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(+)-Phorboxazole A Synthetic Studies. A Highly Convergent, Second Generation Total Synthesis of (+)-Phorboxazole A

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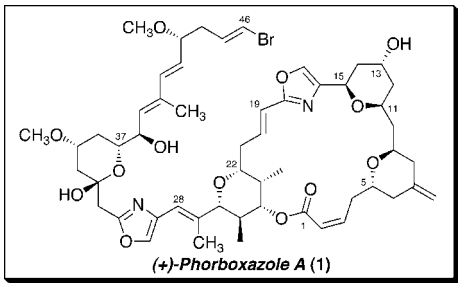
ABSTRACT



A second generation total synthesis of the potent antitumor agent (+)-phorboxazole A (1) has been achieved. The cornerstone of this approach comprises a more convergent strategy, involving late-stage Stille union of a fully elaborated C(1–28) macrocycle with a C(29–46) side chain. The second generation synthesis entails the longest linear sequence of 24 steps, with an overall yield of 4.2%.

In 1995, Searle and Molinski[1] isolated two architecturally complex macrolides, (+)-phorboxazole A and B [epimeric at C(13)], from the Indian ocean sponge *Phorbas* sp., endemic to the waters near the western coast of Australia. The phorboxazoles displayed extraordinary biological properties, including high cell growth inhibitory activity against both fungal and human tumor cell lines, rendering these architecturally complex natural products potentially important pharmacological lead structures. For example, in vitro bioassay of both **1** and **2** against the National Cancer Institute's (NCI) panel of 60 human tumor cell lines reveals a mean GI_{50} of 1.58×10^{-9} M. Not surprisingly, the phorboxazoles have attracted considerable attention from the synthetic community. To date, four total syntheses of phorboxazole A (**1**)[2] and one of phorboxazole B [the C(13) epimer][3] have been reported, along with numerous related synthetic studies.[4]

In 2001, we disclosed our first generation synthesis of (+)-phorboxazole A, relying on the Petasis−Ferrier union/rearrangement tactic, specifically developed to assemble the two highly substituted, *cis*-tetrahydropyran rings embedded in the phorboxazole macrocycle.[5,6] Seven steps were, how-

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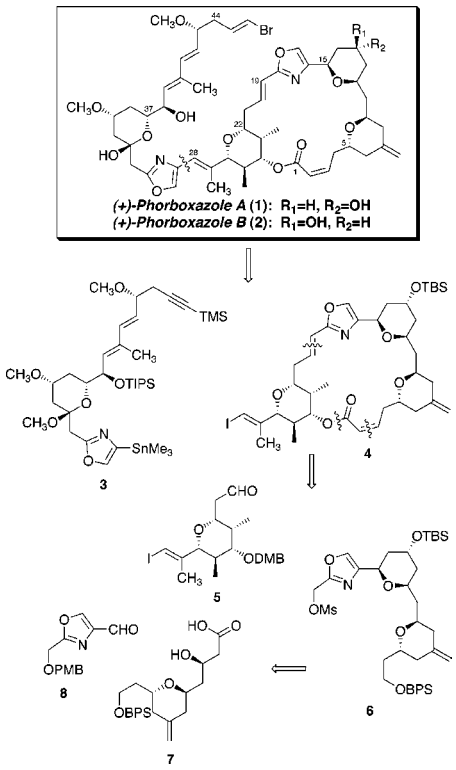
ever, required to complete the total synthesis after Stille union of the macrocyclic precursor and side chain. We, therefore, sought in a second generation approach a more convergent, scalable route, comprising an advanced macrocycle, appropriately functionalized for ready attachment of a more fully elaborated side chain. Success with this venture would reduce the number of post-Stille coupling steps, and thereby increase the overall efficiency. In this, the first of two Letters, we report the successful realization of this goal: a more effective, convergent, and potentially scalable total synthesis of (+)-phorboxazole A (**1**). In the second Letter, we demonstrate the utility of the second generation approach with the design and synthesis of a series of potent phorboxazole congeners possessing structurally modified side chains, one of which proved significantly more active than phorboxazole A.[7]

