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An IMDA Approach to Tigliane and Daphnane Diterpenoids: Introduction of the C-12, C-13 C Ring Oxygenation of Phorbol

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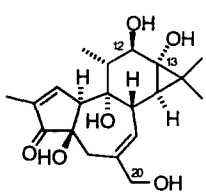
Abstract: A synthesis of the tricyclic ring system of the daphnane and tigliane diterpenes, incorporating the C-12 and C-13 hydroxy groups found in phorbol and its relatives, has been achieved in seven steps using an intramolecular Diels–Alder reaction as the key stereocontrolling process. © 1997 Elsevier Science Ltd.

The daphnane and tigliane groups of natural products are diterpenes containing a tricyclo [9.3.0.0^{2,7}] tetradecane ring system as the basis of their carbon skeleton. The tiglianes contain a fourth, *gem*-dimethylcyclopropane, ring fused to the six-membered ring. A well-known member of the tigliane class is phorbol **1**,[1] which possesses a polyhydroxylated 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.[2] The esters are found in croton oil,[3] from which phorbol was isolated as an hydrolysis product in 1935.[4] The structure was not however elucidated until 1967 by X-ray analysis of a derivative.[5] Phorbol esters are able to activate protein kinase C,[2] and produce a variety of biological responses,[6] but these classes of natural products continue to receive moderate synthetical interest, just one total synthesis, that of Wender, having been published.[7]



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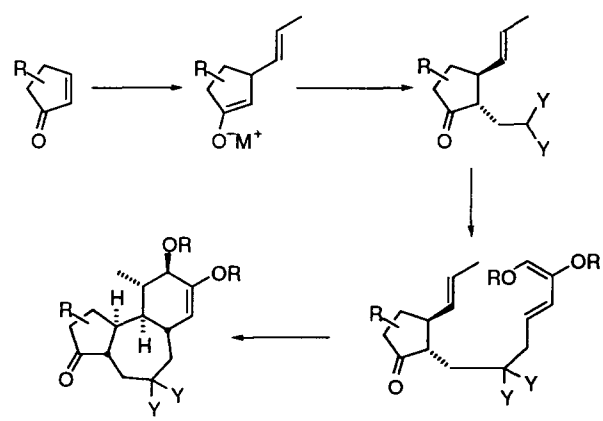
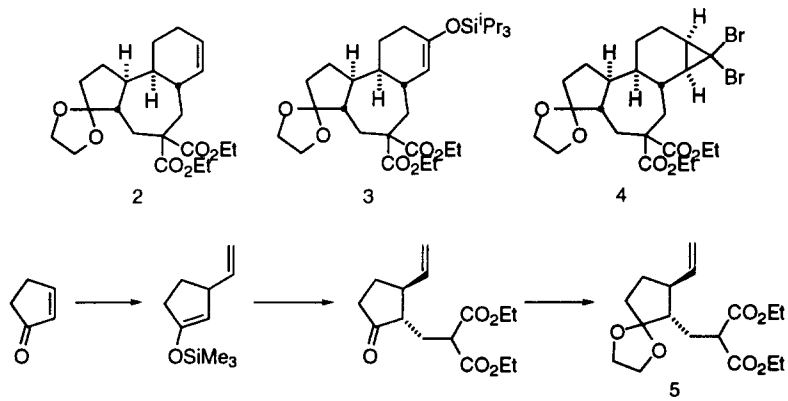


Scheme 1

Our strategy for a general approach to the daphnane and tigliane ring systems revolves around an intramolecular Diels–Alder (IMDA) reaction which constructs the B and C rings, together with a convergent synthesis of the appropriate cyclization precursors, and was suggested by the concentration of asymmetric centres and functionality in the six-membered C ring of phorbol derivatives coupled with the potentially high degree of stereocontrol available through an IMDA reaction.[8] This approach was particularly attractive to us because there remain relatively few examples of IMDA reactions in which the ring system produced is the C_{11} bicyclo [5.4.0] undecane, containing fused six- and seven- membered rings,[9] and the achievable degree of stereoselectivity thus remains to be established.

