Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Total Synthesis of Four Isomers of the Proposed Structures of Cryptorigidifoliol K

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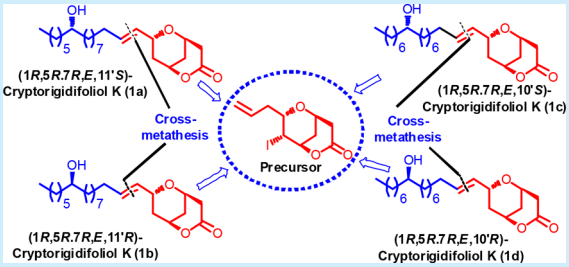
Supporting Information

ABSTRACT: The first asymmetric convergent total synthesis of four isomers of proposed structures of cryptorigidifoliol K (**1a**, **1b**, **1c**, and **1d**) has been achieved from commercially available starting materials. The key steps in this synthesis involve tandem isomerization followed by a C−O and C−C bond-forming reaction for the construction of *trans*-2,6-disubstituted dihydropyran, iodolactonization, isomerization of terminal alkene, and cross-metathesis reaction. The large discrepancies in the spectroscopic data (^{1}H NMR) of synthetic cryptorigidifoliol K from the natural product suggest that the structure of the natural cryptorigidifoliol K requires revision.



The plant genus *Cryptocarya* is distributed throughout the tropic, subtropic, and clement regions of the world.[1a] The class of *Cryptocarya*-derived monocyclic 5,6-dihydro-α-pyrones as well as bicyclic tetrahydropyrone exhibits antimycobacterial,[1b] antiparasitic,[1b] antitumor,[1e] and anticancer activities (Figure 1).[1c,d,f,g,2,3] Cryptorigidifoliols F−K are aliphatic polyketide lactones bearing a bicyclic tetrahydropyrone moiety, isolated from the root wood of *Cryptocarya rigidifolia* (Lauraceae) in 2015 by Kingston et al.[1h] Cryptorigidifoliol K shows antimalarial activity (IC_{50} > 10 μM) against the Dd2 of *Plasmodium falciparum* and antiproliferative activity (IC_{50} > 10 μM) against A2780 human ovarian cancer cells.[1h] Structurally, cryptorigidifoliol K contains a bicyclic tetrahydropyrone moiety with an aliphatic side chain comprising a distal hydroxy group and a proximal olefin. Four stereogenic centers are present in cryptorigidifoliol K, which include three in the bicyclic portion and one in the side chain. The relative stereochemistry at the

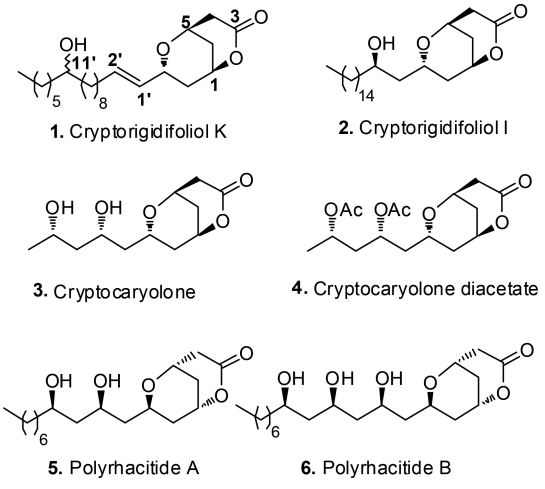
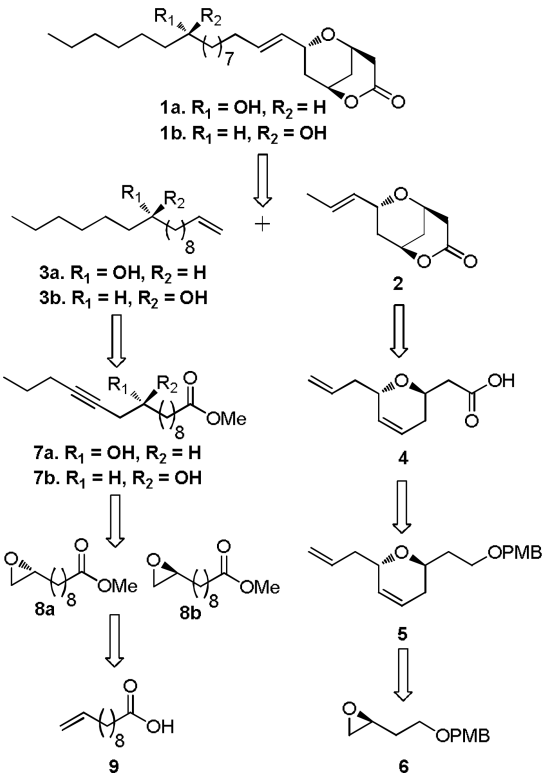


