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Synthesis and Biological Evaluation of Phorboxazole Congeners Leading to the Discovery and Preparative-Scale Synthesis of (+)-Chlorophorboxazole A Possessing Picomolar Human Solid Tumor Cell Growth Inhibitory Activity

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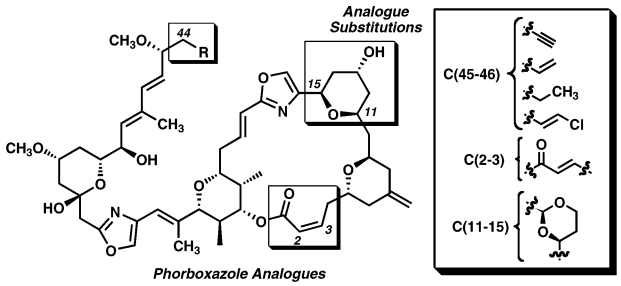

Highly convergent syntheses of eight phorboxazole congeners and their evaluation against a diverse panel of human solid tumor cancer cell lines have been achieved. Specifically, the C(45−46) alkyne, alkene, and alkane phorboxazole A analogues [(+)-**4**−(+)-**6**] were constructed and found to display single digit nanomolar cell growth inhibitory activities in a series of human cancer cell lines. The structurally simplified C(11−15)-acetal congener (+)-**20*Z*** also proved potent albeit reduced (cf. 34.6 nM) when evaluated against the same cell line panel. Importantly, (+)-C(46)-chlorophorboxazole A (**3**) displayed picomolar (pM) inhibitory activity in several cell lines.

Since the isolation and structure elucidation of (+)-phorboxazoles A and B (**1** and **2**) by Searle and Molinski in 1995,[1] a number of studies directed at their synthesis have appeared, including our own contributions to this area.[2−4] Biological studies geared toward identification of the mode of action responsible for the potent tumor cell growth inhibitory activity, however, have been greatly impeded, given the scarcity and structural complexity of the phorboxazoles. As a result, elucidation of their cellular target(s) and biological mechanism of action remained almost completely unknown until the recent study by the Forsyth group employing a fluorescent-labeled phorboxazole analogue demonstrating that the phorboxazoles induce an extranuclear association between the signaling proteins KRIF and cdk4.[5] Specifically, perturbation of cdk4 migration across the nuclear membrane by **1** and **2** precludes retinoblastoma phosphorylation, leading to cell-cycle arrest in the S-phase.[5]

Earlier, the Forsyth group also reported that replacement of the C(45−46) *E*-vinyl bromide structural unit with an alkyne leads to an analogue which retains potent tumor cell growth

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(1) (a) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126. (b) Searle, P. A.; Molinski, T. F.; Brzezinski, L. J.; Leahy, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 9422. (c) Molinski, T. F. *Tetrahedron Lett.* **1996**, *37*, 7879.

(2) Phorboxazole A total syntheses: (a) Forsyth, C. J.; Ahmed, F.; Cink, R. D.; Lee, C. S. *J. Am. Chem. Soc.* **1998**, *120*, 5597. (b) Smith, A. B., III; Verhoest, P. R.; Minbiole, K. P.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 4834. (c) Smith, A. B., III; Minbiole, K. P.; Verhoest, P. R.; Schelhaas, M. *J. Am. Chem. Soc.* **2001**, *123*, 10942. (d) González, M. A.; Pattenden, G. *Angew. Chem. Int. Ed.* **2003**, *42*, *1255*. (e) Pattenden, G.; González, M. A.; Little, P. B.; Millan, D. S.; Plowright, A. T.; Tornos, J. A.; Ye, T. *Org. Biomol. Chem.* **2003**, *1*, 4173. (f) Williams, D. R.; Kiryanov, A. A.; Emde, U.; Clark, M. P.; Berliner, M. A.; Reeves, J. T. *Angew. Chem. Int. Ed.* **2003**, *42*, 1258. (g) Smith, A. B., III; Razler, T. M.; Ciavarri, J. P.; Hirose, T.; Ishikawa, T. *Org. Lett.* **2005**, *7*, 4399. (h) White, J. D.; Kuntiyong, P.; Lee, T. H. *Org. Lett.* **2006**, *8*, 6039. (i) White, J. D.; Lee, T. H.; Kunttiyong, P. *Org. Lett.* **2006**, *8*, 6043.

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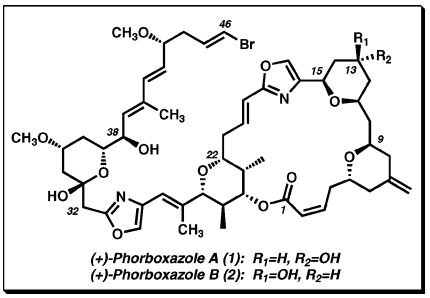


inhibitory activity.[6] In addition, they noted that conversion of the C(33) hemiacetal to the corresponding *O*-methyl analogue yields a slightly less potent analogue, however still retaining nanomolar activity.

Herein we outline our efforts to identify simplified phorboxazole analogues that retain potent tumor cell growth inhibitory activity. Specifically, we will describe the synthesis of a series of C(2−3), C(11−15), and C(45−46) analogues and their evaluation against a diverse panel of human tumor cell lines.[7] In conjunction with these efforts, we have achieved an effective synthesis of (+)-C(46)-chlorophorboxazole A **3**, synthetically a more accessible phorboxazole congener possessing picomolar activity.

Phorboxazole Analogue Syntheses. Having achieved an effective second-generation total synthesis of (+)-phorboxazole A (**1**),[2g] we were in an ideal position to launch a program to identify simplified side-chain and macrocycle analogues that would retain or lead to enhanced inhibitory activity and thereby provide further insight on the functionality required for inhibitory activity. We began the analogue program by considering three regions of the phorboxazole skeleton: the C(45−46) unsaturated unit, the C(2−3) macrocyclic enoate, and the C(11−15) tetrahydropyran (Figure 1). Based upon our second-generation synthesis, these three areas were ideally suited for analogue synthesis. In addition, both electronic and geometric

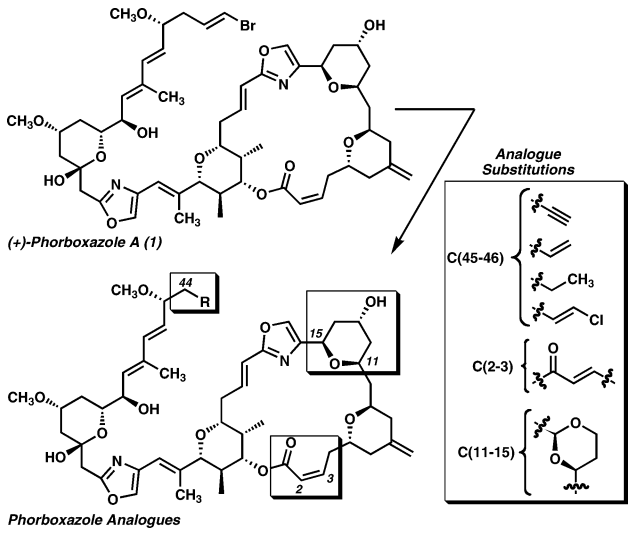
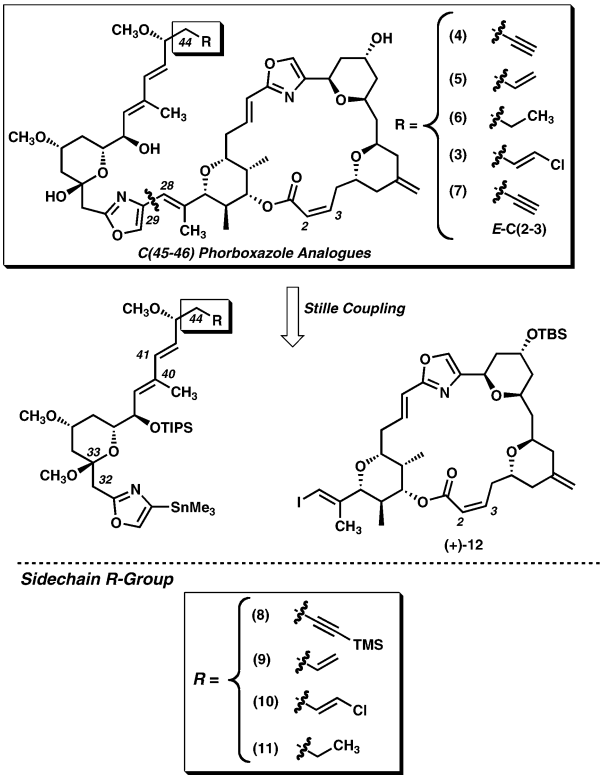


FIGURE 1. Phorboxazole analogues.

effects to the macrocycle could be evaluated at both the C(2−3) and C(11−15) regions.