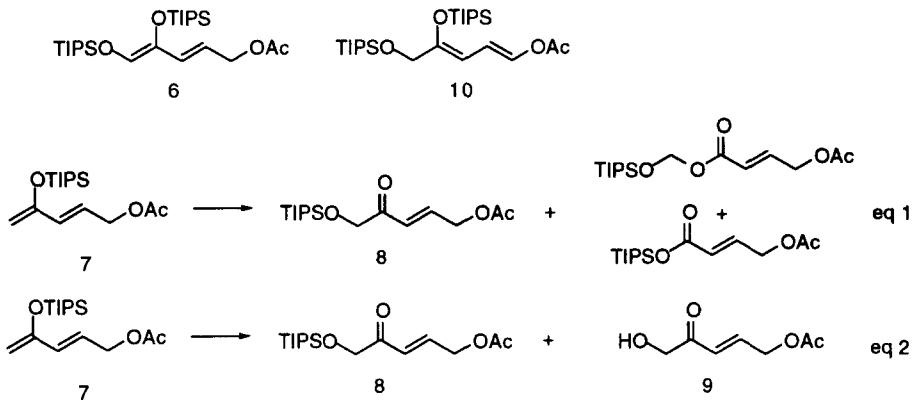
This approach, outlined in Scheme 1, allows very rapid construction of the carbocyclic ring framework of the tigliane/daphnane systems. Conjugate addition of a suitable vinyl anion to a cyclopentenone is followed by addition of the enolate to the C-2 position of a two carbon unit able to sustain an anion 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 success of this approach for the rapid construction of two carbotricycles, **2**[10] and **3**,[11] related to the daphnane and tigliane carbon skeletons, and one carbotetracycle **4**,[12] containing the tigliane ring system. In each case in this series, the IMDA reaction takes place with an unactivated dienophile and gives rise formally to *exo* isomers only, as indicated. We now report the application of this route for the incorporation of the C-12 and C-13 hydroxy groups found in phorbol.



Scheme 2

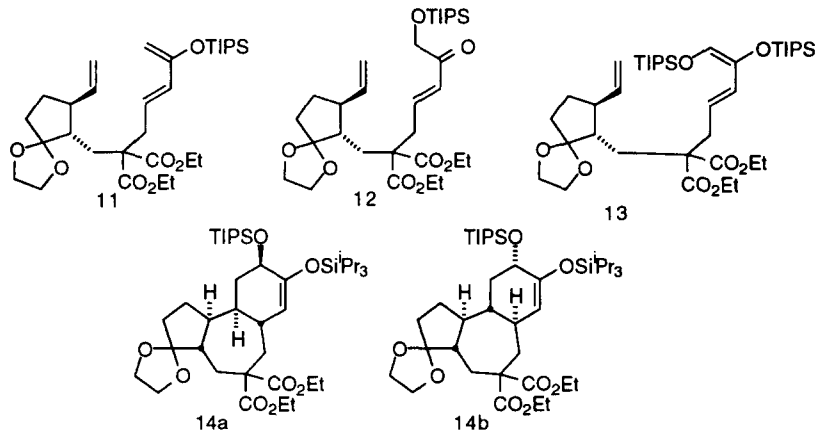
Left hand fragment **5** was constructed as previously described (Scheme 2). Copper-catalysed conjugate addition of vinyl Grignard reagent to cyclopentenone and trapping of the resulting enolate as a silyl enol ether, followed by Lewis-acid mediated Michael addition to methylene malonate provides **5** after suitable protection. We had initially envisaged deprotonation of **5** and palladium-catalysed coupling to a suitably protected dioxygenated diene partner such as **6**, the tactic used successfully for the analogous mono-oxygenated system.[11] Treatment of 2-triisopropylsilyloxy-5-acetoxypenta-1,3-diene **7**, prepared from ethyl laevulinate in four steps as previously reported,[11] with mCPBA[13] however gave rise to complex mixtures of the desired 1-triisopropylsilyloxy-5-acetoxypenta-3-en-2-one **8** with other materials apparently derived from **8** through a Baeyer-Villiger process (Scheme 3, eq 1). Use of dimethyldioxirane gave a cleaner transformation into a mixture of **8** and its protiodesilylated derivative **9** in 95% yield (Scheme 3, eq 2). Unfortunately, treatment of **8** with triisopropylsilyl

triflate gave rise to 1,4-dioxygenated diene **10**, presumably the thermodynamically more stable product, rather than the desired 1,2-dioxygenated **6**.



Scheme 3

A palladium-catalysed coupling of left hand fragment **5** with diene **7** was used previously to construct carbotricycle **3** *via* IMDA substrate **11**.[11] We were pleased to find that treatment of **11** with mCPBA and sodium bicarbonate gave a clean conversion into the expected product **12** uncontaminated by Baeyer-Villiger or other over-oxidation products. Reaction of **12** with triisopropylsilyl triflate at 0 °C now produced the desired new IMDA substrate **13** in 65% yield as a single isomer, together with unreacted **12** (30%). Heating a toluene solution of **13** to 240 °C in a sealed tube for 14 days in the presence of Hünig's base induced a surprisingly clean conversion into the 12,13-dioxygenated tricycle **14** as a *ca* 1 : 1 mixture of two isomers in 80% yield, without hydrolysis of the silyl enol ether. Isomer **14a** has the correct phorbol stereochemistry at C-4, C-8, C-9, C-10, and C-12.



We believe that this seven-step synthesis of the 12,13-dioxygenated daphnane/tigliane nucleus demonstrates the value of this general approach to the daphnane and tigliane groups of diterpenoids.

Acknowledgments

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3 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. in 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 fleshy physician.

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