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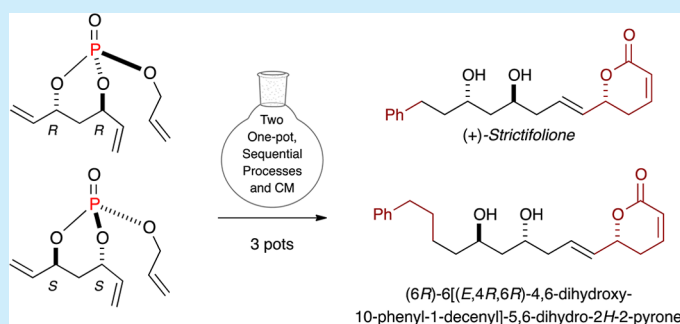
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An Efficient, Modular Approach for the Synthesis of (+)-Strictifolione and a Related Natural Product

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S Supporting Information



ABSTRACT: An efficient, library amenable, “pot economical” total synthesis of (+)-strictifolione and the related natural product, (6R)-6[(E,4R,6R)-4,6-dihydroxy-10-phenyl-1-decenyl]-5,6-dihydro-2H-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 co-workers from the stem bark of *Cryptocaria stritfolia*, 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 co-workers after accomplishing its first total synthesis, employing (S)-malic acid and (S)-glycidol in 18 steps.² A related compound, (6R)-6[(E,4R,6R)-4,6-dihydroxy-10-phenyl-1-decenyl]-5,6-dihydro-2H-2-pyrone (**2**), was isolated by Hostettmann and co-workers in 2001 from the leaves and bark of *Ravensara crassifolia*, which is an endemic genus in Madagascar, along with another structurally similar compound (6S)-5,6-dihydro-6-[(2R)-2-hydroxy-6-phenylhexyl]-2H-pyran-2-one (**3**).³ Krishna and co-workers accomplished the first total synthesis of **2** by iterative use of Jacobsen’s hydrolytic kinetic resolution with a longest linear sequence (LLS) of 17 steps.⁴ All three compounds (**1**–**3**, Figure 1) 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, attenuate its activity.⁵

Among several synthetic methods for the construction of **1**,⁶ notable streamlined efforts have recently been made. In 2003, Cossy and co-workers developed a concise and elegant synthetic pathway consisting of a longest linear sequence of 9

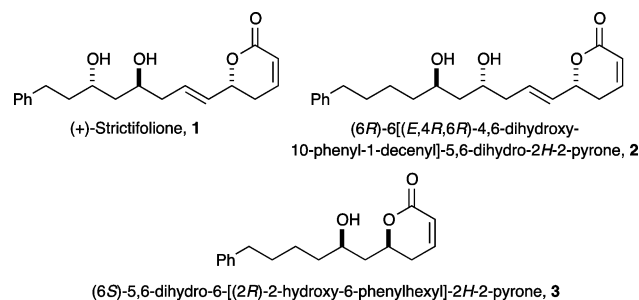


Figure 1. Natural products **1**–**3**.

steps, starting from 3-phenylpropionaldehyde, that utilized the dual use of enantioselective allyltitanation in conjunction with cross metathesis (CM).^{6a} In 2010, Das and co-workers devised a comparable pathway with an LLS of 10 steps using Sharpless kinetic resolution and olefin cross metathesis.^{6b} In 2010, She and co-workers^{6h} developed an efficient route employing a one-pot, double allylboration comprised of a pathway with a 7-step LLS using an Ipc₂BH-derived boryl-substituted allylboration, 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

