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An Efficient, Modular Approach for the Synthesis of (+)-Strictifolione and a Related Natural Product

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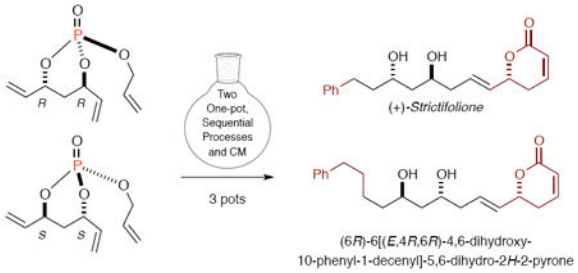
Abstract



An efficient, library amenable, “pot economical” total synthesis of (+)-strictifolione and the related natural product, (6*R*)-6[(*E*,4*R*,6*R*)-4,6-dihydroxy-10-phenyl-1-decenyl]-5,6-dihydro-2*H*-2-pyrone are reported. This modular approach takes advantage of two consecutive phosphate tether-mediated, one-pot, sequential protocols, followed by a final cross metathesis to deliver both antifungal natural products in a three-pot process from the respective enantiomeric (*R*,*R*)- and (*S*,*S*)-trienes with minimal purification. A salient feature of this route is that additional protecting groups are not required as a result of the orthogonal protecting- and leaving-group properties innate to phosphate triesters.

(+)-Strictifolione (**1**) was isolated and structurally characterized by Aimi and coworkers from the stem bark of *Cryptocaria stritifolia*, a member of the family Lauraceae that grows in the rainforests of west Kalimantan, Indonesia.[1] The structure of **1**, including the absolute configuration of the stereogenic centers, was also confirmed by Aimi and coworkers after accomplishing its first total synthesis, employing (*S*)-malic acid and (*S*)-glycidol in 18 steps.[2] A related compound (6*R*)-6[(*E*,4*R*,6*R*)-4,6-dihydroxy-10-phenyl-1-decenyl]-5,6-dihydro-2*H*-2-pyrone (**2**), was isolated by Hostettmann and coworkers in 2001 from the leaves and bark of *Ravensara crassifolia*, which is an endemic genus in Madagascar, along with another structurally similar compound (6*S*)-5,6-dihydro-6-[(2*R*)-2-hydroxy-6-phenylhexyl]-2*H*-pyran-2-one (**3**).[3] Krishna and coworkers accomplished the first total synthesis of **2** by iterative use of Jacobsen’s hydrolytic kinetic resolution with a longest

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linear sequence (LLS) of 17 steps.[4] All three compounds (**1**–**3**) have been shown to possess antifungal activity[3].

Key structural features in **1** and **2** include, a Michael accepting 5,6-dihydro-α-pyrone moiety in the eastern subunit, a central 1,3-*anti* diol, and lipophilic substitution in the western subunit. It is generally believed that the unsaturated pyranone functional group can react with the nucleophilic warhead of a target enzyme, and thus attentuates its activity[5].

Among several synthetic methods for the construction of **1**,[6] notable streamlined efforts have recently been made. In 2003, Cossy and coworkers developed a concise and elegant synthetic pathway consisting of a longest linear sequence of 9-steps, starting from 3-phenyl-propionaldehyde, that utilized the dual use of enantioselective allyltitanation in conjunction with cross metathesis (CM).[6a] In 2010, Das and coworkers devised a comparable pathway with an LLS of 10-steps using Sharpless kinetic resolution and olefin cross-metathesis.[6g] In 2010, She and coworkers[6h] developed an efficient route employing a one-pot, double allylboration comprised of a pathway with a 7-step LLS using an Ipc_2BH-derived boryl-substituted allylborane, derived in two steps from propargyl bromide,[7] 3-butenal, derived in two steps from glyoxal, and a ketal- protected aldehyde.[8] Despite significant attributes of these syntheses,[6] the development of simple, efficient, scalable strategies that are library amenable for installation of key diversity elements in a divergent manner, is notably absent in the literature. In this regard, multi-reaction one-pot protocols have emerged as powerful synthetic strategies to achieve total/intermediate/analog synthesis, due to the ability to form multiple bonds and stereocenters, while invoking step, atom,[9,] green and pot economy,[10] thus saving time and resources. Herein, we disclose an efficient, modular approach for the total synthesis of both naturally occurring antifungal compounds **1** and **2**, highlighting the utility of two consecutive phosphate tether-mediated one-pot, sequential protocols, namely a one-pot, sequential, RCM/CM/chemo-selective hydrogenation protocol,[11] followed by a one-pot, sequential reductive allylic transposition/tether removal method and final CM with overall minimal purification. A critical feature of this strategy is modular installation of the western and eastern 5,6-dihydro-α-pyrone subunits via two facile CM reactions, thus opening future opportunities in library development.

