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Convergent Synthesis of the C31-C46 Domain of the Phorboxazole Natural Products

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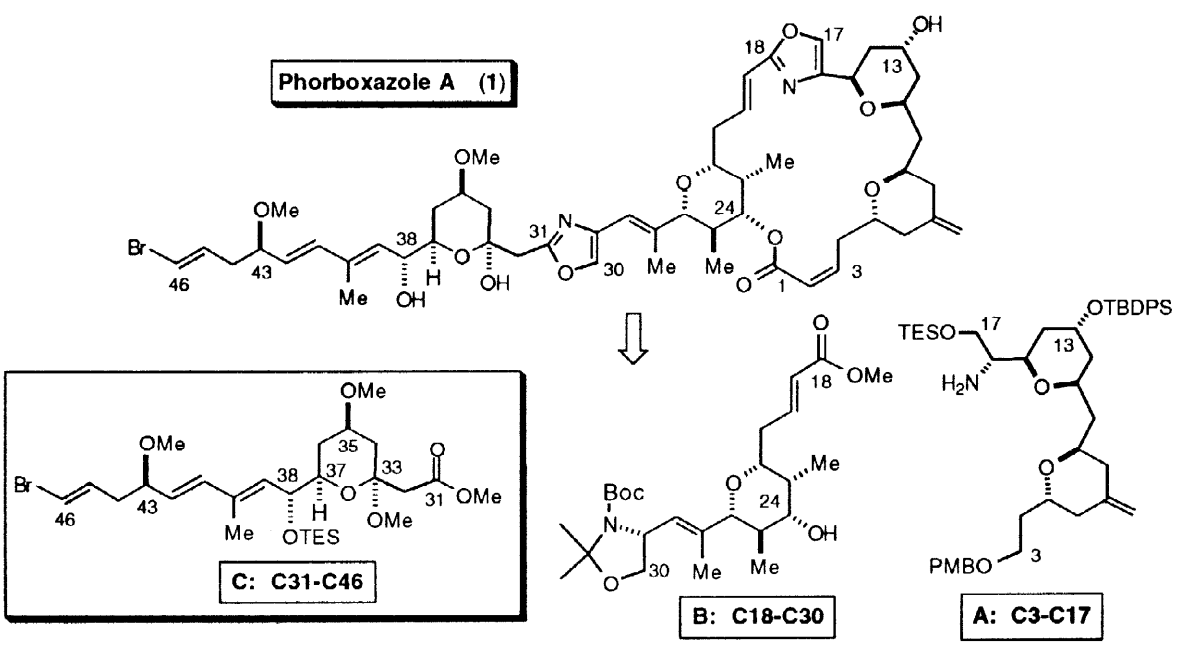
Abstract: A convergent synthesis of the C31-C46 domain of the phorboxazole natural products has been developed. This involved the preparation of a C39-C46 dienyl iodide and a C31-C37 aldehyde, followed by their $CrCl_2$-mediated coupling and final installation of the C46 (*E*)-vinyl bromide via an alkyne hydrostannation-bromination sequence.

Phorboxazole A (**1**) and its C13 epimer phorboxazole B are unique natural products isolated recently from an Indian Ocean sponge *Phorbas* sp.[1] Phorboxazole A has exceptionally potent cytostatic activity against human tumor cell lines, but in contrast to known microtubule-interactive agents, **1** appears to induce cell cycle arrest during S phase.[2] The remarkable levels of cytostatic activity reported for **1** is accompanied by an unprecedented array of structural features. Complete stereochemical assignments have resulted from a combination of extensive NMR, derivatization, degradation, and correlation studies.[1-3] Their structural novelty, limited availability, and intriguing cytostatic activity combine to make the phorboxazoles important and challenging synthetic targets. From this perspective, strategic dissection of the oxazole and (Z)-acrylate moieties yields three fragments of comparable complexity, corresponding to C3-C17 (**A**), C18-C30 (**B**), and C31-C46 (**C**) of the natural products. Syntheses of phorboxazole intermediates **A**[4] and **B**[5] have been reported previously. Described here is a direct and convergent synthesis of the remaining **C** domain of the phorboxazoles.



