate.[9] Elaboration of the C(19−20) *E*-olefin was then expected to arise via an *E*-selective Wittig reaction between aldehyde **8** and the ylide derived from tricycle **9**.[4b,c] As in our first-generation (+)-phorboxazole A total synthesis, both 2,6-*cis*-tetrahydropyran moieties (**8** and **9**) were ideally suited to derive from a Petasis−Ferrier union/rearrangement tactic.[10,11] However, unlike the first-generation campaign, if tens of grams of valuable intermediates were to be subjected to the three-step Petasis−Ferrier sequence, improved conditions would be required to facilitate material advancement.

Results and Discussion

We began the second-generation synthesis with construction of the C(3)−C(19) segment tricycle **9** (Scheme 1). Utilizing the Keck *hetero*-Diels−Alder conditions,[12] treatment of known aldehyde **10**[13] with the Danishefsky diene (Scheme 2),[14]

SCHEME 2



promoted by Ti(O-*i*-Pr)$_4$ and (*R*)-BINOL, followed by treatment with TFA afforded dihydropyranone (−)-**11** in 75% yield with 92% enantiomeric excess (ee). Considerable experimentation was involved to identify reproducible conditions, including temperature, solvent, and drying time of the molecular sieves to define conditions to permit reaction scales at the 50 g level. Drying the molecular sieves for 2.5 h at 100 °C under vacuum followed by introduction of Ti(O-*i*-Pr)$_4$/(*R*)-BINOL and aldehyde **10** and Danishefsky's diene provided the optimal sequence of events. Subsequent experimentation revealed that the Jacobsen chiral chromium(III) catalyst furnished dihydropyranone (−)-**11** with both improved yield (85%) and selectivity (ca. 95% ee) on scales as large as 70 g.[15] In addition, the Jacobsen protocol was operationally more straightforward and less sensitive to water; various molecular sieve drying times (ca. 1 to 24 h) delivered both high yields and enantioselectivity.

Condensation of (−)-**11** with thio-enol ether **12**, promoted by Sc(OTf)$_3$,[16] next furnished the 1,4-addition product, which upon treatment with Cp_2TiMe_2[17] followed by 10% Pd/C and $HSiEt_3$[18] yielded aldehyde (−)-**14** in 73% for the three steps (Scheme 2). Importantly, the Sc(OTf)$_3$-promoted conjugate addition consistently provided the thio-ester in high yield (ca. 95%) as a single diastereomer on scales up to 55 g. Here, solvent water content proved inconsequential as both CH_2Cl_2 with and without drying over molecular sieves consistently provided both excellent yields and diastereoselectivity. In order to orchestrate the C(11) hydroxyl stereogenicity responsible for directing the Petasis−Ferrier rearrangement, a Sn(OTf)$_2$-promoted Nagao acetate aldol reaction was enlisted to provide the corresponding *β*-hydroxy thioimide in 91% yield with good diastereoselectivity (ca. 10:1 dr).[19] In our hands, the reaction was critically dependent on the purity of Sn(OTf)$_2$. Commercial material from several sources proved highly variable, affording a range of yields and diastereoselectivities. With no clear trend identifiable, we opted to prepare Sn(OTf)$_2$ from $SnCl_2$ and TfOH. Immediate use of the snow-white Sn(OTf)$_2$ proved optimal, as prolonged storage afforded both depressed yields and selectivity. Following diastereomer separation, treatment with LiOOH furnished *β*-hydroxy carboxylic acid (−)-**15** in near quantitative yield.

With (−)-**15** in hand, we were poised to explore the large-scale, three-step Petasis−Ferrier union/rearrangement protocol to construct the requisite C(11−15) *cis*-tetrahydropyran (**9**). Following the lead from our 2001 synthesis, treatment of (−)-**15** with HMDS[20] followed by known oxazole aldehyde **16**[4b,f] and TMSOTf furnished dioxanone (−)-**17** in 90−95% yield with good diastereomeric control (ca. 10:1, Scheme 3). Importantly, this reaction was found to be reliable on scales as large as 20 g. Residual HMDS was, however, found to have a detremental effect on the reaction. To avoid quenching the catalytic TfOH arising via hydrolysis of TMSOTf during the reaction, complete removal of HMDS under vacuum at 60 °C was paramount for high conversion.

Treatment of dioxanone (−)-**17** with the Petasis−Tebbe reagent (Cp_2TiMe_2) in THF at reflux for 48 h afforded the desired enol−acetal, albeit in a disappointing yield of 58% (Scheme 3). To facilitate material throughput, we undertook an optimization study. We reasoned that the extended reaction times allowed the excess Cp_2TiMe_2 to react with enol−acetal (−)-**18**

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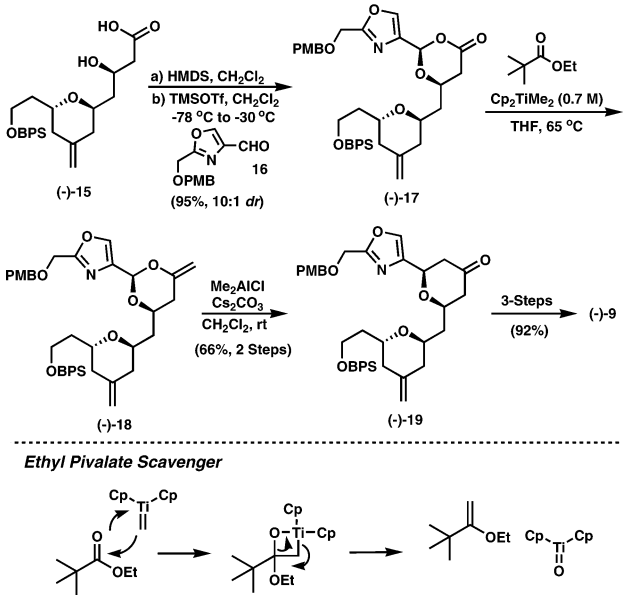
SCHEME 3



in a [2 + 2] fashion, leading to decomposition. In addition, a more concentrated reaction solution would provide an added benefit toward increasing the reaction rate. Indeed, surveying 0.6, 0.7, 0.8, and 1.0 M solutions of the Petasis−Tebbe reagent revealed that the 0.7 M solution of Cp_2TiMe_2 in THF instead of the prescribed 0.5 M improved the yield to 65% in 24 h. Both the 0.8 and 1.0 M conditions provided faster reaction rates; however, reagent stability upon storage was found to be problematic after 48 h freezer storage at 0 °C.

