Studies on Tumor Promoters. 11. A New [5 + 2] Cycloaddition Method and Its Application to the Synthesis of BC Ring Precursors of Phoboids

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Summary: A new method for the generation of oxidopyrylium zwitterions has been developed that allows for its use in the [5 + 2] cycloaddition of substrates incorporating thermally unstable functionalities, providing for the synthesis of previously inaccessible precursors to tiglianes, daphnanes, and ingenanes.

Phorbol (1), daphnane (2), and ingenane (3) derivatives, long recognized as highly potent tumor promoters, have recently found use in numerous other studies ranging from cell differentiation and AIDS virus expression to the biochemical basis of learning.[2,3] The effects caused by these compounds are attributed in most cases to an anomalous activation of one or more isozymes of the protein kinase C family.[2-4] In order to develop an understanding of the structural requirements for this activation process and to obtain information about the physiological role of these isozymes, access to specifically modified derivatives of the above families is required.[5] Recently, we reported two syntheses of phorbol.[6a-c] We describe herein a new advance in this area involving a novel 4-methoxy-3-oxidopyrylium–alkene cycloaddition (Scheme I). This process allows for the facile synthesis of previously inaccessible BC ring precursors of phorbol derivatives and serves more generally to broaden the utility of oxidopyrylium cycloadditions in [5C + 2C] approaches to complex seven-membered rings.

The motivation for this study derived from the view that cycloadduct 4 by virtue of its C-ring unsaturation would serve as a versatile precursor to the tigliane, daphnane, and ingenane derivatives. We previously reported that related cycloadducts can be obtained through a [5 + 2] cycloaddition involving an oxidopyrylium intermediate, produced in situ from a 3-(silyloxy)-4-pyrone through an internal silyl transfer.[6c] In order to test systematically whether this process could be utilized with thermally less robust but synthetically more versatile functionalities such as a tethered diene, the C13–C14 unsaturated and saturated 4-pyrones **6** and **8** were synthesized (Scheme II).[7] Pyrone **8a** was obtained by addition of bromide **7**, prepared from acrolein in two steps (53%), to a solution of potassium kojate[8] and Claisen rearrangement of the resulting allyl ether (90% yield for 2 steps). Silylation of **8a** gave (silyloxy)pyrone **8b** in five steps overall. Pyrone **8c** was prepared similarly, requiring only an additional benzylation step. The synthesis of pyrone **6a** was accomplished in seven steps (36% yield) through a related sequence. Thus, addition of propargylmagnesium bromide to acrolein, followed by palladium-catalyzed coupling with vinyl bromide,[9] and subsequent treatment of the resulting alcohol with $SOBr_2$ gave bromide **10** in 56% yield (3 steps). Treatment of this bromide with potassium kojate afforded the corresponding pyrone–dienyne ether, which was converted to the cis diene **11a** by reduction with activated Zn (72% for 2 steps).[10] Claisen rearrangement and silylation gave pyrone **6a** (89%), while benzoylation and rearrangement provided **6b**, from which **6c** was obtained by silylation.

For comparison purposes, silylated pyrones **8b** and **6a** were heated independently in a sealed tube for 3 days at 200 °C. Pyrone **8b** afforded the expected cycloadduct **9b** (Scheme II) as a single isomer in 74% yield (84% based on recovered **8b**). However, **6a** gave only a trace amount of the desired cycloadduct. Inseparable mixtures of starting material and isomerization products accounted for the majority of the reaction mass. Clearly, the thermal requirements for this transformation preclude its extension to delicately appointed substrates such as **6**.

Given the facility of many oxidopyrylium cycloadditions,[11,12] it was reasoned that silyl transfer from O-3 to O-4 could be the rate-limiting step in the above reactions. Consequently, it was expected that this problematic step could be circumvented through a process involving initial O-4 alkylation,[13] to produce the previously unknown

