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STUDIES ON TUMOR PROMOTERS: V[1]. COMPLEMENTARY 1,4-STEREOCONTROL IN PHORBOID CYCLOHEPTENE SYNTHESIS VIA THE DIVINYLCYCLOPROPANE REARRANGEMENT

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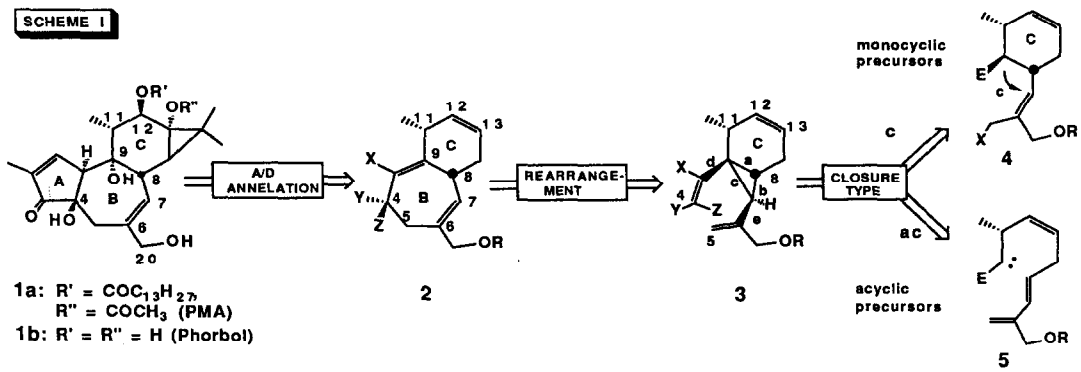
Abstract: Methodology for the synthesis of B-C ring precursors and analogs of the phorbol esters is described which allows for complementary 1,4-stereocontrol in the formation of seven-membered rings through the selective formation and rearrangement of vinyl enol cyclopropanes.

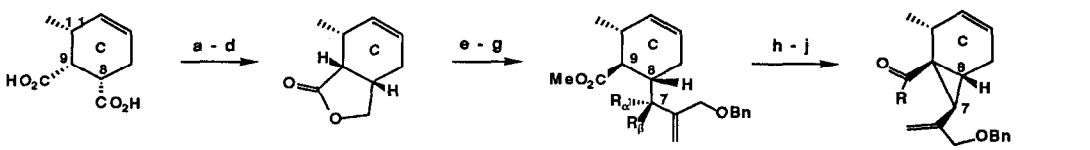
The phorbol esters (PE: e.g. **1a**) have played a crucial role in the evolution of our understanding of multistage carcinogenesis at the molecular level.[3] In studies originating in the 1930s, it was shown that croton oil, a non-carcinogenic plant extract from which the PE are derived, potentiates the activity of certain carcinogens in inducing tumors in mouse skin.[4] In the 1960's, this early finding was placed on a firmer chemical base when the structures of the PE, the active principles of croton oil, were completely established.[5] More recently, the cellular target of the PE has been identified as protein kinase C (PKC), an enzyme of critical importance in the regulation of cell surface signal transduction and cellular proliferation.[6] Biochemical studies have since indicated that diacyl glycerols (DAG) are the endogenous activators of



PKC.[6,7] Several other high affinity but structurally dissimilar PKC activators with tumor promoter activity have also been discovered recently,[8] suggesting that tumor promotion might be a general phenomenon of importance to cancer chemotherapy and prevention. Modeling studies carried out in these laboratories, in collaboration with the National Cancer Institute, have served to elucidate a common relationship amongst the PE, other high affinity PKC activators, and DAG, in which the high affinity exogenous PKC activators are proposed to function as conformationally restricted analogs of DAG.[9] In order to test the generality of this hypothesis, as well as to establish a synthetic route to PE and their analogs, we have developed a method, described herein, for the synthesis of BC ring analogs and potential precursors of the PE, based on one of the most substitutionally complex divinylcyclopropane rearrangements studied to date.[10] This method allows for high complementary stereocontrol and functionality variation at the key sites putatively involved in recognition by and binding to PKC.[9]

