

SYNTHETIC ROUTES TO THE DITERPENOID CORES OF PHORBOL AND RESINIFERATOXIN

Reported by Joseph D. Eckelbarger

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INTRODUCTION

Phorbol (**1**) (Figure 1) is a tigliane diterpene isolated from the seed oil of *Croton tiglium*. The toxicity of croton seed oil has been known for centuries, but its constituents were not isolated and structurally identified until 1967.¹ The structure and relative configuration of phorbol was proposed based on ¹H NMR, MS, IR, UV, and chemical derivatization data and confirmed using X-ray analysis.² The absolute configuration was established by X-ray analysis of a *p*-bromobenzoyl derivative of phorbol and found to be opposite that originally proposed based on circular dichroism measurements.³ Several diester analogues of phorbol are toxic and show potent tumor promoting activity due to activation of protein kinase C.⁴ This property makes phorbols important in the study of carcinogenesis.

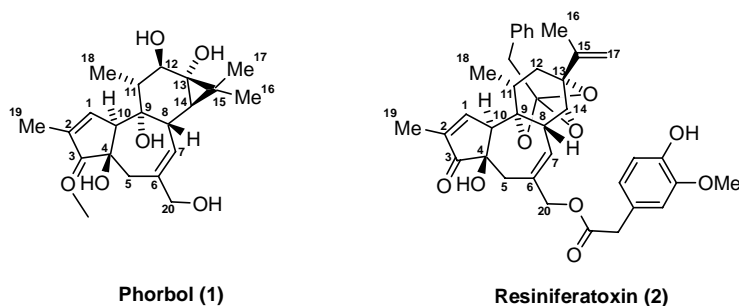


Figure 1. Structures of phorbol and resiniferatoxin

Resiniferatoxin (**2**) is a daphnane diterpene extracted from the latex of *Euphorbia resinifera* in 1975. Its structure and relative configuration were elucidated using a combination of ¹H NMR, MS, IR, UV, and chemical derivatization.⁵ Resiniferatoxin exhibits extremely high irritant activity that mimics capsaicin, the active ingredient in hot peppers.⁶ It has recently garnered interest as a potential analgesic and found use as a vanilloid receptor probe in the study of pain signaling in the central nervous system.⁶

The tigliane and daphnane natural products (Figure 2) share a highly oxygenated tricyclo [9.3.0.0^{2,7}] tetradecane ring system thought to be derived from the biosynthetic precursor casbene.⁷ Despite the structural homology of **1** and **2**, resiniferatoxin does not share the potent tumor promoting activity of the phorbol esters.⁸ The interesting biological activity exhibited by the tiglianes and daphnanes has led to the development of numerous synthetic routes to their diterpenoid core. This review details several recent strategies for the construction

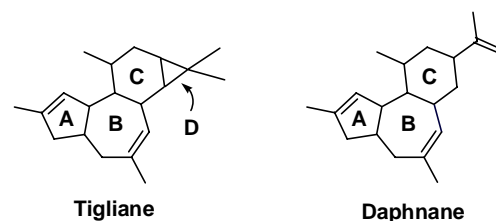


Figure 2. Tigliane and Daphnane Skeletons

of the [9.3.0.0^{2,7}] ring system and their application toward the total synthesis of phorbol and resiniferatoxin.

