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Studies toward the synthesis of phomactin A. An approach to the macrocyclic core

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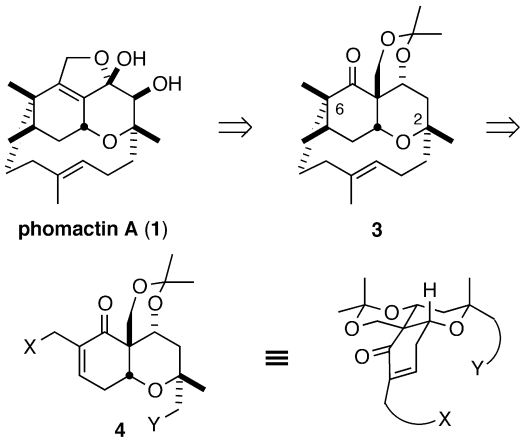
Abstract—An approach to the macrocyclic core of phomactin A is described. Central to this strategy is the use of a cis-fused oxadecalin intermediate, prepared using the dihydropyrone Diels–Alder reaction. The conformational bias inherent to this system is then used to facilitate macrocycle formation via an intramolecular B-alkyl Suzuki coupling.

The phomactins are a group of naturally occurring diterpenes showing specific PAF antagonist activity.[1] Phomactin A (**1**, Scheme 1),[2] the most complex member of this class, has generated considerable attention from the organic chemistry community due to its unique molecular architecture, and the challenge inherent to its synthesis.[3]

Previous efforts from our laboratory have resulted in the preparation of the reduced furanochroman core of this natural product.[4] Based on these findings, we elaborated a strategy for the synthesis of phomactin A whereby the oxadecalin core would be generated at an early stage of the synthesis, with subsequent macrocyclization via formation of the trisubstituted olefin. Generation of the dihydrofuran would then be achieved in the final stages.[5]



Scheme 1.

An obvious concern with this approach lies with the proximity of reactive functionality (e.g., X and Y in **4**) which must span the fused ring system before bond formation can occur. While the feasibility of such a closure had been demonstrated in more fully saturated decalin derivatives,[6] the planarity imposed by the enone moiety (**4**) is potentially problematic. We anticipated, however, that the success of such a closure would be favorably influenced by the inherent conformational bias of a cyclization precursor such as **4**, in which the oxadecalin ring system is cis-fused. Upon cyclization, subsequent introduction of the C6 and C7 methyl groups (**3**) is expected to occur with high levels of stereoselectivity as the α-face of the oxadecalin unit is now shielded by the macrocyclic ring.

In order to evaluate the potential of such substrates to facilitate macrocyclization, we set our sights on the synthesis of a simplified tricyclic macrocyle **5**. Preparation of this compound was envisaged via the intermediacy of bicyclic enone **6**, which in turn could be prepared from an oxadecalin derivative **7** (Scheme 2).

Entry into the oxadecalin system (**7**) was achieved using the dihydropyrone Diels–Alder chemistry previously developed in our laboratory.[7] This transformation accommodates direct incorporation of the requisite C2 vinyl substituent via cycloaddition of dihydropyrone **8**[8]

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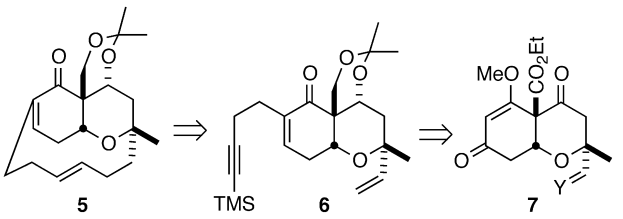
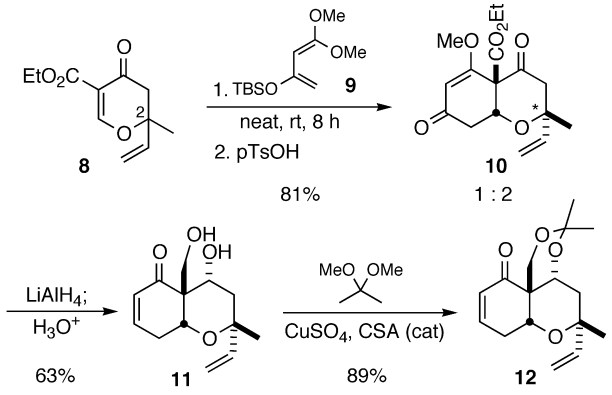


Scheme 2.