From a synthetic perspective, the C(45−46) phorboxazole analogues were envisioned to arise via Stille union of the C(45−46) alkyne **8**, alkene **9**, *E*-vinyl chloride **10**, and alkane **11** side chains with both the *Z*- and *E*-C(2−3)-macrocycles (**12*Z*** and **12*E***, respectively, Scheme 1). Manipulation of the alkyne

SCHEME 1



functionality in **8** would give rise to both C(45−46) alkene **9** and *E*-vinyl chloride **10**.[7a] Alkane **11**, however required a more elaborate synthesis.

(3) Phorboxazole B total syntheses: (a) Evans, D. A.; Cee, V. J.; Smith, T. E.; Fitch, D. M.; Cho, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2533. (b) Evans, D. A.; Fitch, D. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2536. (c) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033. (d) Li, D.-R.; Zhang, D.-H.; Sun, C.-Y.; Zhang, J.-W.; Yang, L.; Chen, J.; Liu, B.; Su, C.; Zhou, W.-S.; Lin, G.-Q. *Chem.*−*Eur. J.* **2006**, *12*, 1185. (e) Lucas, B. S.; Gopalsamuthiram, V.; Burke, S. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 769.

(4) (a) Rychnovsky, S. D.; Hu, Y.; Ellsworth, B. *Tetrahedron Lett.* **1998**, *39*, 7271. (b) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217. (c) Jasti, R.; Vitale, J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 9904. (d) Wolbers, P.; Hoffmann, H. M. R.; Sasse, F. *Synlett* **1999**, 1808. (e) Wolbers, P.; Misske, A. M.; Hoffmann, H. M. R. *Tetrahedron Lett.* **1999**, *40*, 4527. (f) Wolbers, P.; Hoffmann, H. M. R. *Synthesis* **1999**, 797. (g) Wolbers, P.; Hoffmann, H. M. R. *Tetrahedron* **1999**, *55*, 1905. (h) Misske, A. M.; Hoffmann, H. M. R. *Tetrahedron* **1999**, *55*, 4315. (i) Schaus, J. V.; Panek, J. S. *Org. Lett.* **2000**, *2*, 469. (j) Huang, H.; Panek, J. S. *Org. Lett.* **2001**, *3*, 1693. (k) Greer, P. B.; Donaldson, W. A. *Tetrahedron Lett.* **2000**, *41*, 3801. (l) Greer, P. B.; Donaldson, W. A. *Tetrahedron* **2002**, *58*, 6009. (m) White, J. D.; Kranemann, C. L.; Kuntiyong, P. *Org. Lett.* **2001**, *3*, 4003. (n) Paterson, I.; Luckhurst, C. A. *Tetrahedron Lett.* **2003**, *44*, 3749. (o) Paterson, I.; Steven, A.; Luckhurst, C. A. *Org. Biomol. Chem.* ***2004***, *2*, *3026.* (p) Lucas, B. S.; Burke, S. D. *Org. Lett.* **2003**, *5*, 3915. (q) Lucas, B. S.; Luther, L. M.; Burke, S. D. *Org. Lett.* **2004**, *6*, 2965.

(5) Forsyth, C. J.; Ying, L.; Chen, J.; La Clair, J. J. *J. Am. Chem. Soc.* **2006**, *126*, 3858.

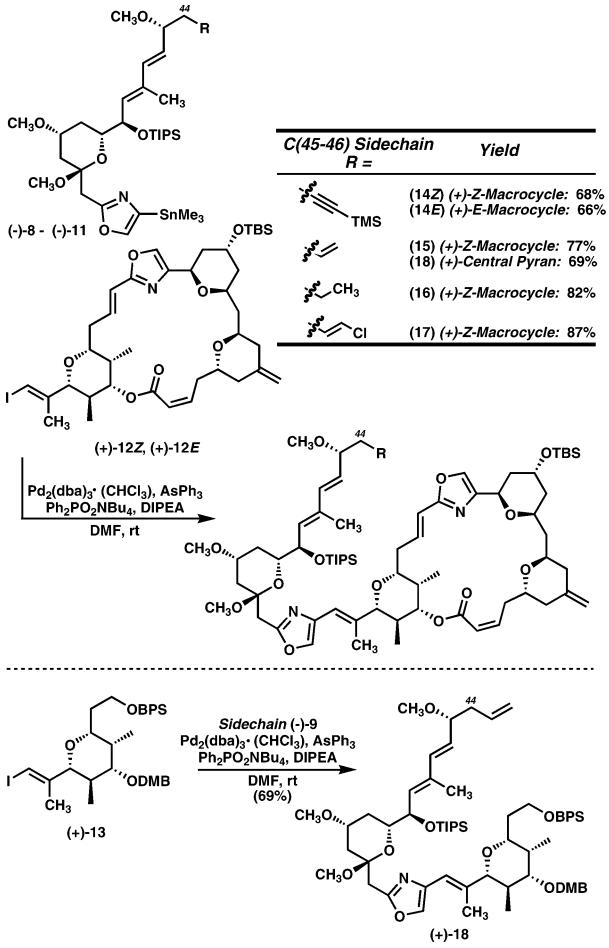
(6) Uckun, F. M.; Forsyth, C. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1181.

(7) (a) Smith, A. B., III; Razler, T. M.; Pettit, G. R.; Chapuis, J.-C. *Org. Lett.* **2005**, *7*, 4403. (b) Smith, A. B., III; Razler, T. M.; Meis, R. M.; Pettit, G. R. *Org. Lett.* **2006**, *8*, 797.

Results and Discussion

Access to the C(45−46) side chain phorboxazole analogues began with Stille union of side chains (−)-**8** to (−)-**11** with the *Z*- and *E*-C(2−3) macrocycles [(+)-**12*Z*** and (+)-**12*E*** (Scheme 2), respectively], as well as with the diminutive C(22−26) central tetrahydropyran (+)-**13**, available from our second-generation phorboxazole synthesis (only the *Z*-macrocycles are shown in Scheme 2). Utilizing the efficient Stille coupling

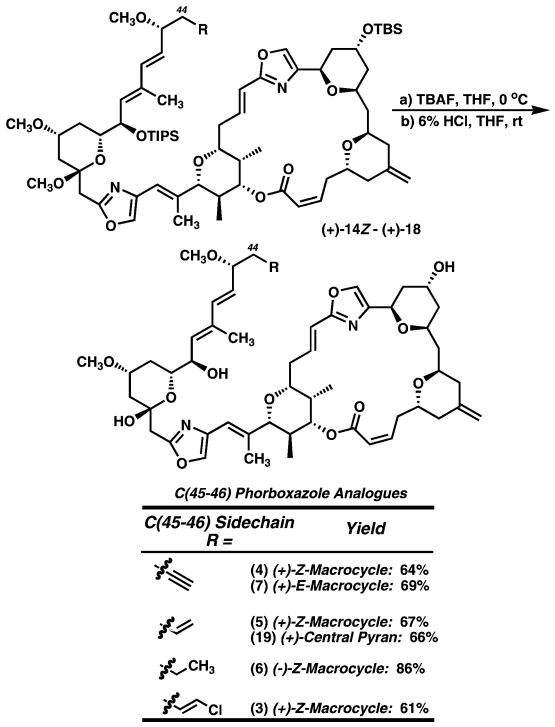
SCHEME 2



protocol developed in our second-generation phorboxazole synthesis,[2g] coupled products consisting of alkyne (+)-**14*Z***, alkene (+)-**15**, alkane (+)-**16**, and *E*-vinyl chloride (+)-**17** were generated in good to excellent yields (cf. 68%, 77%, 82%, and 87% yield, respectively). Similarly, Stille union of the C(45−46) TMS-alkyne side chain (−)-**8** with *E*-C(2−3) macrocycle (+)-**12*E***, and alkene side chain (−)-**9** with the C(22−26) central tetrahydropyran (+)-**13** afforded coupled products (+)-**14*E*** and (+)-**18** in 66% and 69% yield, respectively.

