Formal Synthesis of (+)-Phorbol[1]

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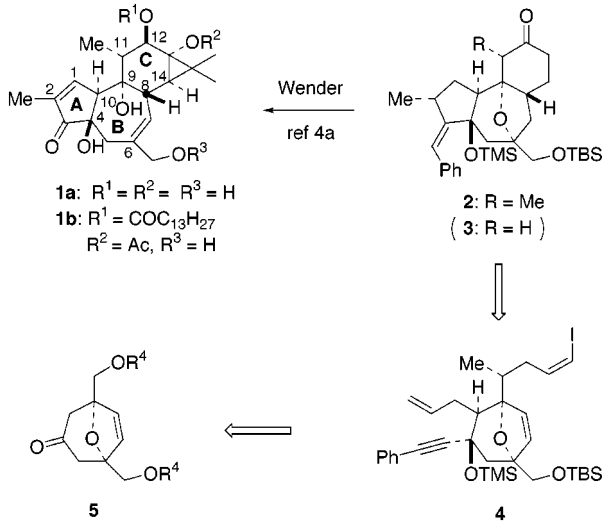
The phorbol esters (e.g., **1b**) have been identified to be among the most potent tumor promoters.[2] High tumor-promoting activity of phorbol derivatives has been correlated to their activation of protein kinase C (PKC) isozymes, which play a central role in cellular signal transduction, and depends on optimal lipophilicities of fatty acid side chains.[3] Recent observations that other phorbol derivatives and structurally related daphnane diterpenes apparently lack tumor-promoting activity but exhibit antitumor, anti-HIV, and analgesic properties have further heightened interest in this important family of natural products. Efforts to elucidate the structural basis for these interesting biological effects of phorbol derivatives and ultimately design inhibitors with optimal specificity for a PKC-signaling pathway have rendered phorbol (**1a**), a tigliane diterpene, an attractive target for synthesis. Several imaginative approaches notwithstanding, to date only the Wender group has achieved a total synthesis by utilizing an elegant application of the oxidopyrylium-olefin [5 + 2] cycloaddition.[4] Herein we report a formal synthesis of (+)-phorbol by intersecting with Wender's advanced intermediate **2**, which could also serve as a pivotal precursor to prostratin and daphnane diterpenes.

As shown in Scheme 1, our synthetic plan was built upon a [4 + 3] oxyallyl cycloaddition and subsequent intramolecular Heck reaction for the stereocontrolled construction of the BC-ring system of phorbol, followed by adaptation of Wender's efficient method for the A-ring construction.[4,5] The utility of this key strategy was previously demonstrated in the synthesis of the tricycle **3**, in racemic form, possessing the ABC-ring skeleton of **1a**.[6] The diastereoselective introduction of the C-11 methyl group, which was required to complete a formal synthesis of **1a**, was deemed challenging. Therefore, we chose to incorporate the C-11 methyl group at an early stage in an enantioselective synthesis of (+)-**1a**.

Our synthesis began with the [4 + 3] cycloaddition of the readily available furan **6**[7] and the oxyallyl generated from 1,1,3-trichloroacetone (**7**) under Föhlisch's conditions,[8] followed by reduction with zinc, to afford the cycloadduct **8** in 80−93% yield (based on consumed starting material) (Scheme 2).[9] After both protecting groups were changed to the acetate, asymmetrization

Scheme 1



of the meso cycloadduct **9** was achieved by means of a lipase from *Candida rugosa* to furnish the alcohol **10** in 90% yield and 80% ee [on the basis of ^{1}H NMR studies with a chiral shift reagent, Eu(hfc)$_3$]. To set the stage for the A-ring annelation by way of enyne cyclization, the two alkyl groups were introduced onto the B-ring.[10] Toward this end, **11** was prepared in 90% overall yield in a straightforward manner. The regio- and stereoselective introduction of the allyl group to nonracemic, yet pseudosymmetric, **11** was realized in a 7:1 diastereoselectivity by asymmetric deprotonation using Simpkins' base **12** in the presence of LiCl.[11] Subsequent Mannich condensation and elimination according to the Eschenmoser's method afforded the enone **13** in 70% overall yield. As a consequence of these two asymmetric transformations, **13** was thus obtained in essentially enantiomerically pure form (≥97% ee). Conjugate addition of vinyl cuprate to **13** and in situ protonation stereoselectively afforded **14** (70%). Alternatively, **14** was prepared on a comparable level of efficiency by means of radical allylation, followed by base-induced equilibration of **15**. The alkyne group was then introduced by addition of phenylacetylide ceriate or lithium phenylacetylide in the presence of lithium bromide from the convex face of **14**, followed by TMS protection, to provide **16**.

