

# Total Synthesis of Phorboxazole A. 1. Preparation of Four Subunits

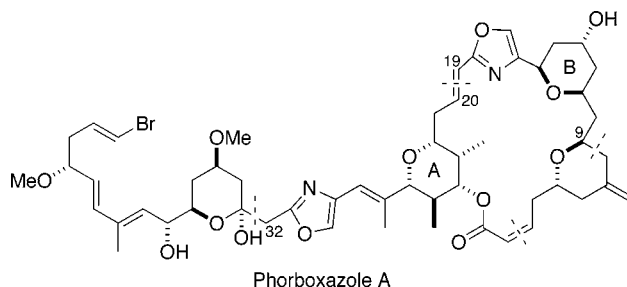
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## ABSTRACT

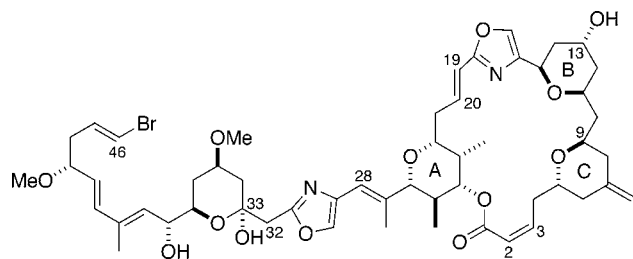


Four subunits of the potent antitumor agent phorboxazole A were constructed; fragments C20–C32 and C9–C19 containing tetrahydropyrans A and B, respectively, were assembled using palladium-catalyzed intramolecular alkoxyacylation.

Phorboxazole A (**1**) and its C13 epimer phorboxazole B were isolated by Molinski from a marine sponge of the genus *Phorbas* sp. and are among the most potent cytotoxic natural products yet discovered.<sup>1</sup> Tumor cell growth is inhibited by **1** at subnanomolar concentration by a mechanism that has been shown to arrest the cell cycle at the S phase. A more detailed description of its mode of action awaits further study, but it is known that **1** has no effect on tubulin polymerization and does not interfere with the integrity of microtubules.

high potency of **1** has invited a broad array of synthetic endeavors that includes completed syntheses of phorboxazole A by Forsyth,<sup>3</sup> Smith,<sup>4</sup> Williams,<sup>5</sup> and Pattenden,<sup>6</sup> as well as syntheses of its C13 epimer (phorboxazole B) by Evans<sup>7</sup> and Lin.<sup>8</sup> In addition, numerous publications have reported syntheses of subunits of **1**.<sup>9</sup>

A striking feature of the structure of phorboxazole A is the presence of three tetrahydropyran units embedded in a 21-membered lactone. Two of these tetrahydropyrans, A and



The structure of phorboxazole A (**1**), including its absolute configuration, was derived by a combination of spectroscopic and degradative studies.<sup>2</sup> The complex architecture and very

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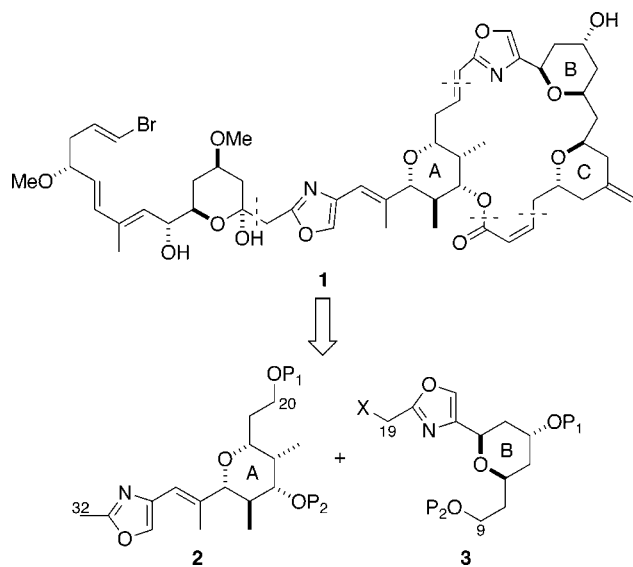
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B, bear substituents in a cis orientation at the C2 and C6 positions, whereas the third tetrahydropyran (C) has a trans 2,6-substitution pattern. This analysis pointed us toward a synthesis strategy for **1** which foresaw two major subunits, **2** and **3**, comprising C20–C32 and C9–C19, respectively, emerging via a pathway that established the cis-2,6-disubstitution in each of the tetrahydropyrans A and B (Scheme 1). Specifically, we envisioned a reaction first described by

