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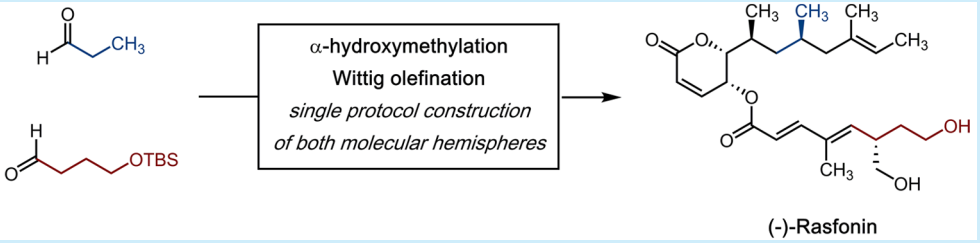
Scalable Synthesis of (−)-Rasfonin Enabled by a Convergent Enantioselective α-Hydroxymethylation Strategy

Robert K. Boeckman, Jr.,* Justin M. Niziol, and Kyle F. Biegasiewicz

Department of Chemistry, University of Rochester, Rochester, New York 14627, United States

Supporting Information



ABSTRACT: A scalable synthesis of the potent antitumor agent, (−)-rasfonin, has been achieved. The synthetic strategy features a highly convergent approach based on a single protocol construction of both major fragments via catalytic enantioselective α-hydroxymethylation of simple aliphatic aldehydes. The route described has been successful in the generation of gram quantities of the natural product and serves as the first synthetic strategy to provide sufficient material to continue studies related to its mechanism of action and potential as a cancer therapeutic.

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The α-pyrone-containing natural product, (−)-rasfonin (**1**), was isolated by Hayakawa and co-workers in 2000 from the fermentation broth of *Taleromyces sp.* 3656-A1.[1] The same year, it was also isolated (and temporarily identified as TT-1) by Ishibashi et al. from the fungi imperfecti *Trichurus terrophilus*.[2] The molecule is now most commonly referred to as (−)-rasfonin, as it has gained a significant amount of attention through its interactions with the G-protein, Ras. *In vivo* studies show that **1** targets and downregulates Ras activity, consequently causing a downregulation of phosphorylation events in the c-Raf/MEK/ERK signaling pathway in proteins. (−)-Rasfonin was also shown to reduce Son of sevenless (Sos1) expression with no change in GEF or GAP activity. It has also been demonstrated that **1** is a potent inhibitor of pancreatic cancers with the K-ras mutation. It has also successfully delayed the growth of xenograft tumors (30 mg/kg) originating from Panc-1 cells, with an eventual reduction in tumor mass after 20 days of treatment.[3] (−)-Rasfonin has even been shown to interact with the autophagic and necrotic pathways of renal cancer cell lines, the former being of extraordinarily high interest in the pursuit of cancer therapeutics.[4−6]

Along with its significance from a biological activity perspective, (−)-rasfonin (**1**) contains a series of synthetically interesting moieties, exemplified by a pendant dihydrtoxylated ester and a tetramethylated alkyl sidechain, both of which stem from the chiral α,β-unsaturated pyranone core on carbon atoms 4 and 5, respectively (Scheme 1).

Apart from our initial synthesis of (−)-rasfonin in 2006, there have only been three other total syntheses reported to date.[1,7−9] While all of these synthetic endeavors have provided uniquely interesting approaches to the construction of **1**, a truly scalable route that would provide enough material for further biological testing has remained elusive. As a result of our ongoing synthetic studies, in combination with our interest in understanding the biological activity associated with **1**, we have now planned and executed a scalable route of **1**. The results of these studies are presented herein.

Retrosynthetically, as previously practiced, we envisioned (−)-rasfonin (**1**) as the product of a Yamaguchi esterification between alcohol **2** and acid **3**. Alcohol **2** is envisioned to be the product of a CBS-catalyzed vinylogous Mukaiyama addition of 2-(trimethylsiloxy)furan to aldehyde **4**. A subsequent DBU-catalyzed furanone-to-pyranone rearrangement would then furnish **2**.

