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A New Approach to Phorbol by [4 + 3] Oxyallyl Cycloaddition and Intramolecular Heck Reaction

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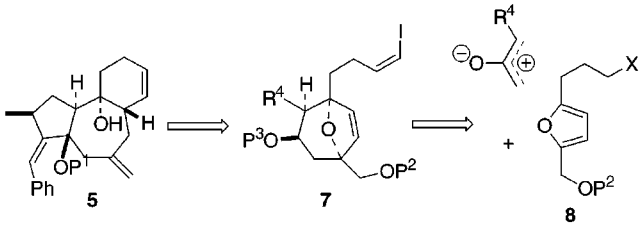
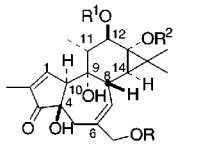
ABSTRACT



A new synthetic strategy for a functionalized tricyclic core of phorbol has been developed by means of a [4 + 3] oxyallyl cycloaddition and subsequent intramolecular Heck reaction. The [4 + 3] oxyallyl cycloadduct 7 was chosen as the B-ring precursor of phorbol. Subsequent elaboration took advantage of its well-defined diastereofacial bias to afford the tricycle 5. This method should be of general value in the construction of 6,7- or 5,7-fused bicyclic systems.

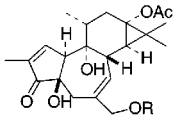
Phorbol (**1b**), a tigliane diterpene, has attracted considerable interest largely because of the high biological activity of its esters.[1] Several esters of phorbol and ingenol (**4**), for



1a: R=R^1=R^2= H

1b: R=H, R^1=COC$_{13}$H$_{27}$

R^2= Ac



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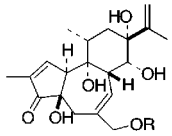

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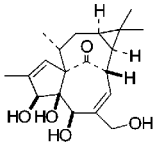

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example, have been identified to be among the most potent tumor promoters. Recent observations that other phorbol derivatives (e.g., prostratin (**2**)) and structurally related daphnane diterpenes (**3**) apparently lack tumor-promoting activity but exhibit promising antitumor, anti-HIV, and analgesic properties have further heightened interest in this important family of natural products. Despite numerous studies and several elegant synthetic approaches, only phorbol and resiniferatoxin have been successfully synthesized by the Wender group by an intramolecular oxidopyrylium−olefin [5 + 2] cycloaddition.[2] As an initial foray into these architecturally complex natural products of current interest, we herein report a convenient synthesis of the tricycle **5** possessing the ABC-ring skeleton of phorbol to exemplify a potentially unified approach to the tigliane, daphnane, and ingenane diterpenes.

The cornerstone of our approach to the phorbol ABC-ring system, outlined in Scheme 1, was an intramolecular Heck reaction of the 8-oxabicyclo[3.2.1]oct-6-ene **7** to assemble the BC-ring compound **6**, where the well-known diastereofacial discrimination engendered by these oxabicycles should result in excellent stereoselectivity. Although the intra-

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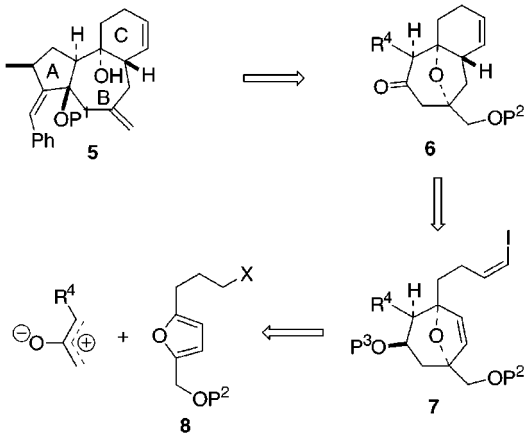
Scheme 1

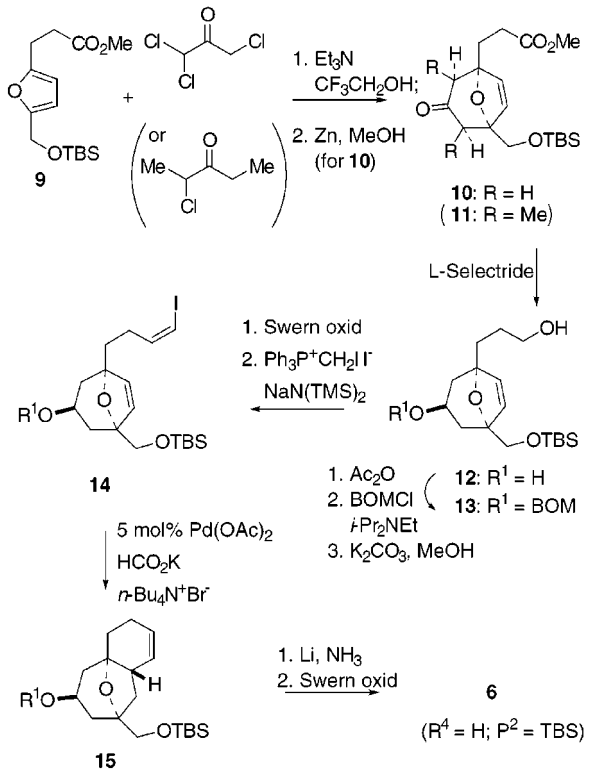


molecular Heck reaction has enjoyed increasingly frequent applications in natural product synthesis, no example has appeared of its use on the [4 + 3] oxyallyl cycloadducts for the stereocontrolled construction of 6,7-fused or 5,7-fused ring systems.[3] The requisite substrate **7** was expected to be readily available by the [4 + 3] oxyallyl cycloaddition of disubstituted furan **8**.[4,5] The cycloadduct **7** was chosen as the B-ring precursor of phorbol because of its rigid conformation possessing the well-defined diastereofacial bias which is useful in post-cycloaddition elaboration.