Figure 1. Natural products with bicyclic lactone motif.

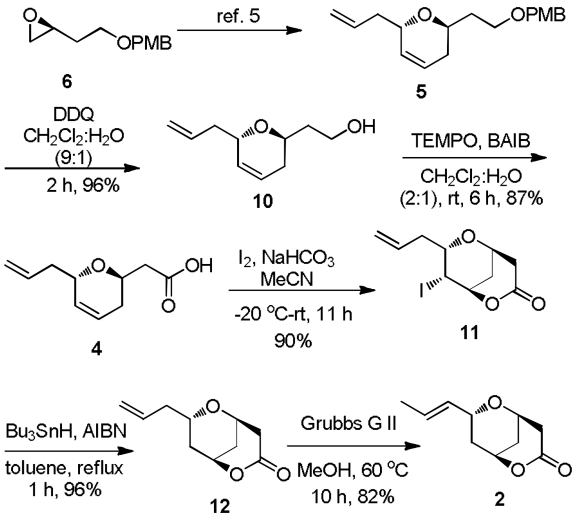
Scheme 1. Retrosynthetic Analysis



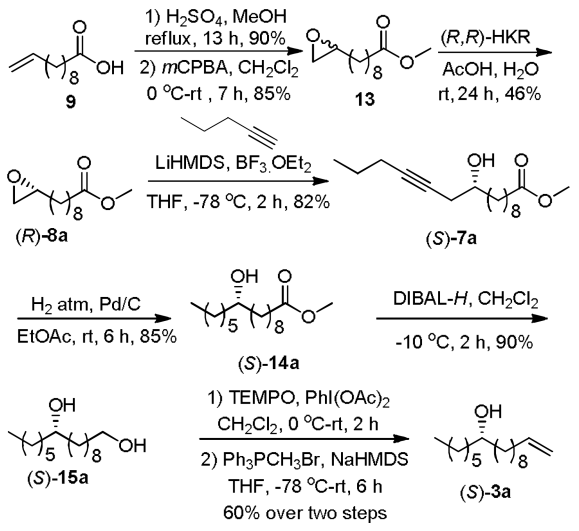
Received: October 11, 2017

DOI: 10.1021/acs.orglett.7b03174
Org. Lett. XXXX, XXX, XXX−XXX

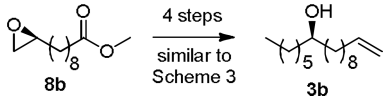
Scheme 2. Synthesis of the Bicyclic Fragment 2



Scheme 3. Synthesis of the Side-Chain Fragment 3a



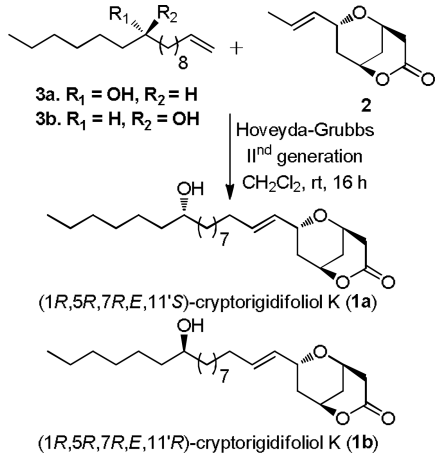
Scheme 4. Synthesis of the Side-Chain Fragment 3b



