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Expedient Route to the Tigliane-Daphnane Skeleton via Oxonium Ylide [1,2]-Shift

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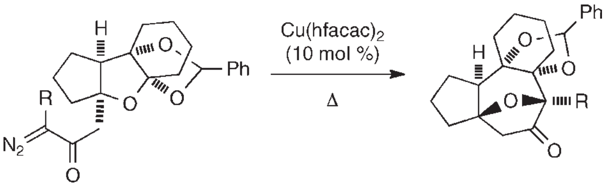
ABSTRACT



A short, stereoselective approach to the fused tricyclic carbon skeleton found in the tigliane and daphnane classes of diterpene natural products is described. Convergent coupling of the A- and C-rings, followed by diastereoselective cerium enolate addition and formation of a double acetal set the stage for generation of an oxonium ylide via a transient metallocarbene. An efficient Stevens [1,2]-shift furnished the 7-membered B-ring, possessing the bridgehead oxygenation pattern found in the natural systems.

The tigliane and daphnane families are complex diterpenoids possessing congested 5-7-6 fused carbocyclic frameworks with multiple contiguous stereogenic centers and extensive oxygenation (Figure 1). The structural complexity and biological significance[1] of these intriguing natural products have piqued substantial interest in the synthetic community, culminating in a number of elegant approaches[2] and several total syntheses.[3] Recent studies of modified phorbol esters[4] and the related natural product prostratin[5] highlight the continuing importance of this target class.

We have previously described a strategy for assembly of oxygenated polycyclic ring systems utilizing the Stevens [1,2]-shift of fused bicyclic oxonium ylides.[6,7] These transient intermediates are generated under catalytic conditions

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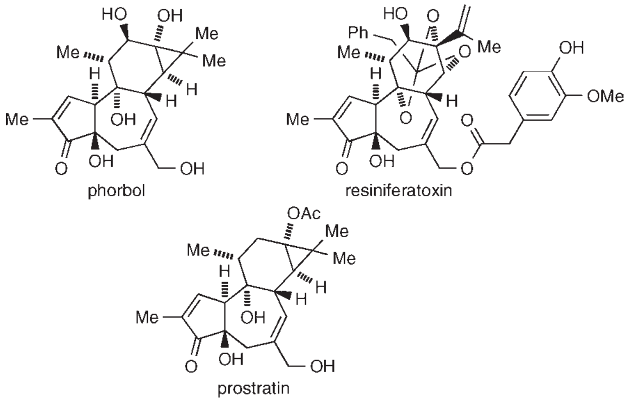
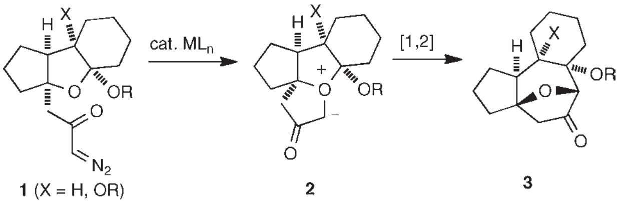


Figure 1. Representative tigliane and daphnane diterpenes.

from readily accessible cyclic ethers or acetals possessing pendent diazoketone side chains. In the context of tigliane and daphnane targets, we envisioned a concise approach employing this methodology, utilizing a tricyclic acetal precursor such as **1** (Scheme 1). Conversion to oxonium ylide intermediate **2** and [1,2]-shift of the anomeric carbon would then furnish **3**, with the 5-7-6 tricyclic carbon skeleton with a bridging ether bound to one of the bridgehead positions that is typically oxygenated in these natural products. More highly oxygenated substrates (X = OR) would lead to products with the required functionality at both oxygenated bridgehead positions. Here we report the results of this study, entailing an efficient 12-step sequence to provide oxygenated phorboids **3** employing a high-yielding and stereospecific [1,2]-shift as the key strategic step.