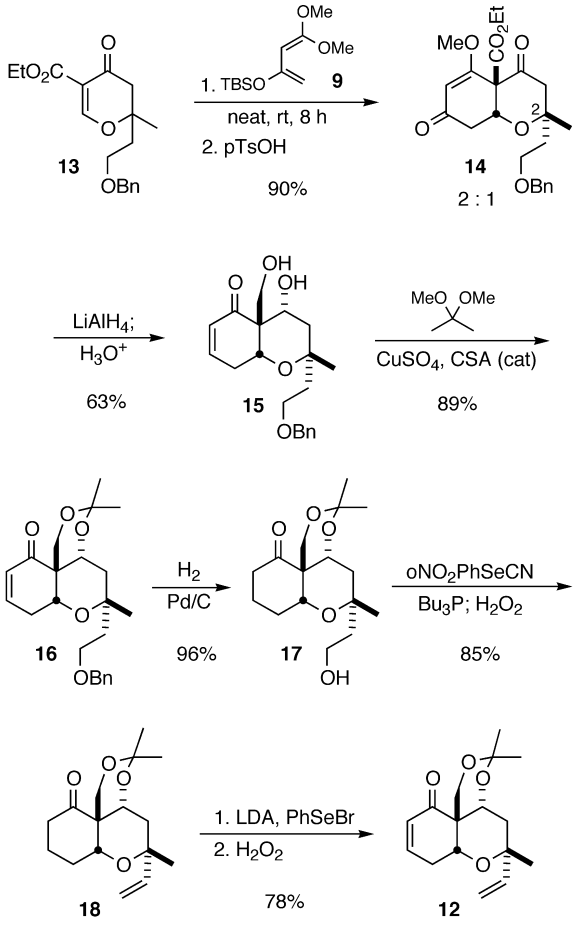
with the highly oxygenated diene **9** (Scheme 3). Subsequent hydrolysis of the intermediate silyl enol ether then gave oxadecalin **10** as a 1:2 mixture of diastereomers (*). Here, differential substitution at C2 of the dihydropyrone does not effectively distinguish the two faces of this dienophile. Reduction of oxadecalone **10** with $LiAlH_4$, followed by an aqueous acidic workup afforded enone **11**, accompanied by small quantities of the corresponding tricyclic ether.[9] Protection of the diol then provided enone **12**.

Alternatively, synthesis of enone **12** could be achieved by a route in which the C2 vinyl function was incorporated after formation of the oxadecalin core. Thus, Diels–Alder reaction of dihydropyrone **13** afforded, upon hydrolysis, oxadecalin **14** as a 2:1 mixture of diastereomers, now favoring the desired stereoisomer (Scheme 4). Incorporation of the hydroxyethyl side chain at C2 of the dihydropyrone may ultimately provide a means to impart stereoselectivity to this transformation by serving as an itinerant tether in an intramolecular cycloaddition process.

Oxadecalin **14** was converted to enone **16** by a reduction/protection sequence analogous to that described above (cf. Scheme 3). Incorporation of the C2 vinyl function was then initiated by cleavage of the benzyl protecting group. Under conditions of palladium catalyzed hydrogenation, deprotection of the primary alcohol was accompanied by reduction of the enone leading to formation of ketone **17**.[10] Elimination of the primary alcohol was effected under Grieco–Sharpless conditions[11] providing ketone **18**, with subsequent reintroduction of the C6/C7 double bond giving enone **12**. Though slightly longer, this route proceeds in an overall yield comparable to that first described.