Ethyl pivalate has been utilized as a Cp_2TiMe_2 scavenger in olefination reactions.[21] In the presence of ethyl pivalate, Cp_2TiMe_2 reacts first with the desired carbonyl in preference to the hindered ethyl pivalate. However, once the olefinated product is generated, ethyl pivalate becomes a more attractive target for Cp_2TiMe_2 and thereby prevents secondary product formation. When applied to the phorboxazole system, ethyl pivalate in conjunction with the higher concentration of the Petasis−Tebbe reagent[21] provided the greatest improvement in yield (ca. 80%, Scheme 3).

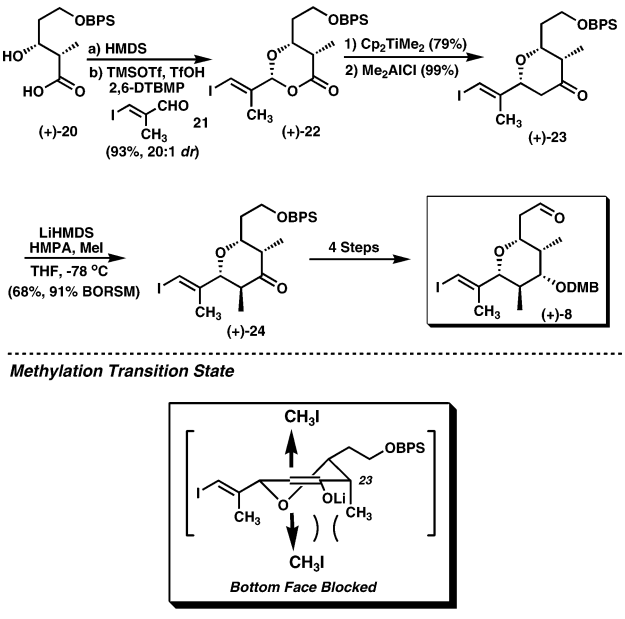
Purification of the unstable enol−acetal also proved to be scale dependent. On a scale less than 1 g, silica gel purification of (−)-**18** was straightforward; however, on larger scales (ca. > 15 g), we began to observe decomposition of (−)-**18** to the corresponding β-hydroxy ketone. Presumably, hydrolysis of the enol−acetal was occurring from the extended exposure to acidic silica gel due to the larger scales. To circumvent enol−acetal decomposition, the titanium byproducts were quickly removed by filtration through a short plug of silica gel, followed by immediate execution of the Petasis−Ferrier rearrangement.

Turning next to the Petasis−Ferrier rearrangement, the conditions utilized in the first-generation synthesis of (+)-phorboxazole A afforded only a modest 37% yield of the desired C(11−15) tetrahydropyranone (−)-**19**, accompanied by a 20% yield of the tetrahydropyranone product without the C(20) *p*-methoxybenzyl (PMB) protecting group. After considerable experimentation, we found that addition of cesium carbonate (Cs_2CO_3) completely suppressed PMB loss during the 2 h reaction time. While the exact nature of this beneficial outcome is still under investigation, a scan of the literature points to the formation of an aluminum−carbonate complex,[22] which slowed both the rate of the Petasis−Ferrier rearrangement as well as the Lewis acid mediated PMB removal. Pleasingly, *cis*-tetrahydropyranone (−)-**19** was obtained in 66% yield for the two steps on scales approaching 10 g. Three steps were then utilized to complete the synthesis of **9**. Reduction of the C(15) ketone to the axial alcohol and protection as the TBS-ether followed by removal of the PMB-group with DDQ furnished (−)-**9** in 92% for the three steps.

Construction of the C(22−26) tetrahydropyranone in our first-generation synthesis also relied upon an efficient Petasis−Ferrier rearrangement in this case of a mixed ethylidene enol−acetal (1:1, *E:Z*) to construct simultaneously the tetrahydropyranone and install the C(25) methyl.[4b,c] Construction of the ethylidene enol−acetal, however, required a somewhat cumbersome four-step sequence from the corresponding dioxanone involving a Julia protocol.[23] At the outset of our second-generation synthesis, it was not clear if this reaction sequence would be well suited for scales as large as 10−15 g. To facilitate material throughput, a more direct approach was desired wherein installation of the C(25) methyl after the Petasis−Ferrier rearrangement would avoid the first-generation ethylidene enol−acetal construction. In addition, we envisioned direct installation of the vinyl iodide during dioxanone formation to avoid the multistep carbometalation sequence utilized in the 2001 campaign.

With this scenario in mind, direct condensation of vinyl iodide aldehyde **21** with β-hydroxy carboxylic acid (+)-**20** afforded dioxanone (+)-**22** (Scheme 4). We first explored direct installation of the C(25) methyl after the Petasis−Ferrier rearrange-

SCHEME 4



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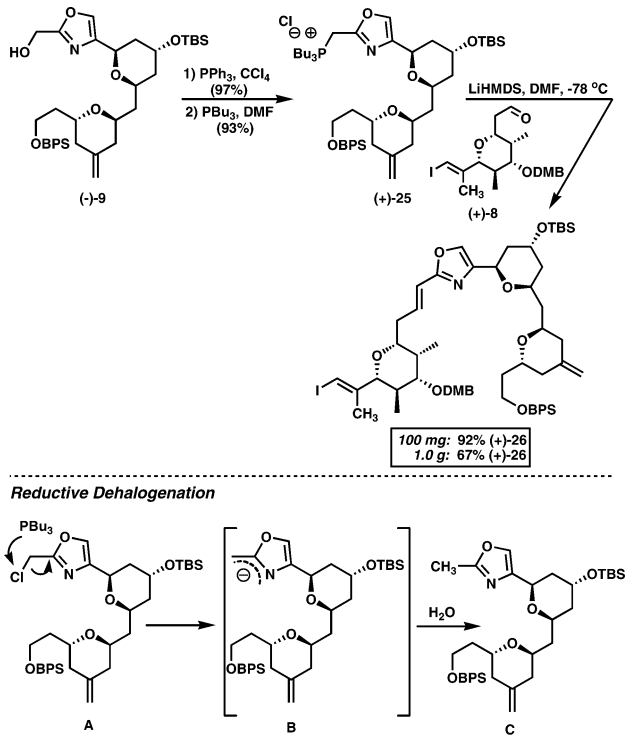
ment. Treatment of dioxanone (+)-**22** with Cp_2TiMe_2 furnished the corresponding enol−acetal in 79% yield after purification by deactivated silica gel.[24] Pleasingly, exposure of the enol−acetal to Me_2AlCl without a carbonate additive provided tetrahydropyranone (+)-**23** in nearly quantitative yield. Both the BPS-protecting group and the vinyl iodide were unaffected by the unbuffered Me_2AlCl conditions. Analysis of the proposed C(25) methylation process revealed that upon kinetic enolization of (+)-**23**, the C(23) methyl should block the bottom face of the molecule, thereby precluding formation of the undesired C(25) axial methyl (Scheme 4). In the event, enolization with LHMDS and HMPA as an additive, preventing higher order lithium aggregates, followed by addition of CH_3I pleasingly afforded the desired C(25) equatorial methyl tetrahydropyranone (+)-**24** as a single diastereomer.[25] A four-step protocol was implemented to complete the synthesis of aldehyde (+)-**8**.[4g]

