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STUDIES ON THE STEREOSELECTIVE CONSTRUCTION OF THE TIGLIANE RING SYSTEM

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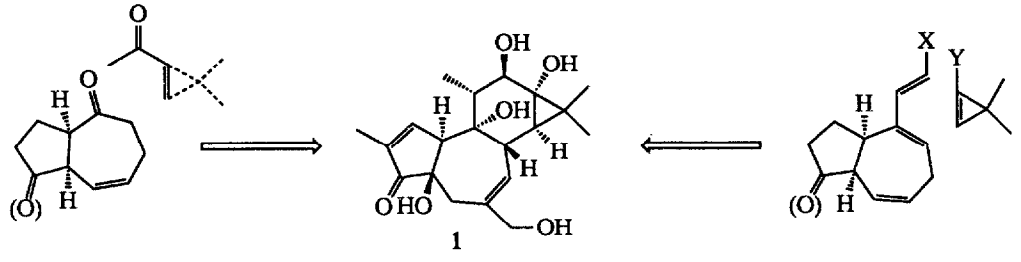
Summary: Complementary strategies for the construction of the tigliane ring system characteristic of the tumor-promoting diterpene phorbol are described. Application of both a Robinson annulation and a Diels-Alder protocol starting from a preformed hydroazulene building block have been examined in this context.

Derivatives of the tigliane diterpene phorbol (1) are the current subjects of intense synthetic and pharmacological investigation.[1] Recently, the phorbol myristate acetate (PMA) receptor was identified as protein kinase C[2] and a number of models for phorbol ester binding to, and activation of, this ubiquitous regulatory enzyme have been forwarded.[3]

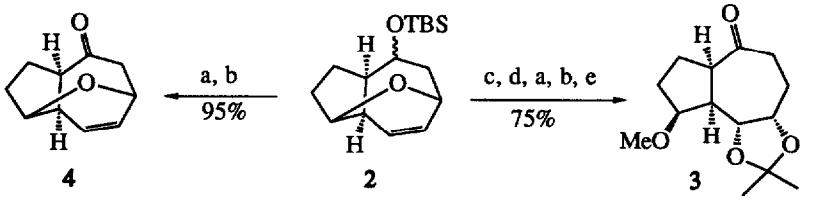


Scheme I

Our general synthetic strategy into the phorbol series exploits the ready availability of functionalized hydroazulene building blocks exhibiting defined stereogenicity upon which the elements of the tigliane C and D rings can be elaborated. Scheme I depicts the complementary Robinson annulative and Diels-Alder cycloaddition protocols for assembling the tigliane architectural features from hydroazulene precursors. A key advantage of this approach is the accessibility of both series from a common intermediate.

We recently disclosed the efficient, stereocontrolled synthesis of bicyclo[4.1.0]heptane systems *via* high-pressure induced cycloaddition of carbonyl activated *gem*-dimethylcyclopropenes.[4] We now describe the application of this technology to the rapid construction of the tetracyclic tigliane skeleton. A noteworthy aspect of

this strategy is the high-level of stereocontrol afforded by the cycloaddition process, particularly in terms of establishing the relative stereogenicity of a number of centers simultaneously.

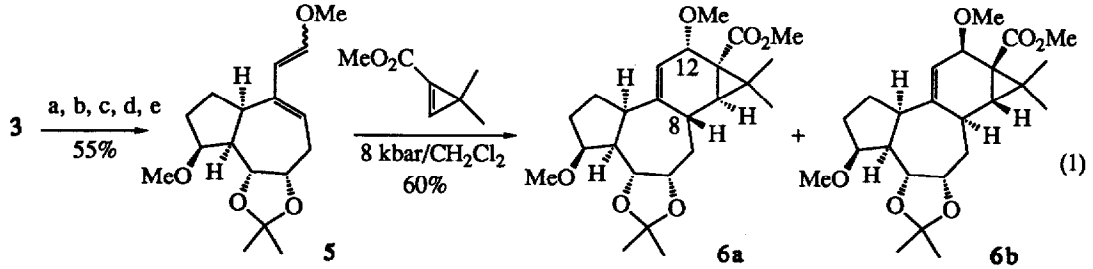


4 2 3

a) Bu_4NF, THF, RT b) Swern Ox c) $Li/MeNH_2$ d) MeI, NaH, THF, 0°C e) OsO_4/Me_3NO, $Me_2C(OMe)_2$, H^+

Scheme II

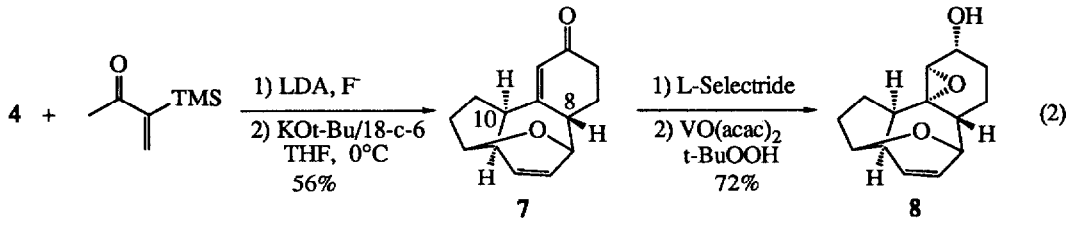
Readily available tricycle **2**[5,6] can be converted in a straightforward fashion into the requisite hydroazulene building block **3**[6] in 75% overall yield as shown in Scheme II. With hydroazulene **3** in hand, routine conversion into the methoxy-diene **5**[6] sets the stage for final fabrication of the C-D rings of the target molecule. This penultimate substrate was produced as a 2:1 *E/Z* mixture of geometrical isomers. It had been previously determined, however, that cyclopropene dienophiles fail to react with *Z* dienes at any appreciable rate under high-pressure conditions.[4]