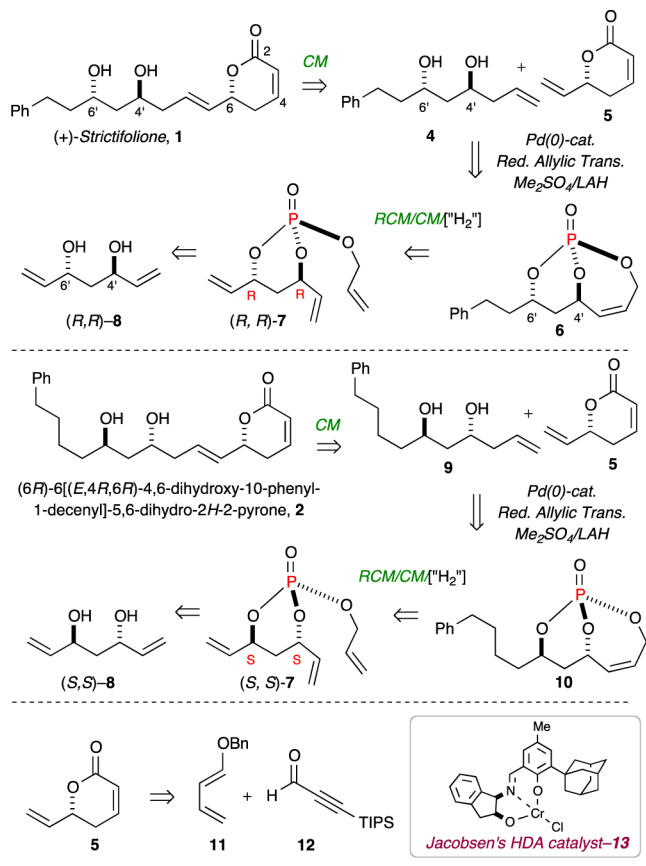
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library amenable for installation of key diversity elements in a divergent manner, is notably absent in the literature. In this regard, one-pot protocols have emerged as powerful synthetic strategies to achieve total/intermediate/analog synthesis, 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

Scheme 1. Retrosynthetic Analysis of Natural Products 1 and 2

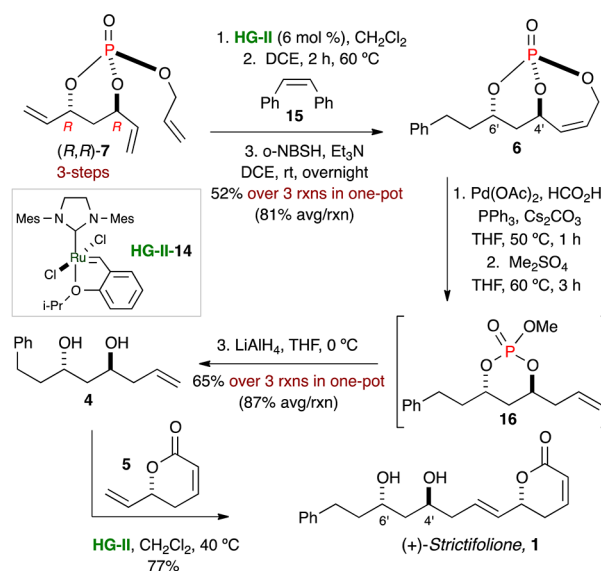


from phosphate **6**, employing a regioselective Pd(0)-catalyzed reductive allylic transposition and phosphate tether removal under reductive conditions. The phenyl substituted bicyclic phosphate **6** can be achieved from triene (R,R)-**7** via a one-pot, sequential RCM/CM/"H₂" with *cis*-stilbene as 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 two steps via sequential tripodal coupling of the C₂-symmetric *anti*-diene diol (R,R)-**8**¹³ and allyl alcohol with POCl₃ or in one step utilizing phosphoramidite chemistry.^{13c} Similarly, phosphate **10** can be synthesized following the same sequence of RCM/CM/"H₂" 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 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/"H₂",¹¹ triene (R,R)-**7** was first subjected to an RCM reaction with the second generation Hoveyda–Grubbs catalyst (HG-II) **14**¹⁵ (6 mol %) in CH₂Cl₂ (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 (Scheme 2). It should be noted that

Scheme 2. Consecutive One-Pot, Sequential Protocols and CM



cross metathesis with styrene was not productive in comparison to *cis*-stilbene due to deleterious homodimerization of styrene, a type I olefin.¹⁶ Subsequent chemoselective diimide reduction by simple addition of *o*-NBSH into the reaction mixture provided the phenyl-substituted phosphate **6** in 52% overall yield, representing an 81% average yield/reaction in the one-pot, sequential protocol.

