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Unusual Oxidative Transformations of a C-Aromatic Taxane Diene and Related Structures

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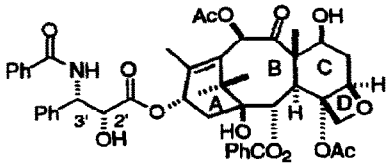
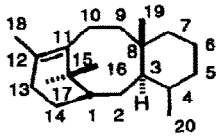
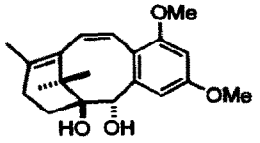
Abstract: The interaction of **1** and related substances with MCPBA, dimethyldioxirane, $VO(acac)_2$–*t*-BuOOH, and $Mo(CO)_6$–*t*-BuOOH affords products with oxygenated A-rings and/or cleaved B-rings through novel oxidative processes.

We recently reported[1] the preparation of potential taxol[2] synthesis[3] intermediate **1** through a convergent intramolecular pinacol coupling strategy.[4] Together with subsequently developed efficiencies,[5] this route has made available quantities of **1** sufficient to investigate the functionalization of important A and B-ring sites. In the pursuit of this objective, we have discovered **1** and related substances to undergo several novel oxidative processes, which we disclose herein.



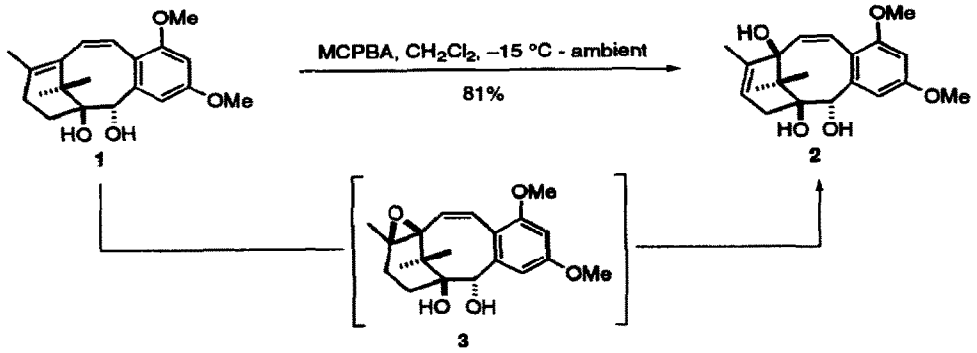
TAXOL

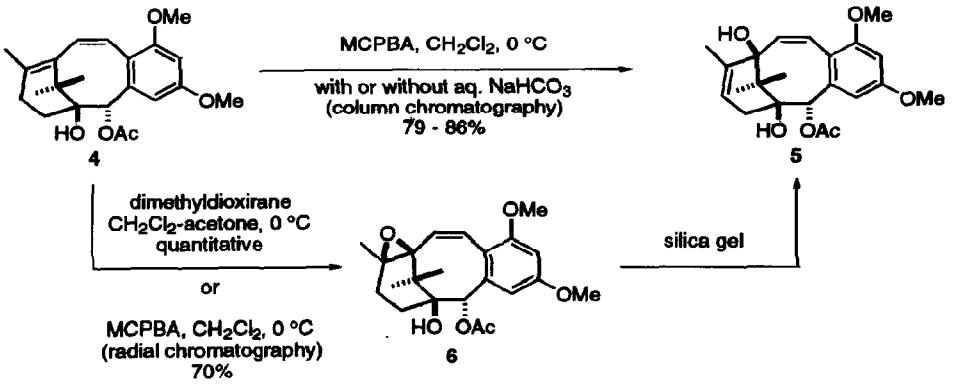




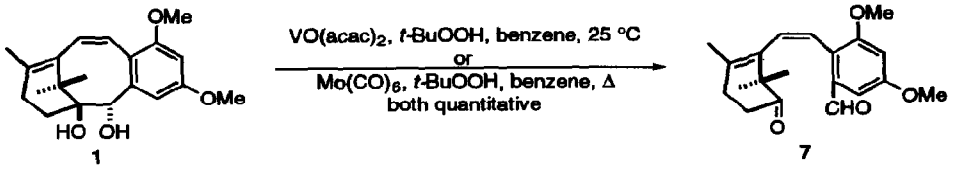
1

The exposure of **1** to *m*-chloroperbenzoic acid (MCPBA) produced triol **2**. We expected that the characteristic low reactivity of the taxane bridgehead olefin and the absence in **1** of a complex, sterically demanding