Scheme 1. Oxonium Ylide Approach to the 5-7-6 Ring System



1 (X = H, OR) **2** **3**

Construction of the required substrates employed the previously described[8] coupling of cyclopentanone and cyclohexene oxide to furnish an inseparable 5:1 mixture of diastereomeric hydroxyketones **4** (Scheme 2). Alcohol acetylation permitted chromatographic separation, and the major diastereomer **5a** underwent aldol addition of the cerium enolate[9] of ethyl acetate, providing a 10:1 mixture of hydroxyester adducts **6**. Following deacetylation to give **7**, oxidation of the secondary alcohol afforded hemiacetal **8**. All attempts to convert **8** to acetal or thioacetal derivatives resulted in elimination to dihydrofuran **9**. Since this process could not be prevented, optimized conditions ($BF_3\cdot OEt_2$) were developed to afford **9**, which was subjected to dihydroxylation to give diol **10** in excellent yield as a single diastereomer. Protection as the benzylidine acetal provided a 1.5:1 mixture of anomers **11a**/**b** in 83% combined yield.[10]

Esters **11a**/**b** were subjected to saponification conditions, followed by conversion to the corresponding mixed anhydrides and treatment with diazomethane to furnish separable diazoketones **12a**/**b** in a combined yield of 76%. Alternatively, reduction of **11a**/**b** to the primary alcohols and oxidation with TPAP provided separable aldehydes **13a**/**b**, which underwent modified Roskamp reaction[11] to the corresponding ketoesters, and Regitz-type diazotransfer reaction[12] then furnished diazoketoesters **14a**/**b** in good yields.

With diazo substrates **12** and **14** in hand, the key oxonium ylide step was next examined. There was some concern about the availability of several ethereal oxygens to the metallocarbene intermediate, leading to different oxonium ylides and several potential products. Moreover, even in the event of formation and rearrangement of the desired oxonium ylide derived from the tetrahydrofuran ring oxygen, the formation of a diastereomeric mixture from migration of the anomeric carbon could occur. In the event, diazoketones **12a** and **12b** were each subjected to the optimized conditions from previous studies (10 mol % $Cu(hfacac)_2$ in CH_2Cl_2 at reflux),[6b] forming in each case a single product in very good yield (Scheme 3). The diastereomeric rearrangement products were assigned as **15a** and **15b**, and the latter was subjected to stereoselective reduction to furnish alcohol **16**, from which crystals suitable for X-ray diffraction analysis were obtained to confirm the relative configuration assigned to the tetracyclic structure. Upon the basis of spectral analogy, **15a** was determined to

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(10) Separation of the anomers **11a** and **11b** could be accomplished by careful chromatography, but in practice they were carried through as a mixture and separated as anomeric diazoketones **12a** and **12b**.

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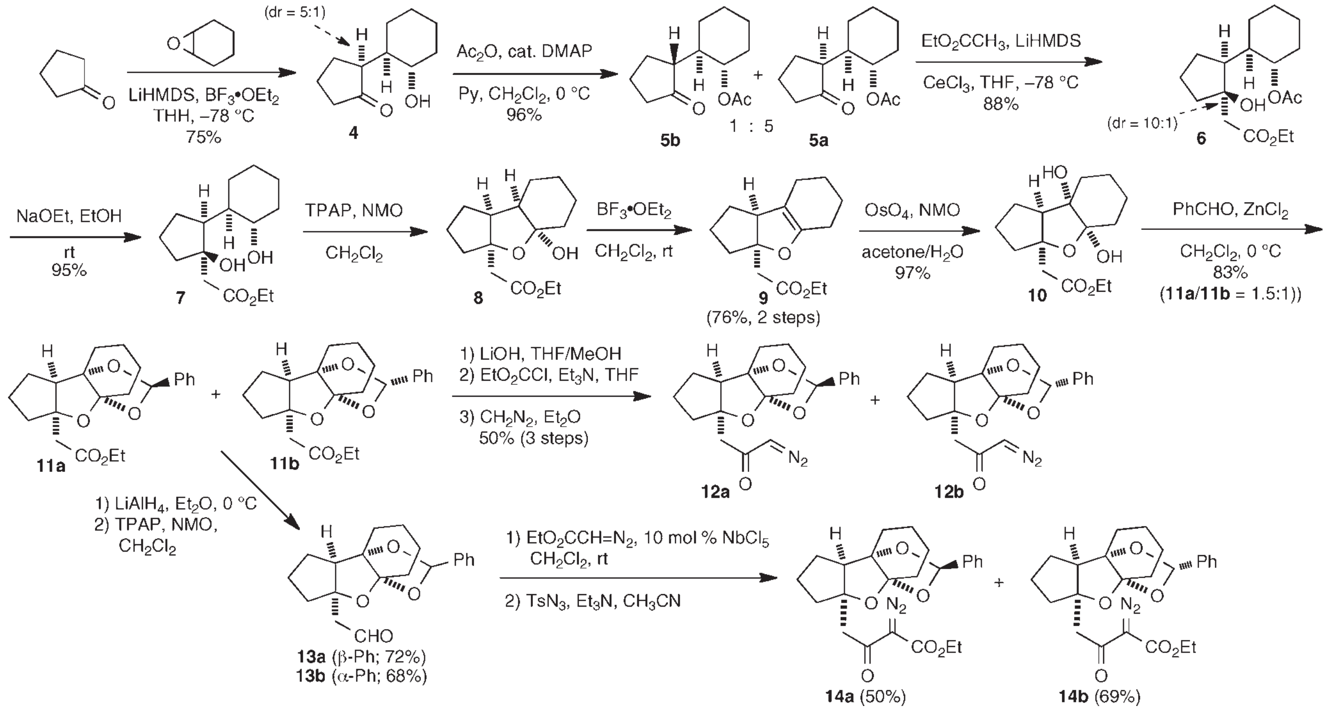
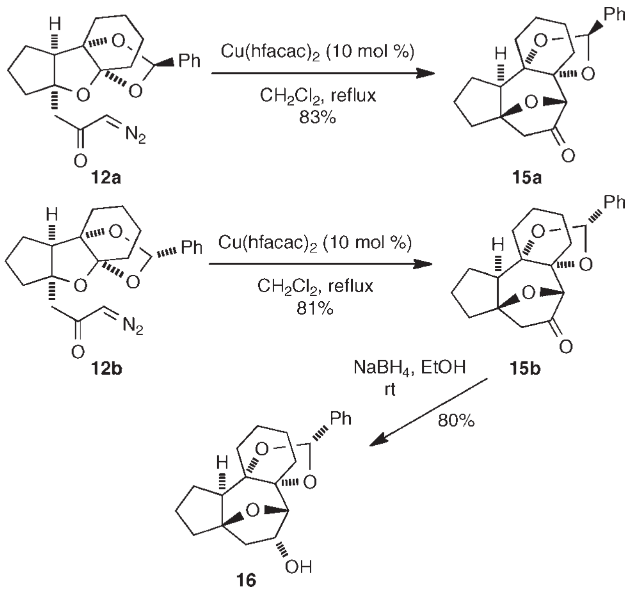
Scheme 2. Synthesis of Substrates