We previously reported three general strategies [11a-c] for the synthesis of the tigliane, daphnane, and ingenane ring systems, one of which is based on the divinylcyclopropane rearrangement (Scheme I).[11a] The value of this rearrangement in approaches to this structural triad arises from its capacity to directly site the C6, C7 double bond of the targets and, as a result of its endo-boat transition state requirement, to control the 1,4- stereorelationship between C4 and C8. Further advantage derives from the flexibility with which the key divinylcyclopropane intermediate can be constructed. In principle, a procedure for forming any of the bonds **a-e** (**3**) or any pair of these bonds (e.g. **ab**, **bc**, **ac**, etc.) could deliver the key intermediate **3** and, thereby, the stereochemically detailed seven-membered ring **2** resulting from its rearrangement. As illustrated, the disconnection involving bond **c** reduces the phorbol problem to that of preparing a suitably substituted six-membered ring precursor, i.e., a problem in Diels-Alder chemistry. With the demonstration in our laboratory that a single C12 or C13 functionality can be used to elaborate the complete CD ring functionality of phorbol,[1] this plan can be further simplified to the elaboration of the commercially available ($) Diels-Alder adduct **6** (Scheme II).

SCHEME II

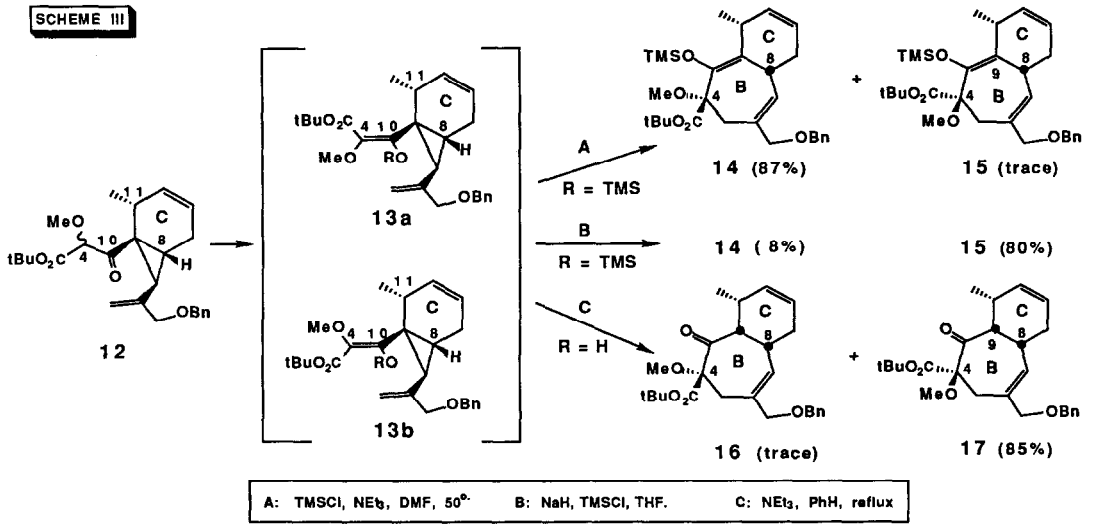


6 ($) **7** **9**: R_β = H, R_α = OH; **10**: R_β = OH, R_α = H **11**: R = OMe **12**: R = $CHOMeCO_2tBu$

a) KI, I_2, 93%; b) BH_3, 96%; c) Zn, EtOH; d) pTsOH, PhH, 84% (2 steps); e) KOMe, MeOH, 86%; f) PCC, 87%; g) $H_2CC(LI)CH_2OBn$ (8), 72%; h) $SOCl_2$, 70%; i) KOtBu, 88%; j) $MeOCH_2CO_2tBu$, LDA, 68%

Implementation of the above analysis proceeded in a straightforward manner. Thus, selective reduction of the C8 carbonyl group of diacid **6** was achieved by protection of the C9 acid in the form of an iodolactone, followed by reduction of the remaining C8 acid and retro-iodolactonization.[12] Alternative procedures, including selective anhydride reduction, were found to be preparatively inferior to this four step sequence. Lactone **7**[13] obtained in this fashion was then hydrolyzed with methoxide and the resulting hydroxy ester oxidized to an aldehyde, which upon treatment with vinyllithium reagent **8**[14] gave allylic alcohols **9** and **10** in a ratio of 10:1. While this high stereoselectivity is mechanistically interesting, it was considered inconsequential in our plans since either configuration at C7 (as well as at C9) was expected to provide the same stereochemistry in the product arising through bond **c** formation. In accord with this expectation, reaction of both **9** and **10** with $SOCl_2$ gave a mixture of primary allylic chlorides, which underwent completely facial-selective S_N2' displacement by the C9 ester enolate to provide a single vinylcyclopropane **11**. The complete stereocontrol achieved in this reaction is a consequence of both the expected preference for the allylic chloride to assume an extended conformation in the alkylation step and the intramolecularity of this process, which permits bond formation on only one enolate face. Subsequent introduction of the remaining pro-B ring subunit was achieved through a crossed Claisen condensation of the cyclopropanation product **11** with the enolate of t-butyl methoxyacetate, providing ester **12** as a 1:1 mixture, epimeric at C4 (the methoxy-substituted carbon).