As part of our new plan, we envisioned access to (*E*,*E*)-acid **3** through a Horner−Wadsworth−Emmons protocol starting from aldehyde **5**. We then anticipate rapid construction of both key intermediate aldehydes **4** and **5** using the same synthetic protocol involving a tandem catalytic α-hydroxymethylation/Wittig olefination sequence from simple aliphatic aldehydes **6** and **7**, respectively (Scheme 1).

We began our synthetic studies with an organocatalytic α-hydroxymethylation sequence recently developed in our laboratory.[10] Propionaldehyde (**6**) was treated with formalin (37% aq) in the presence of the (*S*)-Jørgensen−Hayashi prolinol catalyst **8** (10 mol %) in buffered media (pH = 7), followed by treatment with ethyl 2-(triphenylphosphaneylidene)propanoate which provided unsaturated ester **9** in high yield and enantioselectivity (81%, 94:6 er). The resulting unsaturated ester was subjected to

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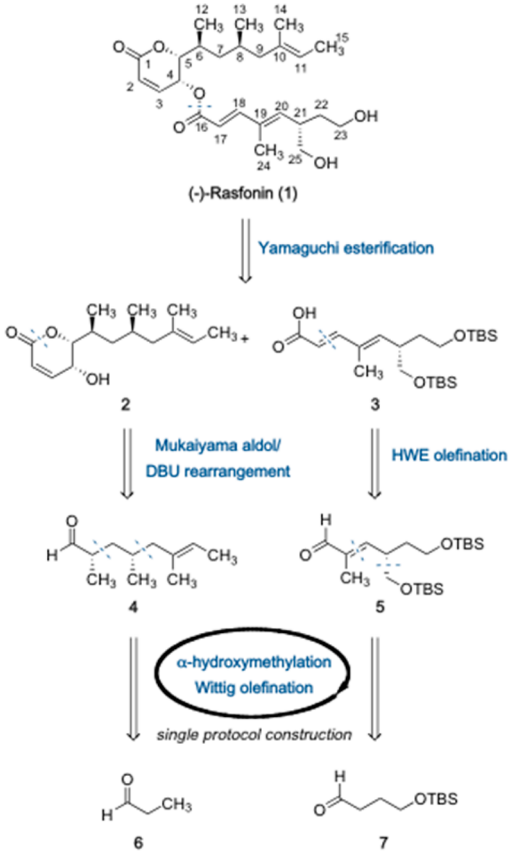
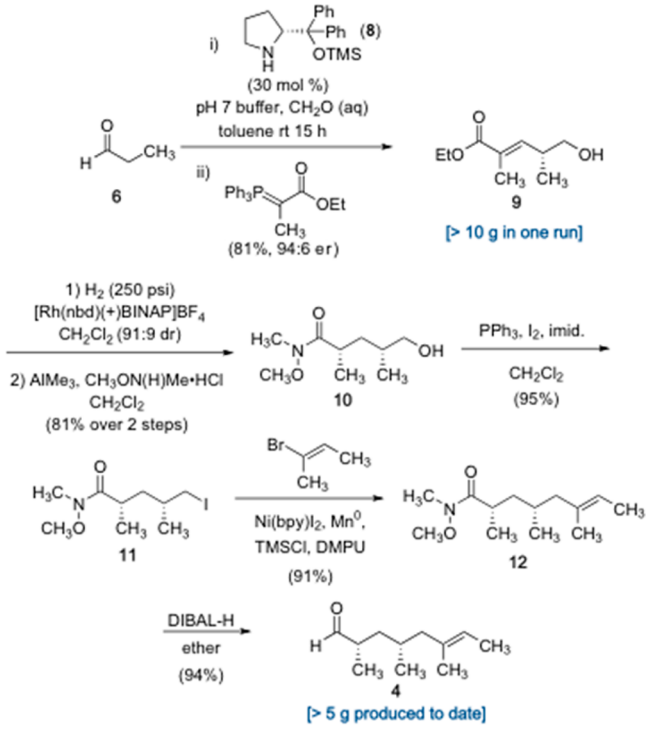
Scheme 1. Retrosynthesis of (−)-Rasfonin (1)