Retrosynthetic analysis reveals that both natural products **1** and **2** can be readily derived from key diol-containing intermediates **4** and **9**, respectively, via CM with vinyl lactone **5** (Scheme 1). The pivotal diol **4** in turn can be synthesized from phosphate **6**, employing a regioselective Pd(0)-catalyzed reductive allylic transposition and phosphate tether removal under reductive conditions. The phenyl substituted bicyclic phosphate **6** can be achieved from triene (*R*,*R*)-**7** via a one-pot, sequential RCM/CM/"H_2" with *cis*-stilbene as the CM partner, followed by chemoselective hydrogenation employing diimide reduction conditions with *o*-nitrobenzenesulfonyl hydrazine (*o*-NBSH).[11,12] Triene (*R*,*R*)-**7** is readily prepared in 2-steps via sequential tripodal coupling of the C_2-symmetric *anti*-diene diol (*R*,*R*)-**8**[13] and allyl alcohol with $POCl_3$ or in one step utilizing phosphoramidite chemistry.[13c] Similarly, phosphate **10** can be synthesized following the same sequence of RCM/CM/"H_2" starting with enantiomeric triene (*S*,*S*)-**7** which is obtained from 1,3-*anti*-diene diol (*S*,*S*)-**8** and employing phenyl-but-3-ene as the cross coupling partner. Vinyl lactone **5** can be readily-

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derived (5 LLS) from diene **11** and TIPS-protected propargyl aldehyde **12** using Jacobsen hetero Diels-Alder chemistry[14].

Following the previously reported optimized conditions for RCM/CM/"H_2",[11] triene (*R*,*R*)-**7** was first subjected to RCM reaction with the second generation Hoveyda–Grubbs catalyst (HG-II) **14**[15] (6 mol %) in CH_2Cl_2 (0.007 M), and upon completion, solvent was evaporated and the cross metathesis partner *cis*-stilbene in DCE was introduced with continued heating for 2 h (Scehme 2). It should be noted that cross metathesis with styrene was not productive in comparison to *cis*-stilbene due to deleterious homodimerization of styrene, a type I olefin.[16] Subsequent chemo-selective diimide reduction by simple addition of *o*-NBSH into the reaction mixture provided the phenylsubstituted phosphate **6** in 52% overall yield, representing an 81% average yield/reaction in the one-pot, sequential protocol.

We next developed a one-pot Pd-catalyzed, reductive allylic transposition[17] and tether removal protocol. In this regard, allylic transposition [$Pd(OAc)_2$, $HCOONH_4$, PPh_3][18] on phosphate **6** generated the requisite terminal olefin that was followed by *in situ* tether removal by consecutive addition of dimethyl sulfate (Me_2SO_4) (reflux 3 h) and $LiAlH_4$ (0 °C), followed by facile Feiser workup,[19] to furnish diol **4** as a single diastereomer in 65% overall yield (87% average yield/reaction)[20].

With the advanced fragment **4** in hand, the total synthesis of **1** was accomplished via CM of diol alkene **4** and the readily-prepared vinyl lactone **5**, *vide infra* (Scheme 2), in the presence of the HG-II catalyst in CH_2Cl_2 in 77% yield and with excellent *E*-selectivity. The spectral data (H^1, C^{13}, IR, HRMS) and optical rotation of **1** were in complete agreement with those reported in the literature.[2] Overall, the three-pot process afforded **1** in 26% yield from triene (*R*,*R*)-**7**.

Since diol **4** was obtained in high purity without chromatography, the protocol outlined in Scheme 2 was further optimized to employ simple cannulation after the aforementioned Feiser workup (i.e. before CM). Thus, after reduction with $LiAlH_4$, and Fieser workup, the resulting THF solution was transfered via cannula, concentrated and subjected to CM with vinyl lactone **5** in CH_2Cl_2 to afford **1** in 26% overall yield (72% average yield/reaction, Scheme 3).