Completion of the C(45−46) side-chain congeners required a final deprotection strategy. Due to the possible sensitivity of such advanced intermediates, both stepwise and global deprotection protocols were examined. Optimal conditions proved to be stepwise treatment with 3 equiv of TBAF to effect initial removal of the TIPS and TBS protecting groups (Scheme 3). Without purification, treatment with 6% HCl then promoted the hydrolysis of the C(33) mixed methyl hemiacetal to furnish the

SCHEME 3



phorboxazole congeners [e.g., (+)-**3**−(+)-**7** and (+)-**19**; again, only the *Z*-macrocycles are shown].[7a]

In addition to the phorboxazole side chain congeners, we also constructed analogues comprising macrocyclic modifications. Substitution of the C(11−15) *cis*-tetrahydropyran for the corresponding C(11−15) acetal, a tactic employed to great advantage by Wender in his bryostatin program,[8] was targeted for synthesis (Figure 2). We reasoned that the acetal would both

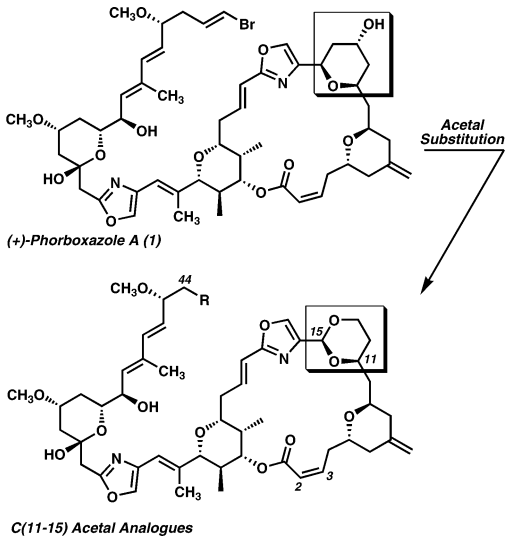
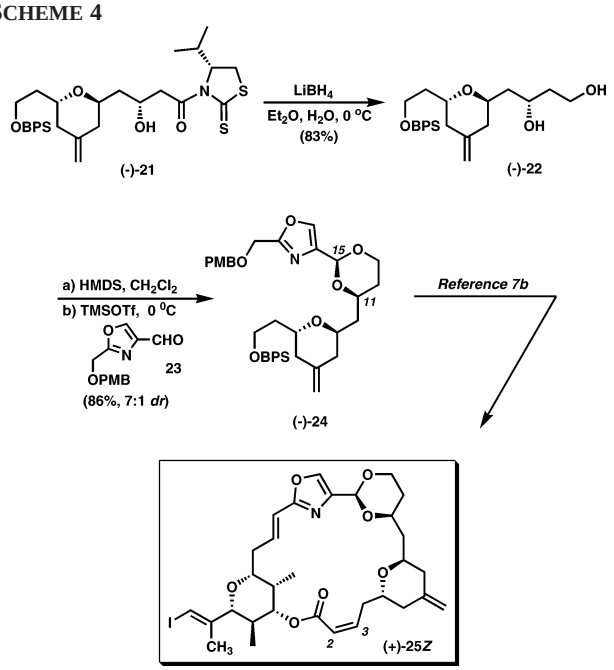


FIGURE 2. C(11−15) acetal analogues.

provide a simplified synthetic target and impart a similar conformational arrangement as the tetrahydropyran. Deletion of the C(13) hydroxyl, however would also provide information on macrocyclic hydrogen-bonding interactions with the phorboxazole cellular targets.[9]

Construction of the *Z*- and *E*-C(2−3)−C(11−15) acetal congeners (**20*Z*** and **20*E***, respectively) began with reduction of *β*-hydroxy imide (−)-**21** with $LiBH_4$ to afford diol (−)-**22** in good yield (Scheme 4).[7b] Bis-silylation with HMDS followed

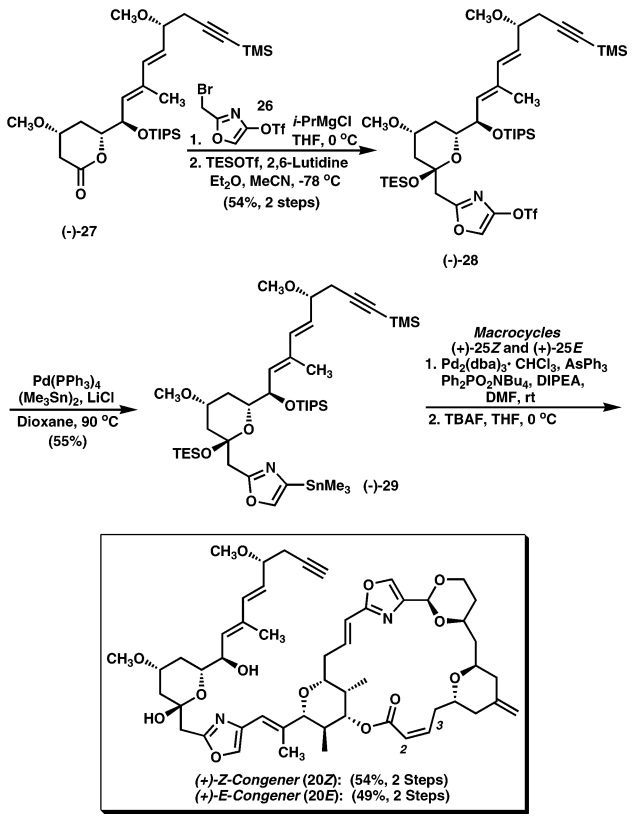
SCHEME 4



by treatment with oxazole aldehyde **23** and TMSOTf at 0 °C then afforded acetal (−)-**24** (86%) as a separable mixture (ca. 7:1) of diastereomers at C(15).[10] Completion of the acetal macrocycles followed a route patterned after our second-generation synthesis: namely, adoption of the Evans protocol to construct the *E*-C(19−20) olefin and the Still−Gennari modified Horner−Emmons olefination to construct the C(2−3) enoate.[2g,3a−c,11] The C(2−3) olefination was not highly selective in our first-generation synthesis;[2g] however, this tactic would provide access to both the *Z*- and *E*-C(2−3) macrocycles (**25*Z*** and **25*E***, respectively), thereby increasing the structural diversity for our SAR study (only the *Z*-macrocycle is shown in Scheme 4).

In our second-generation synthesis,[2g] as well as during the construction of the C(45−46) side-chain analogues, acidic deprotection protocols were employed to effect hydrolysis of the C(33) mixed methyl hemiacetal.[7a] However, given the presence of the C(11−15) acetal in the present series, protection of the C(33) hemiacetal as a silyl ether was undertaken in favor of a fluoride-based tactic[3a−c] to preclude the potential of problematic acidic deacetalization. To this end, addition of the Grignard reagent derived from oxazole **26** to dienyl lactone (−)-**27** gave rise to the corresponding hemiacetal (Scheme 5). After screening several different C(33) protecting groups, including trimethylsilyl and TMS-ethyl, we selected the triethylsilyl (TES)-protecting group for both ease of formation as well as the availability of mild removal conditions. With this scenario in mind, immediate treatment of the corresponding hemiacetal with TESOTf and 2,6-lutidine cleanly provided the C(33) TES-protected hemiacetal (−)-**28**. Conversion to the fully

SCHEME 5



elaborated trimethylstannane (−)-**29** was then achieved employing $Pd(PPh_3)_4$ and $(Me_3Sn)_2$, albeit only in 55% yield, presumably due to decomposition of the TES hemiacetal under the reaction conditions, as lactone (−)-**27** was observed in NMR experiments of the reaction mixture.