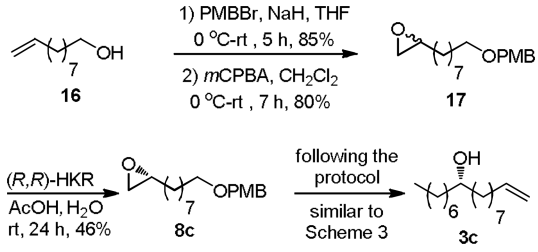
C1, C5, and C7 positions was assigned by the interpretation of ECD spectroscopic data and the Mosher's ester analysis. However, the absolute stereochemistry and position of the hydroxy group in the aliphatic side chain remains unknown. We have developed a versatile protocol for the synthesis of substituted pyrans involving a tandem isomerization followed by C−O and C−C bond-forming reactions. In continuation of our interest in the asymmetric total synthesis of pyran-containing natural products and to assign the stereocenter of the hydroxy group in the side chain, herein we report the stereoselective synthesis of four possible isomers of the proposed structures of cryptorigidifoliol K.

As outlined in Scheme 1, the retrosynthetic approach to **1a**/**1b**, which are diastereomers of cryptorigidifoliol K, relies on the assembly (by olefin cross-metathesis) of bicyclic lactone **2** with side chains **3a** and **3b**, respectively. The bicyclic lactone **2** could

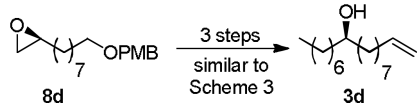
Scheme 5. Synthesis of the First Proposed Structure of Cryptorigidifoliol K



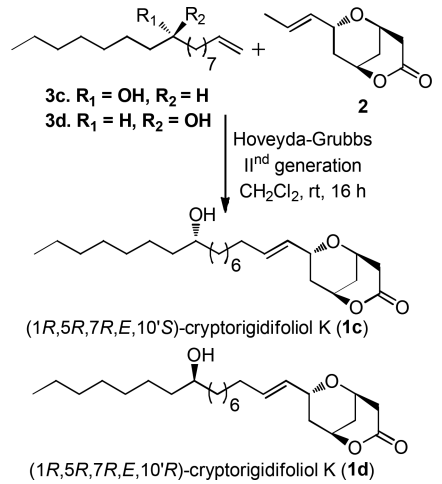
Scheme 6. Synthesis of the Side-Chain Fragment 3c



Scheme 7. Synthesis of the Side-Chain Fragment 3d



Scheme 8. Synthesis of the Second Proposed Structure of Cryptorigidifoliol K



be generated by iodolactonization of acid **4** which, in turn, could be accessed from a known intermediate **5** reported by us following our own developed protocol. The key synthetic intermediates **3a**/**3b** would be prepared from ynoates **7a**/**7b**, which could be readily accessed from the optically pure (*R*)-/(*S*)-chiral epoxides **8a**/**8b**, respectively.

DOI: 10.1021/acs.orglett.7b03174
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Table 1. Comparison of ^{1}H NMR of Natural Product with Synthetic 1a, 1b, 1c, and 1d in $CDCl_3$ (500 MHz)

Hx	natural	synthetic **1a**	synthetic **1b**	synthetic **1c**	synthetic **1d**
4	2.87 br d	2.93 br d	2.93 br d	2.93 br d	2.92 br d
7	4.27 m	4.23 m	4.22 m	4.23 m	4.21 m
8	1.78 m	1.68 m	1.68 m	1.68 m	1.67 m
2′	5.67 m	5.73 m	5.73 m	5.74 m	5.72 m
4′	1.36 m	1.42 m	1.42 m	1.43 m	1.42 m
11′	**3.89 m**	**3.58m**	**3.58 m**	**3.58 m (10′)**	**3.57 m (10′)**
12′	1.63 m	1.67 m	1.68 m	1.68 m	1.67 m

