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STEREOSELECTIVITY IN INTRAMOLECULAR DIYL TRAPPING REACTIONS. MODEL STUDIES DIRECTED TOWARD THE PHORBOLS.

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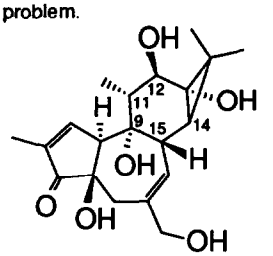
Abstract: The intramolecular diyl trapping reactions, **7** → **9** and **8** → **10**, proceeded reproducibly, in high yield, and with control of both relative and absolute stereochemistry at six contiguous stereogenic centers.

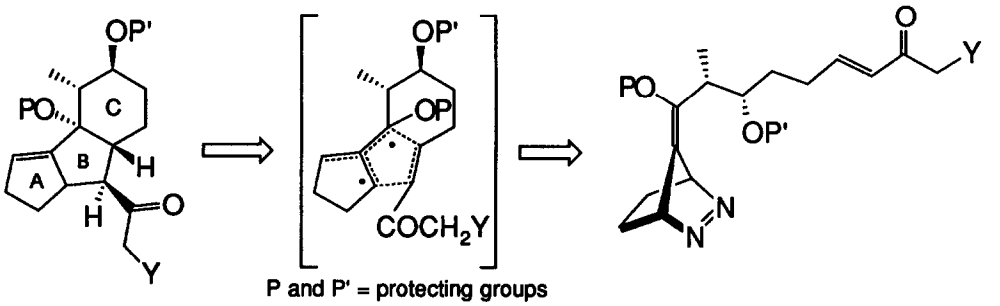
While phorbol was first isolated in 1931,[1] its structure remained unknown until 1968.[2] For many years, interest centered around the observation that certain of the esters, *e.g.*, phorbol myristate acetate, are tumor promoters.[3] Current interest focuses upon their ability to activate protein kinase C (PKC) and upon using the esters to probe in detail the mechanism of the activation process and the sequence of events which follow.[4-6] Despite their extremely interesting and important biological properties, their synthesis has received surprisingly little attention. A notable exception to this observation is, of course, the elegant work of Wender and coworkers.[5] We have become interested in the possibility of designing and constructing simpler PKC activators/inhibitors based upon the use of existing pharmacophore models for the phorbols.[6] This Letter describes the results of essential preliminary studies intended to determine the applicability of the intramolecular diyl trapping reaction to the problem.



1, phorbol

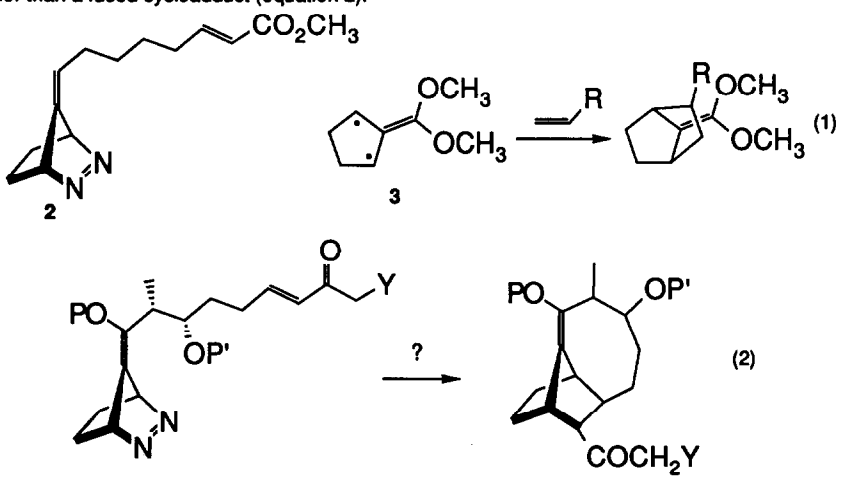
Our plan called for the synthesis of diyl precursors designed in accord with the following considerations: 1. The first carbon exocyclic to the diyl ring must bear an oxygen atom for it is destined to become C_9 (see 1 and the equation shown below); the β-carbon of the diylophile transforms to the other B,C ring junction atom, C_{15}. 2. The tether

constitutes the pro-C_{11}-C_{14} atoms and must be constructed in a manner which will lead to the requisite functionality and stereochemistry found in ring C. 3. The electron withdrawing group attached to the α-carbon of the diylophile is eventually to be used in conjunction with the ring expansion of the initially formed five- to the requisite seven-membered B ring and must be selected to facilitate this process.



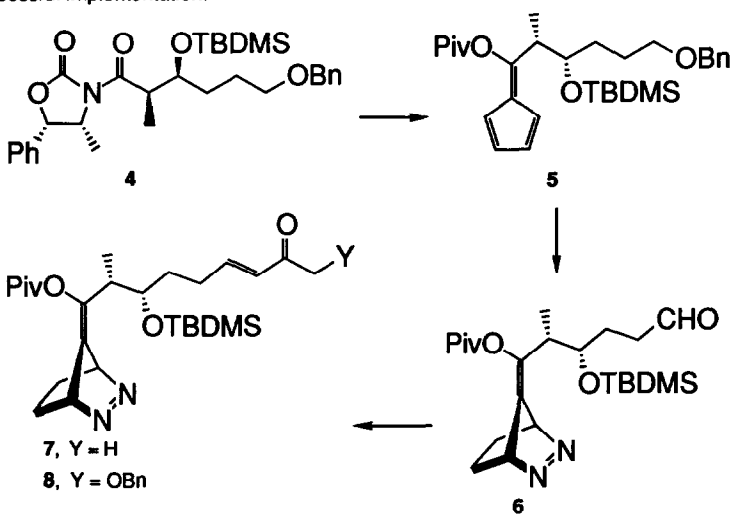
P and P' = protecting groups

Enthusiasm for this approach was tempered by knowledge of the fact that the intramolecular diyl trapping reaction of diazene **2**, one which like the structure illustrated above, possesses a four-carbon tether, did not proceed stereoselectively.[7] Should that prove true in the present instance, then the methodology would certainly not be useful. We were also aware of the fact that the dimethoxy diyl **3** undergoes intermolecular cycloaddition to produce bridged rather than fused cycloadducts; note equation 1.[8] It was possible, therefore, that even the single oxygen atom located on the exocyclic carbon of the diyl would lead to a modification of the course of the intramolecular cycloaddition and provide a bridged, rather than a fused cycloadduct (equation 2).