Access to the fully elaborated *Z*- and *E*-acetal congeners proceeded with union of oxazole stannane (−)-**29** with both the *Z*- and *E*-acetal macrocycles [(+)-**25*Z*** and (+)-**25*E***] exploiting our phorboxazole Stille coupling protocol.[2g] Pleasingly, the *Z*- and *E*-coupled products were obtained in good yield. Final treatment with 4 equiv of TBAF promoted global removal of the C(46) TMS, C(38) TIPS, and C(33) TES protecting groups to furnish the C(11−15) acetal analogues (+)-**20*Z*** and (+)-**20*E*** in 54% and 49% yield, respectively, over the two steps.[7b]

TABLE 1. Human Cancer Cell Line−Analogue Evaluation

GI_{50} (nM)

C(45-46) Sidechain R =	BXPC-3 Pancreatic	MCF-3 Breast	F-268 CNS	NCI-H460 Non-Small Lung	KM20L2 Colon	DU-145 Prostate
(1) 	6.0	7.0	5.5	3.9	2.9	4.8
(6) 	3.2	3.9	3.5	1.6	1.3	5.0
(5) 	5.6	5.6	5.0	2.8	1.8	3.6
(3) 	0.62	1.7	0.49	0.64	0.38	2.5
 (4) *Z-Macrocycle*	4.5	7.0	7.6	4.2	3.0	5.2
(7) *E-Macrocycle*	200	230	510	200	140	410
(20*Z*) *Z-Acetal*	31.2	18.3	44.1	27.9	11.8	74.2
(20*E*) *E-Acetal*	>1076	883	560	>1076	990	>1076
(19) *Central Pyran*	>10,000	>4,800	>10,000	>10,000	>10,000	>10,000

Biological Evaluation of the Phorboxazole Analogues. With (+)-phorboxazole A (**1**) and the eight phorboxazole analogues in hand, evaluation against a diverse panel of human solid tumor cell lines, including BXPC-3 (pancreatic), MCF-3 (breast), F-268 (CNS), NCI-H460 (non-small lung), KM20L2 (colon), and DU-145 (prostate), was undertaken (Table 1). Several

(8) Wender, P. A.; DeBrabander, J.; Harran, P. G.; Jimenez, J. M.; Koehler, M. F. T.; Lippa, B.; Park, C. M.; Shiozaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4534.

(9) We note that both phorboxazole A and B, epimeric at C(13) display similar biological activities.

(10) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899.

(11) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

analogues were found to be as active as, and in several cell lines, significantly more active than, phorboxazole A (**1**). Inactive analogues were also identified, providing direct evidence for the functionality required for tumor cell growth inhibitory effect.

As a control, evaluation of (+)-phorboxazole A (**1**) against the human cancer cell line panel revealed an average growth inhibition (GI_{50}) of 5.0 nanomolar (nM), a value within experimental error of the previously reported results.[1a−c] Screening the (+)-*Z*-C(2−3)−C(45−46) alkyne congener (+)-**4**[6] against the six cancer cell lines furnished an average GI_{50} of 5.2 nM, a value comparable to that observed by Forsyth.[6] Conversely, (+)-*E*-C(2−3)−C(45−46)-alkyne phorboxazole analogue (+)-**7** was found to be significantly less active than (+)-**1** and (+)-**4**. An average GI_{50} of 281 nM was observed, implicating the importance of the conformational geometry imparted by *Z*-C(2−3) macrocyclic enoate for activity.

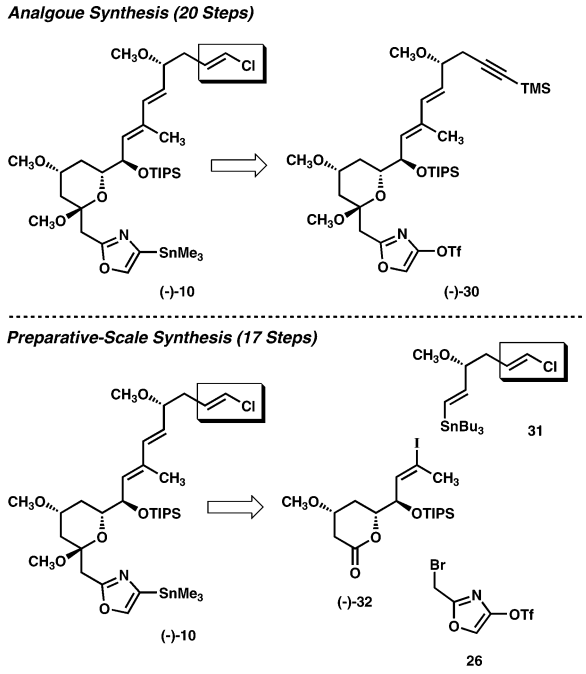
Evaluation of C(45−46) alkene (+)-**5** and alkane (−)-**6** analogues revealed average GI_{50} data of 4.1 and 3.1 nM, respectively, values slightly more potent than (+)-phorboxazole A (ca. 5.0 nM). The alkane congener (−)-**6** was particularly interesting, displaying single digit GI_{50} values of 1.6 and 1.3 nM against the non-small lung and colon cancer cell lines. Not only does the greater flexibility of the C(45−46) alkene and alkane congeners seem not to affect activity, the decreased electronic properties of these substitutions does not appear to play a significant role in their activity. However, when vinyl chloride analogue (+)-**3** was screened, extraordinary activity *in the picomolar range* was observed (cf. 0.62, 0.49, 0.64, and 0.38 nM) against the pancreatic, CNS, non-small lung, and colon cancer cell lines, respectively.

As outlined previously, the structurally simplified C(11−15) acetal congener (+)-**20*Z*** was envisioned to impart a conformation similar to that of the corresponding tetrahydropyran in phorboxazole A (**1**). The importance of the C(13) hydroxyl in phorboxazole A and B [epimeric solely at C(13)], however, was unknown given the equal potency of both phorboxazole A and B.[1a,b] When the *Z*-C(2−3) acetal conger (+)-**20*Z*** was screened against the six cancer cell lines, an average GI_{50} value of 34.6 nM was observed, with breast and colon cancer cell lines displaying values of 18.3 and 11.8 nM, respectively. The *E*-acetal isomer (+)-**20*E***, on the other hand, was significantly less active (cf. an average GI_{50} of 943.5 nM), reinforcing the importance of the *Z*-C(2−3) enoate phorboxazole conformation for potent activity. Given that the *Z*-acetal isomer was only slightly less active than the corresponding C(11−15) tetrahydropyran series, a similar conformation would appear to be present, a fact supported by NMR studies. We also conclude that interactions of the C(13) hydroxyl with the molecular target do not appear to play a significant role in establishing the cytotoxicity of the phorboxazoles.[7a,b,12]

Preparative-Scale Synthesis of (+)-C(46)-Chlorophorboxazole A (3). Given that only 8 mg of the extraordinarily potent (+)-chlorophorboxazole A (**3**) was prepared during the analogue study, greater quantities were required for more in depth evaluation. We therefore set a new goal for our phorboxazole synthetic program: the development of a preparative-scale synthesis of (+)-**3**.

Although the synthesis of (+)-**3** arising from the analogue study was reasonably effective, a more direct route was desired wherein the C(46) chloride would be installed at an early stage in the construction of the side chain (−)-**10** (Scheme 6).