After removal of the BOM-protecting group of **16** and straightforward elaboration of **17** (Scheme 3), the C-11 methyl group was next installed onto **18** diastereoselectively (>20:1) by the powerful enantioselective conjugate addition procedure developed by Hruby to give **19**.[12] By standard methods involving the Wittig olefination variant of Stork,[13] the (*Z*)-vinyl iodide **4** was then prepared in 62% overall yield for the pivotal intramolecular Heck reaction:[14] treatment of **4** with Pd(OAc)$_2$ and HCO_2K yielded **20**, as a single isomer, in 79% yield. Finally, the

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(1) Part 14 in the series of synthetic studies on [4 + 3] cycloadditions of oxyallyls. See also: (a) Part 13: Lee, J. C.; Cha, J. K. *J. Am. Chem. Soc*. **2001**, *123*, 3243. (b) Part 12: Lee, J. C.; Cha, J. K. *Tetrahedron* **2000**, *56*, 10175. (c) Part 11: Sung, M. J.; Lee, H. I.; Chong, Y.; Cha, J. K. *Org. Lett*. **1999**, *1*, 2017.

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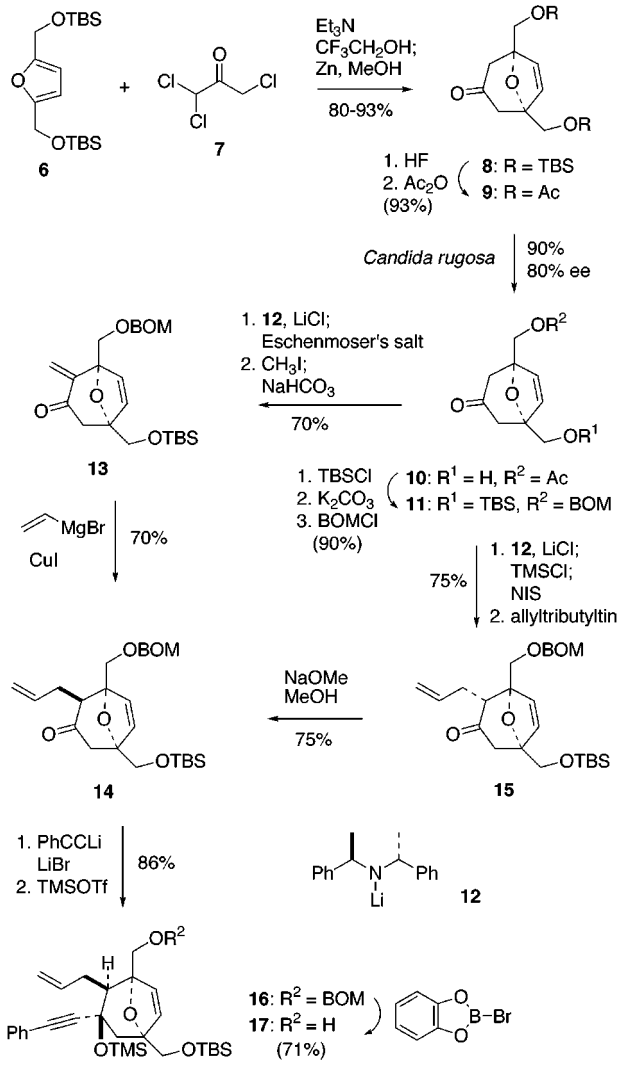
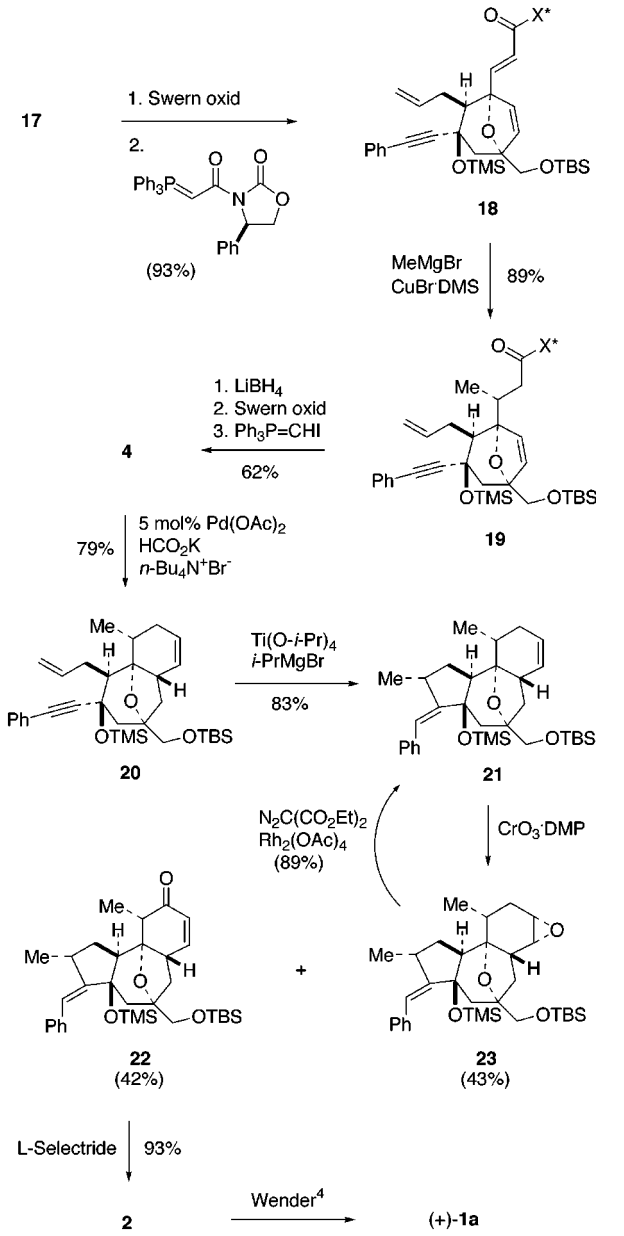
Scheme 2