**Scheme 1.** Two of the Principal Subunits for Assembly into Phorbosazole A



Semmelhack for the synthesis of tetrahydrofurans that employed palladium-mediated intramolecular alkoxy carbonylation of a hydroxy alkene.<sup>10</sup>

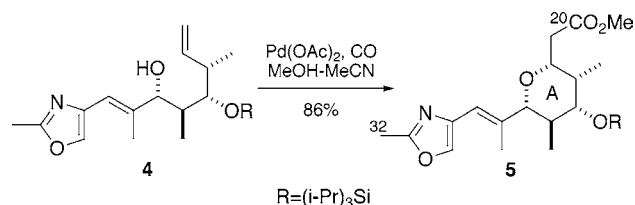
Our initial study of palladium(II)-mediated alkoxy carbonylation of a series of 6-hydroxy-1-octenes in methanol demonstrated that cis-2,6-disubstituted tetrahydropyrans could be prepared by this process but that yields were highly dependent upon the orientation of substituents in the octene chain.<sup>11</sup> A subsequent investigation of palladium-mediated intramolecular alkoxy carbonylation<sup>12</sup> resulted in a high-

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yielding and completely stereoselective synthesis of the C20–C32 subunit from 2-methyloxazole-4-carboxaldehyde<sup>13</sup> via hydroxy alkene **4** (Scheme 2). However, an excess of

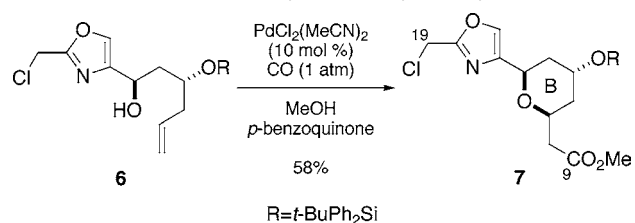
**Scheme 2.** Synthesis of the C20–C32 Domain of **1** via Palladium(II)-Mediated Alkoxy carbonylation



palladium(II) acetate was needed for complete conversion of **4** to **5**. Furthermore, the same conditions, when applied to the synthesis of subunit **3**, resulted in a low yield of the tetrahydropyran.

A problem associated with alkoxy carbonylation of **4** and **6** is reduction of the palladium(II) reagent by carbon monoxide to inactive palladium(0) during the course of the reaction. To prevent this process, we investigated a variety of conditions using a stoichiometric oxidant in the presence of a catalytic quantity of a palladium(II) species. These experiments carried out on **6** prepared from methyl 2-chloromethyloxazole-4-carboxylate<sup>14</sup> showed that exposure of **6** to catalytic palladium dichloride bis(acetonitrile) and excess *p*-benzoquinone<sup>15</sup> in methanol-acetonitrile under an atmosphere of carbon monoxide afforded tetrahydropyran **7** in 58% isolated yield along with 15–20% of recoverable **6** (Scheme 3). The successful conversion of **6** to **7** by this

**Scheme 3.** Synthesis of the C9–C19 Portion of **1** via Palladium(II)-Catalyzed Alkoxy carbonylation



means enabled us to employ this tetrahydropyran subunit in a continuation of our route toward **1**.

Construction of tetrahydropyran C of **1** required a subunit which, when reacted with **7**, would afford a masked 1,5-diol that could be cyclized to the 2,6-trans configuration of

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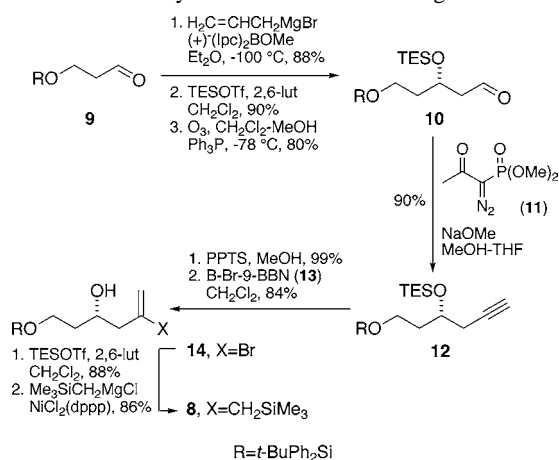
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this heterocycle. The operative species chosen for this was allylsilane **8** (Scheme 4). Asymmetric allylboration<sup>16</sup> of