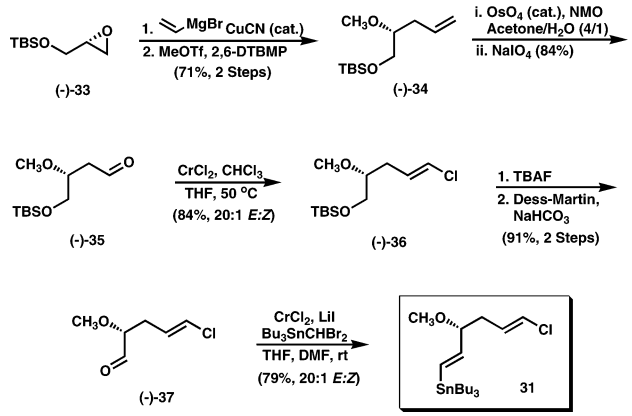
SCHEME 6



Specifically, we envisioned utilizing chlorovinylstannane **31** in the proposed preparative-scale venture. Stille coupling with the vinyl iodide (−)-**32**, followed by oxazole installation and stannylation, would then provide direct access to the chloro side chain (−)-**10**. Assuming success with this scenario, the longest linear sequence for the second-generation chloro side chain construction would be 17 steps, compared to 20 steps employed in the analogue program.

We began construction of chlorovinylstannane **31** by exposure of the TBS-protected epoxide (−)-**33**[2b,c] to vinylmagnesium bromide and CuCN, followed by conversion of the derived secondary alcohol to methyl ether (−)-**34**; the yield for this two-step operation was 71% (Scheme 7). Dihydroxylation with

SCHEME 7



osmium tetraoxide (OsO_4) and methylmorpholine *N*-oxide (NMO), followed by treatment with sodium periodate ($NaIO_4$) to effect diol cleavage then led to aldehyde (−)-**35** in good yield.

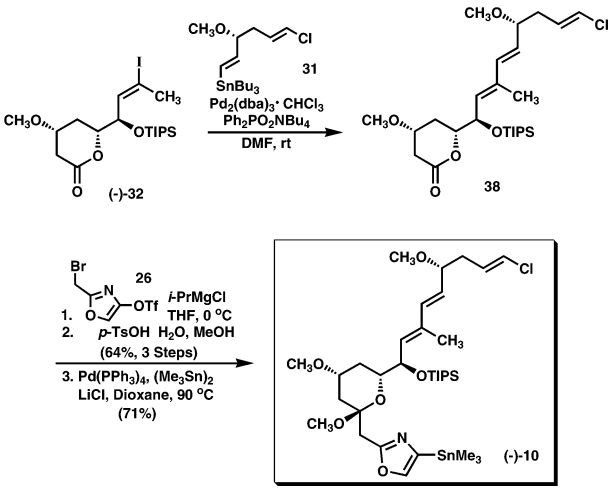
In the analogue program, installation of the C(46) chloride called upon a radical hydrostannylation−chlorination protocol.

(12) We note that the GI_{50} values represent an average of three separate assay trials which incorporate our previously reported results.

We now chose a more direct approach involving a Takai-type homologation of aldehyde (−)-**35** to access directly the C(45−46) vinyl chloride.[13] Toward this end, treatment of aldehyde (−)-**35** with $CrCl_2$ and $CHCl_3$ at 50 °C furnished vinyl chloride (−)-**36** in 84% yield with excellent *E*-selectivity (ca. 20:1 *E*/*Z*). Fluoride-mediated removal of the TBS protecting group (TBAF), followed by oxidation to the corresponding aldehyde and treatment with $CrCl_2$ and $Bu_3SnCHBr_2$ to promote alkenylstannylation then led to chlorovinylstannane **31** in 72% yield for the three steps. Due to facile decomposition upon silica gel chromatography chlorovinylstannane **31** was used without purification.

Completion of the chloro side chain [(−)-**10**] would now entail Stille union of **31** with vinyl iodide (−)-**32** to provide **38** (Scheme 8). Use of excess vinylstannane **31** in the Stille

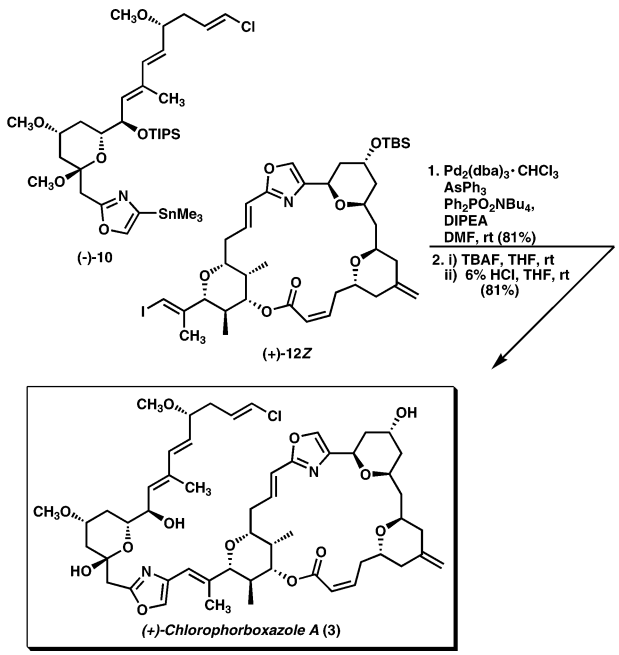
SCHEME 8



coupling, however, resulted in a difficult purification. As a result, lactone **38** was moved forward as mixture of two compounds **31** and **38**. Employing the same two-step protocol as used with other side chain fragments: addition of the oxazole Grignard reagent generated from **26**, followed immediately by treatment with *p*-TsOH·H_2O and methanol furnished the corresponding C(33) mixed methyl hemiacetal. The yield for the three steps was 64%. Silica gel chromatography readily removed all impurities at this stage. A chemoselective palladium-catalyzed conversion of the C(29) enol triflate to trimethylstannane (−)-**10** was then achieved with no observable perturbation of the C(45−46) vinyl chloride (^{1}H NMR).

Employing the now efficient route developed during the second-generation total synthesis of (+)-phorboxazole A, a 1.1 g sample of vinyl iodide macrocycle (+)-**12** was advanced in anticipation of the preparative-scale total synthesis of (+)-chlorophorboxazole A **3** (Scheme 9).[2g] Importantly, the highly successful Stille protocol permitted chemoselective union of the chloro side chain (−)-**10** with vinyl iodide (+)-**12** to furnish fully protected chlorophorboxazole A (+)-**17** in 81% yield on scales as large as 30 mg. Final deprotection, employing the conditions developed in the analogue program, led to ready removal of the C(13) TBS and C(38) TIPS protecting groups. Without purification, exposure to 6% HCl in THF then effected hydrolysis of the C(33) mixed methyl hemiacetal to

SCHEME 9



furnish (+)-chlorophorboxazole A (**3**) in 81% yield; to date, 72 mg of (+)-chlorophorboxazole A have been prepared for future biological evaluation.

In summary, the identification of a series of potent phorboxazole congeners has been achieved. In addition, insight into the importance of the C(13) hydroxyl for biological activity was achieved by replacement of the C(11−15) tetrahydropyran for the corresponding acetal to afford a potent analogue (cf. 34.6 nM). Analogues that possessed the *E*-C(2−3) macrocyclic enoate, however, displayed at best limited biological activity when compared to congeners possessing the natural *Z*-C(2−3) phorboxazole configuration.

Most importantly, we have identified (+)-C(46) chlorophorboxazole A (**3**), a congener which displays picomolar human tumor cell growth inhibitory activity, comparable in potency to the halichondrins[14] and spongistatins.[15] Finally, to gain additional understanding of phorboxazole biology, we have devised and executed a highly effective, preparative-scale synthesis of (+)-C(46)-chlorophorboxazole (**3**), capable of delivering significant quantities for further biological study.