As per the synthetic plan, the first task was to synthesize the *trans*-2,6-disubstituted dihydropyran **5** (Scheme 2). The synthesis of **5** was achieved from the known chiral epoxide **6**[4] using a three-step protocol developed previously by our group in 99:1 dr.[5] Oxidative removal of the PMB group of **5** using DDQ[6] provided primary alcohol **10**, which on subsequent oxidation using TEMPO/BAIB[7] in aqueous CH_2Cl_2 (1:2) furnished the carboxylic acid **4** in 83% yield over two steps. With good quantities of acid **4** in hand, iodolactonization of **4** with I_2 and $NaHCO_3$ in acetonitrile[8] was performed to obtain the bicyclic iodolactone **11** in 90% yield with excellent diastereoselectivity (dr 98:2, analyzed by HPLC). Deiodination was achieved smoothly under Barton−McCombie conditions by treatment of **11** with Bu_3SnH[9] and a catalytic amount of AIBN to furnish compound **12** in 96% yield. Isomerization[10] of the terminal double bond in **12** was carried out using Grubbs' second-generation catalyst and afforded propenyl intermediate **2** successfully in 82% yield.

With the bicyclic lactone **2** in hand, the next step was to synthesize the two enantiomers of the aliphatic side chain. The enantioselective synthesis of (*S*)-enantiomer of the side chain **3a** was started from commercially available undecanoic acid **9** (Scheme 3). Acid-catalyzed esterification followed by *m*-CPBA oxidation afforded epoxide (±)-**13** in 76% yield in two steps.[11] Enantiomerically enriched epoxide (*R*)-**8a** (ee ≥ 99%) was synthesized from (±)-**13** by hydrolytic kinetic resolution[12] in the presence of Jacobsen's (*R,R*)-(salen)Co(III) catalyst in 46% yield. Regioselective ring opening of terminal epoxide (*R*)-**8a** using lithiated-1-pentyne in the presence of $BF_3.OEt_2$ furnished alkynol (*S*)-**7a** in 82% yield.[13] Pd/C-catalyzed hydrogenation of resulting alkynol (*S*)-**7a** led to the formation of saturated ester **14a** in 85% yield.[14]

The absolute configuration of **14a** was assigned by Mosher's modified method.[15] Reduction of the ester group in **14a** using DIBAL-H in CH_2Cl_2 at −10 °C afforded the diol **15a** in 90% yield. A two-step sequence of TEMPO/BAIB oxidation of the primary alcohol followed by one-carbon Wittig olefination produced (*S*)-**3a** in 60% yield over two steps.[16]

The (*R*)-enantiomer **3b** was obtained from (*S*)-epoxide **8b** (ee ≥ 99%) in four steps (Scheme 4) following the identical conditions described in Scheme 3.

The key coupling reaction of the building blocks was carried out between the bicyclic lactone **2** and both the enantiomers **3a**/**3b** (bearing the hydroxyl group on C7) by cross-metathesis[17] using the second-generation Hoveyda−Grubbs' catalyst to afford **1a** and **1b** in 72% and 74% yields, respectively (Scheme 5).

The ^{1}H NMR (as no ^{13}C NMR was given in the literature) data and optical rotation of the synthesized compounds **1a** and **1b** were compared with the natural product which was reported earlier by Kingston et al. The two synthetic products **1a** and **1b** had identical spectra to each other, but showed significant deviation from spectrum of the natural product, with no significant influence of the configuration at the C11′ stereocenter. The optical rotations of the synthetic material **1a** with (*S*)-configured side chain $[\alpha]_D^{21}$ −7.8 (*c* 0.6, MeOH) and **1b** with (*R*)-configured side chain $[\alpha]_D^{21}$ −12.0 (*c* 0.6, MeOH), were in close agreement with the value $[\alpha]_D^{21}$ −8.0 (*c* 0.6, MeOH) reported for the natural product.[1h]

At this juncture, the Kingston group suggested an alternate structure for cryptorigidifoliol K (reported in the SI),[1h] and using a procedure analogous to that described previously, we have synthesized the second possible isomers.