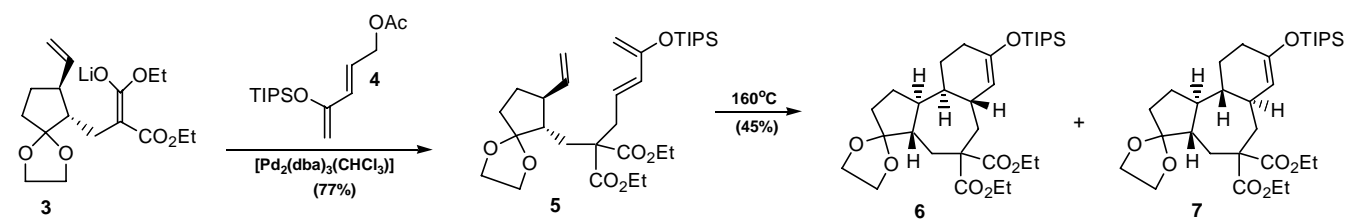
SYNTHETIC APPROACHES

Cycloaddition reactions are valued in organic synthesis for their atom economy and high levels of regio- and stereo-control. Not surprisingly, several different cycloadditions have been utilized in the construction of the tricyclic ring system of the tiglianes and daphnanes. Diels-Alder [4+2]⁹⁻¹¹, nitrile oxide [3+2]¹², oxyallyl [4+3]¹³, and oxidopyrilium [5+2] cycloadditions¹⁴⁻¹⁷ have all been used to successfully construct the tigliane and daphnane skeleton with the correct relative stereochemistry at the ring junctions C(4), C(8), C(9), and C(10). Although various strategies have been employed in the construction of the ring system, assembly with absolute stereocontrol and incorporation of sufficient functionality for elaboration to the natural products has been a challenging task. Described herein are highlights of these efforts.

Intramolecular Diels-Alder Approach

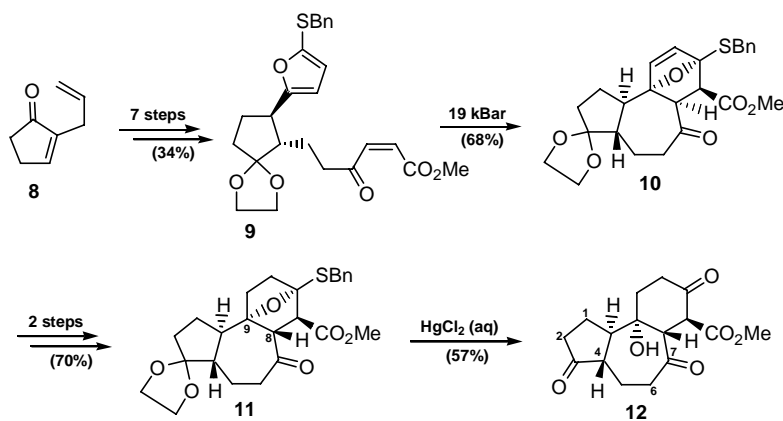
Page and co-workers used an intramolecular Diels-Alder strategy to construct the tigliane/daphnane BC-rings in a single step (Scheme 1).⁹ In this strategy, the diene and dienophile were tethered to a cyclopentane ring in a 1,2-trans orientation in order to produce the stereochemistry of the AB-ring junction. The cycloaddition substrate **5** was prepared by addition of lithium enolate **3** to the palladium π -complex of diene **4**. Heating a toluene solution of **5** to 160° C for 14 days led to the isolation of exo-cycloadducts **6** and **7** as an inseparable 1:1 mixture of diastereomers. Although this approach provides the racemic tricyclic core in only five steps with excellent exo selectivity in the key intramolecular Diels-Alder cycloaddition, there is no inherent facial diastereoselectivity in the transition state. Furthermore, the desired cycloadduct **6** is relatively devoid of functionality, precluding further elaboration to phorbol or resiniferatoxin.

Scheme 1.



Harwood and co-workers were able to construct a racemic tigliane/daphnane core by reacting a tethered furan with a doubly activated dienophile.¹⁰ The cycloaddition substrate **9** (Scheme 2) was prepared from enone **8** in seven steps and 34% overall yield. No cycloaddition was observed at ambient pressure. However, at elevated pressure, the endo-adduct **10** was formed exclusively as a single diastereomer in 68% yield; no exo-adduct was observed. After hydrogenation, the desired ring junction at C(8) was obtained by selective epimerization to **11**. Finally, the oxygen bridge was cleaved by hydrolysis with aqueous mercuric chloride. While the resulting tricycle **12** contains the C(9) hydroxyl and the correct relative configuration at all five stereocenters, it lacks the C(18) and C(19) methyl groups and the angular hydroxyl functionality at C(4), and it requires incorporation of the C(15)-(17) carbons, the C(20) carbon, the C(1)-C(2) olefin, and the C(6)-C(7) olefin.

