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Total Synthesis of (+)-Phomopsolide C by Ring-Size Selective Ring-Closing Metathesis/Cross-Metathesis

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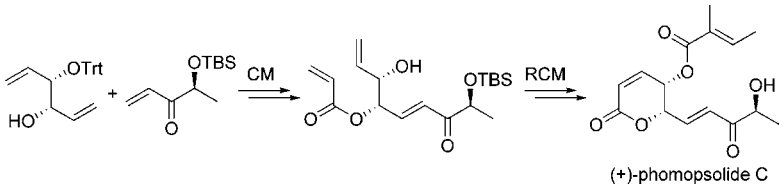
ABSTRACT



A new strategy for the synthesis of chiral 6-substituted 5,6-dihydro-5-hydroxypyran-2-ones by ring-size selective ring-closing metathesis (RCM) and its application to a short total synthesis of (+)-phomopsolide C are described. The key bond-forming reactions in this approach are a chemoselective cross-metathesis (CM) and RCM.

Dutch elm disease can destroy a healthy 100-year-old American elm in as little as two weeks.[1] The fungus responsible for this disease would be quite innocuous, save for its association with the elm bark beetle (Scolytid beetle). The prevention of Dutch elm disease by chemical deterrence of this beetle is therefore of current interest.

The phomopsolides[2] are a new class of natural products possessing an effective antiboring/antifeeding activity against the elm bark beetle (Figure 1). Phomopsolide C is part of a series of related 6-substituted 5,6-dihydro-5-hydroxypyran-2-ones, which were first isolated from fungi found in the bark of the Pacific yew in 1997 by Stierle.[3] In addition to phomopsolides, there exist other natural products possessing a similarly substituted 5,6-dihydro-5-hydroxypyran-2-one core, an example being (+)-diplopyrone (Figure 1).[4]

To date, however, only one synthesis of (+)-phomopsolide C has been reported.[5]

We describe herein the total synthesis of phomopsolide C, the key steps of which involve a regio- and chemoselective

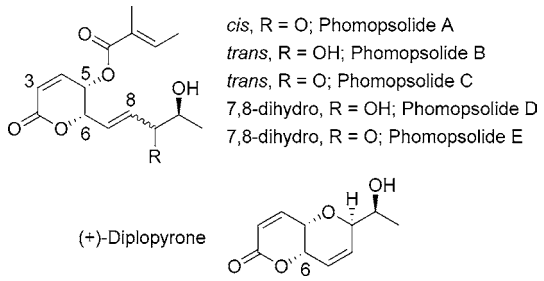


Figure 1. 6-substituted 5,6-dihydro-5-hydroxypyran-2-ones.

CM and a ring-size selective RCM.[6] Our approach is outlined in Scheme 1. To allow for flexibility in our synthetic plan, we envisaged two pathways to phomopsolide C. Pathway A was based on a tandem RCM/CM of **3** and **4**. Selectivity in this conversion would require RCM to occur first, giving exclusively the six-membered ring with only one pendant double bond available for CM.

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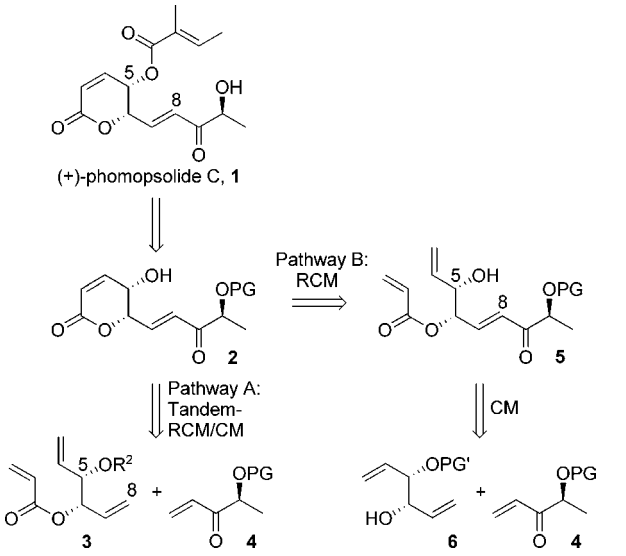
Scheme 1

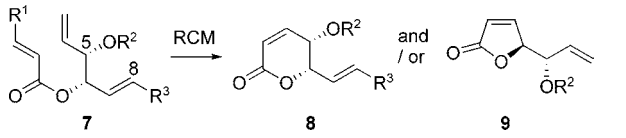


In pathway B, a regioselective CM provides an intermediate that can be converted to the 8-substituted RCM precursor **5** by deprotection and esterification. It was envisaged that the selectivety in the CM of **6** and **4** could be controlled either by chelating effects or by the steric hindrance of the protecting group PG′.[7] Following the synthesis of intermediate **2** by either pathway A or B, esterification and deprotection would then give phomopsolide C.