Scheme 3.

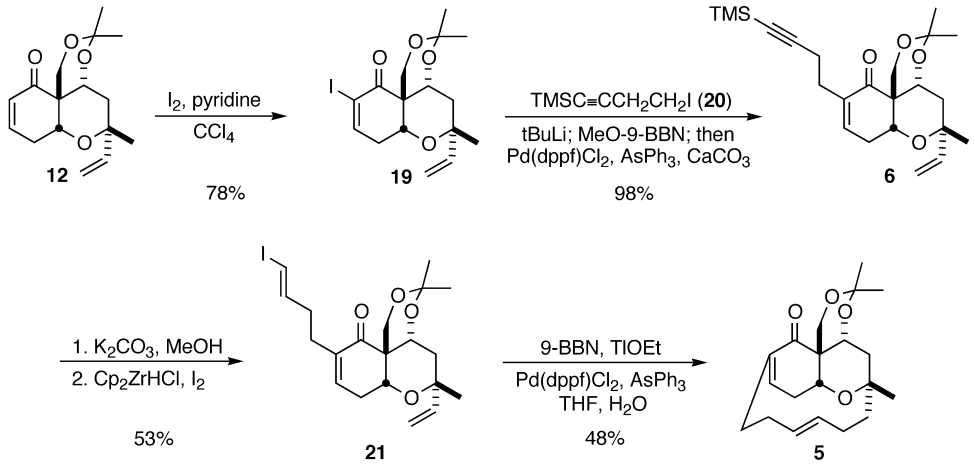


Scheme 4.

With enone **12** in hand, further functionalization of the oxadecalin core required introduction of the C6 side chain (Scheme 5). As such, halogenation of enone **12** provided vinyl iodide **19**, which was subjected to a B-alkyl Suzuki coupling[12] with the organoboron reagent derived from alkyne **20** to give the trisubstituted enone **6**.

From here, macrocyclization substrate **21** was generated by manipulation of the terminal alkyne **6** by deprotection, followed by a hydrozirconation/iodination sequence. Macrocyclization was then effected via Suzuki coupling[13] under high dilution conditions to give the desired product **5** in a respectable 48% yield. While at first glance, cyclization of a substrate (**21**) having an sp^2 hybridized center at C6 seems contrary to a successful macrocyclization, the cis-fused ring system orients the substrate such that there is little strain associated with ring formation.

In conclusion, we have demonstrated feasibility of generating the 12-membered macrocycle found in phomactin A using substrates of type **6** that contain unsaturation at C5–C7. The cis ring fusion of the preformed oxadecalin core is central to this strategy, helping to orient reactive functionality and facilitate macrocyclization. Ongoing efforts in our laboratories are aimed at the total synthesis of phomactin A. These results will be reported in due course.



Scheme 5.

Acknowledgments

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Supplementary data

Experimental procedures and characterization data for compound **5** and all key intermediates. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.122.

References and notes

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5. This approach stands in contrast to those generally set forth by other researchers in which formation of the pyrone unit is effected after macrocycle formation. Exceptions are found in the work of Hsung (Ref. 3j) and Halcomb (Ref. 3m). In the former case, pyrone and macrocycle are formed concurrently. In the latter, macrocyclization is effected with the oxadecalin system in place, albeit in modest yield.
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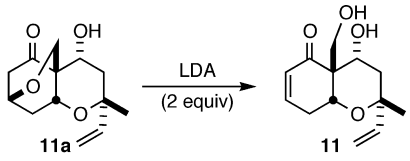
9. Tricyclic ether **11a** is formed via internal Michael addition of the primary alcohol. Regeneration of enone **11** is readily achieved upon treatment of the cyclic ether with an excess of strong base, for example:



10. The use of alternative protecting groups for the primary alcohol was briefly explored. TBDMS, TBDPS, and PMB ethers were found to be incompatible with the reductive conditions used to generate enones of type **15**.
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