The aforementioned vinyl lactone **5** was readily synthesized utilizing Jacobsen hetero-Diels-Alder chemistry as outlined in Scheme 4. The isopropyl acetal alkyne **17** was obtained following the Jacobsen protocol employing hetero Diels-Alder catalyst **13**.[14] Subsequent Lindlar hydrogenation with Pd-$CaCO_3$, in the presence of freshly distilled quinoline in EtOAc under H_2, afforded olefin **18** in 80% yield on gram-scale (Scheme 4). The required vinyl lactone **5** was obtained in good yield via direct oxidation of the isopropyl acetal olefin **18** with PCC in CH_2Cl_2 in the presence of AcOH.

We next highlighted this approach in the synthesis of the natural product (6*R*)-6[(*E*,4*R*, 6*R*)-4,6-dihydroxy-10-phenyl-1-decenyl]-5,6-dihydro-2*H*-2-pyrone (**2**) using the enantiomeric triene (*S*,*S*)-**7** and CM partners **19** and **5** as outlined in Scheme 5. The synthesis of **2** was achieved following a similar sequence starting with the enantiomericlly pure diene

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diol (*S*,*S*)-**8**. After completing the RCM reaction with triene (*S*,*S*)-**7**, CM was carried out with phenyl-but-1-ene (**19**) with subsequent diimide reduction affording phosphate **10** in 54% overall yield in the one-pot, three reaction protocol. Subsequent Pd-catalyzed reductive allylic transposition [$Pd(OAc)_2$, HCOOH, PPh_3 and Cs_2CO_3], followed by tether removal utilizing consecutive additions of Me_2SO_4, and $LiAlH_4$, and final Feiser workup[19] furnished diol **9**, which was transferred via cannula into a new flask and subjected to CM in CH_2Cl_2 with vinyl lactone **5** to furnish the natural product **2** in 28% overall yield (73% average yield/reaction) and excellent *E*-selectivity. Overall, the three-pot process afforded **2** in 15% yield from triene (*S*,*S*)-**8**.

In conclusion, we have reported synthetic routes to the antifungal natural products **1** and **2** employing a three-pot process from the readily-prepared trienes (*R*,*R*)-**7** and (*S*,*S*)-**7**, respectively. Taken collectively, the orthogonal protecting- and leaving group ability of the phosphate triester tether streamlined the synthesis of **1** and **2**. We anticipate that our modular approach can be further exploited for the synthesis of an array of analogues to explore SAR within **1** and **2**.

Supplementary Material

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Acknowledgments

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20. It should be noted that use of Me_2SO_4 facilitated the methylation in the presence of Pd which allowed us to operate using a one-pot sequence, whereas previous use of TMS-diazomethane did not.

