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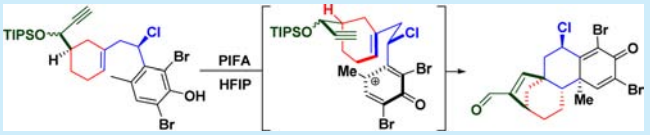
Asymmetric Synthesis of the Main Core of Kaurane Family Members Triggered by an Oxidative Polycyclization–Pinacol Tandem Process

Samuel Desjardins, Gaëtan Maertens, and Sylvain Canesi*

Laboratoire de Méthodologie et Synthèse de Produits Naturels, Université du Québec à Montréal, C.P. 8888, Succ. Centre-Ville, Montréal, H3C 3P8, Québec, Canada

Supporting Information

ABSTRACT: Polycyclization processes represent expeditious routes used in both nature and the laboratory to produce complex polycyclic molecules. A new stereoselective oxidative variant of such a polycyclization has been developed in which the cascade is triggered by a phenol dearomatization and is concluded by a pinacol transposition. This unprecedented avenue combines the synthetic power of a polycyclization and a transposition in tandem and enables the rapid formation of the tetracyclic main core of kaurane diterpenes containing several asymmetric and quaternary carbon centers in a single step from a simple phenol derivative.



Cationic polycyclizations of polyunsaturated compounds have been used in biomimetic syntheses to access complex architectures with excellent diastereoselectivity,[1] for example the remarkable steroid synthesis developed by Johnson et al.[1a] Because of their elegance and efficiency in providing access to complex natural products, such strategies remain the subject of intense interest. The methods are typically triggered by selective generation of an electrophilic species that is then rapidly trapped by several π-bonds in a stereoselective manner. The cascade concludes with nucleophilic capture using an external nucleophile.

Another important transformation that may be performed under similar conditions is the cationic molecular transposition.[2] Despite being first described more than a century ago, these transpositions still represent an appealing and efficient route to elaborated structures via 1,2-substituent shifts such as the Wagner–Meerwein, pinacol, and Prins–pinacol processes. As an illustration, the Prins–pinacol tandem process has often been used as a key strategy in syntheses of natural products, as well demonstrated by Overman and co-workers.[3]

We wondered whether a combination of these powerful synthetic tools could provide a rapid and stereoselective route to the complex structures present in a large family of diterpenes known as the kauranes.[4] These polycyclic natural products have been isolated from numerous natural sources and exhibit a wide range of biological properties.[4a] While some hemisyntheses[4] based on an elaborated natural starting material have previously been reported, no total synthesis of the compounds described in this article has appeared in the literature. However, syntheses of unusual *ent*-kauranes having a different but still interesting and very challenging architecture have been described by leading groups in the field.[5] Indeed, the tetracyclic system contains several quaternary carbon centers as well as contiguous asymmetric centers. The main carbon skeleton of the *ent*-kaurane **1** and two other members of this family, 17-hydroxy-kauran-3-one **2**[4c] and 3-oxo-kaur-15-en-17-al **3**,[4h,i] are illustrated in Figure 1.

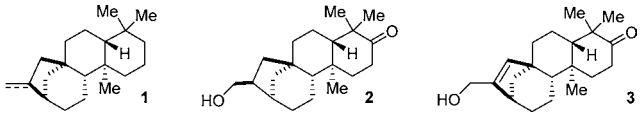


Figure 1. Kaurane diterpenes.

A key attribute of successful polycyclization processes is the capacity to selectively induce an electrophilic species, triggering the synthetic cascade at a specific position within the molecule. The cyclohexanone core of compound **3** could hypothetically be derived from the phenol derivative **15** through chemoselective activation and dearomatization. Our interest in oxidative dearomatization of electron-rich aromatics involving carbon-based nucleophiles[6] led us to question whether the oxidative cationic polycyclization could be triggered by activation of a phenol. Although electron-rich aromatic compounds such as phenols and their derivatives normally react as nucleophiles, oxidative activation can transform these compounds into highly reactive electrophilic species such as **16**. This phenoxonium ion **16** could be intercepted in an intramolecular fashion by appropriate carbon-based nucleophiles such as π bonds, thus initiating a polycyclization via a cationic cascade that would be concluded by a semipinacol process promoting a ring contraction. A combination of these methods enables conversion of the lateral chain into the tetracyclic core of kaurane **17** with the correct configuration for each asymmetric center. Stereoselectivity would be controlled by the benzylic stereocenter, enabling selective formation of the first quaternary carbon via a chairlike transition state **16**, which

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minimizes both steric and electronic interactions. This phenol reversal of reactivity may be thought of as involving "aromatic ring umpolung,"[6] Figure 2.