#### Scheme 4. Synthesis of the C3–C8 Segment of **1**

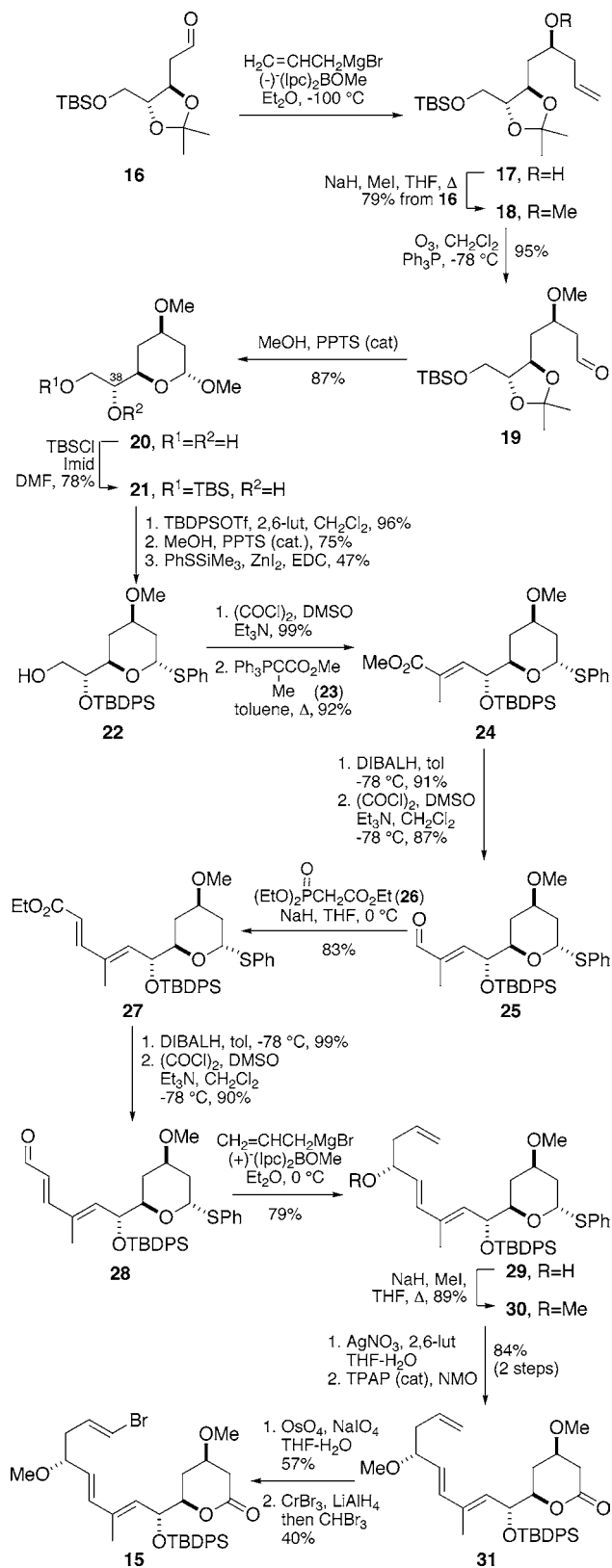


aldehyde **9** followed by silylation of the resultant homoallylic alcohol and then ozonolysis gave aldehyde **10**. Exposure of **10** to diazophosphonate **11**<sup>17</sup> produced alkyne **12**, but bromoboration of this material with 9-bromo-9-borabicyclo-[3.3.1]nonane (**13**) gave an intractable mixture. A cleaner result was obtained with the secondary alcohol from selective cleavage of the TES ether, and the product from reaction with **13** was then resilylated before treating vinyl bromide **14** with trimethylsilylmethylmagnesium chloride in the presence of a nickel(II) catalyst<sup>18</sup> to give **8**.