We next turned attention to union of (+)-**8** with (−)-**9** and ultimately to completion of macrocycle **4** (Scheme 5). On a

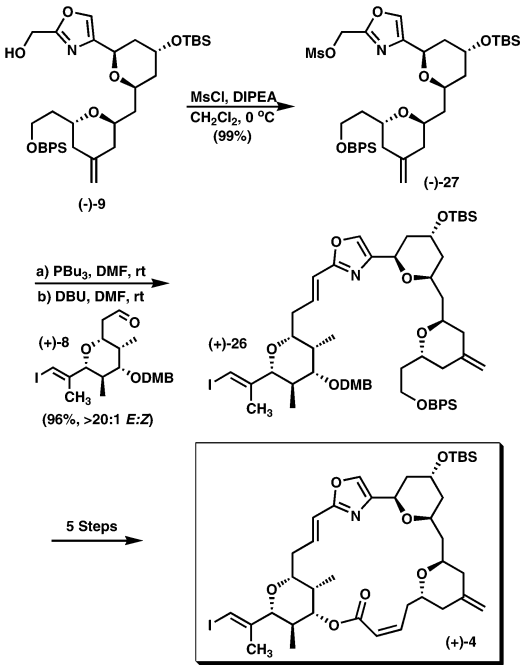
SCHEME 5



small scale, conversion of alcohol (−)-**9** to the corresponding chloride, followed by ylide formation and Wittig olefination with aldehyde (+)-**8**, furnished the *E*-C(19−20) olefin (+)-**26** in 92% yield, with >20:1 *E*:*Z* selectivity. However, conducting the reaction on a gram scale afforded a disappointing 67% yield of (+)-**26**, accompanied by 30% yield of a byproduct identified as methyl oxazole **C**. A similar reductive dehalogenation was observed by Evans et al. in their total synthesis of (+)-phorboxazole B,[5a−c] presumably involving nucleophilic attack of PBu_3 at chloride.

To circumvent this problem, we adopted the Evans protocol to construct the *E*-C(19−20) olefin, for ease of operation, high yield, and selectivity. Conversion of alcohol (−)-**9** to mesylate (−)-**27** proceeded in excellent yield (ca. 99%, Scheme 6). In a

SCHEME 6

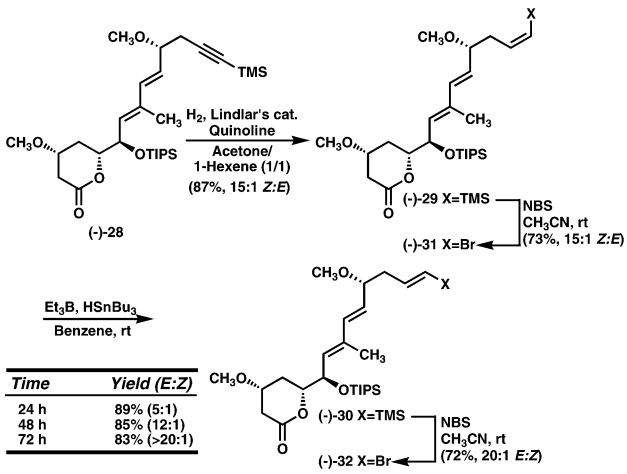


one-flask operation, mesylate (−)-**27** was then treated with tri-*n*-butylphosphine (PBu_3) in DMF to furnish the corresponding ylide without formation of the undesired methyl oxazole **C** (monitored by TLC). Without isolation, introduction of aldehyde (+)-**8**, followed by DBU led to (+)-**26** in excellent yield (96%) with greater than 20:1 *E*:*Z* selectivity. Importantly, this one-flask protocol reproducibly provided (+)-**26** in ca. 96% yield on scales as large as 2 g.

Closure of the macrocyle was accomplished using a five step procedure that relied upon a final Still−Gennari modified Horner−Emmons olefination to fashion the requisite *Z*-C(2−3) enoate in excellent yield, albeit modest selectivity (ca. 96% yield, 2.5:1 *Z*:*E*, Scheme 6).[4g] Pleasingly, construction of macrocycle (+)-**4** was achieved with a longest linear sequence of 20 steps and an overall yield of 20%.

With an efficient synthesis of macrocycle (+)-**4** in hand, we next turned attention to elaboration of the C(29−46) side chain **3**. Beginning with lactone (−)-**28** (Scheme 7), an intermediate

SCHEME 7



Time	Yield (E:Z)
24 h	89% (5:1)
48 h	85% (12:1)
72 h	83% (>20:1)

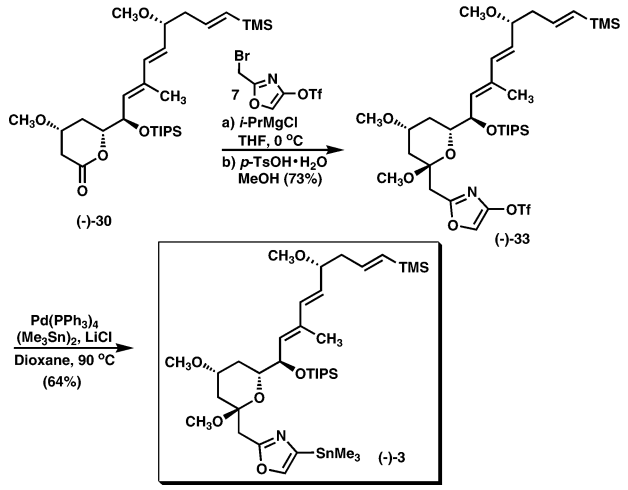
(24) Deactivated silica gel (prepared as a 10% water/silica gel (v/v) slurry) was utilized to mitigate the acidity of silica gel, preventing hydrolysis of the enol−acetal.

