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A Chemoenzymatic Synthesis of the *cis*-Decalin Core Associated with the Novel Anti-Mitotic Agent Phomopsidin: Some Observations Concerning a High-Pressure-Promoted Diels–Alder Cycloaddition Reaction of (1*S*,2*R*)-3-Methyl-*cis*-1,2-dihydrocatechol and the Anionic Oxy–Cope Rearrangement of Compounds Derived from the Adduct*

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The enantiomerically pure and enzymatically derived *cis*-1,2-dihydrocatechol **2** engages in a diastereofacially selective Diels–Alder cycloaddition reaction with commercially available lactone **3** at 19 kbar to afford adduct **4**, which is readily elaborated to the diene-ol **13**. Treatment of this last compound with KH/18[crown]-6 resulted in successive anionic oxy-Cope and 1,2-Wittig rearrangements to afford acyloin **14** embodying the *cis*-decalin core associated with the natural product phomopsidin (**1**). Compound **16** also engages in an anionic oxy-Cope rearrangement reaction to give, depending on the molar equivalents of base used, either the *cis*-decalin **17** or the hexahydroindene **18**. The structure of compound **18** has been established by single-crystal X-ray diffraction analysis.

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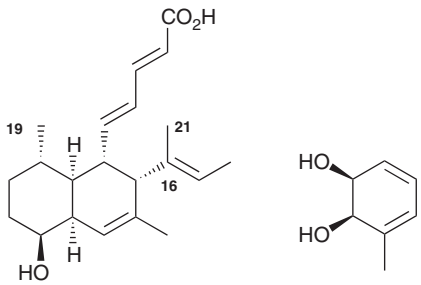
In 1997 Kobayashi and coworkers first reported on a *Phomopsis* sp. (strain TUF95F47) fungus collected from a fallen mangrove branch found on the bottom of a coral reef in Pohnpei, Micronesia.[1] They observed that filtered samples from the cultured broth of this fungus induced deformations of mycelia in germinated conidia of *Pyricularia oryzae* P-2b thus prompting further assay and isolation work.[1,2] As a result the *cis*-decalin **1** (Scheme 1), named phomopsidin, was obtained and identified as the biologically active material. Follow-up studies revealed that phomopsidin exhibits an IC_{50} value of 5.7 μM in a porcine brain microtubule assembly assay and compares well, therefore, with the performance of two prominent and potent anti-mitotic agents, namely rhizoxin (4 μM) and colchicine (10 μM), under the same conditions. Interestingly, the 16*Z*-isomer of phomopsidin is also a natural product (MK8383),[3] isolated from a terrestrial *Phoma* sp., and displays similar anti-microtubule activity (IC_{50} 8.0 μM).[1,2] The constitution and relative stereochemistry of phomopsidin (**1**) follows from extensive spectroscopic studies while the absolute configuration was determined by the exciton chirality method.[2,4]

Since phomopsidin has an unusual structure for a compound that exhibits colchicine-type anti-mitotic activity it clearly warrants further study, especially in terms of the development of a total synthesis that would deliver analogues of value in elucidating the key structural elements responsible for its tubulin-binding properties. On this basis, and because of our ongoing interest in developing methods for the enantioselective preparation of *cis*-decalins via anionic oxy-Cope rearrangement (AOCR) of appropriately functionalized and enantiomerically pure 2-vinylbicyclo[2.2.2]octen-2-ols,[5] we now report on the rapid construction of the carbobicyclic (*cis*-decalin) core of phomopsidin (**1**) from the *cis*-1,2-dihydrocatechol **2** (Scheme 1). Starting material **2** can be obtained on a large scale and in an enantiopure



1 **2**

Scheme 1.

* Dedicated to our colleague Professor Lew Mander on the occasion of his 65th birthday and in recognition of his manifold contributions to the discipline of organic synthesis.