The main challenge in this strategy is controlling the ring-size selectivity of RCM, because of the possibility of either forming the desired six- or the undesired five-membered ring. A number of examples where a six-membered ring has been formed selectively are known, e.g., natural (5′-oxoheptene-1′*E*,3′*E*-dienyl)-5,6-dihydro-2*H*-pyran-2-one,[8] (+)-strictifolione,[9] and spicigerolide[10] by using either the Grubbs catalyst I or II. These examples have two important structural differences to our precursor for RCM as given in pathway A: (1) no substitution in the C5 position and (2) a substituent in the C8 position (see Scheme 1). It has been demonstrated in related systems having no substitution in the C8 position that mixtures of five- and six-membered rings are obtained.[11] RCM of precursors with a protected hydroxy group at the C5 position and no substitution in postion C8 (e.g., (−)-muricatacin[12] and rollicosin[13]) result in the formation of the five-membered ring exclusively when using Grubbs catalyst II.

Bearing these results in mind, we first investigated reaction conditions for the exclusive formation of the six-membered ring **8** when starting from a 5-substituted precursor **7** which may or may not contain a substituent in the C8 position, according to our different retrosynthetic pathways. Our results are summarized in Table 1.

Table 1. Ring-Size Selectivity of RCM



entry	R^1	R^2	R^3	cat. 5 mol %	time (h)	ring size **8**/**9**[a]	conv[a] (%)
1	H	H	H	A[b]	96		5
2	H	H	H	B[c]	17	1/7	80
3	H	H	H	C[d]	96	<1/>99	60
4	H	H	H	D[e]	17	1/6.5	99
5	H	Mom	H	A	96	<1/>99	16
6	H	Mom	H	B	96	1/9	70
7	H	Mom	H	C	96		7
8	H	Mom	H	D	96	1/2.7	55
9	Me	H	H	B	17	<5/>95	75
10	Me	H	H	D	17	<5/>95	>95
11	Me	Mom	H	A−D	96		<5
12	H	H	COR[f]	D	6	>99/<1	>99

[a] Estimated from ^{1}H NMR of the crude reaction mixure. In each case, the remainder was the starting material. [b] Grubbs I: PhCH=$RuCl_2(PCy_3)_2$. [c] Grubbs II: PhCH=$RuCl_2(PCy_3)$(IHMes). [d] Hoveyda: *o*-isopropoxy-PhCH=$RuCl_2(PCy_3)$. [e] See Scheme 2. [f] See **5** (Scheme 1)

In the case where $R^1 = R^2 = R^3 = H$ (entries 1−4), the first-generation Grubbs and Hoveyda catalysts gave exclusively the five-membered ring, in agreement with previously reported studies.[12,13] Interestingly, though, the second-generation catalysts yielded appreciable amounts of **8**. We hypothesised that the double bond on which metathesis commenced governed the size selectivity of the RCM. For this reason, we investigated the use of the methoxymethylene protecting group (Mom) in order to pre-coordinate the catalyst at OR^2 (entries 5−8). We hoped that this would encourage reaction at the neighboring alkene, favoring six-membered ring formation. In most cases, the amount of **8** was increased appreciably. This is the first time that formation of a six-membered ring, for a system substituted at the C5 position but with no substitution at the C8 position, has been observed. We were also interested in the effect of incorporating an electron withdrawing enone at R^3 (entry 12). Gratifyingly, it was found that metathesis with this substrate led exclusively to the six-membered ring **8** in excellent yield.

We now had conditions for RCM that we hoped would give us the core of phomopsolide C. Our model studies indicated that the electron-withdrawing side chain of the natural product precursor **5** would control the reaction outcome, directing the metathesis to the sterically less hindered, more electron rich double bond of the allylic alcohol. This would give the six-membered ring **16** (Scheme 2).

The precursor for CM **12** was available in a few steps starting from commercial diethyl L-tartrate **10**. After protec-