From the synthetic perspective, we trace our second generation approach to the side chain oxazole **3** and a fully elaborated macrocyclic vinyliodide **4** (Scheme 1).[2b,c] Disconnections of **4** in turn at the C(2−3) and C(19−20) olefins reveal a central tetrahydropyran aldehyde **5** and an eastern tricyclic fragment **6**, which in the forward sense would be united via a stereoselective Wittig olefination. The requisite tricycle **6** would be available via a three-step Petasis−Ferrier union/rearrangement of oxazole aldehyde **8** with β-hydroxy acid **7**, the latter assembled via hetero-Diels−Alder[8] and acetate aldol tactics.[9]

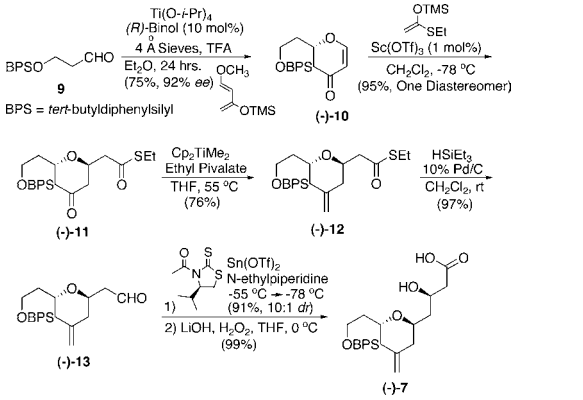
Construction of macrocycle **4** began with the synthesis of β-hydroxy acid **7** (Scheme 2). Condensation of known aldehyde **9**[10] with the Danishefsky diene[11] catalyzed by Ti(O-*i*-Pr)$_4$/(*R*)-Binol furnished the hetero-Diels−Alder[8] adduct (−)-**10** in 75% yield, with 92% enantioselectivity. Scandium triflate-promoted axial delivery of the TMS−thiol enol ether derived from ethylthioacetate led next to *trans*-tetrahydropyranone (−)-**11** as a single diastereomer in excellent yield.[12] Importantly, this reaction was found to be highly reliable on preparative scales up to 50 g.

Chemoselective olefination of (−)-**11** utilizing the Petasis/Tebbe reagent[13] and 10 mol % of ethyl pivalate furnished thiolester (−)-**12** in 76% yield. The ethyl pivalate was employed to prevent deleterious [2+2] side reactions of Cp$_2$-

Scheme 1



Scheme 2



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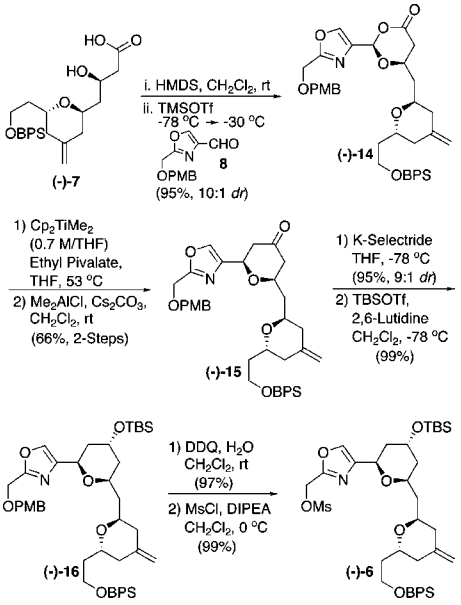
$TiCH_2$ with the resultant *exo*-olefin.[14] Reduction with 10% Pd/C and triethylsilane next afforded aldehyde (−)-**13** in excellent yield.[15] To establish the C(11) configuration required in the C(11−15) tetrahydropyran, we employed the Nagao acetate aldol protocol,[9] promoted by tin triflate, followed by treatment with lithium peroxide, to furnish *β*-hydroxy acid (−)-**7**, with excellent diastereoselectivity (ca. 10:1) and in good yield.

With ample quantities of both *β*-hydroxy acid (−)-**7** and aldehyde **8** available, we turned to the Petasis−Ferrier union/rearrangement (Scheme 3).[5] Bis-silylation of (−)-**7** followed