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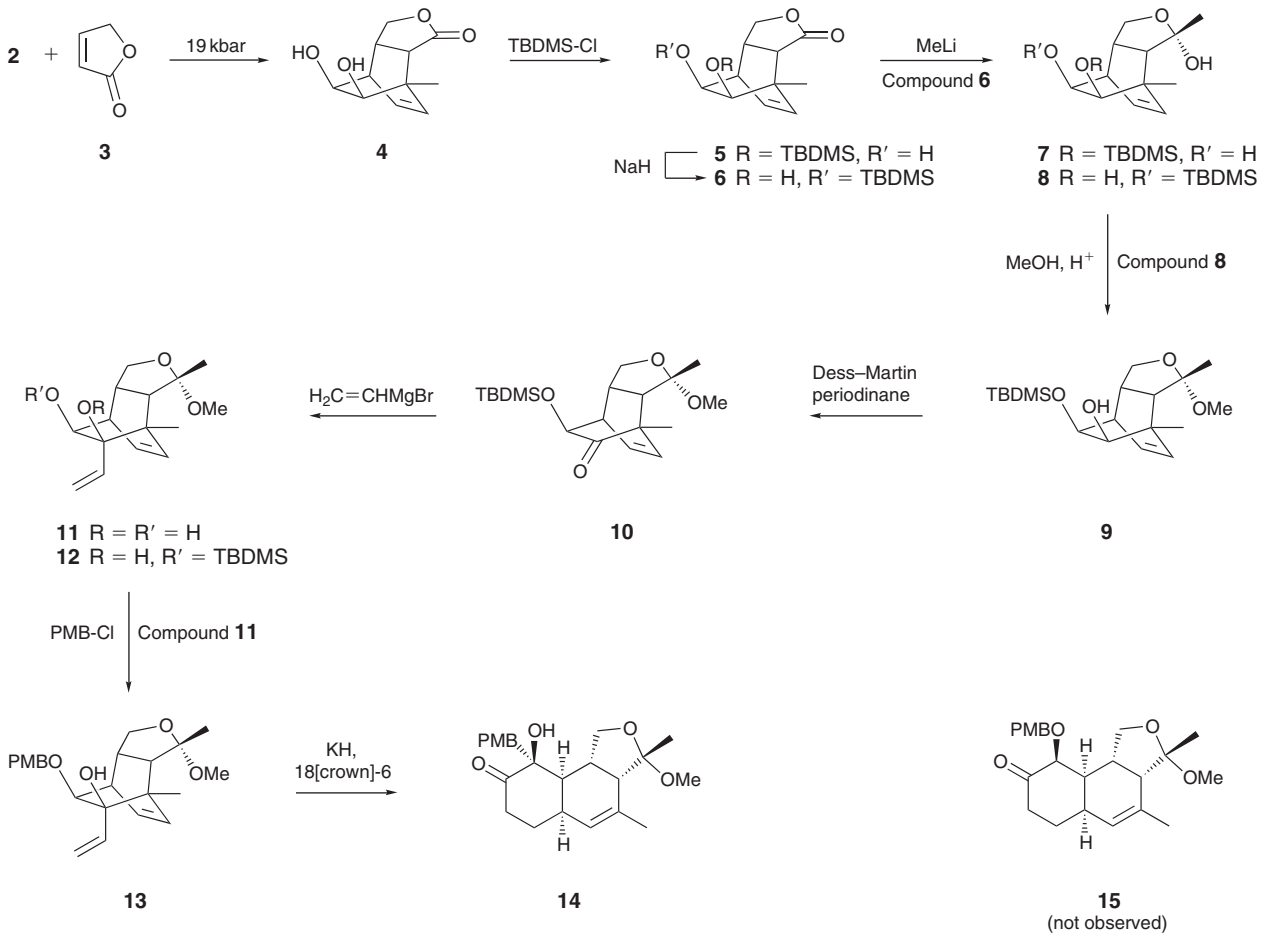
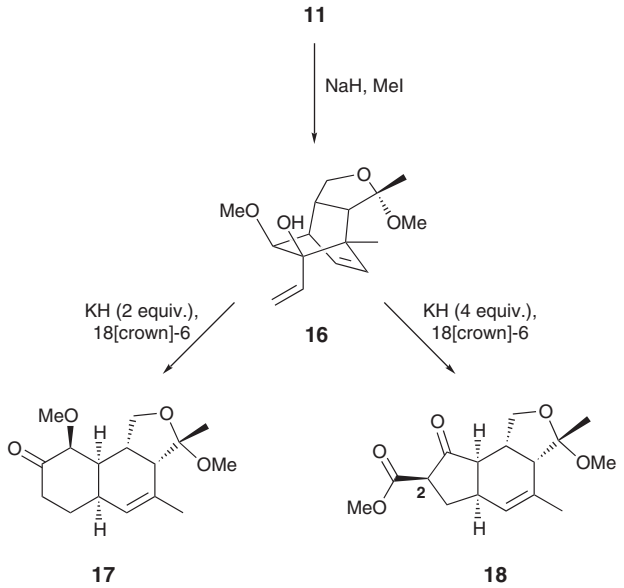