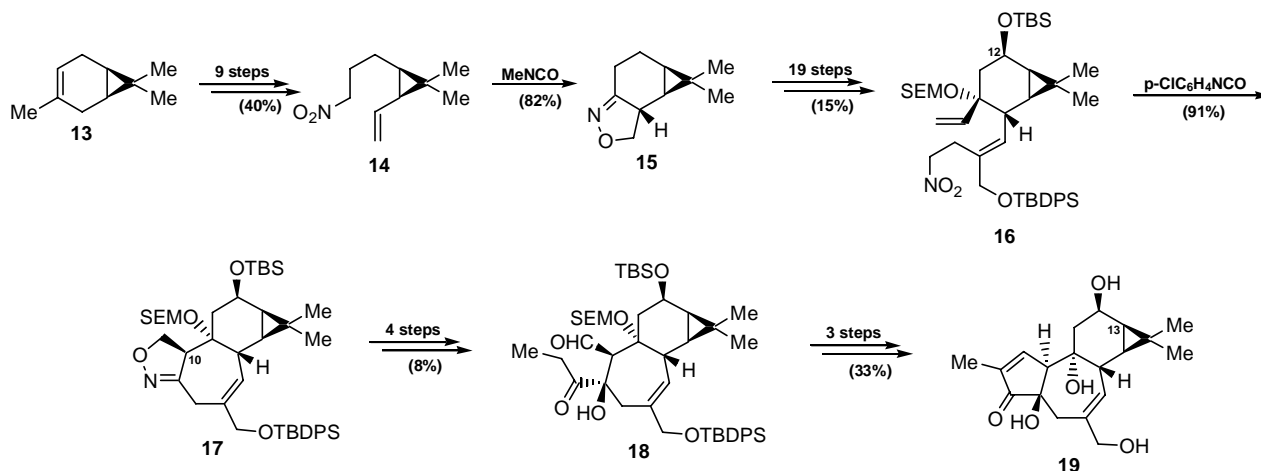
Scheme 2.



Intramolecular Nitrile Oxide [3+2] Cycloaddition Approach

Shibasaki and co-workers constructed the first optically active phorbol skeleton using two intramolecular nitrile oxide [3+2] cycloadditions and an intramolecular aldol condensation as the key transformations.¹² Starting from (+)-3-carene (**13**) (Scheme 3), they prepared the CD-ring system **15** in 10 steps and 33% overall yield. Elaboration to the C(12)-hydroxy BCD-ring system was accomplished

Scheme 3.