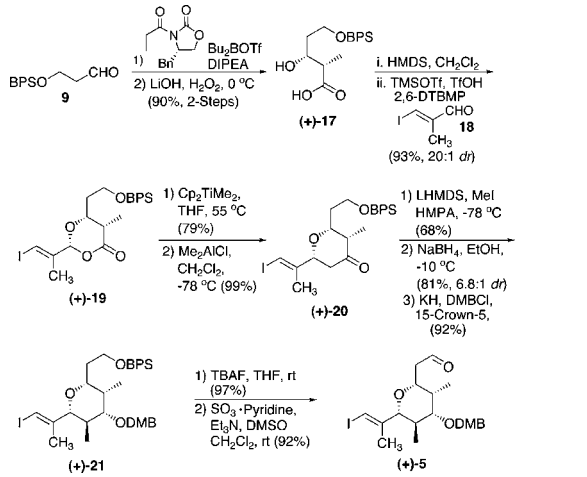
Scheme 3



by TMSOTf-promoted dioxanone formation[16] with oxazole aldehyde **8**[5,17] furnished (−)-**14** in 95% yield, with excellent diastereoselectivity (ca. 10:1) at C(15). Conversion of (−)-**14** to the corresponding enol acetal was again achieved employing the Petasis/Tebbe reagent; however, in this case, a more concentrated solution of the reagent (ca. 0.7 M) was employed, compared to that used in the construction of (−)-**12**. This modification, in conjunction with the use of ethyl pivalate, both shortened the reaction time and greatly reduced side product formation. Execution of the Petasis−Ferrier rearrangement was then achieved by introduction of the enol acetal to a vigorously stirred solution of Me_2AlCl and Cs_2CO_3 at room temperature; pleasingly, tetrahydropyranone (−)-**15** was produced in 66% yield for the two steps.[18] Completion of fragment **6** involved reduction of the C(13) carbonyl with K-Selectride, followed by TBS protection of the resultant axial alcohol to furnish (−)-**16**; in turn, DDQ-mediated oxidative removal of the PMB protecting group and mesylation of the corresponding primary alcohol led to tricycle (−)-**6**, the requisite Wittig salt precursor for union with **5**.

Our next course of action called for the synthesis of the C(22−26) *cis*-tetrahydropyran (**5**, Scheme 4), again employ-

Scheme 4



ing the three-step Petasis−Ferrier union/rearrangement tactic.[6] We began with construction of (+)-**17** via an Evans's *syn*-aldol,[19] employing BPS-protected aldehyde **9**, followed by hydrolysis of the resultant imide with lithium peroxide; the yield for the two steps was 90%. Bis-silylation followed by TMSOTf-promoted condensation with known aldehyde **18**,[20] buffered with 2,6-di-*tert*-butyl-4-methylpyridine, furnished dioxanone (+)-**19** both in excellent yield (ca. 93%) and diastereoselectivity (ca. 20:1). Olefination with the Petasis/Tebbe reagent,[13] followed by exposure of the resultant enol acetal to Me_2AlCl at −78 °C, then led to tetrahydropyranone (+)-**20** in near quantitative yield.

Completion of the C(22−26) central tetrahydropyran (**5**, Scheme 4) proceeded first by kinetic enolization of ketone (+)-**20** with LHMDS, followed by addition of MeI to furnish the equatorial methyl ketone. Axial hydride delivery employing sodium borohydride, followed by protection of the resultant equatorial alcohol with 3,4-dimethoxybenzyl chloride led to (+)-**21**, which upon removal of the BPS protecting group with TBAF, followed by Parikh−Doering[21] oxidation, provided aldehyde (+)-**5**, the requisite coupling partner for union with (−)-**6**.

With aldehyde (+)-**5** and mesylate (−)-**6** in hand, we were in position to effect their union (Scheme 5). The initial capricious yields observed upon Wittig salt formation, presumably due to the reactivity of the initially formed C(19) primary chloride, led us to opt for the one-pot Wittig salt formation/olefination protocol developed by Evans and Fitch