Our initial plan for assembling the C20–C46 portion of phorbaxazole A envisioned capture of the anion derived from deprotonation of the methyl substituent of oxazole **2** by a  $\delta$ -lactone **15** bearing the complete C38–C46 side chain, including the terminal (*E*)-bromoalkene. Toward this end, a route to **15** was devised starting from aldehyde **16** prepared from diethyl (*S,S*)-tartrate (Scheme 5). Asymmetric allylation<sup>19</sup> of **16** gave homoallylic alcohol **17** which was converted to its methyl ether **18** before ozonolytic cleavage to aldehyde **19**. Acidic methanolysis of **19** cleaved both the acetonide and the silyl ether and led directly to ketal **20**, but to attach a robust protecting group selectively at the C38 hydroxyl group, it was first necessary to reprotect the primary alcohol of **20**. After masking the secondary alcohol of **21** and releasing the primary alcohol, it was discovered that subsequent hydrolysis of the methyl acetal and oxidation of the resulting hemiacetal to a  $\delta$ -lactone compromised the integrity of the structure due to silyl group migration.

A solution to this problem was found in conversion of the methyl acetal to its phenylthio acetal **22**,<sup>20</sup> so that Swern

#### Scheme 5



oxidation of **22** followed by Wittig olefination of the resulting aldehyde with ylide **23** afforded (*E*)- $\alpha,\beta$ -unsaturated ester **24** in excellent yield. Reduction of this ester followed by Swern oxidation yielded  $\alpha,\beta$ -unsaturated aldehyde **25** which

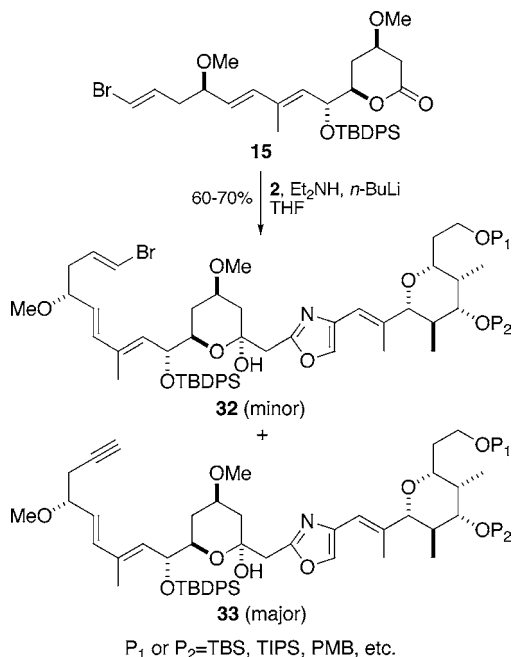
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**Scheme 6.** Attempted Coupling of the C19–C32 Unit **3c** with C33–C46 Fragment **15**



underwent condensation with phosphonate **26** to afford (*E,E*)-dienyl ester **27**. Asymmetric allylation<sup>19</sup> of aldehyde **28** derived from **27** furnished pure triene **29**. After O-methylation of **29**, the phenylthio substituent of **30** was returned to a carbonyl function by treatment with silver nitrate in aqueous THF<sup>20b</sup> followed by oxidation of the intermediate

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hemiacetal with Ley's reagent.<sup>21</sup> The terminal alkene of lactone **31** was cleaved oxidatively to an aldehyde which underwent a Takai reaction<sup>22</sup> with bromoform to yield (*E*)-bromotriene **15**. The use of chromous chloride in this Takai reaction was found to give a mixture of 1-chloro and 1-bromo alkenes that was difficult to separate, and to avoid this problem, chromium(II) bromide was prepared and used in situ by reduction of chromium(III) bromide with lithium aluminum hydride.

Unfortunately, attempts to use **15** in coupling reactions with an anion prepared from **2** under a variety of conditions led to a mixture of the desired product **32** and terminal alkyne **33** resulting from elimination of HBr (Scheme 6). In most instances, **33** was the major product. Separation of **32** from the mixture was tedious, and furthermore, we were unable to convert **33** to **32**.

The difficulties experienced in our attempts to forge the C32–C33 linkage of **1** using lactone **15** as an electrophile caused us to reevaluate our coupling strategy. As a result, a modified assembly plan was devised employing a truncated version of **15**. This and further steps leading to the complete synthesis of phorboxazole A are described in the Letter that follows.

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**Supporting Information Available:** Detailed experimental procedures and characterization data for new compounds; <sup>1</sup>H and <sup>13</sup>C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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