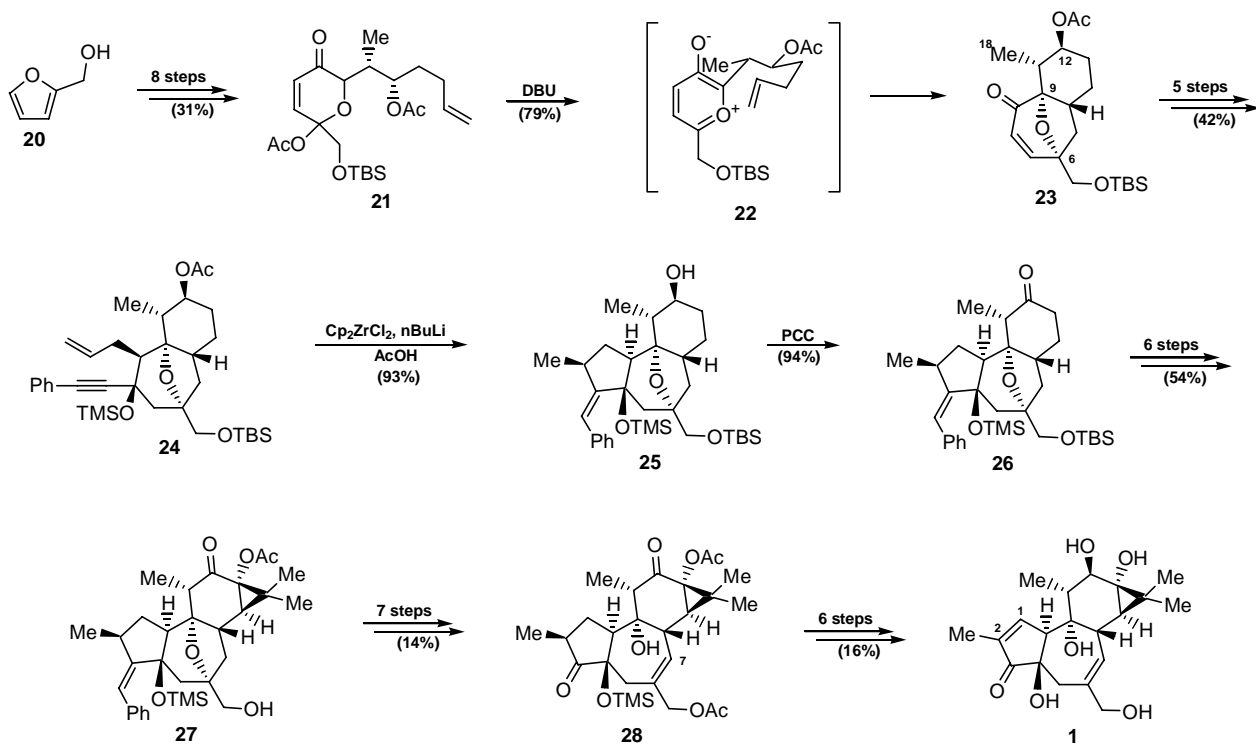


in a 22 step sequence, culminating in an intramolecular nitrile oxide [3+2] cycloaddition to give isoxazoline **17**. The cycloaddition proceeded through a boat-like transition state to give the desired C(10) stereocenter. Unlike the Diels-Alder approaches of Page and Harwood, Shibasaki chose to form the A-ring in the final stages of the synthesis, using an intramolecular aldol condensation. While the phorbol analogue **19** synthesized by Shibasaki and co-workers lacks the C(18) methyl group and C(13) hydroxyl of the natural product, it contains all of the functionality believed necessary for tumor promotion by activation of protein kinase C.¹⁸ However, this synthesis suffered from lack of convergence (37 linear steps) and low overall yield (0.12%).

Intramolecular Oxidopyrilium [5+2] Cycloaddition Approach (The Syntheses of Phorbol and Resiniferatoxin)