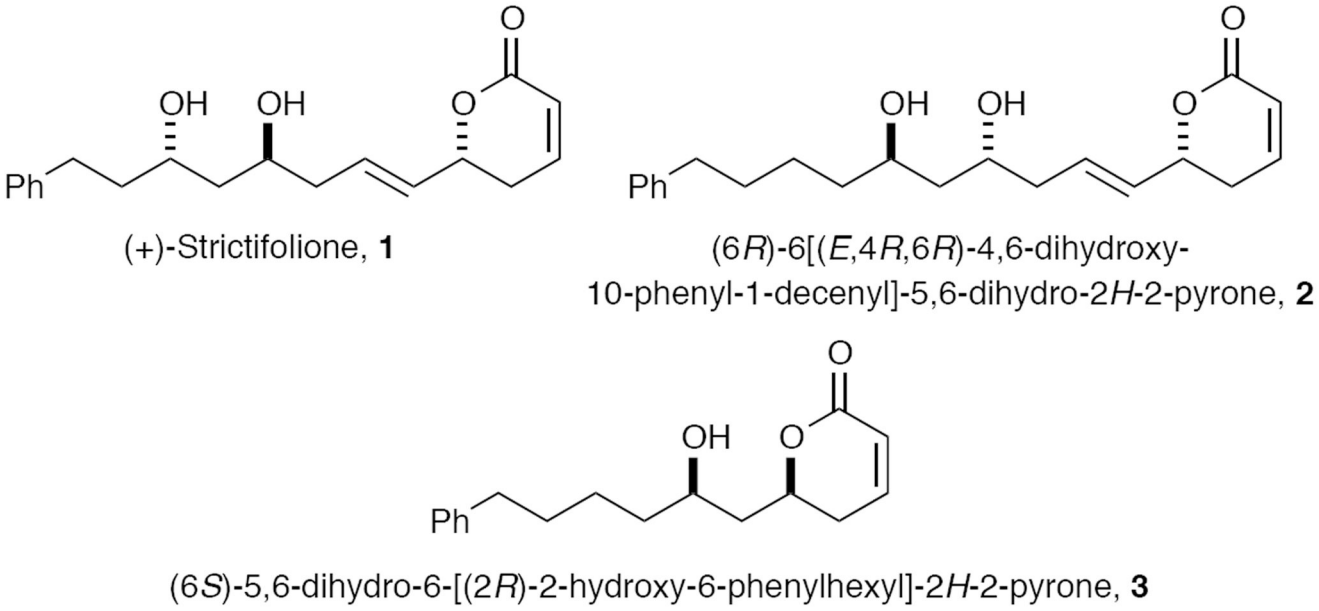

Figure 1. Natural products 1-3

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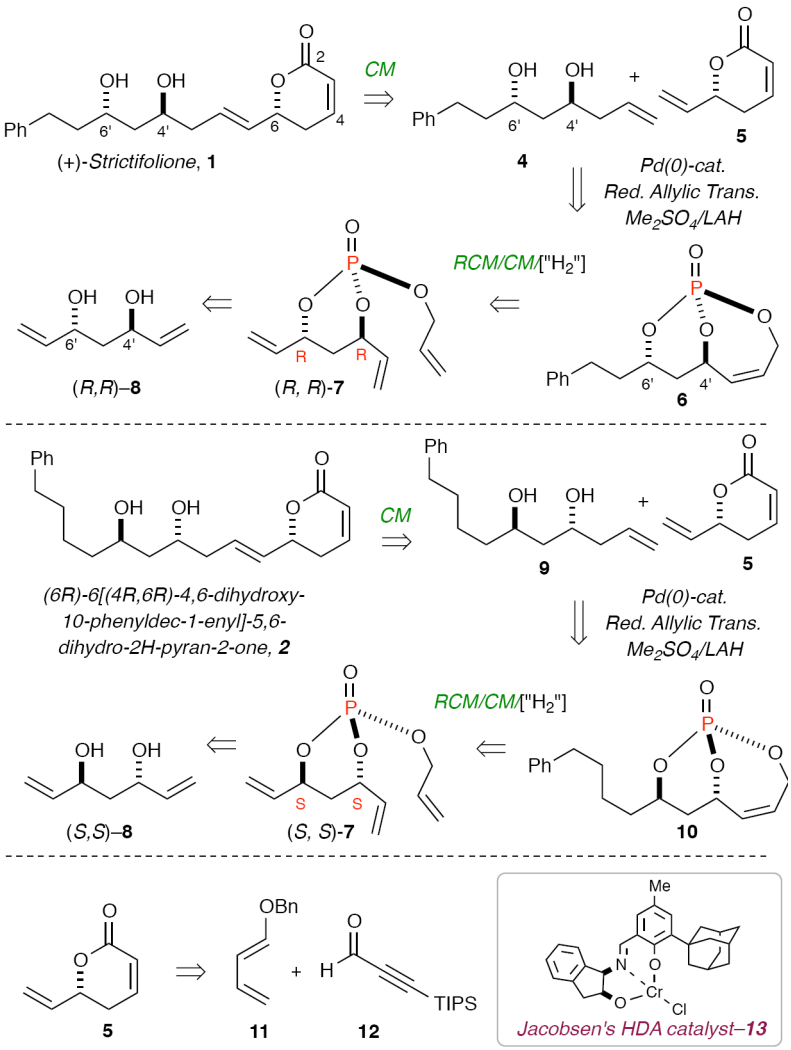