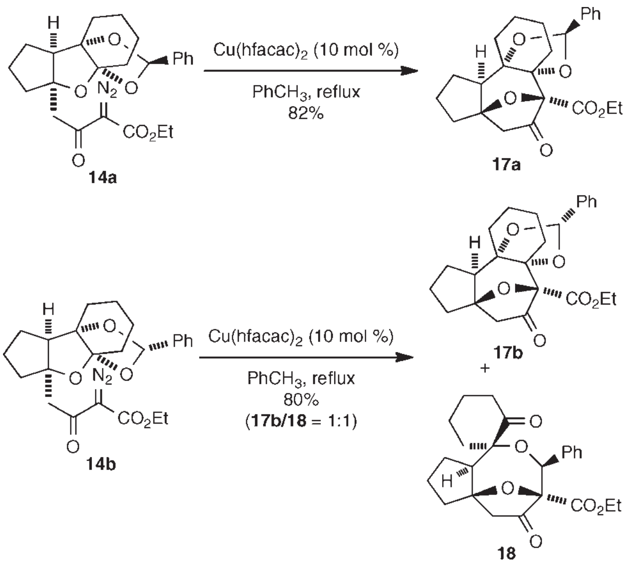
Scheme 3. Rearrangement of Diazoketones **12**



differ from **15b** only at the phenyl-substituted carbon. *Thus, **15a** and **15b** each underwent [1,2]-shift with complete retention of configuration at the migrating center.*

Diazoketoesters **14a**/**b** were found to be much less reactive. Treatment of anomer **14a** under the standard conditions led only to recovered starting material, indicating the need for elevated temperatures (Scheme 4).[6d,13] However, stirring with Cu(hfacac)$_2$ in toluene at reflux