(25) Comparison of the ^{1}HNMR spectrum of (+)-**24** with that of the first generation synthesis confirmed the stereochemical outcome of the methylation.

from our first-generation synthesis, we envisioned installation of an *E*-vinylsilane as a surrogate for the phorboxazole vinyl bromide. After union with macrocycle (+)-**4**, bromo-desilylation was expected to afford protected phorboxazole A. To this end, semi-reduction of (−)-**28** under Lindlar conditions, afforded *Z*-silane (−)-**29** in 87% yield with 15:1 selectivity (*Z*:*E*, Scheme 7). Initial attempts to isomerize (−)-**29** to the desired *E*-silane under acidic conditions met with little success. Careful examination of the literature revealed that Utimoto had reported the isomerization of both *Z*-vinyl trimethylgermanium and the corresponding silane substrates to the corresponding *E*-isomers employing radical conditions initiated by triethylborane (Et_3B) and $HSnBu_3$.[26] Exposure of (−)-**29** to catalytic Et_3B and $HSnBu_3$ for 24 h furnished the desired *E*-silane (−)-**30** in 89% yield as an inseparable mixture (ca. 5:1 *E*:*Z*) of isomers. Extending the reaction time to 72 h led to (−)-**30** in 83% yield with excellent *E*-selectivity (>20:1 *E*:*Z*). The critical bromo-desilylation event was then examined as a model for the late stage bromide installation on the phorboxazole system. Both the *Z*- and *E*-silanes, (−)-**29** and (−)-**30**, were independently exposed to NBS/CH_3CN to afford the corresponding vinyl bromides [(−)-**31** and (−)-**32**, respectively].

Final elaboration of side chain **3** entailed treatment of oxazole **7**[8] with isopropylmagnesium chloride to induce a facile magnesium−halogen exchange (Scheme 8). Exposure of the derived

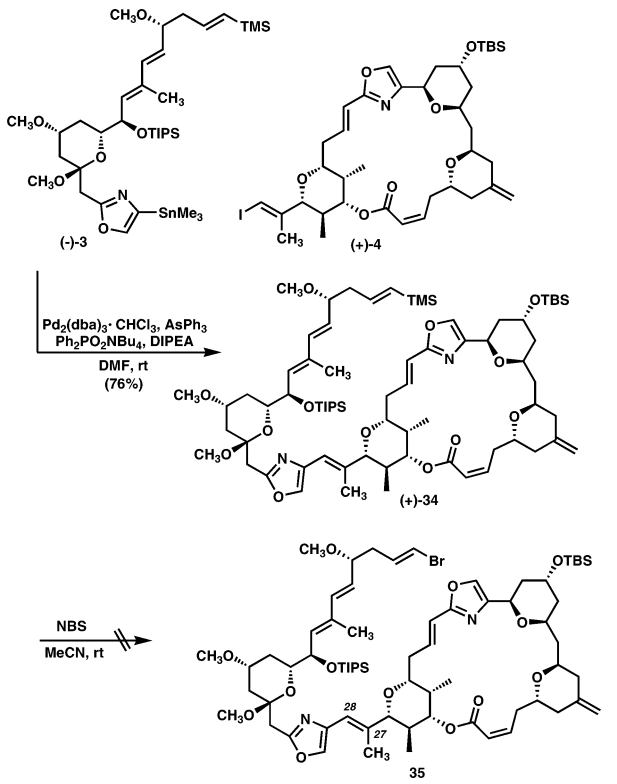
SCHEME 8



Grignard reagent to dienyl lactone (−)-**30** led to the corresponding hemiacetal. Immediate treatment with *p*-TsOH and MeOH provided the expected mixed methyl hemiacetal (−)-**33** in 73% yield for the two steps. Completion of the side chain then called upon a palladium-catalyzed C(29) triflate−trimethylstannane exchange to furnish (−)-**3** in 64% yield. The longest linear sequence to (−)-**3** entailed 17 steps and proceeded in 6.5% overall yield.

Having achieved the syntheses of both the macrocycle and side-chain fragments, we turned to their union, employing a palladium-mediated Stille tactic (Scheme 9).[4g] Exploring a variety of ligands, bases, solvents, and temperature ranges, we found that a catalyst system comprising 1.5 mol % of $Pd_2(dba)_3$·$CHCl_3$ with $AsPh_3$ in combination with diisopropylamine, $Ph_2PO_2NBu_4$, and DMF at room temperature for 15 h

SCHEME 9



provided a 76% yield of the coupled product (+)-**34** on a 5 mg scale. Importantly, isolation entailed direct addition of the reaction mixture to a silica gel column. The additive $Ph_2PO_2NBu_4$ has been shown by Liebeskind to sequester the transmetalation byproduct $XSnR_3$ and prevent entry into the Stille catalytic cycle.[27] In our case, $Ph_2PO_2NBu_4$ afforded a dramatic increase in yield, indicating the involvement of $ISnMe_3$ in the catalytic cycle.[28,29] To complete the second-generation total synthesis of (+)-phorboxazole A, all that remained was bromodesilylation at C(46), followed by global deprotection. However, upon treatment of (+)-**34** with NBS/MeCN, conditions that proved successful in the side-chain model study, the expected protected (+)-phorboxazole A was not obtained. Instead, bromination occurred at the C(27−28) trisubstituted olefin as defined by ^1H NMR. Unable to circumvent the reactivity of the C(27−28)-trisubstituted olefin, we turned to our first-generation route to complete phorboxazole A (**1**), as by this time we recognized C(46)-chlorophorboxazole A to be the more important target for large-scale synthesis; see the accompanying paper.[31]

Stille union of macrocycle vinyl iodide (+)-**4** with the C(45−46) TMS-alkyne side chain (−)-**36** delivered (+)-**37** comprising the full phorboxazole carbon backbone (Scheme 10); the yield was 68%. Treatment with NBS and $AgNO_3$ then provided the corresponding bromoalkyne in excellent yield (95%), which upon exposure to $PdCl_2(PPh_3)_2$ and $HSnBu_3$ delivered an inseparable mixture of external and internal vinyl stannanes (ca. 6:1).[30]

(26) Taniguchi, M.; Nozaki, K.; Miura, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 349.

(27) Alfred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748.

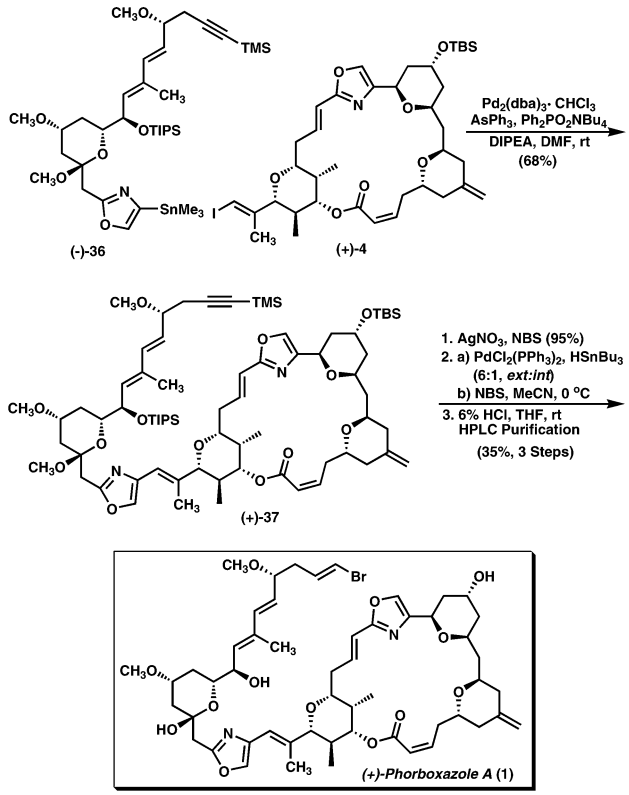
(28) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.