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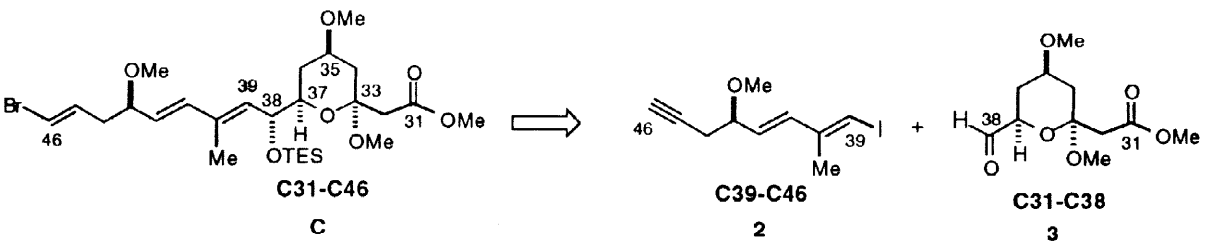
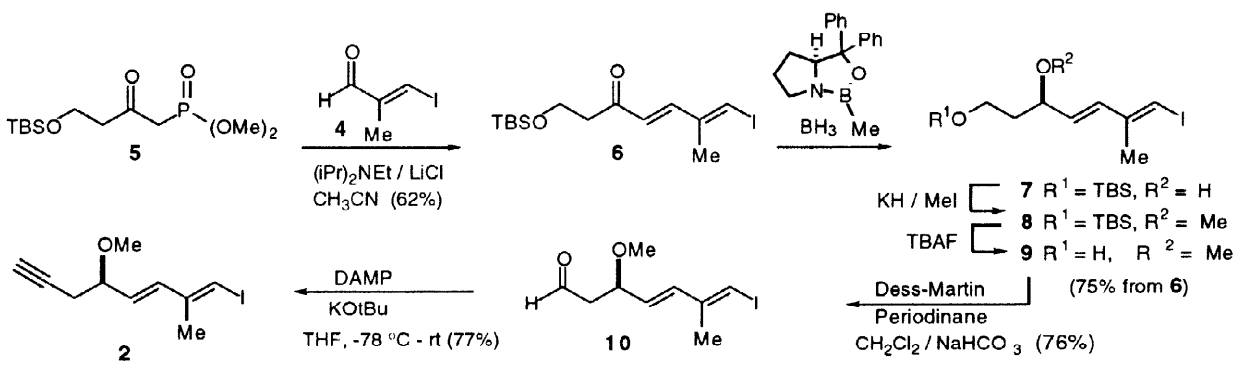
With 5 stereogenic centers and 12 functionalized backbone carbons, the **C** domain of the phorboxazoles presents a challenge for concise assembly. Because the 2,4-disubstituted oxazoles of the phorboxazoles may be constructed from vicinal amino alcohol and carboxylic acid moieties,[6] a carboxylate group was incorporated at C31 of fragment **C**. Dissection of **C** at the C38-C39 bond yields a polyene side chain and a highly substituted hemiketal-oxane ring. The natural products' (38*R*)-configuration would ideally derive from the direct addition of a C39 alkenyl nucleophile to a C38 aldehyde.[3] For this, the use of an organochromium nucleophile[7,8] for chemoselective coupling in the presence of the C31 ester would provide enhanced convergency, but leaves uncertain the stereoselectivity of C38 carbinol formation. Also, installation of the terminal vinyl bromide would best be deferred until after C38-C39 bond formation. Thus, the synthesis of the C31-C46 portion of the phorboxazoles began with the preparation of dienyl iodide **2** and aldehyde **3**, and an examination of their convergent coupling.