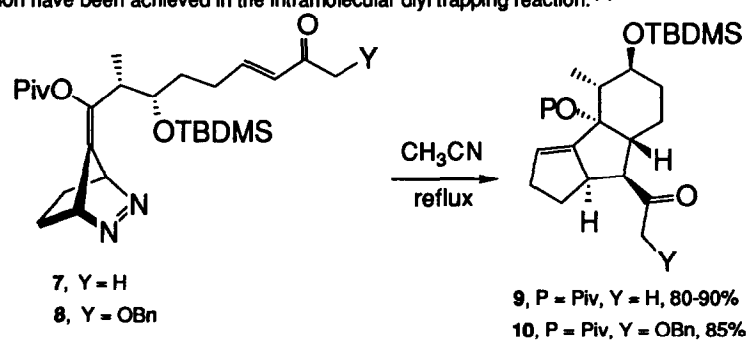


Treatment of the optically active oxazolidinone **4** [9] with hydroperoxide (LiOH, 30 % H_2O_2, 3:1 THF/H_2O, 0 °C, 1.5 h, 87%) served to generate the expected carboxylic acid. Conversion to the corresponding acid chloride ([$COCl]_2$, DMF [cat], PhH, 5 °C to room temp), followed by treatment with CpK [from CpH, $KN(TMS)_2$, degassed THF, 2 equiv HMPA, -78 °C] and 5 equiv of *t*-BuCOCl under carefully-controlled conditions (-42 ≤ T ≤ -32 °C during addition of the acid chloride), led to the formation of fulvene **5** (44-50%, optimized yield, two steps from the carboxylic acid).[10] Diels-Alder cycloaddition between the fulvene and bis-(2,2,2-trichloroethoxy) azodicarboxylate ($CHCl_3$, -4 °C, 12 h, 97%),[11] hydrogenation of the

resulting Δ-4,5 π-bond with concomitant hydrogenolysis of the benzyl group [H_2, $Pd(OH)_2$, EtOH, room temp, 1.5 h, 74%], conversion of the carbamate linkage to the diazene unit [Zn(Cu), MeOH, 0 °C to room temp; 0.3 M aqueous $K_3Fe(CN)_6$, THF/Et_2O, 0 °C, 1.5 h, 80%], and Swern oxidation [$(COCl)_2$, CH_2Cl_2, DMSO, -72 °C, 2 h; Et_3N, -72 °C to room temp, 89%] afforded aldehyde-diazene **6**. A Horner-Emmons-Wadsworth reaction was used to construct both the α,β-unsaturated methyl ketone **7** [$(MeO)_2POCH_2COCH_3$, $KN(TMS)_2$, 1:1 THF/DMSO, 0 °C, 30 min, then add **6**, THF, 1.5 h, 73%] as well as the unsaturated benzyl ether **8** [$(MeO)_2POCH_2COCH_2OBn$, $NaN(TMS)_2$, 0 °C, 1:1 THF/DMSO,1.5 h, 67%], though the latter conversion required considerably more time; the selection of THF/DMSO as solvent proved important for its successful implementation.

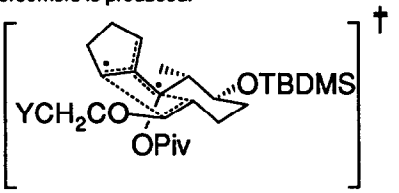


We are exceptionally pleased to report that the intramolecular diyl trapping reactions, **7** → **9** and **8** → **10** (CH_3CN, reflux, 2.5 h), proceeded ***reproducibly, in high yield , with the requisite control of both relative and absolute stereochemistry at six contiguous stereogenic centers, and led to the desired fused tricyclic skeleta.***[12,13] Clearly, the presence of an oxygen atom on the exocyclic carbon of the diyl did not affect the cycloaddition deleteriously (*vide supra*). These examples represent the second instance where useful amounts of asymmetric induction have been achieved in the intramolecular diyl trapping reaction.[14]



It is easy to understand why the cycloadditions of **7** and **8** proceed stereospecifically, while that of **2** does not. Thus, in accord with the previously established model for the intramolecular diyl trapping reaction, one views the

cycloaddition as a kinetically controlled process and focuses upon determining which of a set of possible transition state formulations is most likely to be of lowest energy.[15] Application of this reasoning to the situation in hand reveals that a pseudo-equatorial orientation of the methyl, silyl ether and diyl ring about the periphery of the six-membered ring which is being created leads to the observed stereochemical outcome. The diyl derived from **2** is devoid of substitution on the tether and therefore lacks the conformational bias provided by the substituents; many more transition state conformations are available to it and a mixture of diastereomers is produced.



Cycloadducts **9** and **10** promise to be of utility in conjunction with future plans calling for their conversion to protein kinase C modulators and to the phorbols. The results of these efforts will be reported in due course.

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References and Notes

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