Experimental Section

Preparation of Aldehyde (−)-35. To a stirred solution of terminal olefin (−)-**34** (1.41 g, 6.12 mmol) in an acetone/water solvent solution (4:1, 61 mL) were added osmium tetraoxide (0.2 mL, 0.61 mmol) and *N*-methylmorpholine *N*-oxide (1.43 g, 12.2 mmol). After the solution was stirred for 20 h at rt, solid sodium periodate (3.27 g, 15.3 mmol) was added, and after 2 h at rt, the reaction mixture was filtered and washed with diethyl ether (15 mL, 4×) followed by water (15 mL, 4×). The resultant filtrate was extracted with diethyl ether (10 mL, 3×), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification via silica gel chromatography (15% Et_2O/pentane) afforded aldehyde (−)-**35** as a clear oil (1.19

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g, 84%): $[\alpha]^{20}_D$ −29.8 (*c* 0.96, $CHCl_3$); IR (neat) 2955 (b), 2929 (s), 1728 (s), 1256 (s), 1116 (s), 838 (b), 777 (s) cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$) δ 9.78 (s, 1H), 3.71 (m, 1H), 3.69 (dd, J = 14.7, 4.7 Hz, 1H), 3.58 (dd, J = 10.2, 5.5 Hz, 1H), 3.39 (s, 3H), 2.58 (m, 2H), 0.86 (s, 9H), 0.03 (s, 6H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 202.6, 64.2, 57.8, 46.3, 46.1, 25.9, 18.4, −5.4; high-resolution mass spectrum (CI, NH_3) *m*/*z* 233.1482 $[(M)^+$; calcd for $C_{11}H_{24}O_3Si$ 233.1494].

Preparation of *E*-Vinyl Chloride (−)-36. Under an argon atmosphere, THF (30 mL) was added to a round-bottom flask containing chromium(II) chloride (2.24 g, 18.2 mmol, introduced under an inert atmosphere) at rt. Aldehyde (−)-**35** (0.70 g, 3.0 mmol) in $CHCl_3$ (0.49 mL) was then added via syringe, and the reaction mixture was heated to 50 °C. After 1 h, the reaction was cooled to rt, diluted with aqueous hydrochloric acid (1 N, 10 mL), and allowed to stir for 2 min. The biphasic reaction mixture was poured into a solution of saturated aqueous sodium chloride (15 mL) and extracted with dichloromethane (10 mL, 3×). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification via silica gel chromatography (2% Et_2O/pentane) afforded *E*-vinyl chloride (−)-**36** (0.67 g, 84%, 20:1 *E*/*Z*) as a pale yellow oil: $[\alpha]^{20}_D$ −24.7 (*c* 0.74, $CHCl_3$); IR (neat) 2954 (b), 2929 (s), 1472 (s), 1257 (s), 1113 (b), 776 (s) cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$) δ 6.00 (d, J = 13.3 Hz, 1H), 5.94 (m, 1H), 3.63 (dd, J = 10.5, 5.1 Hz, 1H), 3.53 (dd, J = 10.5, 5.7 Hz, 1H), 3.40 (s, 3H), 3.24 (m, 1H), 2.32 (m, 1H), 2.23 (m, 1H), 0.90 (s, 9H), 0.6 (s, 6H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 130.1, 118.9, 81.1, 64.2, 58.0, 32.8, 26.1, 18.5, −5.2; high-resolution mass spectrum (CI, NH_3) *m*/*z* 265.1378 $[(M)^+$; calcd for $C_{12}H_{25}O_2ClSi$ 265.1390].

Preparation of *E*-Vinyl Chloride Alcohol (−)-SI$_1$. Under an argon atmosphere, tetrabutylammonium fluoride (1.0 M/THF) (5.3 mL, 5.3 mmol) was added dropwise to a solution of *E*-vinyl chloride (−)-**36** (0.70 g, 2.7 mmol) in THF (27 mL) at 0 °C. After 1 h, the reaction was quenched via dropwise addition of saturated aqueous sodium bicarbonate (15 mL) and allowed to warm to rt. The biphasic solution was then extracted with dichloromethane (10 mL, 3×), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification via silica gel chromatography (50% Et_2O/pentane) afforded alcohol *E*-vinyl chloride alcohol (−)-**SI$_1$** (0.38, 95%) as a clear oil: $[\alpha]^{20}_D$ −19.7 (*c* 0.86, $CHCl_3$); IR (neat) 3419 (b), 2932 (b), 2828 (s), 1113 (s), 940 (s) cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$) δ 6.02 (dd, J = 13.2, 1.2 Hz, 1H), 5.88 (m, 1H), 3.64 (m, 1H), 3.47 (m, 1H), 3.39 (s, 3H), 3.28 (m, 1H), 2.28 (m, 1H), 2.22 (m, 1H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 129.4, 119.4, 80.7, 63.4, 57.5, 31.9; high-resolution mass spectrum (CI, NH_3) *m*/*z* 173.0451 $[(M)^+$; calcd for $C_6H_{11}O_2Cl$ 173.0444].

Preparation of *E*-Vinyl Chloride Aldehyde (−)-37. Under an argon atmosphere, the Dess−Martin periodinane (1.8 g, 4.2 mmol) and solid sodium bicarbonate (0.18 g, 2.1 mmol) were added to a solution of *E*-vinyl chloride alcohol (−)-**SI$_1$** (0.32 g, 2.2 mmol) in dichloromethane (21 mL) at 0 °C. After 30 min, the reaction was warmed to rt, and after an additional 45 min, the reaction was quenched with saturated aqueous sodium bicarbonate (8 mL). The biphasic solution was extracted with dichloromethane (10 mL, 3×), and the organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification via silica gel chromatography (50% Et_2O/pentane) afforded *E*-vinyl chloride aldehyde (−)-**37** (0.31 g, 96%) as a clear oil: $[\alpha]^{20}_D$ −23.6 (*c* 1.0, $CHCl_3$); IR (neat) 2932 (b), 2828 (b), 2359 (s), 1733 (s), 1114 (s), 940 (s) cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$) δ 9.66 (app t, J = 1.8 Hz, 1H), 6.07 (dd, J = 13.2, 1.1 Hz, 1H), 5.89 (m, 1H), 3.59 (m, 1H), 3.47 (s, 3H), 2.46 (m, 1H), 2.40 (m, 1H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 203.2, 127.8, 120.6, 84.7, 58.6, 31.5; high-resolution mass spectrum (CI, NH_3) *m*/*z* 149.0367 $[(M)^+$; calcd for $C_6H_9O_2Cl$ 149.0370].

Preparation of *E*-Vinyl Chloride *E*-Vinylstannane 31. Under an argon atmosphere at rt, THF (22 mL) followed by DMF (1.1 mL) were added to a round-bottom flask containing chromium(II) chloride (1.70 g, 13.8 mmol, introduced under an inert atmosphere) with vigorous stirring for 15 min. At this point, a solution of *E*-vinyl chloride aldehyde (−)-**37** and tributyl(dibromomethyl)stannane (1.4 g, 2.9 mmol) in THF (5.4 mL) was added dropwise via cannula. Following the exclusion of light, a solution of lithium iodide (0.72 g, 5.38 mmol) in THF (5.4 mL) was added dropwise via syringe and the reaction stirred at rt in the dark. After 24 h, the reaction was quenched via dropwise addition of saturated aqueous sodium bicarbonate (15 mL) and extracted with diethyl ether (10 mL, 3×). The combined organic extracts were washed with saturated aqueous sodium chloride (15 mL, 1×), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Due to decomposition upon attempted purification, *E*-vinyl chloride *E*-vinylstannane **31** (20:1, *E*:*Z*, ^{1}HNMR) was carried on crude.

Preparation of Lactone *E*-Vinyl Chloride 38. Under an argon atmosphere, tris(dibenzylideneacetone)dipalladium−chloroform adduct $[Pd_2(dba)_3{\cdot}CHCl_3]$ (31 mg, 0.03 mmol) and $Ph_2PO_2NBu_4$ (0.14 g, 0.30 mmol) followed by DMF (3.0 mL) were added to a round-bottom flask containing crude *E*-vinyl chloride *E*-vinylstannane **31** (0.29 g, 1.22 mmol) and lactone vinyl iodide (−)-**32** (0.15 g, 0.30 mmol). After being stirred for 20 h at rt, the reaction mixture was diluted with diethyl ether (5 mL) and washed with water (5 mL, 6×). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Attempted purification via silica gel chromatography (30% EtOAc/hexanes) afforded an inseparable mixture of the desired lactone *E*-vinyl chloride **38** contaminated with *E*-vinyl chloride *E*-vinylstannane (3:1, **38**:**31**) that was carried onto the next step as a mixture.