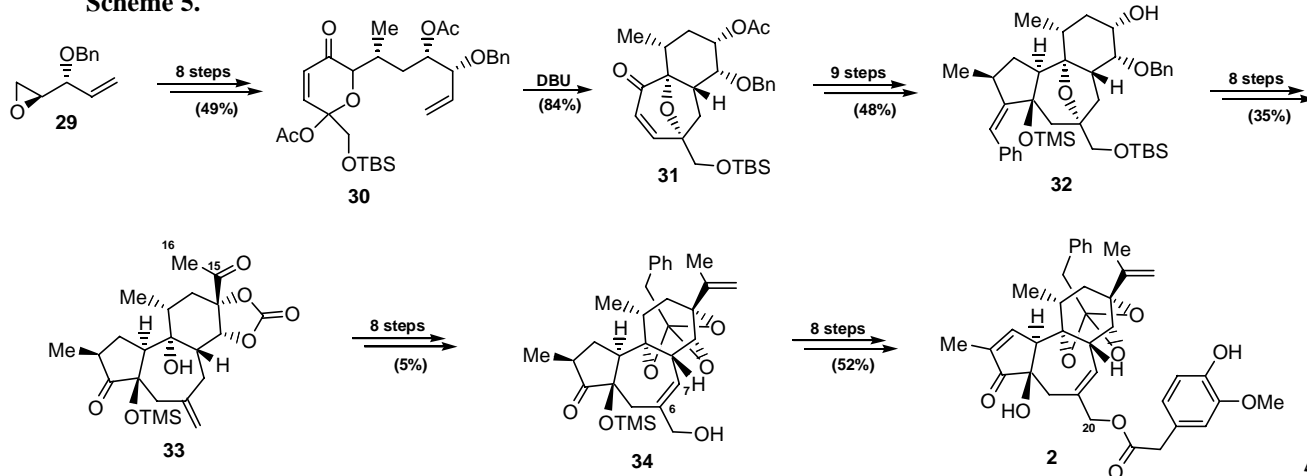
Wender and co-workers published the first asymmetric formal synthesis of phorbol and the only asymmetric total synthesis of resiniferatoxin in 1997.^{16,17} The syntheses relied heavily on their efforts toward the tigliane and daphnane diterpenes during the previous two decades, in which divinylcyclopropane rearrangement²⁰ and zirconium-mediated intramolecular enyne carbocyclization²¹ approaches to the skeleton were developed. They published the first total synthesis of phorbol in 1987, using an intramolecular Diels-Alder cycloaddition and an intramolecular aldol condensation as key steps.¹¹ In 1990, they developed a more efficient second-generation total synthesis by replacing the Diels-Alder and aldol transformations with an oxidopyrilium [5+2] cycloaddition and a zirconium-mediated enyne-cyclization, respectively.^{14,15,19} Wender and co-workers published the first formal asymmetric synthesis of phorbol by the enantioselective synthesis of **26** (Scheme 4), an advanced intermediate in their most efficient racemic synthesis.¹⁶ The optically active cycloaddition substrate **21** was prepared from furan **20** in eight steps and 31% overall yield. Treatment of **21** with DBU generated an aromatic oxidopyrilium zwitterion **22** that participates in a highly selective [5+2] cycloaddition with the tethered terminal olefin. A chair-like transition state, in which the C(18) methyl and C(12) acetate groups adopt equatorial positions, leads to **23** as a single diastereomer. The C(6)-C(9) oxygen bridge adds rigidity to the normally flexible cycloheptane ring, allowing for superior stereocontrol in subsequent reactions. The trans-fused A-ring was completed by elaboration to enyne **24**, followed by zirconocene-mediated cyclization to give **25**. This approach proved far superior to the A-ring closures using aldol¹¹ or nitrile oxide [3+2] cycloaddition¹⁵ strategies previously published by Wender. PCC oxidation of the concomitantly deprotected C(12) hydroxyl gave intermediate **26**, constituting an asymmetric formal synthesis of phorbol. The natural product was completed in 19 additional steps, including introduction of the cyclopropyl D-ring, cleavage of the C(6)-C(9) oxygen bridge, introduction of the C(6)-C(7) olefin, C(1)-C(2) olefin installation, and deprotection.

Scheme 4.



In the total synthesis of resiniferatoxin, Wender and co-workers began with the known optically active epoxide **29** (Scheme 5) and prepared cycloaddition substrate **30** in eight steps and 49% overall yield. Treatment of **30** with DBU at 80 °C gave cycloadduct **31** in 84% yield. As in phorbol, the A-ring of resiniferatoxin was formed using a zirconocene-mediated cyclization to give **32**. With the complete daphnane skeleton in hand, the synthesis diverged from that of phorbol, requiring 24 additional steps for completion of resiniferatoxin. These steps accomplished introduction of the C(15)-C(17) fragment, cleavage of the oxygen bridge, orthoester formation, C(6)-C(7) olefin installation, and C(20) esterification and deprotection.