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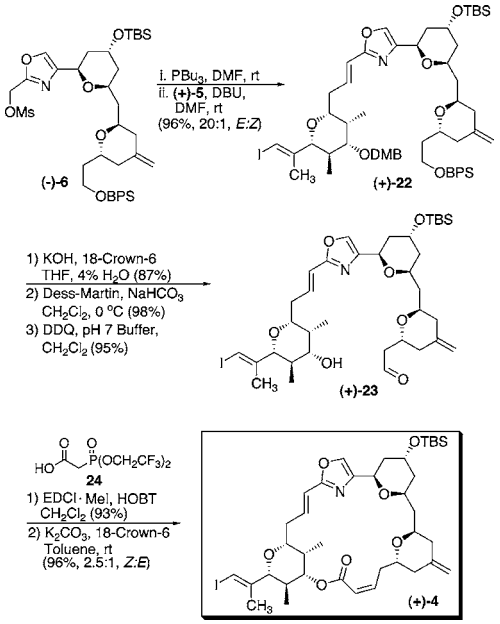
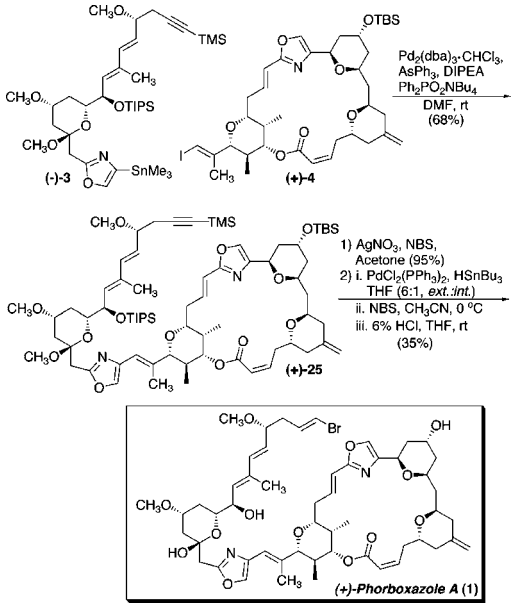
Scheme 5



Scheme 6



in their pioneering (+)-phorboxazole B synthesis.[3,22] Specifically, treatment of mesylate (−)-**6** with tributylphosphine for 36 h, followed by introduction of aldehyde (+)-**5** and DBU, yielded the C(19−20)-*E*-olefin in 96% yield, with greater than 20:1, *E:Z* selectivity. Completion of macrocycle **4** was now in sight. Selective removal of the BPS group with KOH and 18-crown-6[23] furnished the corresponding primary alcohol, which upon oxidation under Dess−Martin conditions,[24] followed by oxidative removal of the DMB protecting group with DDQ, led to alcohol (+)-**23** in 95% yield.

We next enlisted the Still−Genari-modified Horner−Emmons[25] olefination to construct the *Z*-macrolide **4** (Scheme 5). To this end, EDCI·MeI/HOBT-mediated coupling of alcohol (+)-**23** with trifluoroethyl phosphonate acid **24**[26] led to the corresponding phosphonate ester. Exposure of the latter to K_2CO_3/18-crown-6[27] furnished macrocyclic enoate (+)-**4** in excellent overall yield (ca. 89% for the two steps), albeit with only modest 2.5:1, *Z:E* selectivity.

Completion of the phorboxazole skeleton now called for union of the side chain stannane (−)-**3** with (+)-**4**, utilizing the Stille coupling protocol developed by the Liebeskind group,[28] which involves a combination of $Pd_2(dba)_3$·$CHCl_3$/$AsPh_3$, DIPEA, and $Ph_2PO_2NBu_4$ in DMF at room temperature; pleasingly, the coupled product (+)-**25** was obtained in 68% yield (Scheme 6).

Arrival at (+)-phorboxazole A (**1**) and thereby a second generation total synthesis closely followed our first generation approach. Specifically, conversion of TMS-protected alkyne (+)-**25** to the corresponding bromoalkyne with $AgNO_3$/NBS, followed by palladium-catalyzed hydrostannylation,[29] furnished a mixture (ca. 6:1) of external and internal vinylstannanes, which were readily converted to the corresponding vinylbromides using NBS/CH_3CN at 0 °C. Global deprotection enlisting 6% HCl furnished synthetic (+)-phorboxazole A (**1**) in 35% over three steps after HPLC separation of the regioisomeric vinyl bromides.

In summary, we have developed an effective, second generation total synthesis of (+)-phorboxazole A (**1**). Compared to our first generation approach, which required 27 steps (longest linear sequence) and proceeded in 3.1% overall yield, the second generation synthesis proceeds in 24 steps (longest linear sequence) to furnish (+)-phorboxazole A (**1**) in 4.2% overall yield. Importantly, completion of this potentially scalable synthesis of (+)-phorboxazole A provides access not only to **1** but also to significant quantities of advanced intermediates for future analogue synthesis. In the accompanying Letter, we disclose the syntheses and biological evaluation of several structurally simplified analogues which possess equal to or greater tumor cell growth inhibitory activity compared to that of (+)-phorboxazole A (**1**).

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Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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