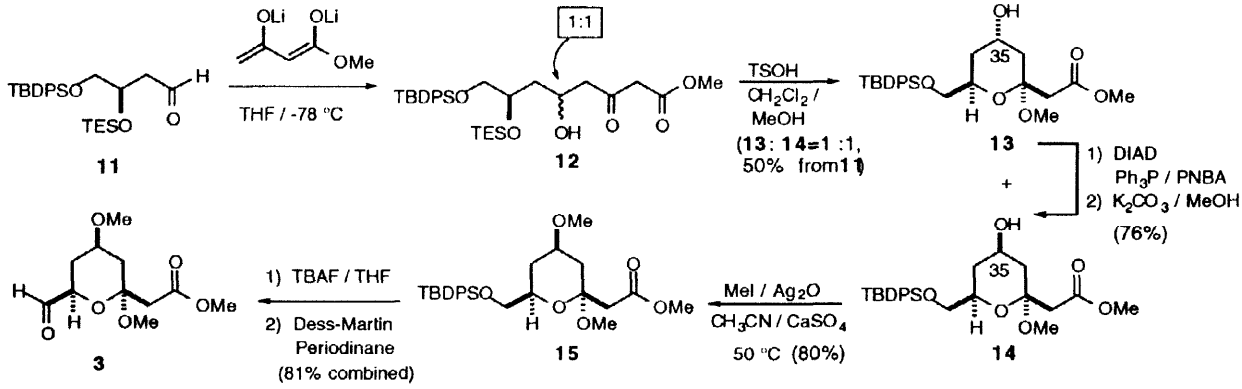
The synthesis of **2** started with a one-pot syn methyl-metallation/iodination of propargyl alcohol,[9] followed by oxidation with Dess-Martin periodinane[10] to give the (*E*)-β-iodoaldehyde **4** (Scheme 1). Coupling[11] of **4** with ketophosphonate **5** provided (*E*,*E*)-dienone **6** as the only stereoisomer.[12] Reduction of **6** using Corey's (*S*)-CBS / BH_3 system[13] gave (*R*)-**7**, which was *O*-methylated then desilylated to yield **9**. Treatment of **9** with Dess-Martin periodinane, followed by alkyne installation[14] completed the synthesis of **2**.

Scheme 1



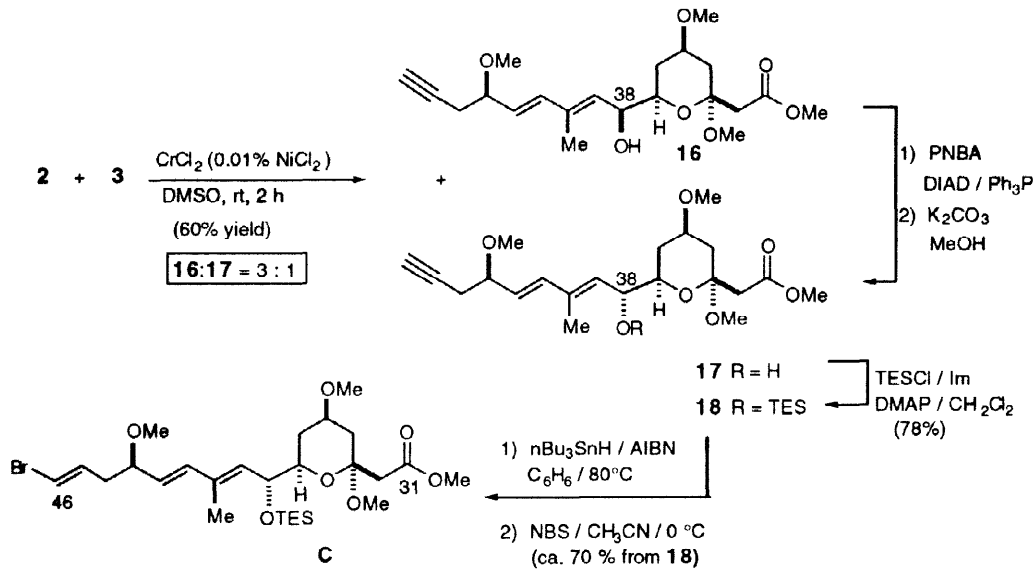
Aldehyde **3** was prepared in a similarly straight-forward manner (Scheme 2). Addition of methyl acetoacetate dianion[15] to aldehyde **11**[16] generated secondary alcohols **12** as a 1:1 diastereomeric mixture. These were cyclized directly to mixed methyl acetals **13** and **14** by treatment with TsOH in MeOH / CH_2Cl_2. In compensation for the lack of diastereoselection in the formation of **12**, the chromatographically separated (35*S*)-carbinol[17] **13** was converted easily into (35*R*)-**14** using a Mitsunobu inversion[18]-saponification sequence. Ag_2O-assisted hydroxyl methylation of **14** gave **15**, which was converted into aldehyde **3** by sequential treatment with TBAF and Dess-Martin periodinane.