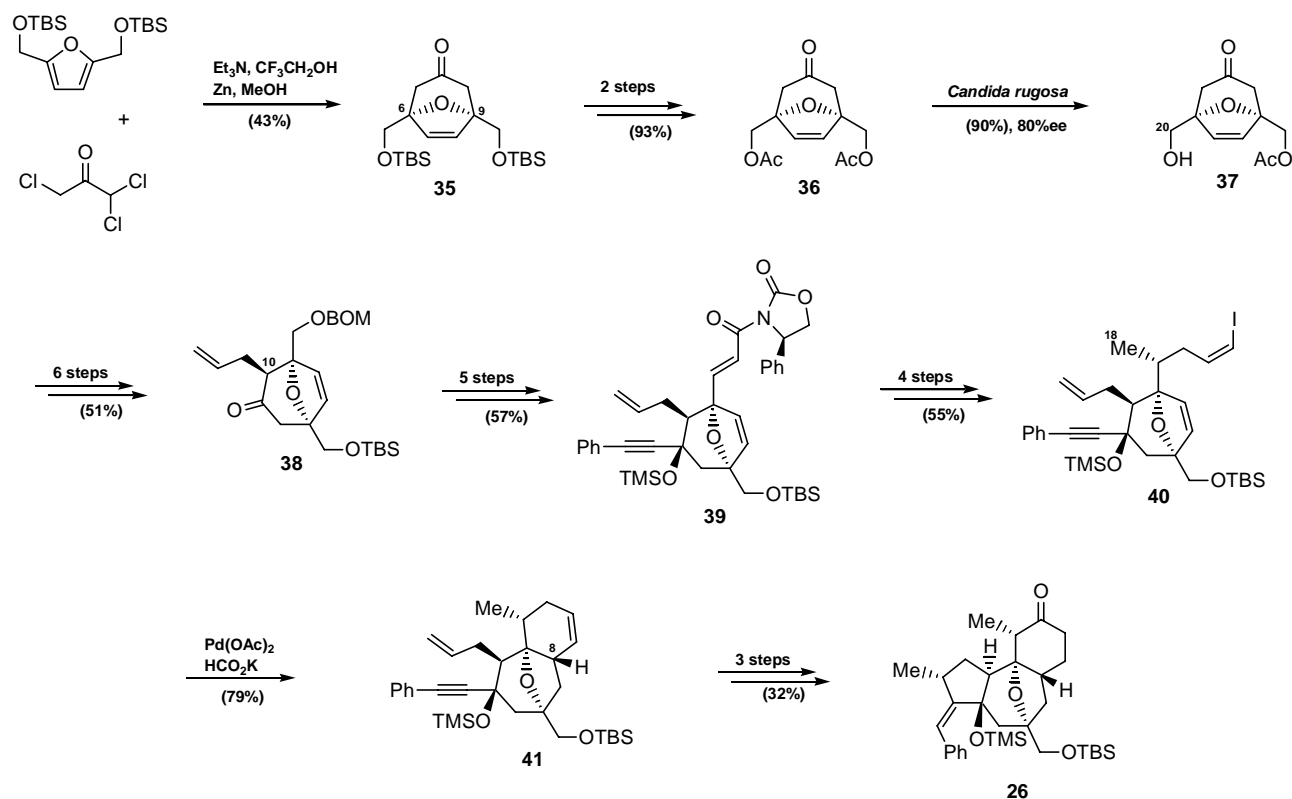
Scheme 5.



Oxyallyl [4+3] Cycloaddition Approach (The Formal Asymmetric Synthesis of Phorbol)

In 2001, Cha and co-workers disclosed a novel approach to the tricyclic daphnane/tigliane core via a formal asymmetric synthesis of phorbol, intercepting Wender's advanced intermediate **26**.¹³ This route commenced with an intermolecular oxyallyl [4+3] cycloaddition to generate the cycloheptane ring of **35** (Scheme 6), possessing a C(6)-C(9) oxygen bridge. Enzyme-catalyzed desymmetrization of the meso bis-acetate **36** generated monoacetate **37** in high yield and good enantioselectivity. Regio- and diastereoselective allylation at C(10) was accomplished in 6 steps and 51% overall yield, providing ketone **38**. Enone **39** was prepared from **38** in 57% overall yield, permitting diastereoselective introduction of the requisite *R*-configured C(18) methyl group. An efficient intramolecular asymmetric Heck reaction was used to form the C-ring and install the C(8) stereocenter in **41**. Finally, a three-step sequence involving 1) titanium-mediated enyne cyclization, 2) regioselective allylic oxidation, and 3) enone reduction provided **26**, constituting a formal asymmetric synthesis of phorbol. Cha's synthesis of

Scheme 6.

