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A Carbonyl-Ylide Approach to the Tigliane Diterpenes

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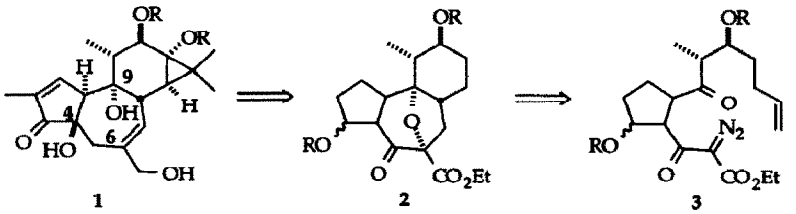
Abstract: *A simple tricyclic oxo-bridged phorbol analog has been synthesized via a 1,3-dipolar cycloaddition from a rhodium initiated metallocarbenoid ylide.*

A recent report by Dauben[1] involving the use of α-diazocarbonyl ylides for the synthesis of an advanced phorbol intermediate has prompted us to present our studies[2] directed toward similar phorbol analogs. Despite a number of attempts at total synthesis and many groups involved in the development of methodology directed toward phorbol,[3a-i] Wender, only recently accomplished a total synthesis of phorbol via similar cycloaddition methodology.[4a-f]

Phorbol (1) and phorbol esters are a family of tigliane diterpenes isolated from *Croton Tiglium*, the source of croton oil. These compounds have received considerable synthetic attention because they behave as tumor promoters, inducing carcinogenesis in animal models that have received a subeffective dose of a known carcinogen.[5a,b] It is postulated that the activity of these novel compounds arises from their ability to mimic their endogenous counterparts, the diacyl glycerols, and activate protein kinase C. The increased activity of this powerful phosphorylating enzyme results in the expression of certain oncogenes.[6]

Scheme I

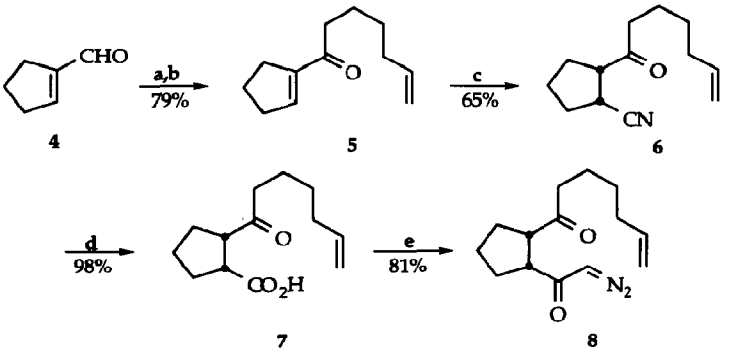


As part of an ongoing effort in our group to utilize rhodium-mediated metallocarbenoid species for the synthesis of carbocyclic and nitrogen containing natural products,[7] it was determined that a carbonyl ylide promoted cyclization[8a-g] might provide a facile entry into the tigliane skeleton. A potential retrosynthetic sequence based upon this key transformation is presented in Scheme I. Cyclization of 3 might provide a rigid tricyclic moiety 2 that supplies the correct stereochemistry at the newly formed stereocenters of the phorbol

skeleton.[9] This will generate a transannular attachment of the C9 (phorbol numbering) hydroxyl group to C6 to produce a temporary ether linkage across the B-ring. This bridged ether will be formed during a 1,3-dipolar cycloaddition of a carbon tethered olefin to an intermediate carbonyl ylide. The carbonyl ylide will in turn be generated by the nucleophilic attack of a carbonyl oxygen on an electrophilic metallocarbenoid center formed from the corresponding α-diazocarbonyl moiety.

At this time, we wish to report a successful cyclization of this type to produce a simple phorbol analog devoid of most of the oxygenation (**Schemes II, III**).

