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An IMDA Approach to Tigliane and Daphnane Diterpenoids: Generation of the Tetracyclic Ring System of the Tiglianes

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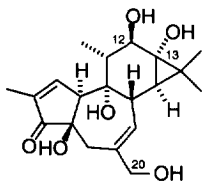
Abstract: A synthesis of the tetracyclic ring system of phorbol and other tigliane diterpenes has been achieved in six steps using an unusual intramolecular Diels–Alder reaction both as the key stereocontrolling process and to introduce a double bond appropriately positioned for functionalization as a cyclopropane. © 1997 Published by Elsevier Science Ltd.

The tigliane group of natural products are diterpenes containing a tetracyclo [10.3.1^{5,7}.0.0^{2,8}] pentadecane ring system as the basis of their carbon skeleton. The most well-known member is phorbol **1**,[1] which possesses a polyhydroxylated tigliane carbon skeleton containing eight contiguous asymmetric centres, six of which are sited around the six-membered C ring. Phorbol occurs naturally in the form of its 12,13-diesters and 12,13,20-triesters, which are potent tumour-promoting agents, inducing susceptibility at levels of carcinogen below the normal threshold. The most potent of the diesters is phorbol myristate acetate (PMA, TPA); paradoxically, a 12,13-diester has been shown to exhibit antitumour activity,[2] and the parent molecule phorbol is neither a carcinogen nor a cocarcinogen.[3] Phorbol esters are found in croton oil,[4] ubiquitous 400 years ago as a purgative, from which phorbol was isolated as an hydrolysis product in 1935.[5] The structure was not however elucidated until 1967 by X-ray analysis of a derivative.[6]

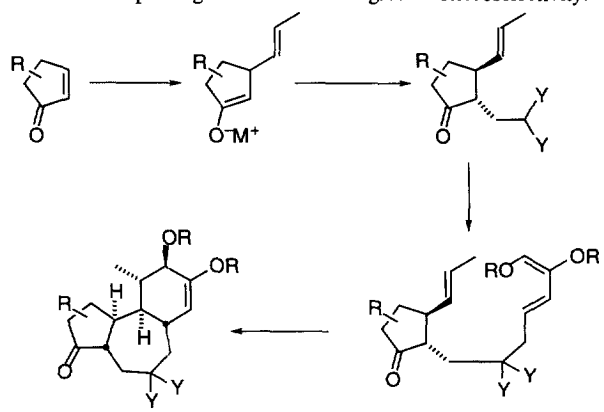


1

Phorbol esters are able to activate protein kinase C,[7] a calcium-dependent enzyme involved in the regulation of threonine and serine phosphorylation. They produce a variety of biological responses, including roles in cardiovascular disease and cystic fibrosis,[8] as well as carcinogenesis; prostratin, a 12-deoxy species, displays cytoprotective behaviour in human lymphocytes infected with the HIV-1 virus.[9] Despite their range of interesting biological activity however, this group of natural products continues to receive surprisingly moderate synthetical interest, only one total synthesis, that of Wender, having been published.[10]

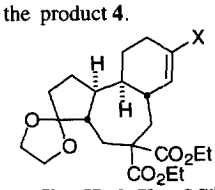
Our strategy for a general synthetic approach to the tigliane/daphnane ring systems, outlined in Scheme 1, was suggested by the concentration of asymmetric centres in the six-membered C ring of phorbol derivatives coupled with the potentially high degree of stereocontrol available through an intramolecular Diels–Alder (IMDA) reaction.[11] It is built around the use of an IMDA reaction to construct the B and C rings, coupled with a

convergent synthesis of the appropriate cyclization precursors. Such an approach was particularly attractive to us because there remain relatively few examples of IMDA reactions in which the ring system formed is the C_{11} bicyclo [5.4.0] undecane, containing fused six- and seven- membered rings, as is found in the tiglianes and daphnanes,[12] and we are interested in probing the achievable degree of stereoselectivity.

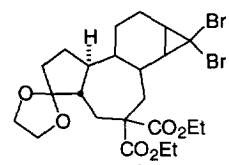


Scheme 1

This approach allows very rapid but flexible construction of the carbocyclic ring framework of the tigliane/daphnane systems. Conjugate addition of a suitable vinyl anion to a cyclopentenone is followed by addition of the enolate to the C-2 position of a two carbon unit able to sustain an anion at C-1. Coupling of such an anion with a pre-formed diene subunit provides the substrate for the crucial intramolecular Diels-Alder (IMDA) reaction which sets up most of the remaining asymmetric centres and which provides a suitably functionalized product of considerable synthetic potential, for example containing a double bond suitably positioned for introduction of the cyclopropane D ring of phorbol. We have previously demonstrated the value of this approach for the rapid construction of two simple carbotricycles **2a**[13] and **3**[14] related to the daphnane and tigliane carbon skeletons, the latter involving an oxygenated diene coupled using palladium chemistry. We report herein elaboration into the tetracyclic tigliane ring framework by cyclopropanation of **2**, and establishment of the stereochemistry of the product **4**.