Scheme 1. Retrosynthetic analysis of natural products 1 and 2

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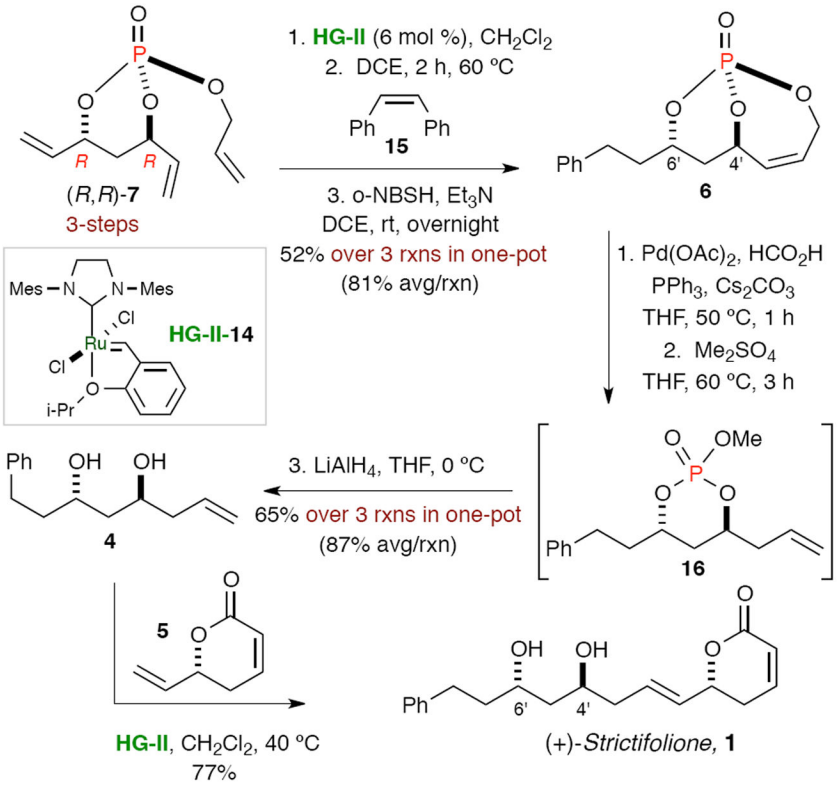

Scheme 2. Consecutive one-pot, sequential protocols, and CM

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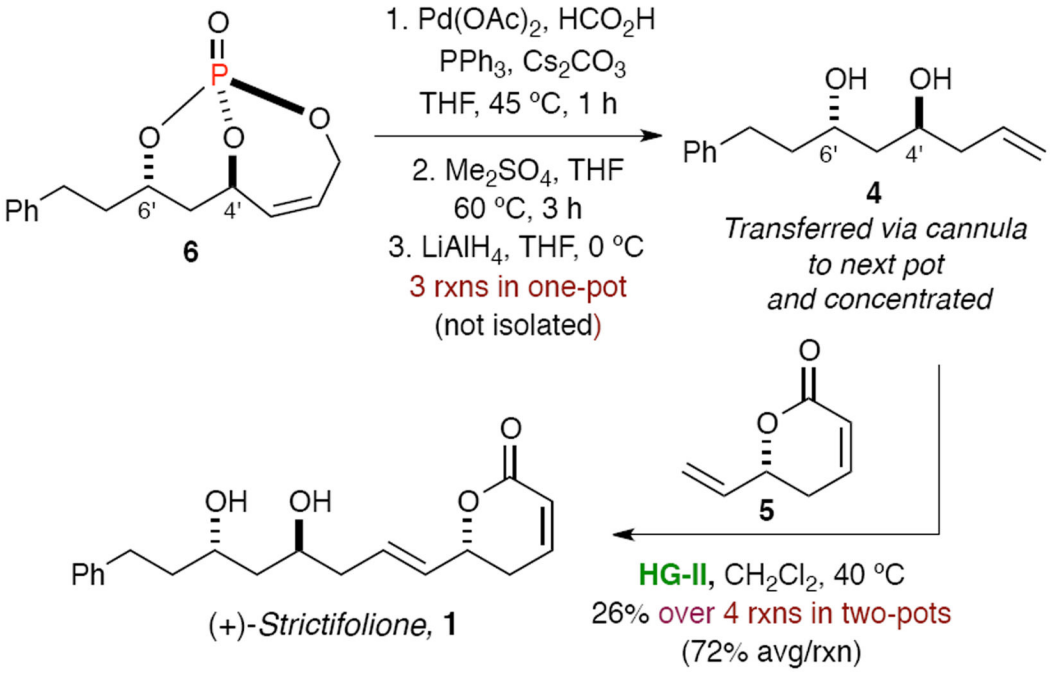