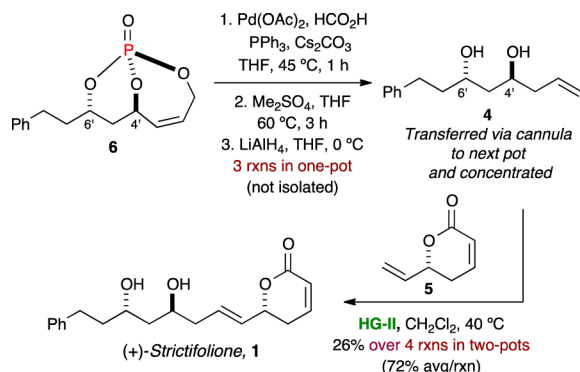
We next developed a one-pot Pd-catalyzed, reductive allylic transposition¹⁷ and tether removal protocol. In this regard, allylic transposition [Pd(OAc)₂, HCOONH₄, PPh₃]¹⁸ on phosphate **6** generated the requisite terminal olefin that was followed by *in situ* tether removal by consecutive addition of dimethyl sulfate (Me₂SO₄) (reflux 3 h) and LiAlH₄ (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 CH₂Cl₂ in 77% yield and with excellent *E*-selectivity. The spectral data (¹H, ¹³C, 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**.

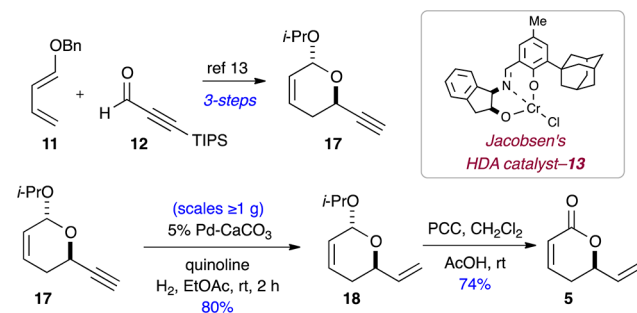
Since diol **4** was obtained in high purity without chromatography, the protocol outlined in Scheme 2 was further optimized to employ simple cannulation after the aforementioned Feiser workup (i.e., before CM). Thus, after reduction with LiAlH₄, and Fieser workup, the resulting THF solution was transferred via cannula, concentrated, and subjected to CM with vinyl lactone **5** in CH₂Cl₂ to afford **1** in 26% overall yield (72% average yield/reaction, Scheme 3).

Scheme 3. One-Pot, Pd-Catalyzed Reductive Allylic Transposition, Tether Removal Protocol, and CM



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

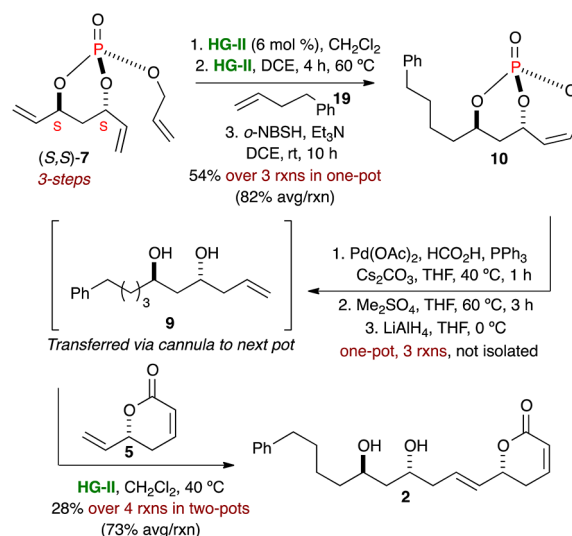
Scheme 4. Synthesis of Vinyl Lactone 5



following the Jacobsen protocol employing hetero-Diels–Alder catalyst **13**.¹⁴ Subsequent Lindlar hydrogenation with Pd–CaCO₃, in the presence of freshly distilled quinoline in EtOAc under H₂, 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 CH₂Cl₂ 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 enantiomerically pure diene diol (*S,S*)-**8**. After completion of 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,

Scheme 5. Consecutive One-Pot, Sequential Protocols and CM



PPh₃, and Cs₂CO₃], followed by tether removal utilizing consecutive additions of Me₂SO₄, and LiAlH₄, and final Feiser workup¹⁹ furnished diol **9**, which was transferred via cannula into a new flask and subjected to CM in CH₂Cl₂ 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**.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic data of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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