Preparation of Oxazole Triflate *E*-Vinyl Chloride (−)-SI$_2$. To lactone *E*-vinyl chloride **38** (93.0 mg, 0.18 mmol) in a flame-dried round-bottom flask under argon at rt in freshly distilled THF (8.7 mL) was added oxazole **26** (0.29 g, 0.92 mmol) and the solution cooled to 0 °C. Isopropylmagnesium chloride (2.0 M/THF, 0.23 mL, 0.46 mmol) was then added dropwise over 30 min. After the mixture was stirred for 20 min, another addition of isopropylmagnesium chloride (2.0 M/THF, 0.23 mL, 0.46 mmol) was introduced over 20 min. After a third addition of isopropylmagnesium chloride (0.23 mL, 0.46 mmol) and stirring for 30 min, the reaction was quenched via dropwise addition of saturated aqueous sodium bicarbonate (5 mL). The solution was warmed to rt, at which point the layers of the biphasic mixture were separated and the aqueous layer was extracted with ethyl acetate (8 mL, 3×). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resultant pale yellow oil was then dissolved in anhydrous methanol (25 mL) followed by the addition of *p*-TsOH·H_2O (60 mg, 0.31 mmol) under an argon atmosphere. After stirring for 20 h at rt, the reaction was quenched via dropwise addition of aqueous saturated sodium bicarbonate (12 mL). The biphasic mixture was extracted with ethyl acetate (15 mL, 3×), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification via silica gel chromatography (25% EtOAc/hexanes) afforded oxazole triflate *E*-vinyl chloride (−)-**SI$_2$** (0.15 g, 64%, three steps) as a pale yellow oil: $[\alpha]^{20}_D$ −31.3 (*c* 0.41, $CHCl_3$); IR (neat) 2942 (b), 2864 (s), 1594 (s), 1432 (s), 1231 (s), 1138 (s), 1094 (b), 854 (b) cm^{-1}; ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.60 (s, 1H), 6.17 (d, J = 15.7 Hz, 1H), 6.00 (d, J = 13.3 Hz, 1H), 5.89 (m, 1H), 5.45 (dd, J = 15.7, 7.8 Hz, 1H), 5.42 (d, J = 9.4 Hz, 1H), 4.60 (dd, J = 8.8, 6.2 Hz, 1H), 3.64 (app q, J = 6.5 Hz, 1H), 3.56 (m, 2H), 3.31 (s, 3H), 3.30 (s, 3H), 3.27 (s, 3H), 3.25 (d, J = 14.9 Hz, 1H), 2.98 (d, J = 14.9 Hz, 1H), 2.37 (m, 1H), 2.27 (m, 1H), 2.17 (dd, J = 12.6, 3.5 Hz, 1H), 1.99 (ddd, J = 10.0, 4.2, 2.1 Hz, 1H), 1.76 (s, 3H), 1.38 (d, J = 12.3 Hz, 1H), 1.36 (d, J = 11.4 Hz, 1H), 1.06 (m, 21H); ^{13}CNMR (125 MHz, $CDCl_3$) δ 159.0, 145.0, 137.4, 134.3, 133.1, 129.8, 128.3, 127.1, 119.1, 99.9, 81.7, 74.3, 73.5, 71.8, 56.5, 55.7, 48.1, 39.3, 37.4, 36.1, 32.2, 18.2, 18.1, 13.8, 12.6; high-resolution mass spectrum (ES^+) *m*/*z* 769.3469 $[(M + Na)^+$; calcd for $C_{32}H_{51}F_3NO_9SSiClNa$ 769.3474].

Preparation of Oxazole Stannane *E*-Vinyl Chloride (−)-10. Oxazole triflate *E*-vinyl chloride (−)-**SI$_2$** (42 mg, 0.059 mmol) was combined with hexamethylditin (0.017 mL, 0.082 mmol) in a sealed tube (100 mL), azeotroped from benzene (5 mL, 3×), and dried for 1 h under vacuum. In a glove bag under an inert argon atmosphere was added flame-dried lithium chloride (39 mg, 0.941 mmol) followed by tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$] (10 mg, 0.009 mmol) and dioxane (0.6 mL, freeze pump thawed, 3×). The tube was sealed and the reaction mixture heated to 80 °C behind a blast shield. After 12 h, the reaction was cooled to rt and introduced directly onto a silica gel column (15% EtOAc/hexanes) to afford oxazole stannane *E*-vinyl chloride (−)-**10** (30.5 mg, 71%) as a colorless oil: $[\alpha]^{20}_D$ −28.4 (*c* 0.32, CH_2Cl_2); IR (neat) 2940 (s), 2863 (s), 1556 (s), 1460 (s), 1378 (b), 1244 (s), 1095 (b), 990 (s), 883 (s), 773 (s), 681 (s); ^{1}HNMR (500 MHz, C_6D_6) δ 7.21 (s, 1H) 6.12 (d, J = 15.7 Hz, 1H), 5.90 (ddd, J = 13.3, 7.5, 7.4 Hz, 1H), 5.69 (d, J = 13.3 Hz, 1H), 5.51 (d, J = 8.9 Hz, 1H), 5.38 (dd, J = 15.7, 7.8 Hz, 1H), 4.72 (dd, J = 8.8, 6.3 Hz, 1H), 3.74 (m, 1H), 3.66 (m, 1H), 3.45 (d, J = 14.9 Hz, 1H), 3.43 (s, 3H), 3.35 (app q, J = 6.4 Hz, 1H), 3.06 (s, 3H), 3.03 (s, 3H), 2.56 (dd, J = 12.7, 3.0 Hz, 1H), 2.12 (m, 2H), 1.99 (app q, J = 6.1 Hz, 1H), 1.68 (s, 3H), 1.30 (dd, J = 23.6, 11.9 Hz, 2H), 1.14 (m, 22H), 0.24 (s, 9H); ^{13}CNMR (125 MHz, C_6D_6) δ 161.5, 145.4, 137.5, 134.7, 133.8, 130.5, 129.3, 119.5, 100.9, 81.9, 74.7, 74.2, 72.8, 56.4, 55.6, 48.3, 40.5, 37.8, 36.4, 33.2, 18.7, 18.6, 14.1, 13.2, −9.3; high-resolution mass spectrum (ES^+) *m*/*z* 784.2787 [$(M + Na)^+$; calcd for $C_{34}H_{60}ClNO_6SiSnNa$ 784.2645].