Scheme 2. Synthesis of Aldehyde 4



asymmetric hydrogenation conditions developed by Evans using [Rh(nbd)(+)BINAP]BF_4 under 250 psi of H_2 (nbd = norbornadiene).[11] It was found that the catalyst loading for this reaction could be as low as 0.3 mol % while retaining full conversion. Theoretically, this number can be reduced even further if the reaction vessel could be more strictly purged of moisture and oxygen. We suggest that to attain full conversion a sufficient quantity of the rhodium catalyst must be introduced to compensate for catalyst deactivation by exogenous moisture in the reaction vessel. Upon reaction completion and analysis of the products, the rhodium catalyst was found to have promoted partial lactonization (~40%), owing to its strong Lewis acid properties. This result was easily accommodated by direct conversion of the mixture solely to the desired chiral Weinreb amide **10** using standard conditions[12] in 81% yield over two steps.

Conversion of the primary alcohol **10** to the corresponding iodide **11** via an Appel reaction[13] provided the precursor for a Ni-catalyzed coupling reaction recently described by Weix.[14] In the presence of (bpy)NiI_2 (bpy = bipyridyl) and Mn^0, primary iodide **11** is readily coupled to commercially available (*E*)-2-bromo-2-butene to provide amide **12** in high yield (91%). Use of undistilled commercial TMSCl was found to be important for reproducibly high conversion of **11** to **12**. We surmise that traces of HCl in the TMSCl serve to activate the manganese metal surface. Use of freshly distilled TMSCl led, as expected, to lower conversion to **12** after the indicated reaction time. Reduction of the Weinreb amide **12** with DIBAL-H in ether at −78 °C then provided aldehyde **4** in nearly quantitative yield (Scheme 2).

As employed in our initial 2006 synthesis,[7] completion of the pyranone subunit of **1** from aldehyde **4** was carried out via a CBS-catalyzed vinylogous Mukaiyama aldol reaction with (furan-2-yloxy)trimethylsilane and the Corey oxazaborolidine catalyst **13**. The TMS-furan is easily generated from the Dakin oxidation of furfural followed by soft enolization of the resulting butenolide. Catalyst **13** is generated *in situ* from the oxazaborolidine (obtained from the dehydration of diaryl prolinol and *o*-tolylboroxine) and triflic acid at −78 °C.

Introduction of aldehyde **4** followed by (furan-2-yloxy)-trimethylsilane cleanly provides nearly a single diastereomer of aldol adduct **14** in good yield (74% yield, > 20:1 syn:anti, > 20:1 dr).[7] Successive reduction of **14** with DIBAL-H, stirring with DBU, and oxidation with MnO_2 in a 3-step sequence provide a mixture of the desired pyranone **15** (34% yield or 70% average yield over 3 steps at 45% conversion for a single pass) along with starting material **14**, as we have previously described.[7] The starting material **14** can be recycled, increasing the overall conversion. Unsaturated pyranone **15** was then treated with 1 M HCl in THF to provide the desired unsaturated pyranone alcohol **2** in 95% yield (Scheme 3).

Our further optimized synthesis of the side chain carboxylic acid **3** commenced with the mono-TBS protection of 1,4-butanediol (**16**) followed by Swern oxidation, providing aldehyde **7** in high yield (88% over two steps).[15] An ensuing α-hydroxymethylation of **7**, followed by a one-pot successive treatment with ethyl 2-(triphenylphosphanylidene)propanoate and then TBS protection conditions, provided the expected chiral ester **18** in high yield and enantioselectivity (94%, 93:7 er). Reduction with excess DIBAL-H followed by Parikh−Doering oxidation[16] furnished aldehyde **19** with the α-olefin intact. Horner−Wadsworth−Emmons olefination[17] gave methyl ester **20** which was efficiently hydrolyzed with excess LiOH·H_2O in THF:CH_3OH:H_2O (2:2:1) to provide the acid chain **3** of (−)-rasfonin in excellent yield. Yamaguchi esterification[18] of

