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Communication

Oxidative Spirocyclization

Spiroketal Formation by Cascade Oxidative Dearomatization: An Approach to the Phorbaketal Skeleton

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Abstract: Addition of $PhI(OAc)_2$ to phenols that have *meta*-linked hydroxy ketones results in cascade oxidative dearomatizing spirocyclization to give tricyclic spiroketals. This framework is found in the phorbaketal family of natural products.

Introduction

The sesterterpenoid phorbaketal A (**1**) was reported by Rho and co-workers[1] as an isolate from a Korean marine sponge Phorbas *sp.* that exhibited cytotoxicity against human colorectal, heptoma and lung cancer cell lines as well as stimulating differentiation of human stem cells.[2] Contemporaneously, an isomeric natural product alotaketal A (**2**)[3] was found to activate the cAMP cell signaling pathway. Despite being isolated > 3500 miles apart, their remarkable similarity suggests a common biogenesis. Rho et al. proposed that cyclization of geranylfarnesyl pyrophosphate creates the phorbane carbon skeleton,[4] oxidation of which gives the γ-hydroxycyclohexenone **3** (Figure 1).[5]

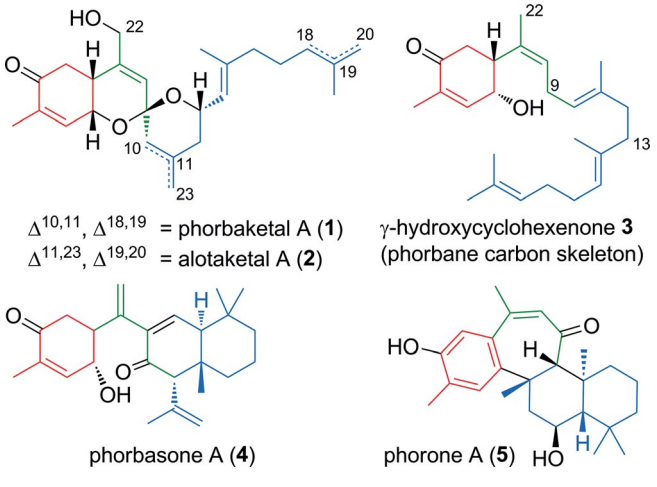
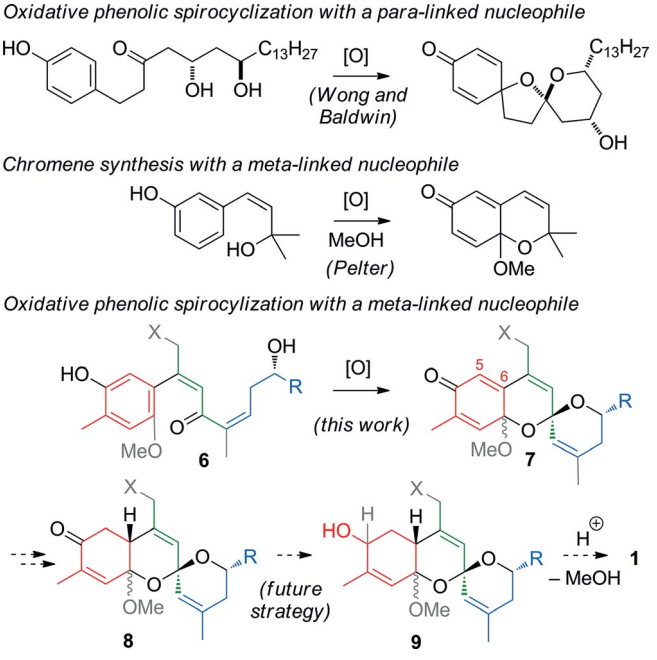


Figure 1. Marine-derived sesterterpenoid natural products.

Phorbaketal A (**1**) might then be formed by oxidation of C9 to a ketone and similarly to alcohols at C13/22, followed by acid-catalyzed dehydrative spirocyclization. Isomerization of the $\Delta^{10,11}$ and $\Delta^{18,19}$ alkenes would hence give alotaketal A (**2**). In terms of total synthesis, a route patterned along such a biogenetic pathway was of concern since acid-catalyzed elimination of the alcohol at C22 and/or aromatization of the γ-hydroxycyclohexenone would likely compete with spiroketal formation under protic conditions. The respective existence of phorbasone A (**4**)[4] and phorone A (**5**)[6] provides biosynthetic evidence for such predispositions.