(29) (a) Casado, A. L.; Espinett, P. *J. Am. Chem. Soc.* **1998**, *120*, 8978. (b) Amatore, C.; Bahsoun, A. A.; Jutand, A.; Meyer, G.; Nededi Ntepe, A.; Ricard, L. *J. Am. Chem. Soc.* **2003**, *125*, 4212.

(30) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.

(31) Smith, A. B., III; Razler, T. M.; Meis, R. M.; Pettit, G. R. *J. Org. Chem.* **2008**, *74*, 1201.

SCHEME 10



Without purification, treatment with NBS/MeCN furnished the desired brominated product, which again proved inseparable via silica gel chromatography. Global deprotection employing 6% HCl/THF at room temperature, conditions developed in our first-generation synthesis, led to the fully deprotected product as a 6:1 external/internal mixture of vinyl bromides. Separation by reversed-phase chromatography delivered (+)-phorboxazole A (**1**) in a combined yield of 35% for the three steps.[4g]

In summary, an effective second-generation total synthesis of (+)-phorboxazole A (**1**) has been achieved, with an improved longest linear sequence of 24 steps and an overall yield of 4.6%, compared to our first-generation route (27 steps and 3.1%). Importantly, improved Petasis−Ferrier union/rearrangement conditions were developed, permitting access to multigram quantities of the C(11−15) tetrahydropyranone (−)-**19**. In addition, a convenient method to access both *E*- and *Z*-vinyl bromides from TMS-protected alkynes was developed employing a highly stereoselective radical vinylsilane isomerization. Robust Stille coupling conditions were also identified which enabled the efficient union of the advanced fragments, vinyl iodide macrocycle (+)-**4**, and oxazole stannane sidechains (−)-**3** and (−)-**36**.

Importantly, our second-generation synthesis of (+)-phorboxazole A provided the resources to initiate an analogue program. In the following publication,[31] we will detail the design, total synthesis, and biological evaluation of a series of C(45−46), C(11−15), and C(2−3) phorboxazole congeners. Through these studies, the more readily available C(46)-chlorophorboxazole A was identified as an analogue possessing picomolar tumor cell growth inhibitory avtivity. The C(46) chloro congener thus became our target for preparative-scale elaboration.

Experimental Section

In the sections to follow, key transformations are described; for full details of this synthetic venture, see the Supporting Information.

Preparation of Cyclic Enone (−)-11 (Keck Procedure). Trifluoroacetic acid (TFA, 0.029 mL, 0.384 mmol) was added to a solution of *R*-(+)-BINOL (5.50 g, 19.2 mmol), distilled Ti(O-*i*-Pr)$_4$ (2.83 mL, 9.60 mmol), and 4 Å molecular sieves (36.9 g) in Et_2O (320 mL) at rt under an atmosphere of argon.[32] After the reaction mixture was heated for 1 h at 35 °C, the slurry was cooled to rt, where aldehyde **10** (30.0 g, 96.0 mmol) in Et_2O (107 mL) was added via cannula as a steady stream. The reaction mixture was then cooled to −78 °C, and Danishefsky's diene (28.0 mL, 144 mmol) was added via cannula. After being stirred for 10 min, the reaction mixture was warmed to rt and stirred for 24 h. A solution of saturated $NaHCO_3$ (20 mL) was added, and the reaction mixture was stirred for 1 h. At this point, the reaction mixture was filtered through a pad of Celite and the filtrate was washed with saturated $NaHCO_3$ (200 mL, 1×) and brine (200 mL, 1×), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was dissolved in CH_2Cl_2 (600 mL) and cooled to 0 °C. TFA (40 mL) was added via syringe and the reaction mixture stirred for 1 h, quenched with saturated $NaHCO_3$ (800 mL), and extracted with CH_2Cl_2 (1 L, 3×). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. Removal of BINOL was accomplished via silica gel chromatography (90/10/1, $CHCl_3$/Et_2O/Et_3N). Further purification of the resultant oil via silica gel chromatography (20% EtOAc/hexanes) afforded enone (−)-**11** (27.4 g, 75% yield, 92% ee) as a clear oil. Enantiomeric excess was determined by chiral HPLC: Chiralcel OD, 98:2 hexanes/iPrOH, 0.75 mL/min, 50 μL injection loop); $[\alpha]^{20}_D$ −35.8 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 2980 (s), 1670 (s), 1595 (w), 1280 (s), 1100 (s) cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.64 (m, 4H), 7.30 (m, 6H), 7.26 (d, J = 6.0 Hz, 1H), 5.37 (dd, J = 6.0, 1.0 Hz, 1H), 4.66 (m, 1H), 3.85 (ddd, J = 13.0, 10.5, 8.2 Hz, 1H), 3.78 (ddd, J = 10.7, 5.5, 5.3 Hz, 1H), 2.46 (m, 2H), 2.00 (m, 1H), 1.88 (m, 1H), 1.02 (s, 9H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 192.4, 163.0, 135.5, 133.5, 129.8, 127.7, 107.1, 59.2, 41.9, 37.2, 29.8, 19.1; high-resolution mass spectrum (ES, NH_3) *m*/*z* 381.1888 [(M + H)$^+$; calcd for $C_{23}H_{29}O_3Si$: 381.1885].

Preparation of Cyclic Enone (−)-11 (Jacobsen Procedure). A solution of aldehyde **10** (70.5 g, 226.0 mmol) in acetone (100 mL) was added via cannula to a slurry of 4 Å molecular sieves (45 g) and Jacobsen's Cr(III) catalyst (1.53 g, 3.38 mmol) in acetone (350 mL). The reaction mixture was stirred at rt for 3 h, at which point Danishefsky's diene (65.8 mL, 338.0 mmol) was added and the reaction mixture was stirred for 15 h. The reaction mixture was diluted with THF (400 mL) and cooled to 0 °C, and TFA (23.5 mL) was added over 1.5 h via syringe. After the addition was complete, the reaction mixture was stirred for an additional 30 min, warmed to rt, and diluted with 2/1 hexanes/ether (1 L). The reaction mixture was then washed with water (1 L, 2×), followed by saturated aqueous $NaHCO_3$ (1 L, 1×) and saturated aqueous NaCl (1 L, 1×). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification via silica gel chromatography (10% EtOAc/hexanes) afforded cyclic enone (−)-**11** (73.1 g, 85% yield, 95% ee) as a clear oil. Enantiomeric excess was determined by chiral HPLC: Chiralcel OD, 98:2 hexanes/iPrOH, 0.75 mL/min, 50 μL injection loop).