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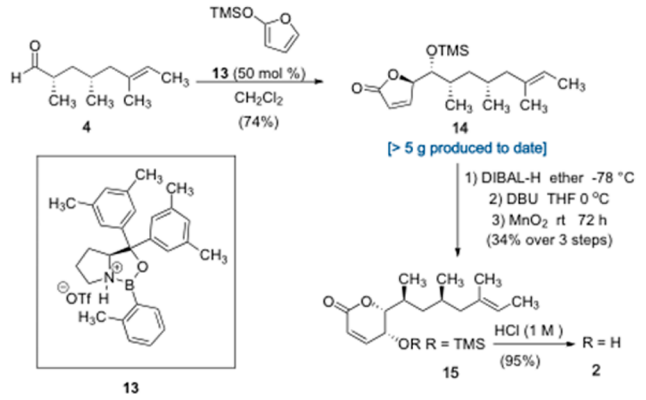
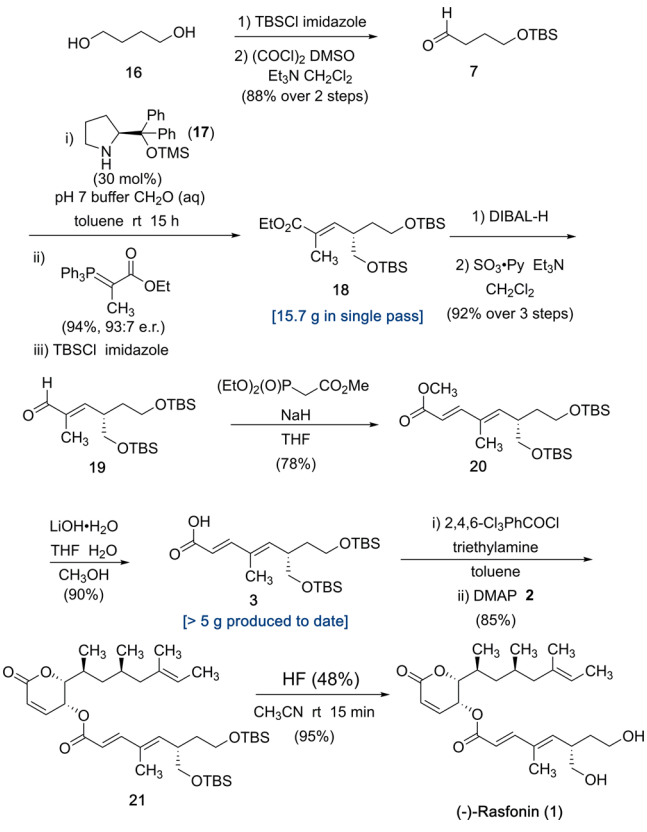
Scheme 3. Completion of Pyranone 2



acid **3** with alcohol **2** proceeded without remark, and a final treatment with HF (48% in water) in acetonitrile[8] afforded (−)-rasfonin (**1**) i whose spectroscopic data were in complete agreement with those of authentic (−)-rasfonin and our previously prepared synthetic sample in nearly quantittive yield (Scheme 4).[1]

Scheme 4. Completion of (−)-Rasfonin (1)



Thus, employing the enantioselective α-hydroxymethylation protocol from which both subunits of **1** originate as the nucleus of our synthetic design, we have successfully executed a new scalable and practical route to (−)-rasfonin (**1**). The current route required three fewer steps than our prior route (13 vs 16 linear steps) exhibiting generally high atom economy and affording very good to excellent yields (overall yield 10%), while employing inexpensive starting materials. We anticipate that scale-up and further optimization of this route is possible, making available the necessary quantities of **1** to hopefully realize the full potential of (−)-rasfonin (**1**) as a novel cancer therapeutic agent.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02222.

Experimental procedures (PDF)

Spectral data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rkb@rkbmac.chem.rochester.edu.

ORCID

Robert K. Boeckman, Jr.: 0000-0001-7230-4642

Notes

The authors declare the following competing financial interest(s): (−)-Rasfonin generated via the outlined synthesis is currently undergoing biological profiling at the Max-Planck Institute of Molecular Physiology in Dortmund Germany by Dr. Herbert Waldmann and his group.

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