Scheme 2



Joining of **2** and **3** under $CrCl_2$ / $NiCl_2$-mediated conditions[7] gave a 3 : 1 ratio of allylic alcohols (38*S*)-**16** and (38*R*)-**17** (Scheme 3).[19] The configuration at C38 of **16** could be inverted[18] as before to provide additional **17**. After silylation of the C38 hydroxyl of **17**, the terminal alkyne was hydrostannated under standard conditions to give the (*E*)-vinyl stannane (*E*:*Z*=5:1), without interference of the conjugated diene system. Whereas direct bromination of the vinyl stannane using Br_2 in CH_2Cl_2 yielded several by-products in addition to bromide **C**, facile tin-bromine exchange using NBS in CH_3CN at 0 °C provided **C** cleanly.

Scheme 3



A fully functionalized synthetic fragment representing the C31-C46 domain of the phorboxazole natural products was thus prepared in ca. 15-steps in the longest linear sequence from dimethyl (*R*)-malate.[16] Although the initial generation of intermediates **14** and **17** lacked favorable diastereoselectivity, this direct synthetic route provides practical access to the third and final **C** domain of the phorboxazoles. This work, coupled with previous results,[4,5] will promote continuing efforts towards the development of an efficient total synthesis of the phorboxazole natural products.

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References and Notes

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(12) Yields indicated in the schemes refer to chromatographically and spectroscopically homogeneous products, unless otherwise noted.

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(16) Compound **11** was prepared from dimethyl (*R*)-malate (Henrot, S.; Larcheveque, M.; Petit, Y. *Synth. Commun.* **1986**, *16*, 183-190.) as follows: (*i*) BH_3·DMS / $NaBH_4$ (Saito, S.; Hasegawa, T.; Inaba, M.; Nishida, R.; Fujii, T.; Nomizu, S.; Moriwake, T. *Chem. Lett.* **1984**, 1389-1392.), (*ii*) TBDPSCl / Im, (*iii*) TESCl / Im, (*iv*) DIBAL.

(17) The C35 configurations of **13** and **14** were assigned on the basis of an oxidation / diastereoselective reduction sequence [oxidation of **14** with Dess-Martin periodinane followed by Li(*s*-Bu_3BH) reduction of the resultant ketone gave **13**] and comparison of vicinal coupling constants with data reported for **1**.[1]

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(19) The C38 configurations (phorboxazole numbering) were assigned by reference to the work of Searle *et al.*[1,3] and comparison of vicinal coupling constants: (38*R*)-**17**: $J_{37H\text{-}38H}$ = 6.5 Hz, (38*S*)-**16**: $J_{37H\text{-}38H}$ = 3.5 Hz, (38*R*)-**1**: $J_{37H\text{-}38H}$ = 7.9 Hz[1] ($CDCl_3$).