5 6a 6b

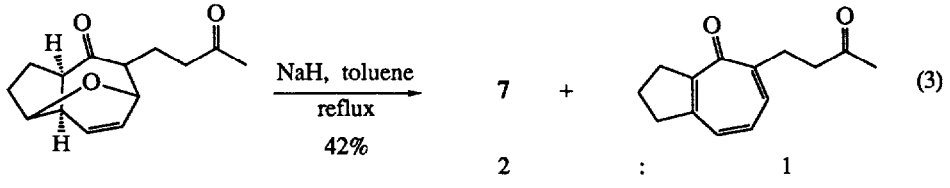
a) Lithium tetramethyl piperdide/Tf_2NPh[7] b) $Pd(OAc)_2/CO/Ph_3P/Et_3N/MeOH$[8] c) DIBAL, -78°C
d) Swern oxidation e) $Ph_3P^+CH_2OMe\ Cl^-$/n-BuLi, 0°C.

Exposure of dienes **5** to an excess of readily accessible methyl *gem*-dimethylcyclopropenecarboxylate provided the tigliane tetracycle in 60% yield (based on *E* content of starting mixture) as an easily separable 2:1 mixture of isomers in which the desired compound **6a**[6] prevailed. Precedent for a high degree of facial selectivity in previous reactions of these *cis*-fused hydroazulenes suggests that the presence of the acetonide moiety influences the facial bias of this system.[5] None the less the sequence described above represents a particularly rapid entry into the tigliane skeleton.



Attempts to bring the corresponding Robinson annulation sequence to fruition as depicted in Scheme I met with two difficulties. Considerable experimentation failed to reveal an effective method for preparing useful quantities of the requisite acetyl substituted cyclopropene.[4] This limitation was easily overcome by employing α-trimethylsilyl methyl vinyl ketone as the four carbon source.[9] It was reasoned that the cyclopropane could be introduced subsequently. More important was the question of exercising a sufficient level of stereocontrol during the Robinson annulation. This issue could be addressed effectively using the simpler enone reaction partner. Efforts to perform the projected cyclization sequence on a *cis*-hydroazulenone resulted in the production of a myriad of products and was deemed inappropriate for the purposes at hand. This situation was easily remedied by employing the rigid and facially biased hydroazulene equivalent 4[5] (Scheme II).

The critical issue upon which the validity of this strategy rests is the production of a tricyclic species that displays the correct relative configurations at C_8 and C_{10}. The restricted conformational options available to ketone 4 should assure production of the requisite relative stereochemistry at the centers in question. In the event, kinetic enolate generation followed by trapping with the modified methyl vinyl ketone equivalent and base mediated aldol condensation yielded a single compound in 56% overall yield. The structural identity of the product was ascertained by single crystal X-ray analysis and determined to be the desired enone 7[6]. If harsher base conditions were employed in the aldol step, a considerable quantity of a tropone derivative[6], ostensibly derived from multiple, competitive β-elimination processes, was obtained as depicted in equation (3).



To demonstrate the utility of compound 7 in phorbol synthesis, studies were initiated to introduce the crucial C_9 tertiary oxygen. An important aspect of this intermediate in terms of elaborating the C ring substitution pattern is the range of possible stereochemical relationships that can be conveniently developed. To this end, methods have been devised for introducing the tertiary oxygen with complementary relative stereochemistry. Reduction of 7 with L-Selectride at -78°C provided a mixture of alcohols with the desired pseudoaxial alcohol as the preferential isomer (3:1) in 98% yield[6]. In contrast, lithium aluminum hydride reduction gave the

pseudoequatorial isomer (20:1) in 96% yield.[6,10] The α-alcohol was treated under directed epoxidation conditions to give epoxy-alcohol **8** as the only isolable product in 96% yield. The β-isomer was converted into the isomeric epoxide in a similar fashion. The epimeric nature of the two epoxides was verified by conversion into the corresponding keto-epoxides which were shown not to be identical.

With the developments described herein, the notion of elaborating hydroazulenes into complex, highly substituted tigliane-like carbon systems in a stereoselective fashion has been established as a viable fundamental strategy for diterpene synthesis. Further work on extending these approaches to the total synthesis of phorbol is currently underway in our laboratory.

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References and Notes

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10. The stereochemical assignments of these reduction products were based on molecular modeling using MM2 calculations which indicated that the dihedral angle between the vinyl proton and the alcohol methine proton was nearly 90° in the β-alcohol, whereas, a much smaller angle was predicted for the α-isomer. The observed coupling constants were J=1.2 Hz and J=4.7 Hz, respectively.

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