Preparation of *trans*-Tetrahydropyranone Thio-ester (−)-SI$_1$. To a solution of enone (−)-**11** (50.4 g, 132.4 mmol) and scandium triflate [Sc(OTf)$_3$] (0.65 g, 1.32 mmol, added as a solid) in dichloromethane (662 mL) under argon was added dropwise the TMS-enol ether derived from ethyl thioacetate (35.0 g, 198.6 mmol) at −78 °C over 2 h. Once the addition was complete, the reaction

(32) The 4 Å molecular sieves were purchased as an activated powder (< 50 μm). Activation at 100 °C for 2.5 h under atmospheric pressure proved optimal.

mixture was stirred for an additional 15 min at −78 °C. When the starting enone was consumed (as monitored by TLC), a solution of methanol/pyridine (1/1, 750 mL) was added dropwise over 3 h. Once the addition was complete, the −78 °C bath was removed and the reaction was warmed to rt. After 1 h and 30 min at rt, the layers of the biphasic mixture were separated and the aqueous layer was extracted with dichloromethane (300 mL, 3×). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification via silica gel chromatography (10% EtOAc/hexanes) afforded *trans*-tetrahydropyranone thio-ester (−)-**SI$_1$** (60.9 g, 95%) as a light yellow oil: $[\alpha]^{20}_D$ −9.1 (*c* 2.3, $CHCl_3$); IR ($CHCl_3$) 2931 (m), 2857 (m), 1719 (s), 1685 (s), 1472 (w), 1428 (m), 1112 (s), 998 (w), 823 (w), 739 (m), 614 (m) cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.65 (m, 4H), 7.38 (m, 6H), 4.50 (m, 1H), 4.41 (ddd, J = 8.6, 5.7, 5.5 Hz, 1H), 3.79 (ddd, J = 10.5, 7.8, 5.4 Hz, 1H), 3.71 (m, 1H), 2.84 (m, 3H), 2.65 (dd, J = 14.9, 5.8 Hz, 1H), 2.58 (ddd, J = 14.5, 5.3, 1.1 Hz, 1H), 2.53 (ddd, J = 14.5, 4.7, 1.3 Hz, 1H), 2.33 (ddd, J = 14.7, 7.6, 1.1 Hz, 1H), 2.30 (ddd, J = 14.5, 6.2, 1.3 Hz, 1H), 1.89 (m, 1H), 1.68 (m, 1H), 1.20 (app t, J = 7.4 Hz, 3H), 1.05 (s, 9H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 206.2, 195.7, 135.5, 133.7, 133.6, 129.6, 129.5, 127.7, 70.0, 68.7, 59.9, 48.7, 46.5, 46.2, 36.7, 26.9, 23.5, 19.2, 14.5; high-resolution mass spectrum (ES^+) *m*/*z* 507.2024 [$(M + Na)^+$; calcd for $C_{27}H_{36}O_4SSiNa$ 507.2001].

Preparation of Tetrahydropyranone (−)-19. Under an argon atmosphere, Cp_2TiMe_2 (0.7 M/THF, 206.5 mL, 144.6 mmol) was added to a solution of dioxanone (−)-**17** (17.2 g, 24.1 mmol) and ethyl pivalate (1.94 mL, 12.0 mmol) in THF (240 mL). The orange solution was heated to 65 °C with stirring in the absence of light and monitored by TLC. After 15 h, an additional charge of Cp_2TiMe_2 (0.7 M/THF, 137.7 mL, 96.4 mmol) was added along with ethyl pivalate (1.94 mL, 12.0 mmol), and the dark orange solution was allowed to stir at 65 °C. After an additional 10 h of stirring, Cp_2TiMe_2 (0.7 M/THF, 68.9 mL, 48.1 mmol) was added in addition to ethyl pivalate (1.94 mL, 12.0 mmol). After 15 h of additional stirring at 65 °C, the reaction was deemed complete by TLC. The dark orange reaction mixture was cooled to rt and diluted with hexanes (0.5 L) in order to precipitate Cp_2TiO. The orange reaction slurry was filtered through a pad of silica gel and washed with 40% EtOAc/hexanes (2.5 L). The resultant filtrate was concentrated under reduced pressure to afford enol−acetal (−)-**18** (14.5 g) as a light orange, clear oil that was used as is in the subsequent Petasis−Ferrier rearrangement.

Me_2AlCl (1 M/hexanes, 26.5 mL, 26.5 mmol) was added dropwise over 30 min to a stirring slurry of Cs_2CO_3 (10.6 g, 32.6 mmol) in CH_2Cl_2 (500 mL) at rt under an argon atmosphere. After stirring for 1 h, a solution of enol−acetal (−)-**18** (14.5 g, 20.4 mmol) in CH_2Cl_2 (317 mL) was added to the Me_2AlCl/Cs_2CO_3 solution at rt via cannula as a steady stream over 10 min. After 2 h, the reaction was quenched by dropwise addition of a saturated aqueous solution of $NaHCO_3$ (263 mL), and the bisphasic mixture was stirred vigorously at rt. After 15 min, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (150 mL, 2×). The combined organic extracts were washed with a saturated solution of NaCl (1×, 150 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford a clear, colorless oil. Purification via silica gel chromatography (40% EtOAc/hexanes) afforded tetrahydropyranone (−)-**19** (11.2 g, 66% yield over two steps) as a clear oil: $[\alpha]^{20}_D$ −14.7 (*c* 0.20, $CHCl_3$); IR ($CHCl_3$) 2940 (s), 1720 (s), 1105 (s) cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.65 (m, 4H), 7.49 (s, 1H), 7.38 (m, 6H), 7.25 (m, 2H), 6.87 (dd, J = 6.6, 2.1 Hz, 2H), 4.72 (s, 2H), 4.52 (s, 2H), 4.51 (s, 2H), 4.50 (m, 1H), 4.00 (m, 1H), 3.92 (m, 1H), 3.82 (m, 1H), 3.79 (s, 3H), 3.74 (m, 1H), 3.67 (m, 1H), 2.69 (dd, J = 14.4, 11.8 Hz, 1H), 2.58 (dt, J = 14.3, 2.6 Hz, 1H), 2.49 (ddd, J = 14.5, 2.3, 2.1 Hz, 1H), 2.33 (m, 3H), 2.16 (m, 1H), 2.02 (m, 2H), 1.78 (m, 1H), 1.65 (m, 2H), 1.04 (s, 9H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 205.6, 161.3, 159.5, 141.7, 140.4, 135.9, 135.5, 133.9, 129.7, 129.6, 129.2, 127.7, 113.9, 110.5, 74.3, 72.3, 72.8, 71.7, 69.0, 68.2, 63.5, 60.5, 55.3, 47.2, 46.3, 39.6, 39.5, 39.4, 36.4, 26.9, 19.2; high-resolution mass spectrum (ES, NH_3) *m*/*z* 732.3359 [$(M + Na)^+$, calcd for $C_{42}H_{51}O_7NSiNa$ 732.3333].