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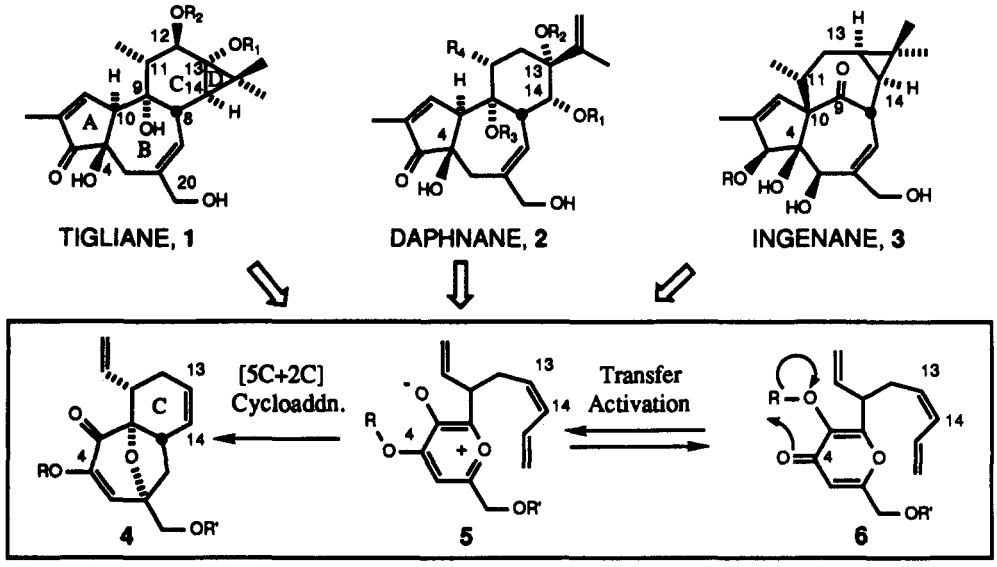
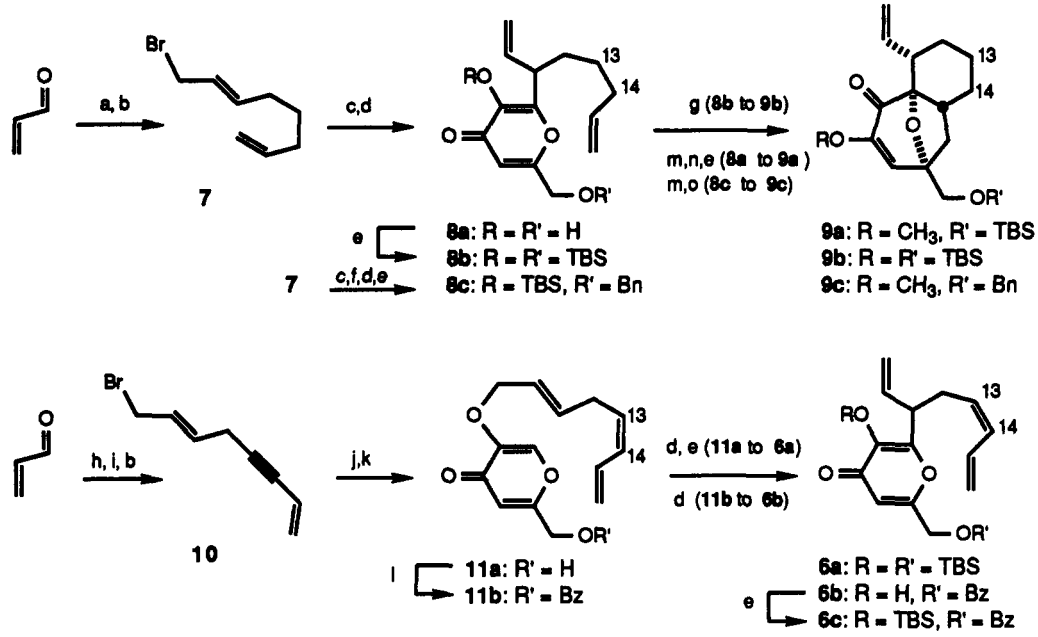
Scheme I

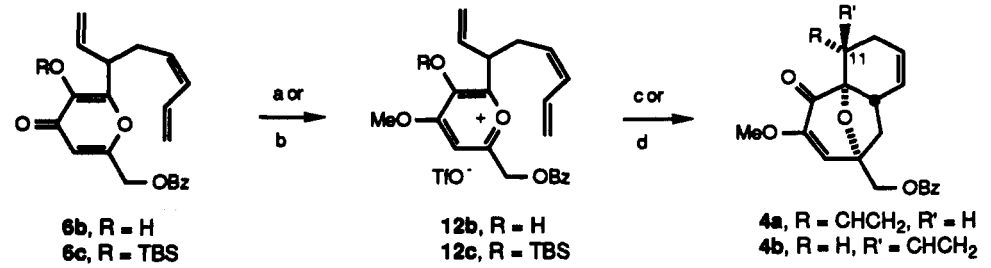


Scheme II[a]



[a] (a) CH_2=$CH(CH_2)_3MgBr$, ether, 20 °C; (b) 1.5 equiv of $SOBr_2$, 1.3 equiv of propylene oxide, CH_2Cl_2, 0 °C; (c) potassium kojate, MeOH, 20 °C; (d) EtOH, reflux, 60 h; (e) TBSCl, imidazole, DMF; (f) NaH, BnBr, *n*-BuN_4I, THF, 20 °C; (g) 200 °C, sealed tube, toluene, 60 h; (h) $HCCCH_2MgBr$, ether, 20 °C; (i) 10 equiv of CH_2=$CHBr$, 3 equiv of $HN[CH(CH_3)_2]_2$, 0.02 equiv of $Pd(PPh_3)_2Cl_2$, 0.06 equiv of CuI, 20 °C; (j) potassium kojate, MeOH, 20 °C; (k) Zn, $Cu(OAc)_2{\cdot}H_2O$, $AgNO_3$, $MeOH/H_2O$, 20 °C, 48 h; (l) BzCl, NEt_3, DMAP, CH_2Cl_2; (m) 1.7 equiv of MeOTf, CH_2Cl_2, 40 °C, 7 h; (n) 2 equiv of 2,2,6,6-tetramethylpiperidine, CH_2Cl_2, 20 °C, 4 h; (o) excess CsF, DMF/CH_2CL_2 (1:1), 8 h.

