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A Stereoselective Oxidative Polycyclization Process Mediated by a Hypervalent Iodine Reagent

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ABSTRACT

Activation of phenol derivatives with a hypervalent iodine reagent promotes the formation of bicyclic and tricyclic products via a cationic cyclization process. The method allows efficient one-step syntheses of scaffolds present in several natural products and occurs with total stereocontrol, governed by 1,3 allylic strain interactions and by the configuration of the side chain double bonds.

The use of cationic polycyclizations of polyunsaturated compounds in biomimetic syntheses allows rapid access to complex architectures with excellent diastereoselectivity. The first remarkable examples can be attributed to Johnson et al. for the syntheses of steroids in 1976;[1] however such strategies are still under intensive investigation.[2] Our own interest in oxidative dearomatization of electron-rich aromatics involving carbon-based nucleophiles[3] led us to question whether an 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[4,5] can transform these compounds into highly reactive electrophilic species such as **2**. This phenoxonium ion[6] **2** could be intercepted in an intramolecular fashion by appropriate carbon-based nucleophiles such as π bonds, thus initiating a diastereoselective polycyclization leading to tricyclic core **3**. This phenol reversal of reactivity may be thought of as involving an "aromatic ring umpolung". The oxidative process could rapidly generate the core of several natural products such as the human

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steroidal hormone skeleton **4**,[1] or cassaic acid **5** and its derivatives,[7] Figure 1.

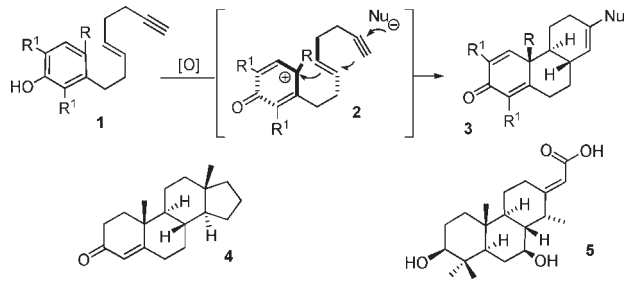

Figure 1. Oxidative cationic polycyclization cascade.

An indication of how the necessary phenol activation can be efficiently achieved is apparent in the work of Kita,[8] who demonstrated that phenols react under the influence of hypervalent iodine reagents[9] such as (diacetoxyiodo)benzene (DIB), an environmentally benign and inexpensive reagent. This reaction is best performed in solvents such as hexafluoroisopropanol (HFIP).[8f] In our first study, an oxidative vicinal fused carbocycle formation was performed with a terminal alkyne on a lateral chain at the *meta*-position relative to the phenol group **6**. During the umpolung activation, we speculate that a strained half-chair intermediate **8** was generated which strongly favored nucleophile capture, leading to the unsaturated decalin system **9**, Scheme 1.

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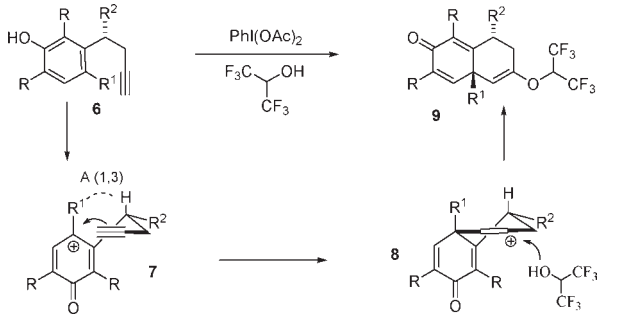
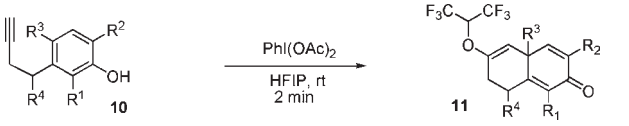
Scheme 1. Formation of Functionalized Decalin Cores



The strain created by the transient *sp*-hybridized carbonium ion in species **8** resulted in the intermediate being highly electrophilic and enabled it to react with the weakly reactive nucleophile HFIP,[8f] normally used as an inert solvent. This reaction produced the highly functionalized bicyclic system **9** containing a quaternary carbon center, a dienone functionality, and an enol-ether as a masked carbonyl. In order to determine the scope and limitations of this new transformation, substituents were introduced on the lateral chain, on the aromatic ring, and at the *para* position to produce the elaborated bicyclic cores **11**. In addition, the new process can efficiently afford the tricyclic core **11h** in excellent yield from a simple tetralone derivative **10h**, Table 1.

Table 1. Oxidative Bicyclization Process



entry	R^1	R^2	R^3	R^4	R^3/R^4	yield (%)
a	H	H	Me	H		43
b	Br	Br	Me	H		86
c	H	H	Me	Me	*trans*	50
d	H	Br	Me	Me	*trans*	70
e	Br	Br	Et	H		91
f	Br	Br	Bn	H		85
g	Br	Br	*n*-Pr	H		79
h	Br	Br	$H_2C-CH_2-CH_2$		*cis*	90

This bicyclization reaction produced vicinal fused carbocycles in very good yields. However, the oxidation of compounds containing open *ortho*-positions (entries **10a** and **10c**) occurred in lower yields compared to the dibromo analogs. This may be explained by considering that the first intermediate is a highly delocalized carbonium ion, which can be represented by **7** (Scheme 1, R = Br) as one of its resonance structures. We believe that because of the presence of the electron-withdrawing bromine atoms, **7** is the more dominant resonance form rather than the *ortho* mesomer. Consequently the cyclization occurs mainly at

the desired *para*-position when bromines are protecting the *ortho*-positions. An added advantage is that the bromine atoms could be used subsequently to introduce others substitutents, using transition metal chemistry. Furthermore, entries **10c** and **10d** (R^4 = Me) led exclusively to the *trans* diastereoisomer.[10] This stereoselectivity could be explained by the required minimal 1,3 allylic strain interactions between the two methyl groups during the transition state **7** (Scheme 1, R^2 = Me). These observations demonstrate the high diastereoselectivity of this new process and could have applications in asymmetric synthesis governed by the *meta* first stereogenic benzilic center. Such scaffolds are present in numeral natural products such as anominine[11] **12**, andrographolide[12] **13**, or the decalin core of azadirachtin[13] **14**, Figure 2.