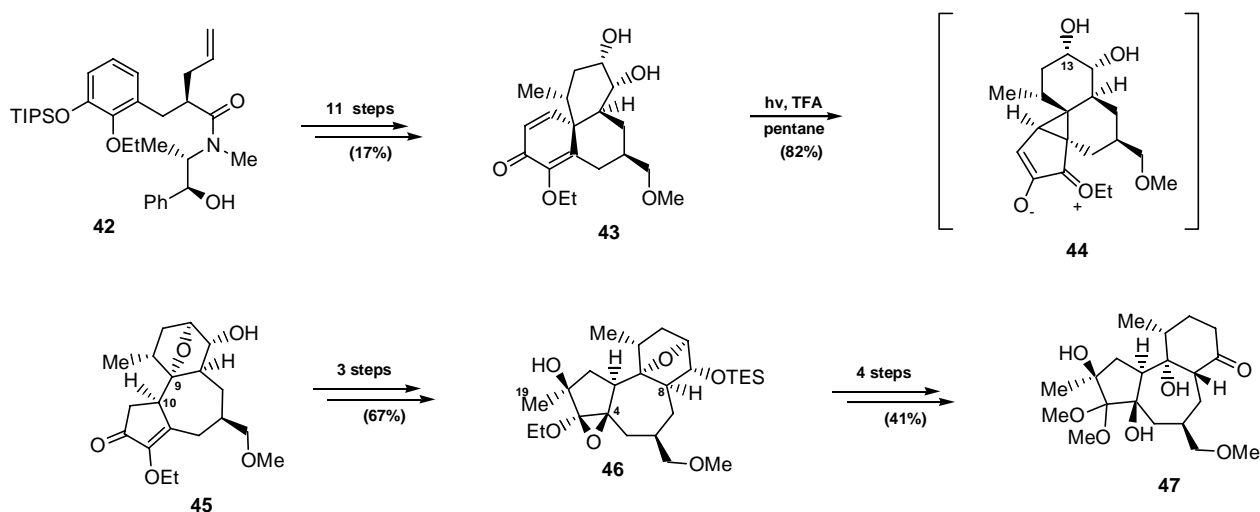


phorbol intermediate **26** (23 steps in 1.6% overall yield) required more transformations and was less efficient than that of Wender and co-workers (16 steps in 8.9% overall yield). However, the applicability of this strategy to the tiglianes and daphnanes was aptly demonstrated.

Photorearrangement Approach

In 2001, Carreira and co-workers published an alternative route to the tigliane and daphnane skeleton that employs a highly efficient photorearrangement inspired by the widely studied photochemical transformation of santonin to isophotosantonin lactone.^{22,23} Starting from the pseudoephedrine amide **42** (Scheme 7), they prepared the optically active photorearrangement precursor **43** by a high-yielding 11 step procedure. Upon irradiation with ultraviolet light, dienone **43** undergoes a rearrangement to the transient cyclopropane **44**, which fragments proximal to the C(13) hydroxyl, affording the C(9)-C(13) oxygen bridged daphnane skeleton **45**. The C(19) methyl group and C(4) hydroxyl functionality were then installed to give epoxide **46**. Further elaboration, including epimerization at C(8) and cleavage of the oxygen bridge, provided the advanced intermediate **47** in 19 total steps and 3.8% overall yield from **42**. Like previous successful approaches, this photorearrangement strategy allows for the facile incorporation of various functional groups, which should permit further elaboration toward the total synthesis of resiniferatoxin.

Scheme 7.



CONCLUSION

The fascinating biological properties and complex molecular architecture of the tigliane and daphnane diterpenes, embodied by their highly oxygenated tricyclo [9.3.0.0^{2,7}] tetradecane ring system, have fueled numerous studies by organic chemists. The difficulties associated with absolute stereocontrol and incorporation of necessary functionality have only recently been overcome. Wender accomplished both the asymmetric total synthesis of resiniferatoxin and a formal asymmetric synthesis of phorbol in 1997, using an oxidopyrilium [5+2] cycloaddition strategy.^{16,17} In 2001, Cha used an oxyallyl [4+3] cycloaddition strategy to complete a formal asymmetric synthesis of phorbol,

intercepting an advanced Wender intermediate.¹³ Later in 2001, Carriera reported the asymmetric synthesis of a highly functionalized resiniferatoxin core, using a photorearrangement as the key step.²²

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