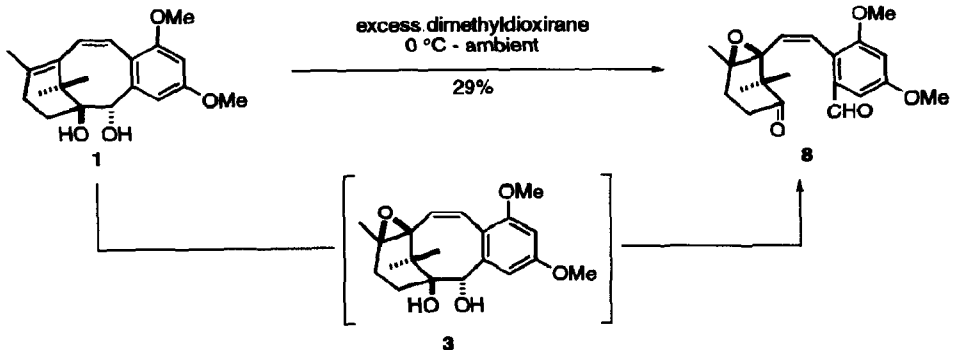




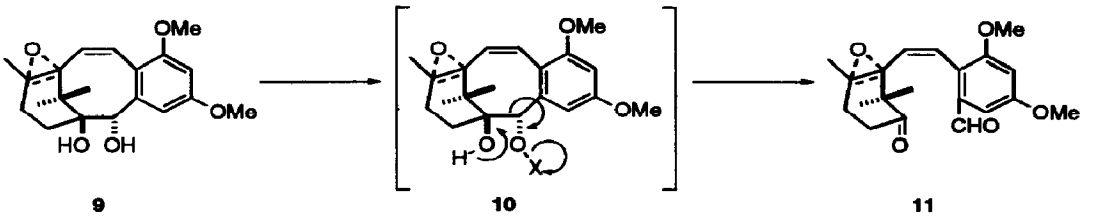
saturated C-ring substructure might direct epoxidation to the B-ring olefinic site. However, **2** apparently arises from the rearrangement *in situ* of intermediate A-ring epoxide[6] **3** since acetate **4** behaved similarly toward MCPBA, but under appropriate conditions provided metastable epoxide **6** whose isolation and spectroscopic characterization proved possible. Epoxide **6** readily isomerized into **5** when exposed to silica gel. These epoxide rearrangement processes presumably are aided by the conversion of the C-11 bridgehead site to a conventional sp^3 center uninvolved with an epoxide ring. Following the experience with **4**, the careful reexamination by TLC of the MCPBA oxidation of **1** then revealed the involvement of a labile intermediate, which we believe to be epoxide **3**.



Oxidation substrate **1** behaved unusually toward other epoxidation reagents, as well. The attempted $VO(acac)_2$[7] and $Mo(CO)_6$–catalyzed[7] epoxidations of **1** with *t*-BuOOH led instead to oxidative cleavage product **7**, readily recognized as the pinacol coupling substrate that had acted as the precursor to **1**.[1] Similarly, dimethyldioxirane[8] produced epoxidation-oxidative cleavage product **8** when **1** was exposed to a large excess

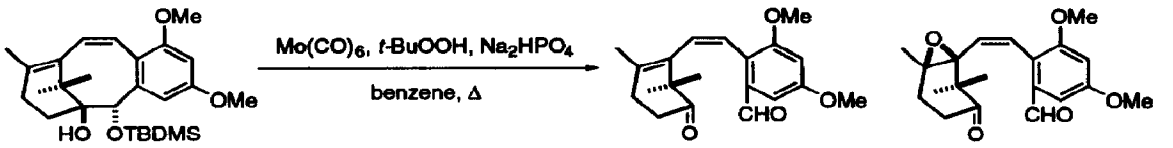


of the reagent and the reaction mixture allowed to warm. Epoxide **8** showed no propensity to undergo facile rearrangement to an allylic alcohol. Its structure was confirmed by synthesis from **7** through sequential reduction to the corresponding diol ($NaBH_4$), epoxidation (MCPBA), and oxidation (TPAP–NMO[9]) to **8**. Keto aldehyde **7** was unreactive toward dimethyldioxirane, thus confirming the sequence of events in **1** → **3** → **8**.