The synthesis of olefin-coupling partners (bearing the hydroxyl group at C8) commenced with commercially available decen-1-ol **16** (Scheme 6). The hydroxyl group in **16** was protected as its PMB ether by using *p*-anisyl bromide and NaH in THF followed by the epoxidation of terminal olefin with *m*-chloroperoxybenzoic acid (*m*-CPBA) afforded a racemic epoxide (±)-**17**. The hydrolytic kinetic resolution of the (±)-epoxide **17** in the presence of Jacobsen's catalyst[12] (*R,R*)-(salen)Co(III) furnished epoxide **8c** in 46% yield (98% ee). The compound **3c** was obtained from (*R*)-epoxide **8c** by following the protocol as described in Scheme 3.

In an identical manner as outlined in Scheme 3, the side chain **3d** was obtained from (*S*)-epoxide **8d** in three steps in 48% yield (~99% ee) (Scheme 7).

With both coupling partners **3c**/**3d** (having hydroxyl group on C8) in hand, the final cross-methathesis[17] reaction was carried out with bicyclic lactone **2** by using Hoveyda−Grubbs' second-generation catalyst to obtain two isomers **1c** and **1d** of the second proposed structure (by Kingston and co-workers) of cryptorigidifoliol K in 70% and 74% yields, respectively (Scheme 8).

Comparison of the ^{1}H NMR data of **1c** and **1d** with the known stereochemistries of the hydroxyl group at C10′ on the side chain revealed that they are identical to each other, but they do not match with the reported spectral data for the natural product (Table 1). In **1c** and **1d**, the proton attached to the hydroxyl functionality resonated at 3.57 ppm, while it appeared at 3.89 ppm in the natural product, which suggests an allylic CH proton rather than an aliphatic CH proton. The optical rotations of the synthetic material **1c** with (*S*)-configured hydroxy side chain was $[\alpha]_D^{21}$ −6.5 (*c* 0.6, MeOH) and **1d** with (*R*)-configured side chain was $[\alpha]_D^{21}$ −20.0 (*c* 0.6, MeOH), while the reported value for the natural product was $[\alpha]_D^{21}$ −8.0 (*c* 0.6, MeOH).

In summary, we have achieved the first asymmetric total synthesis of four isomers of the proposed structures for cryptorigidifoliol K. The key steps in the synthesis involved our own developed protocol for the construction of *trans*-2,6-disubstituted dihydropyran, iodolactonization, isomerization of the terminal alkene to internal alkene, and olefin cross-metathesis. The discrepancies between the spectroscopic data

DOI: 10.1021/acs.orglett.7b03174
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of the synthetic isomers of cryptorigidifoliol K and the isolated natural product, particularly with respect to the hydroxyl group position, suggests that the structure proposed for the natural product needs revision.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03174.

Experimental procedure and characterization of new compounds (^{1}H, ^{13}C NMR spectra, 2D NMR spectra)-(PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Council of Scientific and Industrial Research (CSIR), New Delhi, India, for financial support as part of the XII Five Year plan programme under the title ORIGIN (CSC-0108). G.S.R., B.P., and Y.B. thank CSIR and UGC, New Delhi, India, for financial assistance in the form of fellowships.

■ DEDICATION

This manuscript is dedicated to Dr. Mukund K. Gurjar, CSO, Emcure Pharmaceuticals Pvt., Ltd., on the occasion of his 65th birthday.

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DOI: 10.1021/acs.orglett.7b03174
Org. Lett. XXXX, XXX, XXX−XXX