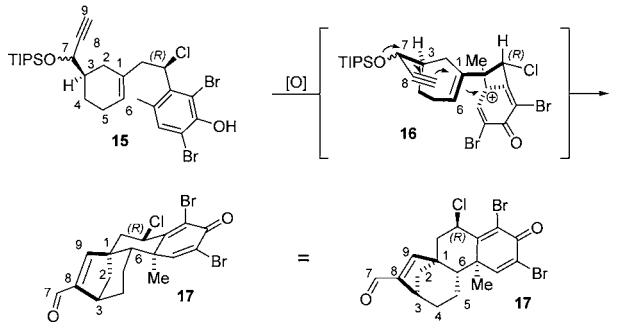


Figure 2. Oxidative polycyclization–pinacol tandem process.

The formation of species similar to the phenoxonium ion **16** is brilliantly described in the work of Kita,[7] who has reported that phenols may be activated under the influence of environmentally benign hypervalent iodine reagents[8,9] such as iodobenzene diacetate (DIB) or phenyliodine bis(trifluoroacetate) (PIFA). This reaction is generally best performed in solvents such as hexafluoroisopropanol (HFIP).[7f] The aromatic ring umpolung approach provides new synthetic strategies by extending several well-known reactions in aliphatic chemistry to aromatic systems. In this paper, we present a rapid stereoselective synthesis of the main tetracyclic core of kaurane diterpenes **17** mediated by an oxidative polycyclization–pinacol tandem process, Figure 3.

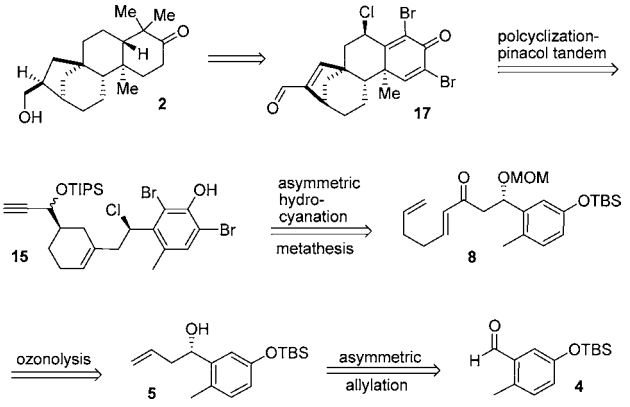
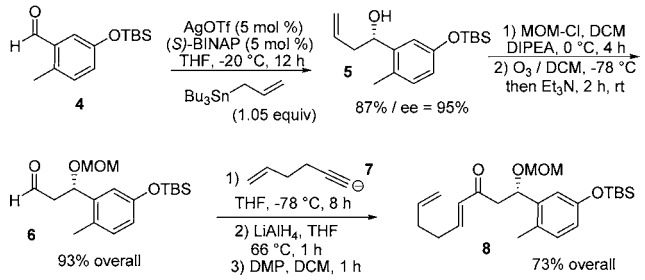


Figure 3. Retrosynthetic pathway.

Starting from known compound **4**,[10] the first asymmetric center was produced using a Yamamoto allylation process,[11] leading to alcohol **5** in 87% yield and 95% ee. This compound was protected with MOMCl, and subsequent ozonolysis yielded aldehyde **6** in 93% overall yield. Nucleophilic capture of **6** with the anion of alkyne **7**[12] produced an epimeric mixture of propargylic alcohol, and further treatment with $LiAlH_4$ stereoselectively reduced the alkyne moiety into a *trans* alkene with the assistance of the hydroxyl group. The alcohol mixture was oxidized with Dess–Martin periodinane (DMP), leading to ketone **8** in 73% yield over three steps, Scheme 1.

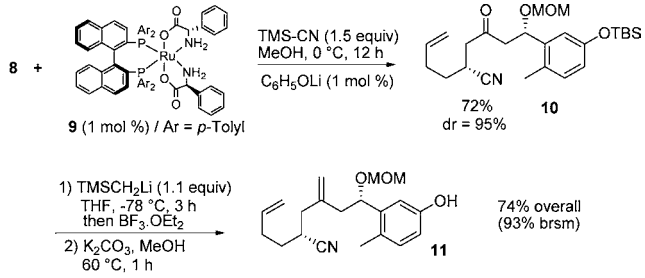
An asymmetric hydrocyanation mediated by a ruthenium catalyst developed by Ohkuma et al.[13] controlled the formation of a new stereocenter in 72% yield and 95% ee. Peterson olefination of ketone **10** followed by TBS deprotection under

Scheme 1. Formation of the First Stereocenter



basic conditions afforded phenol **11** in 74% overall yield (or 93% overall yield, based on recovered starting material), Scheme 2.