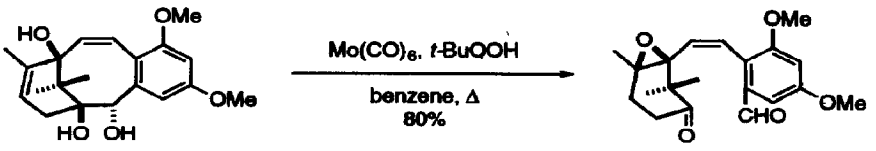
9 **10** **11**

It seems likely that these three vicinal diol oxidative cleavage reactions occur through fragmentations of intermediates like **10**, which, like the epoxide rearrangements above, are driven by relief of strain associated with the tricyclic carbon skeleton. The X-group in **10** could represent the remainder of peroxide or hydroperoxide substituents, or ligated V and Mo centers in the respective $VO(acac)_2$ and $Mo(CO)_6$-catalyzed processes. Since no reaction occurred between **1** and *t*-BuOOH, $VO(acac)_2$, or $Mo(CO)_6$ alone, the metal catalysts could serve to mediate peroxide exchange, or the *t*-BuOOH to turn over the V and Mo catalysts.

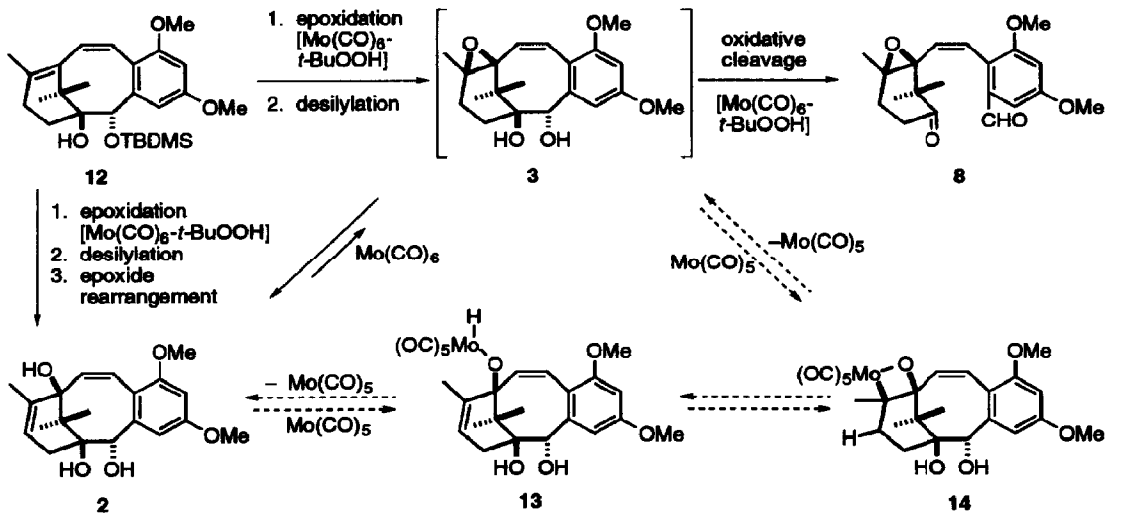


12 **7** 53% **8** 29%

With the knowledge that **1** could not be expected to interact usefully with $Mo(CO)_6$–*t*-BuOOH, we investigated the oxidation of its *t*-$BuMe_2Si$-ether derivative **12** with this reagent, which produced previously encountered **7** and **8**. Their formation was not substantially altered whether or not the Na_2HPO_4 buffering agent was included, although its inclusion led to cleaner reaction mixtures. Keto aldehyde **7** apparently is the product of the *in situ* desilylation of **12** and the subsequent oxidative cleavage of the resulting **1**, as above. However, **8** is not simply a secondary oxidation product derived from **7** since **7** proved to be unreactive toward $Mo(CO)_6$–*t*-BuOOH. We eventually were led to investigate the reaction of **2** with this reagent and were surprised to discover that it, too, served as a precursor to **8**. Neither $Mo(CO)_6$ nor *t*-BuOOH alone effected these transformations. Therefore, we speculate that the sequence of events in these intriguing processes is as portrayed on the next page. Again, a key factor in the oxidative cleavage of vicinal diol **3** appears to be the relief of strain imposed by the epoxide, which acts as a bridgehead olefin surrogate. Thus **2** itself does not undergo



2 **8**



oxidative cleavage. It is the fortuitous vicinal diol cleavage of **3** to give stable **8** that reports the unusual $Mo(CO)_6$-mediated interconversion of **2** and **3**, for which we are aware of no precedent. This equilibration might involve thermally generated $Mo(CO)_5$ through the mechanistic course indicated.

The novel oxidative processes reported herein probably are, in part, the consequence of the special features of the taxane skeleton. However, they might find parallels in other unusual structural contexts, and could be of some value to the many ongoing programs directed at the synthesis of taxol and related structures.

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