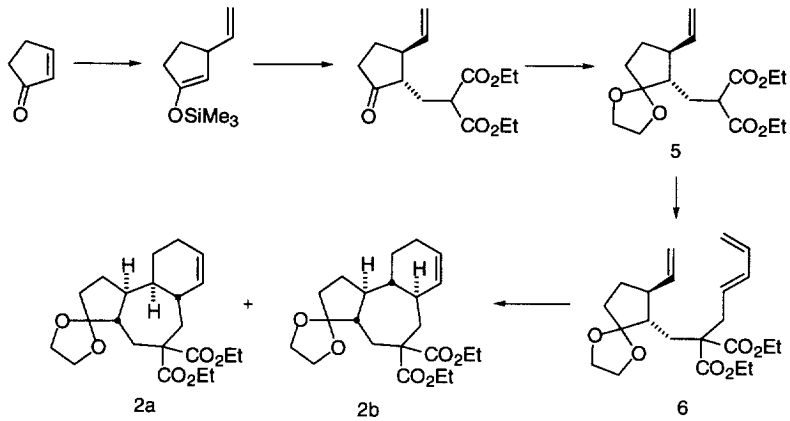
2a, X = H; 3, X = OSi^{i}Pr$_3$



4

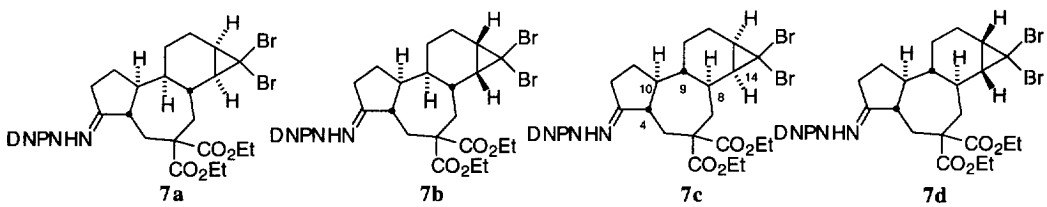
Carbotricycle **2** was constructed as shown in scheme 2 by copper-catalysed conjugate addition of a vinyl Grignard reagent to cyclopentenone and trapping of the resulting enolate as a silyl enol ether. Lewis-acid mediated Michael addition to methylene malonate provides left hand fragment **5** after suitable protection, which is deprotonated and coupled with 5-bromopenta-1,3-diene, producing IMDA precursor **6**. The crucial Diels–Alder reaction takes place over 14 days at 160 °C in toluene in a sealed tube to give the product in 70% yield as a *ca* 1 : 1 mixture of *exo* isomers **2a** and **2b**.

Dimethylcarbene metal complexes have been reported to react with alkenes to provide *gem*-dimethylcyclopropanes, as found in phorbol itself, but these reactions generally take place in low yields.[15] Attempts to introduce the cyclopropane unit into **2** using a Simmons–Smith procedure[16] proved unsuccessful, and we therefore chose to introduce a *gem*-dibromocyclopropane unit in our first synthesis of the basic tetracycle of the natural product, with a view to potential future introduction of the *gem*-dimethylcyclopropane unit, for example through treatment with a higher order organocuprate reagent.[17]



Scheme 2

Thus, treatment of **2a,b** with dibromocarbene, generated from bromoform and sodium hydroxide in the presence of benzyltriethylammonium bromide as a phase transfer catalyst in dichloromethane/water at 0 ℃,[18] provided the tetracycle **4** in up to 91% total yield as an inseparable mixture of isomers, in some cases partially deprotected at the ring A acetal.



In order to establish the relative stereochemistry of the products, the ring A acetal moiety of **4** was hydrolysed to afford the ketone, which was then converted into the 2,4-dinitrophenylhydrazone derivatives **7**, enabling the products to be partially separated. Fractional crystallization from hot ethanol separated the isomers into two pairs, **7a/7b** and **7c/7d**, in a *ca* 1 : 1 ratio, mirroring the ratio of **2a** and **2b**, and each containing *trans* fused AB and BC ring junctions, but differing in the relative stereochemistry between C9 and C10, and in the cyclopropane stereochemistry. Isomers **7a** and **7b**, from reaction of **2a**, were precipitated from the solution as an inseparable mixture, while isomers **7c** and **7d**, from reaction of **2b**, remained in the mother liquor. Further separation by thin layer chromatography provided isomers **7c** and **7d** in a ratio of 3.4 : 1.

The stereochemistry of each of **7a-d** was established using a combination of NMR experiments, with through space interactions observed between the protons located at C-4 and C-9, at C-8 and C-10, and at C-8 and C-14 in the 500 MHz NOESY spectrum being important factors in the structural elucidation of **7c**. We were pleased to find that the major components of the mixture were formed by attack of the dibromocarbene at the β-face of **2a,b**.

Compound **7a** contains the correct phorbol stereochemistry at C-4, C-8, C-9, C-10, C-13 and C-14. The nucleus of the tigliane ring system has therefore been constructed in only six steps from very simple starting materials.

Acknowledgments

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4 The oil expressed from the seeds of the purging croton, the leafy *Euphorbia* succulent *Croton tiglium*, native to south-east Asia. The seeds, formerly known as molucca grains, were in common use in Europe from the sixteenth century as a purgative and emmanagogue, having been introduced from China by the Dutch: Ainslie, W., quoted by Lindley, J. in *A Natural System of Botany*, Longman, Rees, Orme, Brown, Green, and Longman, London, 1836 (senior author's collection); Graves, G.; Morries, J. D. *Hortus Medicus*, Adam & Charles Black, Edinburgh, 1834. Many of the fleshy *Euphorbia* species have found uses in folk medicine; indeed, they were given their name by King Juba II of Mauretania, from Euphorbus, his equally fleshy physician.

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