Scheme 3. One-pot, Pd-catalyzed reductive allylic transposition, tether removal protocol and CM

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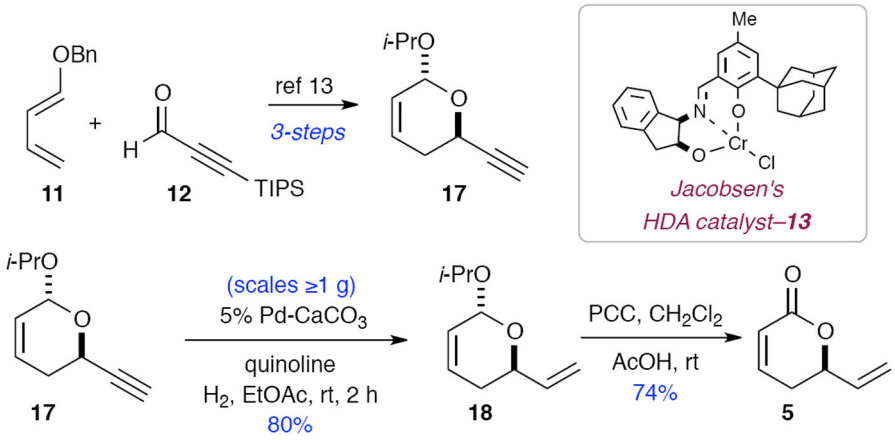

Scheme 4. Synthesis of vinyl lactone 5

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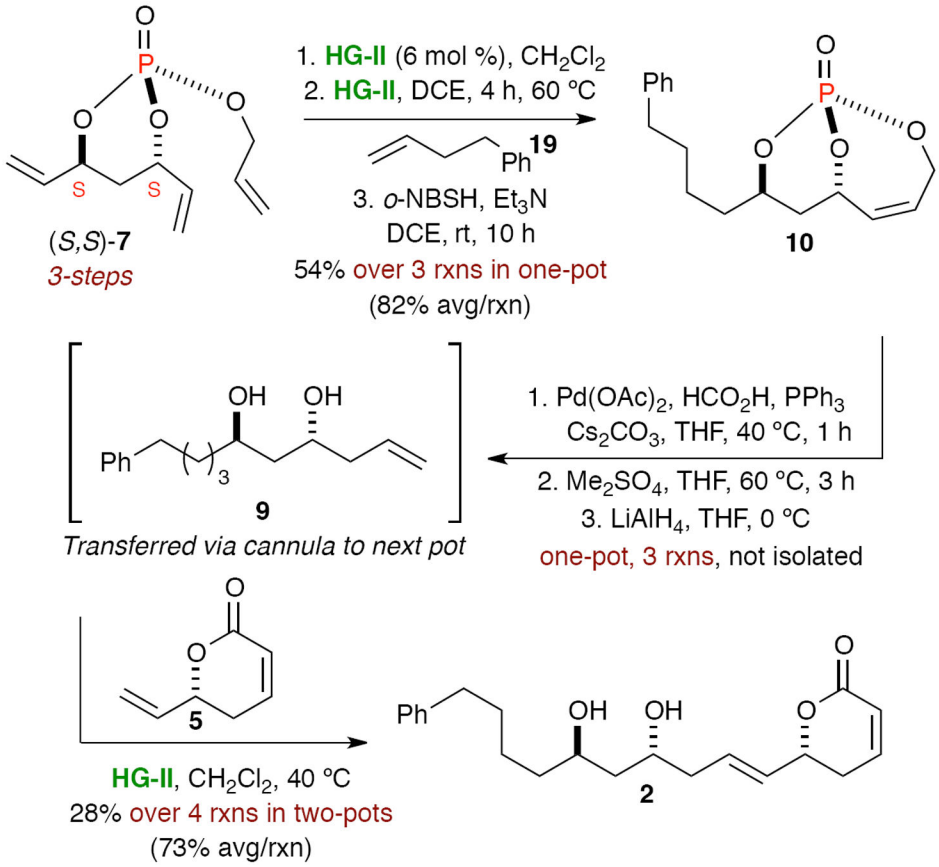

Scheme 5. Consecutive one-pot, sequential protocols and CM

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