Preparation of Methylated Tetrahydropyranone (+)-24. Under an argon atmosphere in a flame-dried 250 mL round-bottom flask at rt, lithium hexamethyldisilazane (LiHMDS) (1.19 M/THF) (9.92 mL, 11.8 mmol) was diluted with THF (9.92 mL). and the solution was cooled to −78 °C with stirring. After 20 min, a solution of tetrahydropyranone (+)-**23** (6.03 g, 10.7 mmol) in THF (53.5 mL) was added dropwise via cannula over 45 min to the diluted LHMDS solution. After 30 min at −78 °C, the solution was warmed to −20 °C and stirred for 1 h. A cooled solution (−20 °C) of methyl iodide (2.00 mL, 32.2 mmol) and HMPA (5.60 mL, 32.2 mmol) in THF (21.5 mL) was then added dropwise via cannula over 1 h, and the reaction mixture was stirred at this temperature. After 2 h, the reaction was quenched at −20 °C with saturated aqueous NH_4Cl (130 mL), warmed to rt, stirred for 30 min, and then extracted with Et_2O (150 mL, 3×). The combined organic extracts were washed with saturated aqueous NH_4Cl (200 mL) followed by saturated aqueous NaCl (200 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification via silica gel chromatography (2.5% EtOAc/hexanes) furnished methylated tetrahydropyranone (+)-**24** (4.20 g, 68%; 91% based on recovered starting material), as a colorless oil and starting material (+)-**23** (1.53 g, 25%). (+)-**24**: $[\alpha^{20}]_D$ +12.6 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 2930 (m), 2857 (m), 1715 (s), 1457 (w), 1428 (m), 1282 (w), 1197 (w), 1112 (s), 822 (w), 738 (m), 701 (s) cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.64 (m, 4H), 7.40 (m, 6H), 6.25 (d, J = 0.6 Hz, 1H), 3.93 (ddd, J = 8.8, 4.0, 2.4 Hz, 1H), 3.77 (ddd, J = 10.0, 10.0, 4.7 Hz, 1H), 3.70 (ddd, J = 10.0, 4.9, 4.9 Hz, 1H), 3.66 (d, J = 10.5 Hz, 1H), 2.65 (dddd, J = 14.4, 10.5, 6.6, 3.9 Hz, 1H), 2.43 (dddd, J = 11.8, 7.1, 4.7, 2.4 Hz, 1H), 1.90 (d, J = 0.5 Hz, 3H), 1.85 (m, 1H), 1.64 (m, 1H), 1.15 (d, J = 7.1 Hz, 3H), 1.04 (s, 9H), 0.86 (d, J = 6.6 Hz, 3H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 211.8, 145.5, 135.5, 133.7, 133.6, 129.6, 129.4, 127.7, 88.0, 81.7, 75.7, 60.0, 49.3, 43.2, 34.6, 26.8, 19.2, 18.8, 11.2, 9.3; high-resolution mass spectrum (ES^+) *m*/*z* 599.1467 [$(M + Na)^+$, calcd for $C_{28}H_{37}O_3SiINa$ 599.1454].

Preparation of Vinyl Iodide (+)-26. To a solution of mesylate (−)-**27** (2.02 g, 2.57 mmol) in anhydrous DMF (549 mL) at rt under an argon atmosphere was added dropwise tri-*n*-butylphosphine (2.57 mL, 10.3 mmol). After 36 h of stirring at rt, aldehyde (+)-**8** (1.25 g, 2.57 mmol) in anhydrous DMF (295 mL) was added dropwise via cannula over 10 min followed immediately by dropwise addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.77 mL, 5.14 mmol) via syringe over 15 min. After being stirred at rt for 3 h, the reaction mixture was diluted with diethyl ether (400 mL) and poured into water (400 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (150 mL, 5×). The combined organic extracts were washed with saturated aqueous NaCl (350 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification via silica gel chromatography (20% EtOAc/hexanes) afforded vinyl iodide (+)-**26** (2.86 g, 96%, 20:1, *E*:*Z*) as a white foam: $[\alpha]^{20}_D$ +22.7 (*c* 1.0, $CHCl_3$); IR (neat) 2967 (b), 2930 (s), 1487 (m), 1258 (s), 1110 (s), 776 (s) cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.64 (m, 4H), 7.35 (m, 6H), 6.89 (d, J = 1.9 Hz, 1H), 6.82 (dd, J = 8.2, 1.9 Hz, 1H), 6.58 (m, 1H), 6.32 (d, J = 16.0 Hz, 1H), 6.23 (s, 1H), 4.82 (dd, J = 11.2, 1.9 Hz, 1H), 4.70 (s, 2H), 4.56 (d, J = 11.2 Hz, 1H), 4.26 (d, J = 11.2 Hz, 1H), 4.24 (m, 1H), 3.95 (m, 3H), 3.87 (s, 3H), 3.65 (m, 2H), 3.50 (d, J = 10.4 Hz, 1H), 3.45 (ddd, J = 14.1, 7.1, 1.8 Hz, 1H), 3.12 (dd, J = 10.4, 4.5 Hz, 1H), 2.52 (m, 1H), 2.34 (m, 3H), 2.08 (m, 1H), 2.00 (dd, J = 13.0, 7.0 Hz, 1H), 1.93 (dd, J = 13.0, 7.0 Hz, 1H), 1.86 (m, 2H), 1.82 (s, 3H), 1.80 (m, 2H), 1.75 (m, 4H), 1.61 (m, 3H), 1.48 (m, 3H), 1.06 (s, 9H), 0.97 (d, J = 6.7 Hz, 3H), 0.91 (s, 9H), 0.76 (d, J = 6.3 Hz, 3H), 0.06 (s, 6H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 160.7, 149.0, 148.6, 146.3, 143.3, 142.3, 135.6, 135.5, 135.1, 134.2, 133.9, 133.8, 130.9, 129.5, 127.6, 120.2, 118.8, 111.1, 110.1, 87.5, 82.8, 80.9, 77.4, 77.2, 69.9, 69.0, 68.8, 67.4, 64.7, 60.6, 55.9, 55.7, 39.6, 39.3, 39.2, 38.9, 38.2, 36.6, 36.2, 33.7, 33.5, 33.3,

30.3, 26.8, 25.8, 19.1, 18.0, 13.5, 5.7, −4.8, −4.9; high-resolution mass spectrum (ES^+) *m*/*z* 1182.4735 [$(M + Na)^+$, calcd for $C_{61}H_{86}INO_9Si_2Na$ 1182.4886].