Scheme 2. Formation of the Second Stereocenter



The bromine atoms introduced on the aromatic moiety **11** serve a dual purpose. They are first used to protect the *ortho*-positions of the phenol moiety, forcing the polycyclization to occur at the *para* position, which is assumed to bear the largest LUMO coefficient of the phenoxonium species **16** (Figure 2). Due to their electron-withdrawing effect, the bromine atoms destabilize the resonance positive charge at the less hindered *ortho* position. Second, the bromine atoms could be used in combination with a transition metal catalyst to introduce one of the methyl groups required at this position during synthesis of kaurane derivatives. During the synthesis, it appeared that compound **11** was the best precursor for introducing halides; attempts on later intermediates were unsuccessful, probably for steric reasons. It was found more convenient to protect the phenol moiety using TBS before performing a metathesis reaction on compound **12** using a Hoveyda–Grubbs second generation catalyst to produce the desired cyclohexene core. Subsequent treatment with DIBAL-H yielded the aldehyde **13** in 86% overall yield. In the presence of the TMS-acetylene anion, a mixture of secondary propargylic alcohols was obtained in a 1:1 ratio, both of which led to the same aldehyde **17** following the polycyclization–pinacol process (Figure 2). The alcohol moiety was protected with a hindered TIPS group to avoid trapping of electrophilic species generated during the cationic cascade by the propargylic alcohol moiety rather than the alkyne segment. The MOM group was selectively cleaved under mildly acidic conditions and the TBS and alkyne TMS groups were selectively removed under basic conditions, producing **14** in 68% yield over four steps, Scheme 3.

At this stage, the secondary alcohol functionality **14** was substituted with a chlorine atom with stereochemical inversion and rapidly engaged in the next key transformation. It should be noted that the configuration of this benzylic stereocenter is very important, as it provides control over the stereocenters generated during the umpolung activation by favoring the

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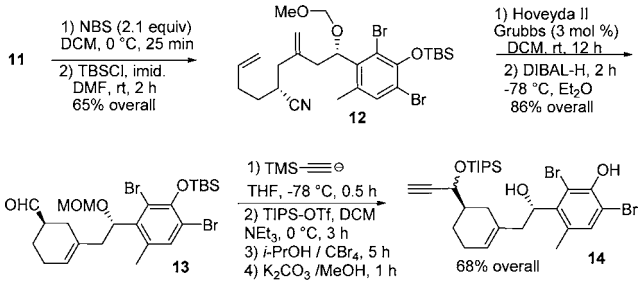
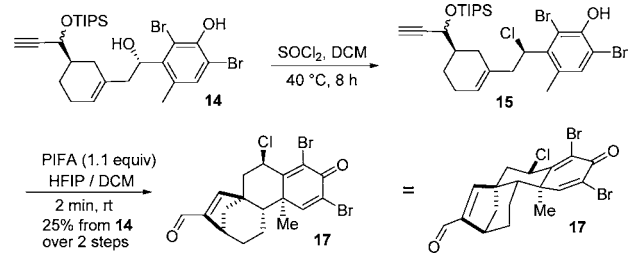
Scheme 3. Elaboration of the Key Phenol Precursor



chairlike transition state **16**, Figure 2. Phenol **15** (containing a previously elaborated lateral chain for the cascade) represents the key intermediate enabling the one-step stereoselective formation of the tetracyclic kaurane system **17**. The transformation was triggered by PIFA and occurred in 25% yield over two steps, Scheme 4 and Figure 2.

Scheme 4. Oxidative Polycyclization–Pinacol Tandem Process



In summary, the main tetracyclic core of a large class of compounds belonging to the kaurane family has been enantioselectively synthesized in one step from an elaborated phenol derivative. This key step is based on a previously unreported oxidative cascade (tandem polycyclization–pinacol process) mediated by a hypervalent iodine reagent. This first example demonstrates the utility of the "aromatic ring umpolung" concept for the rapid elaboration of complex polycyclic structures.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, NMR spectra, and characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: canesi.sylvain@uqam.ca.

Notes

The authors declare no competing financial interest.

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