The success of our plan at this point required that the enol or enol ether of ketoester **12** (Scheme III) rearrange to the deconjugated enol or enol ether of the cycloheptadiene product. The loss of electronic stabilization accompanying this reaction was expected to be offset by strain release. Importantly, if the geometry of the C10, C4 double bond arising

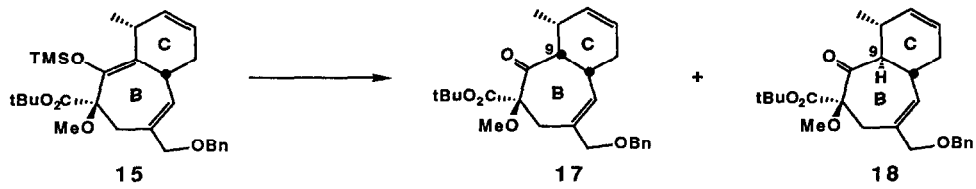


from the enolization of **12** could be controlled, it was expected that the 1,4-stereorelationship between C4 and C8 would be similarly regulated, due to the mechanistic requirements of the divinylcyclopropane rearrangement. Our studies revealed that this result can indeed be achieved with high selectivity through simple experimental variations, to produce either stereorelationship between C4 and C8. Thus, treatment of **12** with Et_3N and trimethylsilyl chloride in DMF at 50°C produced the rearranged product **14** in 87% yield, ostensibly through the intermediacy of enol ether **13a**; only a trace of the C4 epimer (**15**) arising from **13b** was detected. Since enolate chelation was expected to favor formation of **13b** over **13a**, ketoester **12** was also treated with sodium hydride followed by TMSCl. In accord with the preferential formation of **13b**, rearrangement product **15** was now obtained in 80% yield while **14** (the major product obtained previously) and its precursor were formed in a combined yield of only 8%. Finally, it was also possible to effect selective rearrangement by simply heating **12** in a 3:1 mixture of benzene and Et_3N. Under these conditions, ketone **17**, possessing the same C4, C8 relative stereochemistry as that in **15** (and in phorbol) was obtained in 85% yield with only a trace of the C4 epimer. This direct rearrangement is expected from a Et_3N- induced formation of an internally hydrogen bonded enol of **12**. Such an intermediate would have the same C10, C4 geometry as that in the sodium chelated enolate and its silylation product **13b** and, consequently, would give the same C4, C8 product stereochemistry.

A further consequence of the success of this methodology is found in the versatility which it provides in regulating the stereochemistry and functionality at C9 of the phorbol system. It is noteworthy in this context that the role of the C9 hydroxyl of PE in recognition by and binding to PKC[9] has unfortunately not been evaluated since all known PE bear a C9 hydroxyl;[3a] the C9 deoxy control compounds have not as yet become available through partial synthesis. However, the above methodology allows selective access to not only the β–C9 deoxy analog **17** (Scheme III, method C), but also to the α-C9 deoxy analog **18** (Scheme IV). For the latter, **15** was treated with n-Bu_4NF to produce the trans-fused isomer **18** in high yield and greater than 50:1 selectivity over the cis-fused isomer **17**. In this series of phorbol precursors, this selectivity is found to be thermodynamically controlled. Finally, it has also been possible to introduce oxygenation at C9 as would be required in the continuation of these studies toward a synthesis of phorbol.[15]

In summary, this study describes the successful application of the divinylcyclopropane rearrangement to the preparation of intermediates suitably functionalized for the synthesis of PE and analogs. The methodology for easily

SCHEME IV



AcOH, H_2O, THF 87% 4 : 1

TBAF 95% < 1 : > 50

regulating enol, enol ether, and enolate geometry and thereby the stereochemistry of the cycloheptadiene product should have general use in the synthesis of stereochemically complex seven-membered ring systems. As it applies to synthetic studies on the phorboids, this strategy provides excellent and complementary control over C4 and C8 stereochemistry and comparable control over C9 stereochemistry and substitution. On the practical side, this sequence allows for the production of the key intermediates **15** and **17** in 11 steps and 14% overall yield from commercially available materials, involving operations which can be easily conducted on a large scale. Pharmacological and further synthetic studies based on these intermediates will be reported in due course.

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