Of interest to us were the syntheses of the aculeatin family of spiroketals from the groups of Wong[7] and Baldwin[8] that revealed that spirocyclization[9] could be initiated by oxidative dearomatization[10] of a phenol that had a pendant *para*-linked hydroxy ketone (Scheme 1).



Scheme 1. Existing oxidative cyclization strategies vs. our work.

Also of note is the chromene syntheses of Pelter et al.[11] who had oxidized phenols with *meta*-linked allylic alcohols in the presence of MeOH as an exogenous nucleophile to form

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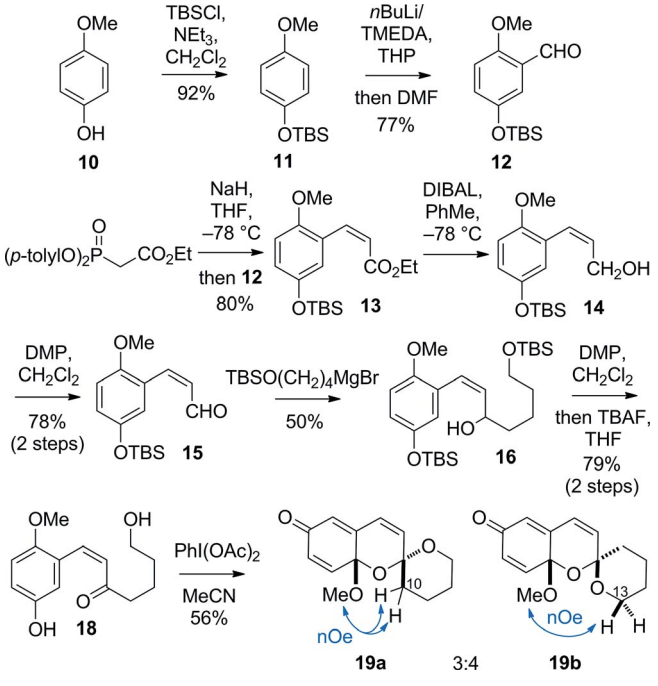
cyclohexadienone ketals.[12] Integrating these concepts, we envisaged a synthesis of the phorbaketal skeleton based on a cascade spirocyclization of a phenol **6** pending the requisite *meta*-linked hydroxy ketone and a pre-incorporated methoxy group.[13] Oxidative dearomatization of this precursor would lead to the formation of two acetals and two rings in a single synthetic operation. A spirocyclization strategy of this kind has not been reported before.[14] Furthermore, there was the future possibility that all the stereocentres of phorbaketal A (**1**) might ultimately be established by relay from the distal alcohol.[15] The end game would involve hydroxy-directed reduction of the C5–C6 double bond of **7** (X = OH) and the C4 ketone of **8** to give **9**. Elimination of MeOH/tautomerization would lead to phorbaketal A (**1**). In the present work though we have simply sought to establish the validity of the proposed spirocyclization methodology.

Results and Discussion

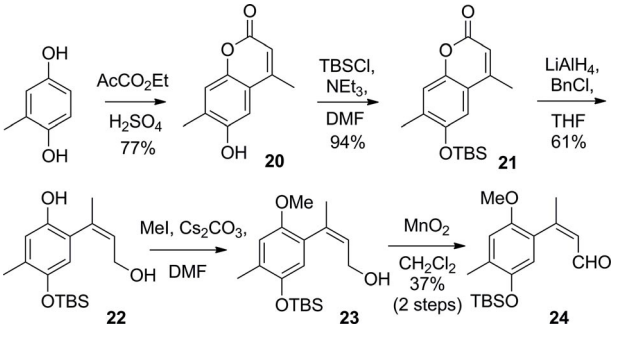
We selected (*Z*)-phenolic hydroxy ketone **18** as the substrate on which to initially examine the feasibility of the anticipated cyclization (Scheme 2).



Scheme 2. Proof of concept for a new spiroketalization strategy.