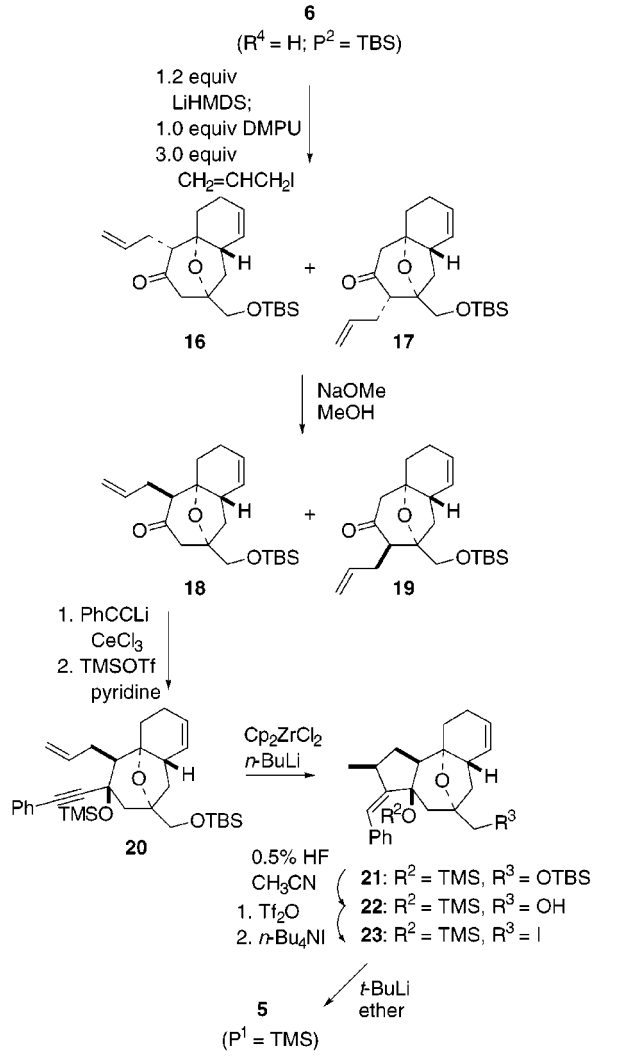
Our synthesis began with the readily available furan **9** (Scheme 2).[6] The [4 + 3] cycloaddition of **9** to the oxyallyl generated from 1,1,3-trichloroacetone under Föhlisch's conditions,[7] followed by reduction with zinc, gave the cycloadduct **10** in 83−98% yield (based on consumed starting material). The Föhlisch procedure was chosen because of convenient execution, as well as the commercial availability of the oxyallyl precursor. Similarly, use of 2-chloro-3-pentanone afforded the corresponding cycloadduct **11** in good yield. Global reduction with L-Selectride gave the diol **12** in 90% yield. By standard functional group manipulation, **13** was then obtained in 87% yield. Swern oxidation and subsequent olefination by the method of Stork[8] produced the (*Z*)-vinyl iodide **14** (80% yield). The pivotal step, an intramolecular Heck reaction, took place smoothly by the action of $Pd(OAc)_2$ and HCO_2K[9] to stereoselectively yield **15** in 75% yield. It is noteworthy that intramolecular carbanionic ring opening of the oxabicyclo[3.2.1] compounds bearing four-carbon tethers failed to provide the corresponding bicyclo[5.4.0]undecenes, in marked contrast to the facile preparation of bicyclo[5.3.0]decenes by use of three-carbon tethers.[10]

Toward the A-ring construction, the keto group at C-4 (phorbol numbering) was first restored to furnish ketone **6** (75% yield) by standard methods (Scheme 3). Alkylation of the ketone enolate with allyl iodide produced an insepa-

Scheme 2



Scheme 3



rable 2.5:1 mixture of the two regioisomers **16** and **17** in 64% yield, along with recovered starting ketone (16%). Equilibration with NaOMe and chromatographic separation then afforded the β-allyl ketone **18**. We decided to defer to later study the ultimate regiocontrol which would be achieved by way of an intramolecular process of oxyallyl cycloaddition or enolate alkylation. The structural assignment of **18** and **19** rests upon the $^1H-^1H$ COSY experiments and difference NOE measurements: diagnostic evidence for the stereochemistry of the allylic side chain in **18** was obtained by an NOE between the methine proton (δ 2.44) at C-10 (phorbol numbering) and the α-proton (δ 2.70) at C-5. The A-ring was then constructed by adaptation of Wender's method.[2,11] Stereoselective addition of phenylacetylide ceriate, followed by alcohol protection, gave **20** in 96% yield. Zirconocene-mediated enyne cyclization under Negishi's conditions[12] took place smoothly to yield the A-ring annulation product **21** (91%). Selective desilylation by the action of aqueous HF in CH_3CN afforded the primary alcohol **22** in 70% yield. Following conversion to the iodide **23** (76%), cleavage of the oxa bridge was achieved by reductive elimination involving iodine−lithium exchange to furnish the initial target compound **5** (69%) containing the ABC-ring skeleton of phorbol.[13]

In summary, we have developed a new synthetic strategy for a suitably functionalized tricyclic core of phorbol by means of a [4 + 3] oxyallyl cycloaddition and subsequent intramolecular Heck reaction. This method should be of general value in the stereocontrolled construction of 6,7- or 5,7-fused bicyclic systems which are frequently found in bioactive natural products. Further refinement toward a total synthesis of phorbol, with particular emphasis on regio- and stereocontrolled alkylation at C-10, is currently in progress.

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