Preparation of Protected Chlorophorboxazole A (+)-SI$_3$. In a round-bottom flask (5 mL), vinyl iodide macrocycle (+)-**12*Z*** (24.9 mg, 0.031 mmol) and oxazole stannane *E*-vinyl chloride (−)-**10** (35.0 mg, 0.045 mmol) were combined, azeotroped from benzene (3 mL, 3×), and dried under vacuum. After 1 h, under an inert argon atmosphere, tris(dibenzylideneacetone)dipalladium−chloroform adduct [$Pd_2(dba)_3$·$CHCl_3$] (6.3 mg, 0.0061 mmol), triphenylarsine ($AsPh_3$) (11.4 mg, 0.036 mmol), and $Ph_2PO_2NBu_4$ (21.5 mg, 0.046 mmol) were added followed by anhydrous DMF (0.31 mL, sparged with argon, 1 h) and diisopropylethylamine (0.004 mL, 0.031 mmol). After 1 min, the black solution turned light brown and was allowed to stir at rt. After 17 h, the light brown solution was purified directly via silica gel chromatography (20% EtOAc/hexanes → 25% EtOAc/hexanes) to afford protected chlorophorboxazole A (+)-**SI$_3$** (31.2 mg, 81%) as an off-white foam: $[\alpha]^{20}_D$ +14.3 (*c* 0.37, $CHCl_3$); IR (neat) 2933 (s), 2866 (s), 1716 (s), 1644 (b), 1461 (b), 1370 (b), 1254 (s), 1187 (s), 1153 (s), 1096 (s), 1043 (b), 879 (s), 836 (s), 807 (b) cm^{-1}; ^{1}HNMR (500 MHz, C_6D_6) δ 7.15 (s, 1H), 6.96 (s, 1H), 6.87 (m, 1H), 6.35 (s, 1H), 6.19 (d, J = 15.8 Hz, 1H), 6.14 (d, J = 15.8 Hz, 1H), 5.91 (m, 1H), 5.79 (dd, J = 11.5, 2.9 Hz, 1H), 5.70 (d, J = 13.3 Hz, 1H), 5.53 (d, J = 8.6 Hz, 1H), 5.45 (ddd, J = 10.6, 10.6, 2.8 Hz, 1H), 5.41 (dd, J = 15.7, 7.7 Hz, 1H), 5.17 (s, 1H), 4.94 (d, J = 11.2 Hz, 1H), 4.73 (m, 2H), 4.61 (dd, J = 11.2, 4.4 Hz, 1H), 4.38 (br s, 1H), 4.24 (app t, J = 10.7 Hz, 1H), 4.06 (m, 1H), 4.02 (s, 1H), 3.94 (m, 1H), 3.77 (dd, J = 6.1, 1.9 Hz, 1H), 3.69 (m, 1H), 3.43 (d, J = 10.0 Hz, 1H), 3.40 (s, 3H), 3.37 (d, J = 6.7 Hz, 1H), 3.33 (d, J = 14.8 Hz, 1H), 3.07 (s, 3H), 3.04 (s, 3H), 2.94 (d, J = 14.8 Hz, 1H), 2.64 (app t, J = 5.8 Hz, 1H), 2.56 (dd, J = 13.0, 4.4 Hz, 1H), 2.39 (m, 3H), 2.13 (m, 2H), 2.08 (s, 3H), 2.00 (m, 3H), 1.70 (s, 3H), 1.63 (m, 2H), 1.48 (d, J = 13.2 Hz, 1H), 1.32 (m, 5H), 1.14 (m, 25H), 1.03 (d, J = 6.8 Hz, 3H), 0.92 (s, 9H), 0.76 (d, J = 6.4 Hz, 3H), 0.01 (s, 3H), −0.01 (s, 3H); ^{13}CNMR (125 MHz, C_6D_6) δ 165.9, 161.8, 160.2, 145.8, 144.0, 143.2, 139.4, 138.4, 137.7, 136.9, 134.9, 134.5, 134.0, 133.9, 130.7, 121.6, 120.4, 120.1, 119.7, 119.6, 110.7, 101.0, 90.2, 82.1, 81.6, 80.4, 78.9, 74.9, 74.3, 73.9, 72.9, 70.1, 69.4, 67.9, 66.1, 56.6, 55.8, 48.5, 42.6, 40.7, 40.6, 40.1, 38.1, 38.0, 36.5, 35.1, 33.3, 32.6, 31.3, 30.7, 26.5, 18.9, 18.7, 14.8, 14.2, 13.9, 13.3, 6.8, −4.2, −4.3; high-resolution mass spectrum (ES^+) *m*/*z* 1285.7001 [$(M + Na)^+$; calcd for $C_{69}H_{107}ClN_2O_{13}Si_2Na$ 1285.6997].

Preparation of Chlorophorboxazole A (+)-3. Fully protected chlorophorboxazole A (+)-**SI$_3$** (31.2 mg, 0.025 mmol) was introduced into a flame-dried round-bottom flask, azeotroped from benzene (3 mL, 3×), and dried under vacuum. After 1 h, under an inert argon atmosphere, (+)-**SI$_3$** was dissolved in freshly distilled THF (24.7 mL) and cooled to 0 °C, and tetrabutylammonium fluoride (1.0 M/THF) (0.074 mL, 0.074 mmol) was added dropwise. After 1 h, the reaction was quenched via dropwise addition of saturated aqueous sodium chloride (5 mL) and allowed to stir for 1 min. The layers of the biphasic mixture were separated, and the aqueous layer was extracted with ethyl acetate (5 mL, 4×). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resultant off white amorphous solid, under an argon atmosphere, was dissolved in freshly distilled THF (30.8 mL) followed by dropwise addition of 6% hydrogen chloride solution (11.9 mL). After being stirred for 36 h at rt, the reaction was cooled to 0 °C and poured into saturated aqueous sodium bicarbonate (5 mL). The resultant layers were separated, and the aqueous layer was extracted with dichloromethane (5 mL, 4×) followed by ethyl acetate (5 mL, 2×). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification via silica gel chromatography (100% EtOAc → 10% CH_3OH/EtOAc) afforded chlorophorboxazole A (+)-**3** (19.6 mg, 81%) as a white amorphous solid: $[\alpha]^{20}_D$ +47.8 (*c* 0.39, CH_2Cl_2); IR (neat) 3411 (b), 2926 (s), 1720 (s), 1647 (b), 1443 (b), 1375 (b), 1186 (s), 1156 (s), 1088 (s), 991 (b) cm^{-1}; ^{1}HNMR (500 MHz, C_6D_6) δ 7.04 (s, 1H), 6.91 (s, 1H), 6.87 (m, 1H), 6.22 (d, J = 15.7 Hz, 1H), 6.21 (s, 1H), 6.10 (d, J = 15.7 Hz, 1H), 5.98 (m, 1H), 5.80 (dd, J = 11.0, 2.9 Hz, 1H), 5.74 (d, J = 13.3 Hz, 1H), 5.55 (d, J = 8.8 Hz, 1H), 5.45 (ddd, J = 12.7, 12.6, 1.2 Hz, 1H), 5.37 (dd, J = 15.7, 7.8 Hz, 1H), 5.24 (s, 1H), 4.81 (d, J = 11.1 Hz, 1H), 4.78 (s, 1H), 4.61 (dd, J = 11.1, 4.3 Hz, 1H), 4.37 (m, 2H), 4.08 (m, 2H), 3.96 (m, 2H), 3.80 (m, 2H), 3.41 (m, 1H), 3.39 (d, J = 9.9 Hz, 1H), 3.36 (app q, J = 7.3 Hz, 1H), 3.08 (s, 3H), 3.04 (s, 3H), 3.00 (dd, J = 11.1, 0.9 Hz, 1H), 2.86 (d, J = 15.3 Hz, 1H), 2.74 (d, J = 15.3 Hz, 1H), 2.65 (app t, J = 5.2 Hz, 1H), 2.42 (m, 4H), 2.30 (dd, J = 12.1, 4.3 Hz, 1H), 2.11 (m, 1H), 2.01 (m, 6H), 1.92 (d, J = 0.5 Hz, 3H), 1.63 (d, J = 0.9 Hz, 3H), 1.54 (m, 4H), 1.29 (m, 6H), 1.05 (d, J = 6.8 Hz, 3H), 0.73 (d, J = 6.4 Hz, 3H); ^{13}CNMR (125 MHz, C_6D_6) δ 165.1, 161.0, 160.5, 145.1, 143.1, 142.4, 138.4, 137.7, 136.9, 136.6, 135.6, 133.6, 133.2, 131.2, 129.9, 127.2, 120.7, 119.6, 119.2, 118.1, 109.8, 96.6, 89.1, 81.1, 79.4, 78.1, 73.1, 72.6, 70.7, 69.3, 68.5, 66.9, 64.0, 55.7, 55.0, 41.6, 40.7, 39.5, 39.4, 39.0, 37.4, 37.3, 34.8, 34.3, 33.6, 33.2, 32.4, 31.7, 30.5, 14.1, 14.0, 13.1, 6.0; high-resolution mass spectrum (ES^+) *m*/*z* 1002.5813 [$(M + Na)^+$; calcd for $C_{53}H_{71}ClN_2O_{13}Na$ 1002.5801].

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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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