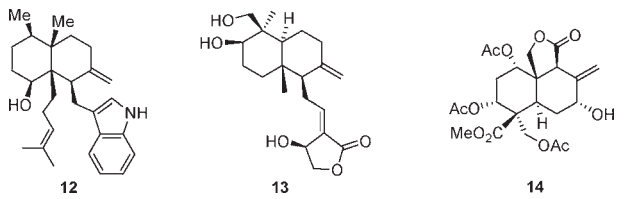
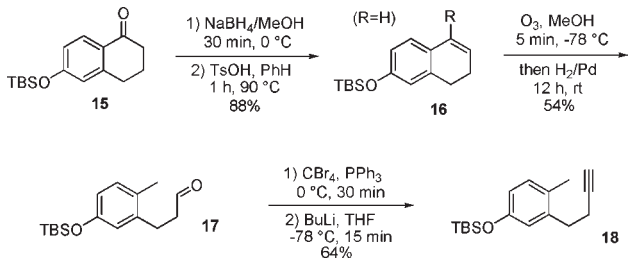


Figure 2. Natural products containing a decalin core.

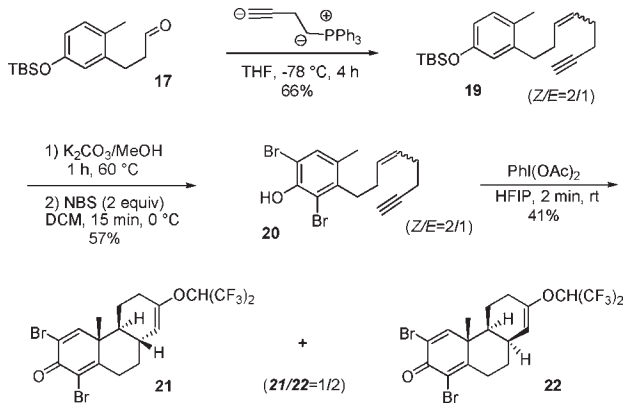
The required starting materials were obtained from tetralone **15**, via a reduction/elimination sequence[14] leading to **16** followed by ozonolysis and reductive treatment with H_2/Pd to provide aldehyde **17** in 54% overall yield. This substrate was further easily transformed into product **18** using a Corey–Fuchs strategy,[15] Scheme 2.

Scheme 2. Formation of Starting Materials



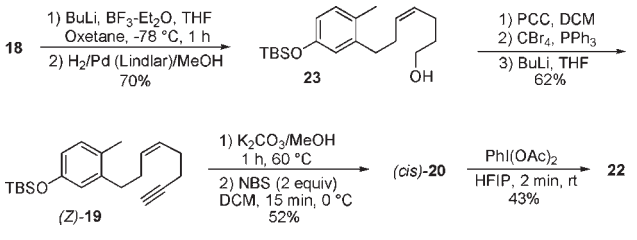
We were also interested in the possible extension of this process to the formation of tricyclic systems as well as in the diastereoselectivity of the cyclization with respect to the configuration of the central double bond in compound **20**. A Wittig reaction transformed aldehyde **17** into an inseparable mixture of *cis* and *trans* alkenes **19** in a 2:1 ratio in favor of the (*Z*)-isomer. The mixture was further transformed in two steps into a diastereoisomeric mixture of phenols **20**. The same umpolung activation led to the desired tricyclic systems **21** and **22** in 41% yield.[16] The cyclization reaction occurred with total stereocontrol in agreement with the configuration of the starting olefin (*Z* or *E*), since a 2:1 mixture of diastereomers[10] was obtained. It should be stressed that compound **21** represents the main core of cassaic acid **5**, Scheme 3.

Scheme 3. Oxidative Tricyclization Process



To verify the high diastereoselectivity of this process, *cis*-**20** was efficiently synthesized by a Lindlar reduction of an internal triple bond. The requisite alkyne was prepared via oxetane ring opening by the lithium salt of **18** (made directly from the dibromoalkene precursor) and then further transformed into the *cis* compound **19** via a Corey–Fuchs reaction in 62% overall yield from compound **23**. The oxidation of *cis*-**20** led exclusively to the tricyclic core **22** in 43% yield,[10] Scheme 4.

Scheme 4. Diastereoselective Tricyclization Process



In summary, an unprecedented oxidative polycyclization process has been developed that enables rapid access to bicyclic and tricyclic systems present in several natural

(10) The stereoselectivity was verified and attributed by ^{1}H NMR and ^{1}H NMR NOE.

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(15) Synthetic details are provided as Supporting Information.

(16) The two diastereomers were separated by chromatography at this point.

products, from inexpensive phenol derivatives. This method is an efficient means of diastereoselectively introducing several stereogenic centers in one step, with total stereocontrol, governed by 1,3 allylic strain interactions and by the configuration of the side chain double bonds. Ongoing investigations of this process and potential applications will be disclosed in due course.

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Supporting Information Available. Experimental procedures and spectral data for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.