Scheme 2.

form through the whole-cell biotransformation of toluene using the genetically engineered micro-organism *E. coli* JM109(pDTG601) that over-expresses the responsible enzyme, namely toluene dioxygenase (TDO).[6] The present work serves to further highlight the potential of compound **2** as a starting material in natural products synthesis[7] and its capacity to participate in facially selective Diels–Alder cycloaddition reactions with various dienophiles at high pressure.[8] The novel base-promoted rearrangements of some of the 2-vinylbicyclo[2.2.2]octen-2-ols derived from the products of such Diels–Alder reactions is another noteworthy feature of the work presented here.

The reaction sequence leading to a 2-vinylbicyclo[2.2.2]-octen-2-ol capable of engaging in the required AOCR is shown in Scheme 2. Thus, in the opening stages, reaction of a dichloromethane solution of an approximately 1 : 2 mixture of compounds **2** and **3** at 19 kbar for 24 h afforded the *syn*-Diels–Alder adduct **4** (mp 186–187°C, 56% based on **2**) as the major product of reaction. Only 9% of the corresponding *anti*-adduct was isolated. The selective formation of compound **4**, the structure of which was confirmed by a single-crystal X-ray diffraction analysis that will be detailed elsewhere,[8*b*] is attributed to a stabilizing interaction between the C—O bonds within diene **2** and the π*-orbital of dienophile **3** at the transition state for the relevant Diels–Alder process.[9,10] Selective mono-protection of the diol **4** as the corresponding *tert*-butyldimethylsilyl (TBDMS) ether was achieved under standard conditions to give a chromatographically separable mixture of the undesired mono-ether **5** (22%) and the desired isomer **6** (62%). The assigned structures follow from an X-ray crystallographic study (see below) and the selective formation of compound **6** is presumably the result of a kinetic and/or thermodynamic preference for introduction of the bulky TBDMS protecting group at that hydroxy group, within **4**, remote from the bridgehead methyl group. Consistent with this notion, treatment of the minor regioisomer **5** with sodium hydride effected its equilibration to a 3 : 1 mixture favoring the required isomer **6**. Installation of what would become the C21 methyl group of phomopsidin **1** was achieved by treating compound **6** with six equivalents of methyllithium and in this manner a chromatographically separable mixture of the two isomeric lactols **7** (17%) and **8** (59%) was obtained. The structures of these products follow from nuclear Overhauser effect (nOe) difference measurements which establish that in each isomer the newly introduced methyl group is in the less hindered β-orientation. Protection of the labile lactol moiety within compound **8** was necessary at this point and could be achieved by its reaction with methanol at 0°C in the presence of catalytic amounts of camphorsulfonic acid. In this way the acetal **9** (84%) was obtained as a single diastereoisomer, the configuration of which follows from X-ray studies and is presumably determined through operation of the anomeric



Scheme 3.