Preparation of Protected C(45−46)-TMS-alkyne-phorboxazole (+)-37. Vinyl iodide macrocycle (+)-**4** (13.8 mg, 0.017 mmol) and C(45−46)-TMS-alkyne side chain (−)-**36** (21.0 mg, 0.026 mmol) were combined in a flame-dried round-bottom flask (5 mL), azeotroped from benzene (2 mL, 3×), and dried under vacuum for 2 h. To the flask under an argon atmosphere were added tris(dibenzylideneacetone)dipalladium−chloroform adduct [$Pd_2(dba)_3$•$CHCl_3$] (3.6 mg, 0.003 mmol), triphenylarsine ($AsPh_3$) (6.4 mg, 0.021 mmol), and $Ph_2PO_2NBu_4$ (12 mg, 0.026 mmol) followed by introduction of DMF (0.17 mL, sparged with argon, 30 min) and diisopropylethylamine (DIPEA) (0.003 mL, 0.017 mmol). After being stirred for 16 h at rt, the light brown reaction mixture was introduced directly onto a silica gel column (20% EtOAc/hexanes → 30% EtOAc/hexanes) to afford protected C(45−46)-TMS-alkynyl-phorboxazole (+)-**37** (14.9 mg, 68%) as a light yellow oil: $[\alpha]^{20}_D$ +1.3 (*c* 0.2, $CHCl_3$); IR (neat) 2925 (b), 1718 (s), 1456 (b), 1250 (s), 1187 (s), 1091 (s), 1053 (b), 840 (s) cm^{-1}; ^{1}HNMR (500 MHz, C_6D_6) δ 6.96 (s, 1H), 6.90 (m, 1H), 6.37 (s, 1H), 6.32 (d, *J* = 15.7 Hz, 1H), 6.20 (d, *J* = 15.9 Hz, 1H), 5.79 (dd, *J* = 11.2, 2.3 Hz, 1H), 5.69 (dd, *J* = 15.7, 7.3 Hz, 1H), 5.57 (d, *J* = 8.9 Hz, 1H), 5.47 (ddd, *J* = 10.7, 10.5, 2.9 Hz, 1H), 5.18 (s, 1H), 4.96 (dd, *J* = 11.3, 2.0 Hz, 1H), 4.77 (m, 2H), 4.62 (dd, *J* = 11.2, 4.4 Hz, 1H), 4.39 (m, 1H), 4.25 (app t, *J* = 10.4 Hz, 1H), 4.08 (m, 1H), 4.03 (d, *J* = 2.6 Hz, 1H), 3.95 (m, 1H), 3.76 (m, 1H), 3.69 (app t, *J* = 6.9 Hz, 1H), 3.68 (m, 1H), 3.52 (dd, *J* = 9.4, 4.6 Hz, 1H), 3.45 (d, *J* = 10.1 Hz, 1H), 3.41 (s, 3H), 3.34 (d, *J* = 14.7 Hz, 1H), 3.28 (app t, *J* = 4.8 Hz, 1H), 3.23 (app t, *J* = 5.0 Hz, 1H), 3.09 (s, 3H), 3.08 (s, 3H), 3.04 (d, *J* = 11.4 Hz, 1H), 2.95 (d, *J* = 14.8 Hz, 1H), 2.66 (app t, *J* = 6.3 Hz, 1H), 2.60 (m, 1H), 2.58 (dd, *J* = 16.7, 5.7 Hz, 1H), 2.44 (dd, *J* = 16.7, 6.8 Hz, 1H), 2.42 (m, 2H), 2.37 (dd, *J* = 12.8, 5.5 Hz, 1H), 2.17 (dd, *J* = 10.0, 7.7 Hz, 1H), 2.10 (m, 1H), 2.09 (d, *J* = 0.6 Hz, 3H), 2.02 (d, *J* = 11.8 Hz, 1H), 1.98 (d, *J* = 13.0 Hz, 1H), 1.77 (d, *J* = 0.8 Hz, 3H), 1.65 (m, 3H), 1.49 (d, *J* = 13.2 Hz, 1H), 1.35 (m, 3H), 1.17 (m, 22H), 1.05 (d, *J* = 6.9 Hz, 3H), 0.94 (s, 9H), 0.77 (d, *J* = 6.5 Hz, 3H), 0.24 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}CNMR (125 MHz, C_6D_6) δ 165.8, 161.7, 160.0, 145.5, 143.8, 143.0, 139.2, 138.2, 137.3, 136.8, 135.0, 134.4, 133.8, 133.5, 121.4, 120.1, 119.5, 110.5, 104.6, 100.8, 90.0, 86.8, 81.0, 80.2, 78.7, 74.7, 74.1, 73.7, 72.7, 69.9, 69.3, 67.7, 65.9, 56.7, 55.6, 48.3, 42.4, 40.5, 40.4, 40.0, 37.9, 36.4, 36.3, 34.9, 33.1, 32.4, 31.2, 30.5, 27.9, 26.3, 18.7, 18.6, 14.6, 14.1, 13.7, 13.2, 6.6, 1.7, 0.6, −4.5, −4.4; high-resolution mass spectrum (ES^+) *m*/*z* 1321.7641 [$(M + Na)^+$, calcd for $C_{72}H_{114}N_2O_{13}Si_3Na$ 1321.7626].

Preparation of Phorboxazole A (+)-1. Protected phorboxazole A, under an argon atmosphere, was dissolved in freshly distilled THF (1.7 mL) followed by the dropwise addition of 6% HCl (0.67 mL) at rt. After 96 h, the reaction mixture was cooled to 0 °C and poured into saturated aqueous sodium bicarbonate (5 mL) and extracted with dichloromethane (5 mL, 3×) followed by ethyl acetate (5 mL, 3×). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification via silica gel chromatography (100% EtOAc → 10% methanol/EtOAc) afforded phorboxazole A (+)-**1** (1.1 mg, 6:1 C(46)/C(45) vinyl bromide). Further purification via reverse phase HPLC (Zorbax C_{18} column, acetonitrile/H_2O (55/45) eluent) afforded phorboxazole A (+)-**1** (0.90 mg, 35% over three steps after HPLC purification) which matched the ^{1}HNMR, $[\alpha]^{20}_D$, and high-resolution mass spectrum of natural (+)-phorboxazole A: $[\alpha]^{20}_D$ +43.4 (*c* 0.04, CH_2Cl_2); high-resolution mass spectrum (ES^+) *m*/*z* 1045.4029 [$(M + Na)^+$, calcd for $C_{53}H_{71}N_2O_{13}BrNa$ 1045.4037].

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Supporting Information Available: Experimental procedures and analytical data for all new compounds. Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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