Scheme 4. Rearrangement of Diazoketoesters **14**



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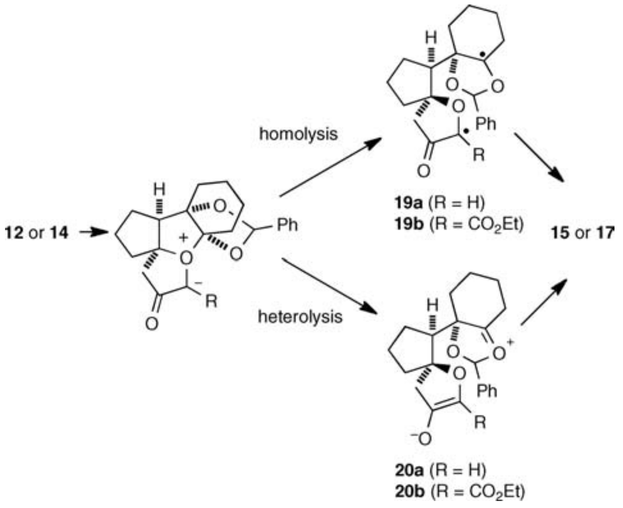
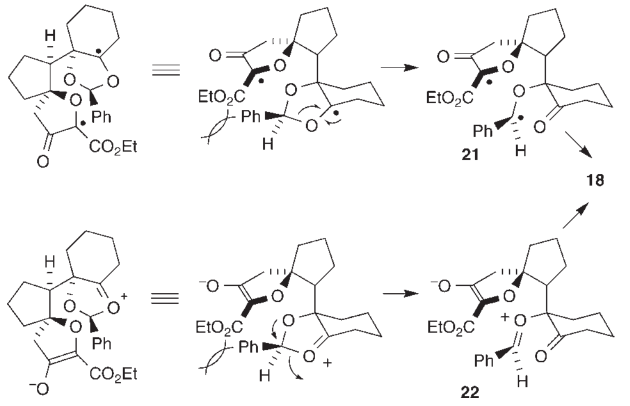
Scheme 5. Homolytic and Heterolytic Mechanisms



yielded **17a** in good yield. Anomer **14b** was unique among the substrates examined, as it gave rise to two products in roughly equal amounts: expected [1,2]-shift product **17b**, and a constitutional isomer that seemed to contain an α-alkoxycyclohexanone fragment and no benzylidene acetal. Both **17b** and the unexpected product were crystalline solids suitable for X-ray diffraction, allowing for confirmation of the stereochemical assignment of the [1,2]-shift product, and assignment of the isomeric compound as spirocyclic oxacanone **18**.

Previous mechanistic studies of the Stevens [1,2]-shift of ammonium ylides implicated a stepwise process involving radical intermediates.[14] In simplified oxonium ylide systems, we have also observed homodimeric products indicative of radical pair intermediates.[15] If this homolytic mechanism were operant for the more complicated substrates in the present study, biradicals **19a** and **19b** would intervene (Scheme 5). On the other hand, with acetal-derived oxonium ylides, an alternative heterolytic mechanism can also be considered, which would proceed via zwitterions **20a** and **20b**. Regardless of mechanism, the complete stereospecificity observed in these reactions is notable. Other fused bicyclic oxonium ylides have displayed high stereochemical retention during [1,2]-shifts,[6b,16] but randomization is also common.[6d,17] Here, the migrating center is at the bridgehead of a fused bicyclic system, which precludes recombination with inversion.

Scheme 6. Possible Mechanism for the Formation of **18**



The origin of the unusual rearrangement product **18** also merits discussion (Scheme 6). An apparent fragmentation of the biradical or zwitterionic intermediate to form a cyclohexanone substituted with either a benzylic radical (**21**) or a benzylic oxocarbenium ion (**22**) seems probable. Recombination would then provide the ring-expanded product. Observation of this unique pathway with **14b** but not **14a** may be the result of the added steric demand imposed by the anomeric phenyl group in the initial homolysis (or heterolysis) product, slowing the rate of recombination relative to the fragmentation pathway. Failure to observe a similar outcome with the analogous anomer **12b** is likely due to the much lower reaction temperature, as well as the absence of the ester group.

A short and stereoselective synthetic route to the 5-7-6 tricyclic core of the tigliane and daphnane diterpenes has been developed. An oxonium ylide [1,2]-shift installs the central 7-membered B-ring with oxygenation at two key bridgehead positions. Formation of the oxonium ylide is chemoselective in favor of the desired fused tetracyclic intermediate, and rearrangement is efficient and stereospecific. In one instance, an unexpected competing fragmentation process was observed. Application of this strategy using more highly functionalized A- and C-ring building blocks is currently under investigation, and results will be disclosed in due course.

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Supporting Information Available. Experimental procedures, physical data, and NMR spectra for all compounds and synthetic intermediates, and X-ray crystallographic data for **16**, **17b**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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