Scheme III[a]



[a] (a) 1.7 equiv of MeOTf, CH_2Cl_2, 40 °C, 11 h; (b) 2 equiv of MeOTf, CH_2Cl_2, 20 °C, 14 h; (c) 2 equiv of 2,2,6,6-tetramethylpiperidine, CH_2Cl_2, 20 °C, 10 h; (d) excess CsF, DMF/CH_2Cl_2 (1:1), 10 h.

4-alkoxypyrylium salt, followed by O-3 desilylation to give the desired oxidopyrylium intermediate. Of the several alkylating agents screened to test this possibility, methyl trifluoromethanesulfonate (MeOTf) proved to be the reagent of choice. When **6c** in CH_2Cl_2 was treated with MeOTf at 20 °C for 8 h, O-4 alkylation occurred readily to give pyrylium salt **12c** (Scheme III).[14] Gratifyingly, when this salt[15] in CH_2Cl_2/DMF was exposed to anhydrous cesium fluoride, cycloaddition proceeded smoothly *at room temperature* to give cycloadducts **4a/b** (3.8:1 mixture) in 84% yield. A variant of this protocol allowed for the direct use of hydroxypyrones. Thus, when **6b** in CH_2Cl_2 was treated with MeOTf for 11 h, the pyrylium salt **12b**[14] was produced. Upon reaction with the nonnucleophilic base 2,2,6,6-tetramethylpiperidine, **12b**[15] gave at 20 °C cycloadducts **4a/b** (3.8:1, respectively, 82% yield, 94% based on recovered **6b**).

The novel protocols developed for the cyclization of substrates **6b** and **6c** were also applicable to pyrones **8a** and **8c** (Scheme II). The respective cycloadducts **9a** and **9c** were obtained again at room temperature in 83% and 88% yield as single isomers. The differences in stereoselectivity observed in the cycloadditions of substrates **8** and **6** are potentially a reflection of the relative energy differences between pro-axial and pro-equatorial C-11 substituents on the developing C rings in the cyclization transition states (cyclohexanyl for **8** and cyclohexenyl for **6**).[6a,c]

In summary, a new method has been developed for the synthesis of complex seven-membered rings based on the novel generation and cycloaddition of 4-methoxy-3-oxidopyrylium intermediates. The mild conditions involved with the method create new opportunities for its use with thermally unstable functionalities, as required in the synthesis of phorbol derivatives and other highly functionalized seven-membered carbocycles. In the present case, this process delivers cycloadducts incorporating C ring unsaturation directly amenable to elaboration into diterpenoid promoters, including those bearing oxidation at the C-11 group. Further studies on the scope and limitations of this methodology are in progress.

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(14) ^1H and ^{13}C NMR spectra indicate that the pyrylium salt is the major product in the crude reaction mixture (>80%).

(15) In order to obtain a efficient cycloaddition, complete elimination of the excess MeOTf (under vacuum at room temperature) from the crude pyrylium salt is required.

Dipolar Cycloaddition of Cyclic Rhodium Carbenoids to Aromatic Heterocycles

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Summary: Cyclic diazo 1,3-dicarbonyl compounds are decomposed by rhodium carboxylate salts in the presence of furans, dihydrofurans, pyrroles, and indoles to generate 7-oxatricyclo[6.4.0.0^{2,6}]dodecane derivatives.

Rhodium-mediated decomposition of diazo carbonyl compounds has become an important methodology in organic synthesis.[1] The reactions in which the putative intermediate metal–carbene participates include ylide formation,[2] O–H and C–H insertion,[3] cyclopropanation,[4] and dipolar cycloaddition.[5] Acyclic diazo ketones and diazo β-keto esters[6] have been widely used for these processes. In reactions of carbenoids derived from these compounds with furans, the products are (*Z*)-α,β,γ,δ-dienals or dienones.[7] It has been postulated that they are produced via initial cyclopropanation followed by electrocyclic ring opening (eq 1). Much less study has been made of the reactions of cyclic metal carbenoids. In this paper we report that cyclic diazo β-diketones preferentially yield dipolar cycloaddition products in rhodium-mediated reactions with aromatic heterocycles such as furan. The

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