Scheme II



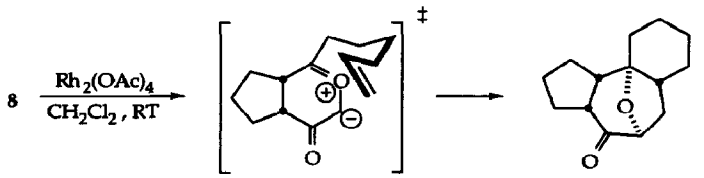
4 5 6 7 8

(a) CH_2=$CH(CH_2)_3CH_2MgBr$, THF (b) DMSO, $(COCl)_2$, Et_3N (c) Et_2AlCN, PhH (d) 20% NaOH, CH_3OH/H_2O (e) $(COCl)_2$, Et_3N, then CH_2N_2

The construction of a simple cyclization precursor commences with the known cyclopentene-1-carboxaldehyde.[10] Addition of the Grignard reagent derived from 6-bromo-1-hexene followed by Swern oxidation of the resulting alcohol furnishes the enone **5** in excellent overall yield. Conjugate addition of cyanide by action of diethylaluminum cyanide[11] produces the nitrile **6** as a mixture of *cis* and *trans* isomers (6-9:1) that can be separated easily by flash column chromatography.[12] The relative stereochemistry was determined by a combination of NOE difference and NOESY NMR spectroscopy.[13a,b] Basic hydrolysis of the resultant nitrile produces acid **7**. It appears that there is no loss of stereochemical integrity during the basic hydrolysis. Acid **7** is converted to the acid chloride by reaction with oxalyl chloride and then immediately treated with diazomethane to generate diazo ketone **8**.[14]

Reaction of diazoketone **8** with a catalytic amount (2 mole%) of dirhodium tetraacetate is assumed to produce a rhodium stabilized metallocarbenoid intermediate which is attacked by the carbonyl oxygen at C9 to produce a transient oxonium ylide **9**. The ylide is then trapped by the tethered olefin in a 1,3-dipolar cycloaddition reaction to form tetracyclic ether **10** in 55% yield (unoptimized) as a single isomer (**Scheme III**).

Scheme III



9 10

An X-ray structure analysis[15] of crystalline **10** (**Figure 1**) showed the C8 hydrogen to be placed in a *syn* relationship with the protons found to be *cis* at the A-B ring fusion. The stereochemical selectivity of addition of the tethered olefin to the 1,3-dipole is attributed to non-bonded interactions in the transition state where the olefinic side chain can adopt a chair-like conformation in the *exo* mode. Simple Molecular Mechanics calculations suggest that the alternative approach of the olefin (*endo* to the 1,3-dipole) is a higher energy transition.[16]

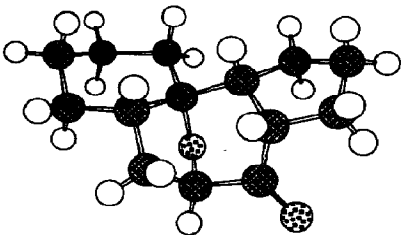


Figure 1. Representation of **10** from X-Ray Coordinate File.

This tandem cyclization-cycloaddition strategy has been demonstrated to be effective for the construction of the basic phorbol skeleton. Current efforts are centered around the construction and cyclization of more complex substrates and regioselective cleavage of the ether bridge to unveil the angular hydroxyl group at C9.

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† Author to whom questions regarding the X-Ray structure should be directed

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15. X-ray structure determination of **10**: crystal dimensions: 0.45x0.32x0.11mm^3, colorless, Siemens P2$_1$ diffractometer, CuK$_a$ radiation, T=125 K, monoclinic, a=5.570(2), b=24.101(4), c=8.689(1)Å, b=92.07(3)°, V=1165.7(3)Å^3, Z=4, d_{cal}=1.25 g cm^3, m=0.570mm^{-1}, SG: P2$_1$, 2112 reflections collected, 1985 unique reflections ($2q_{max}$=138°)1456 reflections with $F_o > 3s(F_o)$, R-value=0.063, GOF=1.59. Detailed X-ray crystallographic data are available from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ U.K.

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