The synthesis of this compound began with 4-methoxyphenol (**10**), which was *O*-protected as the *tert*-butyldimethylsilyl ether **11**. Lithiation *ortho* to the methoxy group was achieved with *n*BuLi/TMEDA, and the subsequent anion was quenched with DMF to give **12**. Ando's olefination[16] of **12** proceeded with 85:15 (*Z*)/(*E*) stereocontrol, the isomers being readily separable by column chromatography. The (*Z*)-ester **13** was reduced to an alcohol **14** with DIBAL-H and then oxidized with the Dess–Martin periodinane to give (*Z*)-enal **15**. Addition of $TBSO(CH_2)_4MgBr$[17] gave the allylic alcohol **16**, which was reoxidized with Dess–Martin periodinane (**17**) before desilylation with TBAF gave the desired (*Z*)-phenolic hydroxy ketone **18**. Treatment of **18** with $PhI(OAc)_2$ in anhydrous MeCN at room temperature led to rapid spirocyclization. Key evidence for the success of the cyclization was an upfield shift of the MeO signal in the ^1H NMR spectrum [from δ_H = 3.80 (**18**) to 3.18 (**19a**) and 3.28 ppm (**19b**)] and the appearance of characteristic enone and acetal signals in the ^{13}C NMR spectrum [δ_C = 185.9, 92.6, 96.3 (**19a**), 186.0, 90.8 and 95.3 ppm (**19b**)]. These spiroketals were isolated by flash column chromatography in 24 % and 32 % yield, respectively. The stereochemistry of the major isomer **19b** was assigned based on nOe enhancements observed between the protons of the methoxy group and one of those on C13, and for the minor isomer between both protons at C10. The slight diastereochemical preference for spiroketal **19b** over **19a** could be attributed to triple *pseudo*-anomeric effects in the former as opposed to only a double interaction in the latter. Such a preference has been noted before.[18] Of interest to the current study (vide infra) was the fact that the chemical shift of the methoxy group signals in the ^1H and ^{13}C NMR spectra of spiroketal **19b** were both shifted upfield compared to those of **19a**. Overall, this sequence demonstrated the validity of our proposed methodology, albeit with a pendant alcohol that was primary rather than secondary and allylic.

Having demonstrated this strategy as a plausible method for spiroketal formation we further explored its utility for the total synthesis of the phorbaketal natural products. We next synthesized the enal **24** (Scheme 3) that would be required for phorbaketal A (**1**).

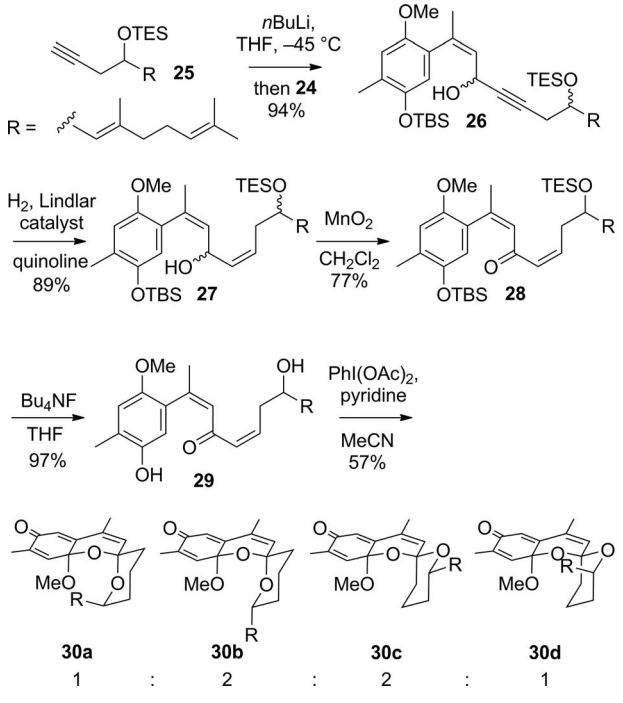


Scheme 3. Synthesis of the enal **24**.

Work began with a Pechmann condensation of 2-methylhydroquinone with ethyl acetoacetate to form coumarin **20**.[19] This established the necessary C7–C8 (*Z*) stereochemistry, which would have been otherwise difficult to achieve in an acyclic system. The coumarin **20** was then *O*-protected as the *tert*-butyldimethylsilyl ether. The protected coumarin **21** could be regioselectively oxidized with SeO_2 and then reduced with $NaBH_4$ to provide a means to install the alcohol needed at C22 in the natural products.[20] For ease though, further steps were carried out by using coumarin **21**. Reduction with a range of typical hydride sources failed, but the use of BnCl and $LiAlH_4$ for the in situ formation of AlH_3[21] gave allylic alcohol **22** in 61 % yield. Base-mediated chemoselective methylation of the phenol with MeI and subsequent oxidation of the remaining alcohol with MnO_2 gave enal **24**, for which the (*Z*)-alkene geom-

etry was confirmed by nOe experiments and also X-ray crystallographic analysis.