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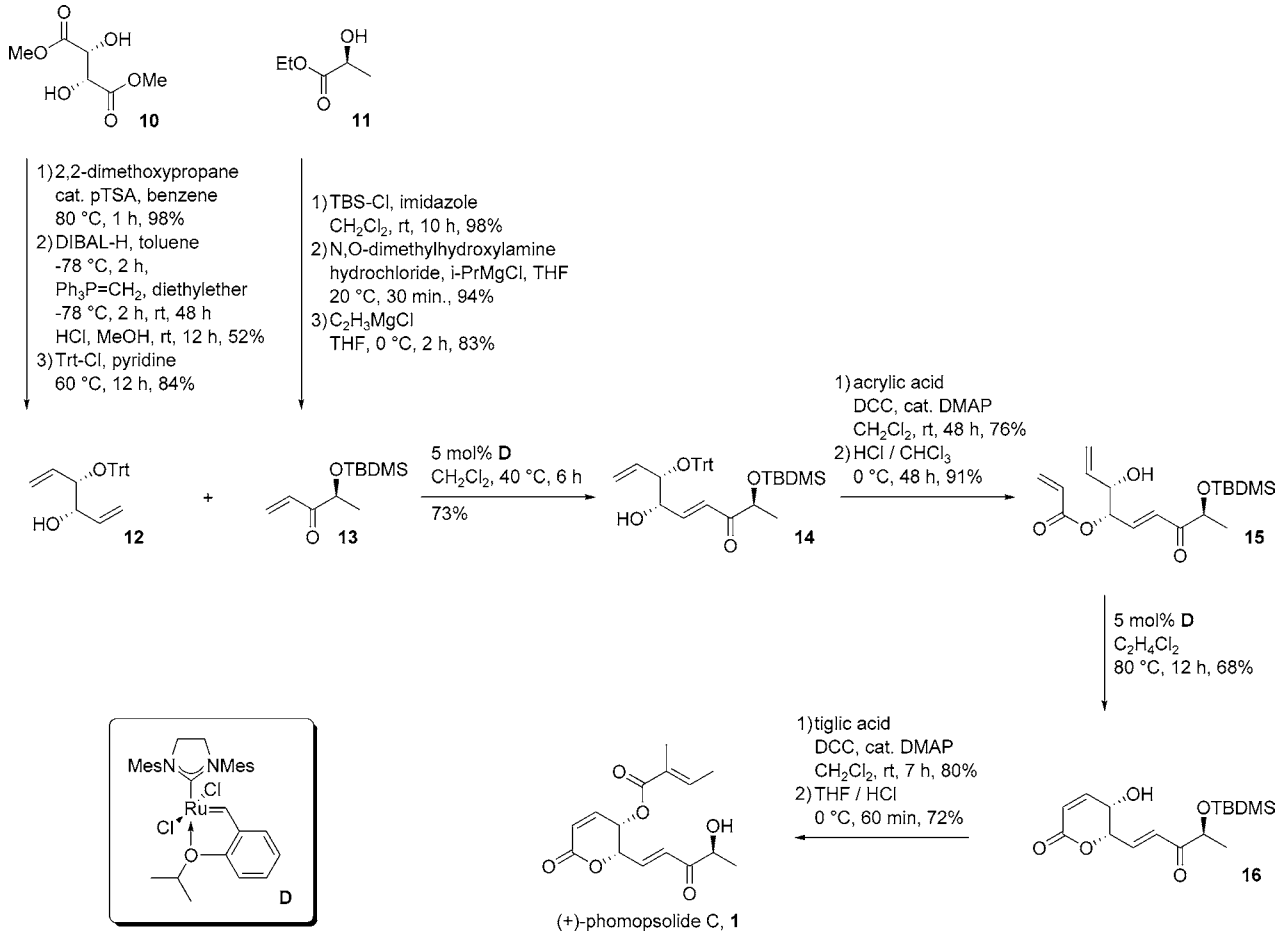
Scheme 2



tion of the 1,2-diol in **10** as a cyclic ketal,[14] subsequent ester reduction and double Wittig olefination[15] were conducted in one pot due to the instability of the intermediate aldehyde. Deprotection[16] leading to the C_2-symmetric dienediol and monotritylation of one of the hydroxy groups afforded diene **12** in 43% yield over five steps.

Starting with methyl *S*-(−)-lactate **11**, the coupling partner **13**[17] was synthesized by protection of the hydroxy functional group,[17] followed by Grignard reaction[18] of the Weinreb amide[19] in 68% overall yield.

The ruthenium-catalyzed cross metathesis of **12** and **13** occurred with exclusive formation of the desired regioisomer using catalyst D (Scheme 2), giving **14** in 73% yield, exclusively as the *trans* isomer, as well as the dimer of **12** in 24% yield. Recycling of the dimer by CM with **13** gave additional cross product **14**, increasing the yield to 89%. The chemoselectivity may result from steric hindrance by the bulky trityl group.[6] CM with an ester substituent as a chelating controlling feature instead of the trityl group led to a 4:1 mixture in favor of the desired regioisomer.

Acrylation and trityl removal of **14** gave the precursor for RCM **15**. Migration of the acryl group during the deprotection under either too acidic or basic conditions (i.e., during the workup process) was suppressed by using a saturated HCl solution in $CHCl_3$, and the deprotection succeeded under these conditions in good yield.

Using the optimized reaction conditions, RCM of **15** proceeded in complete conversion, although the isolated yield of **16** was 68%, suggesting partial decomposition during chromatography. Esterification with tiglic acid and subsequent deprotection then yielded phomopsolide C, the spectroscopic data of which was identical (IR, ^1H and ^{13}C NMR) to the literature.[5] Thus, a concise synthesis of (+)-phomopsolide C has been achieved in good overall yield.

This synthesis demonstrates the power of CM and RCM in skeletal C−C bond-forming. Selectivity in CM was obtained by tuning the relative steric environments of the double bonds. Furthermore, we have shown that we are able to control the size selectivity of the RCM by altering the electronic environment of double bonds. We are currently working on

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establishing control of the ring size in RCM with $R^3 = H$. We are also synthesising further natural products with related structures to expand the scope of this methodology.

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Supporting Information Available: Full experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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