effect. In anticipation of introducing the vinyl moiety necessary for the AOCR, alcohol **9** was oxidized to the corresponding ketone **10** (91%) using the Dess–Martin periodinane. Reaction of the latter compound with vinyl magnesium bromide then afforded a chromatographically separable mixture of the desired vinyl alcohol **11** (89%) and traces (<5%) of the mono-ether **12**. The facial selectivity of the nucleophilic addition process leading to compound **11** is dictated by the bulky TBDMSO moiety adjacent to the ketone carbonyl unit within substrate **10** and leads to the stereochemistry required for operation of the pivotal AOCR process. However, before examining this step, diol **11** was first converted into the corresponding *p*-methoxybenzyl (PMB) ether **13** (97%) under standard conditions. In keeping with expectations, the latter compound engaged in a smooth reaction on exposure to two molar equivalents of KH in the presence of 18[crown]-6 although the product of reaction proved to be the acyloin **14** (50%) and not the anticipated ether **15**. The structure of compound **14** follows from, among other things, extensive nOe difference, HMBC, and HMQC experiments. Presumably, compound **14** arises through initial operation of the expected AOCR process but the resulting enolate then engages in an in situ enolate equilibrium followed by a [1,2]-Wittig rearrangement to give, after protic work-up, the observed product. The operation of related sequences has been noted by Paquette during the course of his work on the synthesis of taxoids.[11]

In seeking to exploit the above-mentioned and unanticipated [1,2]-Wittig rearrangement for the purposes of introducing the C19 methyl group of phomopsidin (**1**), the diol **11** was converted (Scheme 3) into the corresponding mono-*O*-methyl ether **16** (76%) by standard methods. However, in contrast to the situation detailed above, subjection of compound **16** to the same rearrangement conditions as applied to substrate **13** afforded only the AOCR product **17** (45%). Thus, no material arising from a subsequent [1,2]-Wittig

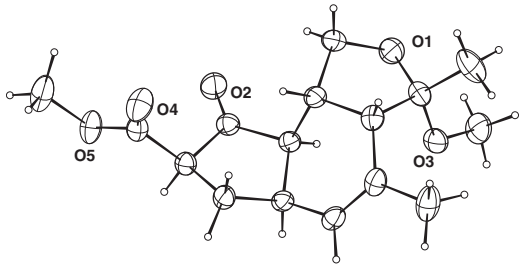


Fig. 1. A molecule of compound **18** derived from a single-crystal X-ray diffraction analysis.

rearrangement process, which would have served to introduce the C19 methyl group, was observed. In an effort to promote the tandem AOCR/[1,2]-Wittig rearrangement sequence substrate **16** was treated with four equivalents of each of KH and 18[crown]-6. However, under such conditions an interconverting mixture of the tetrahydroindanone **18** and its C2 epimer (43% combined yield) was observed and the structure of the former product was established by single-crystal X-ray diffraction analysis (Fig. 1).[12] The origins of this material are not entirely clear at this stage but a Favorskii-type ring-contraction process[13] operating on a species such as the enolate derived from ketone **17** might be involved. Furthermore, the anion arising from methoxide ion-promoted cleavage of the intermediate cyclopropanone could react with adventitious dioxygen as part of a process leading to introduction of the ketone carbonyl moiety observed in product **18** and its C2 epimer. Alternately, the more highly substituted enolate derived from compound **17** could be trapped with dioxygen providing, after protonation, a peroxyhemi-acetal. This last species could then react, via initial nucleophilic addition of methoxide ion to the carbonyl moiety, to give a ring-cleaved diester which subsequently engages in a Dieckmann cyclization[14] thus affording compound **18**.

The reaction sequences outlined above provide an efficient means for the construction, in enantiomerically pure form, of the pivotal *cis*-decalin moiety associated with phomopsidin (**1**). Work aimed at exploiting such results in developing a total synthesis of this fascinating natural product and certain analogues will be reported in due course.

Note added in proof (21 May 2004): The first total synthesis of (+)-phomopsidin has been reported. T. Suzuki, K. Usui, Y. Miyake, M. Namikoshi, M. Nakada, *Org. Lett.* **2004**, *6*, 553. doi:10.1021/OL036338Q

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