Synthesis of the side chain began from homopropargyl silyl ether **25**, which was synthesised by Reformatsky reaction of propargyl bromide with geranial followed by *O*-protection as the triethylsilyl ether (Scheme 4). The lithium acetylide of **25** was added to enal **24**, and the resultant propargyl alcohol **26** was selectively reduced to the (*Z*)-allylic alcohol **27**.[22] This alcohol was then oxidized with MnO_2 before the silyl protecting groups were removed with TBAF to give the phenolic hydroxy ketone **29**, which has a norphorbane carbon skeleton. Confirmation of the key (*Z*,*Z*)-olefin geometries was achieved through careful analysis of coupling constants and a series of nOe experiments. Unhelpfully, compound **29** was found to degrade to a variety of polyolefinic compounds under normal laboratory conditions and needed to be stored at –80 °C in the dark. Nevertheless, we were now in a position to examine the proposed spiroketalization on a substrate remarkably close to the one needed for the synthesis of phorbaketal A (**1**) and importantly one that was pendant with a secondary allylic, rather than a more nucleophilic primary alcohol.



Scheme 4. Spirocyclization to form a phorbaketal-like tricycle.

Treatment of norphorbane **29** with $PhI(OAc)_2$ led to rapid consumption of the starting material but also extensive decomposition, as judged by TLC analysis. Monitoring of the reaction by in situ ^1H NMR spectroscopy ([D_3]MeCN) once again revealed rapid loss of the original methoxy signal (δ_H = 3.74 ppm) with the concomitant appearance of a complex set of signals between δ_H = 5 and 6 ppm. Over several hours there was decomposition of these initially formed products with a significant amount of MeOH being released. This indicated the spirocycle-containing products were prone to acid-catalyzed elimination of the methoxy group by the acetic acid being generated during the course of this reaction. Fortunately, the addition of pyridine as a buffer led to the desired product being isolated in 57 % yield. This was found to be a ca. 1:2:2:1 mixture of four diastereomers. Analysis of the ^1H NMR spectrum revealed that two of the diastereomers gave signals for their methoxy groups (δ_H = 3.29 and 3.26 ppm) at much higher chemical shift than the other two (δ_H = 2.96 and 2.88 ppm). By comparison with the spiroketals **19a**/**b** and in line with previous studies,[18] the diastereomers with more deshielded methoxy groups were tentatively assigned as **30a** and **30b** that are subject to a triple anomeric effect. The diastereomers with more shielded methoxy groups were hence assigned as **30c** and **30d**. The stereochemistry of the epimers at C13 within these sets of diastereomers was based on the expectation that the geranyl chain (R) would preferentially be orientated in an equatorial position. Extensive efforts were made to separate the various acid-sensitive diastereomers, but the spirocycles **30** proved to be very unstable to a large variety of chromatographic techniques. Partial purification was possible using freshly prepared grade III Brockmann alumina to give predominantly the two major diastereomers **30b** and **30c**. Overall this was encouraging since the acetal stereocenter at C1 would ultimately be removed (cf. Scheme 1) for the synthesis of phorbaketal A (**1**).

Conclusions

This study demonstrates that oxidative cascade dearomatization of phenols with *meta*-linked nucleophiles is a feasible strategy for the synthesis of complex spiroketals. A high degree of molecular complexity is established in this process with two new rings and two new stereocentres being generated in a single step. This method provides an alternative strategy to the traditional acid-catalyzed cyclization of dihydroxy ketones for the synthesis of spiroketals and might be similarly useful for a variety of other ring sizes. In light of the instability of tricycle **30**, elaboration of this method to phorbaketal A (**1**) will require in situ conversion of the initially formed spirocycles to the desired cyclohexenone motif.

Acknowledgments

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Keywords: Spiro compounds · Cyclization · Oxidation · Dearomatization · Hypervalent iodine

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