A-ring was constructed by adaptation of Wender's method.[4,5] Zirconocene-mediated cyclization of the enyne **20** under Negishi's conditions[15] afforded an inseparable 4:1 mixture (81%) of the ABC-ring tetracycle **21** and the C-2 epimer. On the other hand, Sato's enyne cyclization protocol[16] gave **21** as the sole isomer (83%).[17]

To intersect with Wender's advanced intermediate **2**, allylic oxidation of **21** was next undertaken; CrO_3-3,5-dimethylpyrazole produced a 1:1 mixture of enone **22** and epoxide **23** in 85% yield.[18−20] Efficient deoxygenation of **23** by the procedure of

Scheme 3



Ganem allowed recycling to **21**.[21] Finally, L-Selectride reduction of **22** smoothly gave the key intermediate **2** in 93% yield. This synthetic substance, $[\alpha]_D = -55°$ (*c* 0.47, CH_2Cl_2) {lit[4c] $[\alpha]_D = -54.7°$ (*c* 1.28, CH_2Cl_2)} was found to exhibit physical and spectroscopic data identical to those reported by Wender.[4]

In summary, we have developed a formal synthesis of phorbol (**1a**) and also a general strategy for the stereocontrolled construction of 6,7- or 5,7-fused bicyclic systems by means of a [4 + 3] oxyallyl cycloaddition and subsequent intramolecular Heck reaction.

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Supporting Information Available: Experimental procedures and the ^{1}H and ^{13}C NMR spectra of key intermediates (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) We believe that the C-2 methyl group of **21** has the α-configuration, as shown in Scheme 3, on the basis of difference NOE measurements: when the resonance of the −OTMS group was irradiated, a significant NOE was observed for the methine hydrogen (δ 2.85 ppm) at C-2. Since the C-2 stereocenter is destined to become the olefin functionality, however, this stereochemistry is inconsequential for the synthesis of **1a**.

(18) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057.

(19) The epoxide **23** was obtained as a single isomer, and the α-configuration was tentatively assigned on the basis of difference NOE measurements.

(20) A more expedient route to the incorporation of the alcohol functionality at C-12 should be available by oxidatively trapping the enolate intermediate in the conjugate addition of **18**.

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