Communication

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Enantioselective Chemical Syntheses of the Furanosteroids (–)-Viridin and (–)-Viridiol

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Supporting Information Placeholder

ABSTRACT: Herein we describe concise enantioselective chemical syntheses of (–)-viridin and (–)-viridiol. Our convergent approach couples two achiral fragments of similar complexity and employs an enantioselective intramolecular Heck reaction to set the absolute stereochemical configuration of an all-carbon quaternary stereocenter. To complete the syntheses of these base- and nucleophile-sensitive natural products, we conduct carefully orchestrated site- and diastereoselective oxidations and other transformations. Our work is the first generate these targets as single enantiomers.

Wortmannin (**1**),[1] viridin (**3**),[2] and other furanosteroids have been the subjects of structural and limited biological studies for over seven decades.[3] However, biological investigations involving wortmannin exploded in 1994, following three independent reports documenting its ability to selectively and irreversibly inhibit phosphatidylinositol 3-kinases (PI3Ks) at single-digit nanomolar concentrations.[4] Unsurprisingly, wortmannin became the reagent of choice in fundamental biochemical studies of PI3Ks. Also, given the increasing awareness and understanding of PI3K's role in cancer development and progression,[5] medicinal chemistry efforts ensued based on this steroid scaffold.[6] Wortmannin's direct use in therapeutic applications, however, is precluded by two problems: it is rapidly degraded in serum, and despite its high affinity for PI3Ks, its potency as an irreversible covalent inhibitor leads to general toxicity.[7] In response, Wipf developed PX-866 (**2**), a prodrug, from wortmannin, and this agent has advanced to Phase II clinical trials.[8] Alongside semisynthesis studies by Wipf and others, several groups have also pursued a total synthesis of **1**, with only Shibasaki's efforts reaching fruition.[9,10]

In principle, viridin (**3**) may also be a viable candidate for PI3K inhibition-based chemotherapy. It, too, bears the hallmark 2,4-diketofuran that imbues wortmannin with its potent, PI3K-alkylating activity. Remarkably, in a side-by-side comparison *it was found that wortmannin and demethoxyviridin, also a natural product, inhibited mammalian PI3K activity at single-digit nanomolar concentrations.*[11] Taken together, the biological profile and untapped medicinal chemistry potential of viridin and its congeners provide strong motivation for synthesis studies. Sorensen duly completed the first total syntheses of each viridin and viridiol (**4**)[2c] in racemic form in 2004.[12] Herein we report our own enantioselective syntheses of (–)-viridin and (–)-viridiol. Our ultimate goal is to be able to generate viridin analogs with deep-seated changes to the C- and D-rings (e.g. heterocyclic isosteres) because even subtle modifications in this region of wortmannin leads to significant changes in potency[6] and because this region embeds itself most deeply in the PI3K active site.[13] Importantly, while medicinal chemists have largely exhausted all reasonable synthetic modifications to wortmannin,[6] our late-stage fragment coupling approach may permit broader SAR studies with the aim of addressing PI3K/target specificity. However, before such long-term goals can be pursued, we wish to establish the feasibility of a fragment coupling strategy by completing a total synthesis of viridin itself.

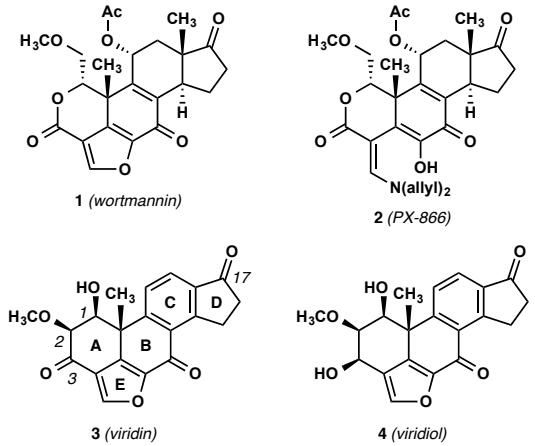
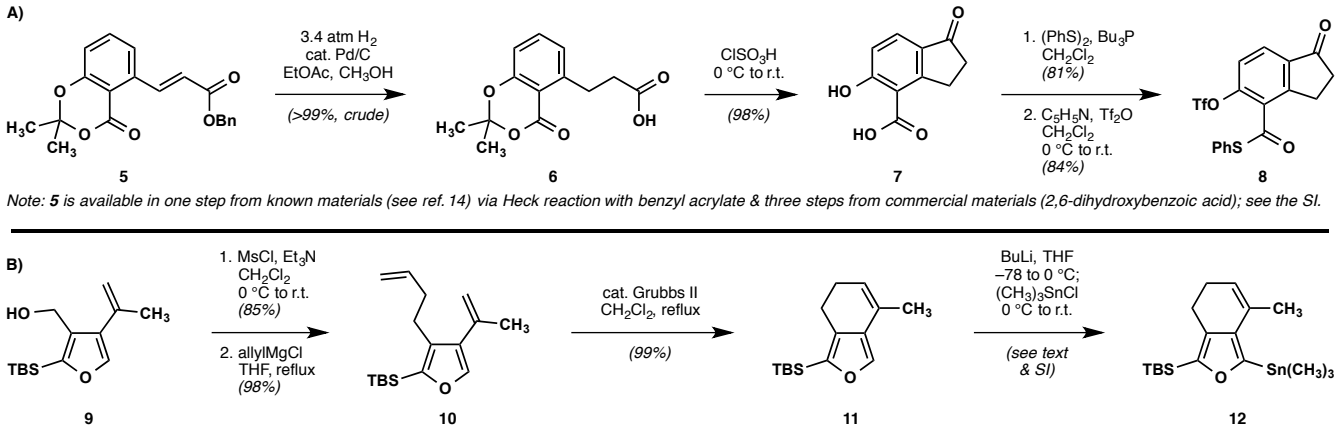


Figure 1. Furanosteroid natural products.

As shown in Scheme 1A, our synthesis begins with acrylate **5**, generated in one step from a known aryl triflate[14] via Heck alkenylation. Hydrogenation (3.4 atm

Scheme 1. Preparation of coupling partners **8** and **12**



*Note: **5** is available in one step from known materials (see ref. 14) via Heck reaction with benzyl acrylate & three steps from commercial materials (2,6-dihydroxybenzoic acid); see the SI.*

*Note: **9** is a known material (see ref. 15) and is available in three steps from commercial materials (furan-3-methanol); see the SI.*

H_2 over Pd/C) reduces the alkene and removes the benzyl group, furnishing dihydrocinnamic acid **6**. This intermediate is then directly dissolved in neat chlorosulfonic acid, stirred at ambient temperature for 12 hours, and quenched into ice-cold water, enabling isolation of indanone **7** by simple trituration. Finally, thioesterification and triflation yields functionalized indanone **8**.

The A-ring furan fragment is prepared starting from furan **9**,[15] previously prepared by Keay in his own studies[9] toward viridin (see Scheme 1B). The hydroxyl group is converted to the chloride using methanesulfonyl chloride and triethylamine, which is then displaced by allylmagnesium chloride, furnishing unconjugated diene **10**. Ring-closing metathesis catalyzed by Grubbs's second-generation Ru-alkylidene catalyst gives **11** and subsequent lithiation-stannylation provides furan **12**, which was used directly as obtained in subsequent chemistry due to slow destannylation upon storage.

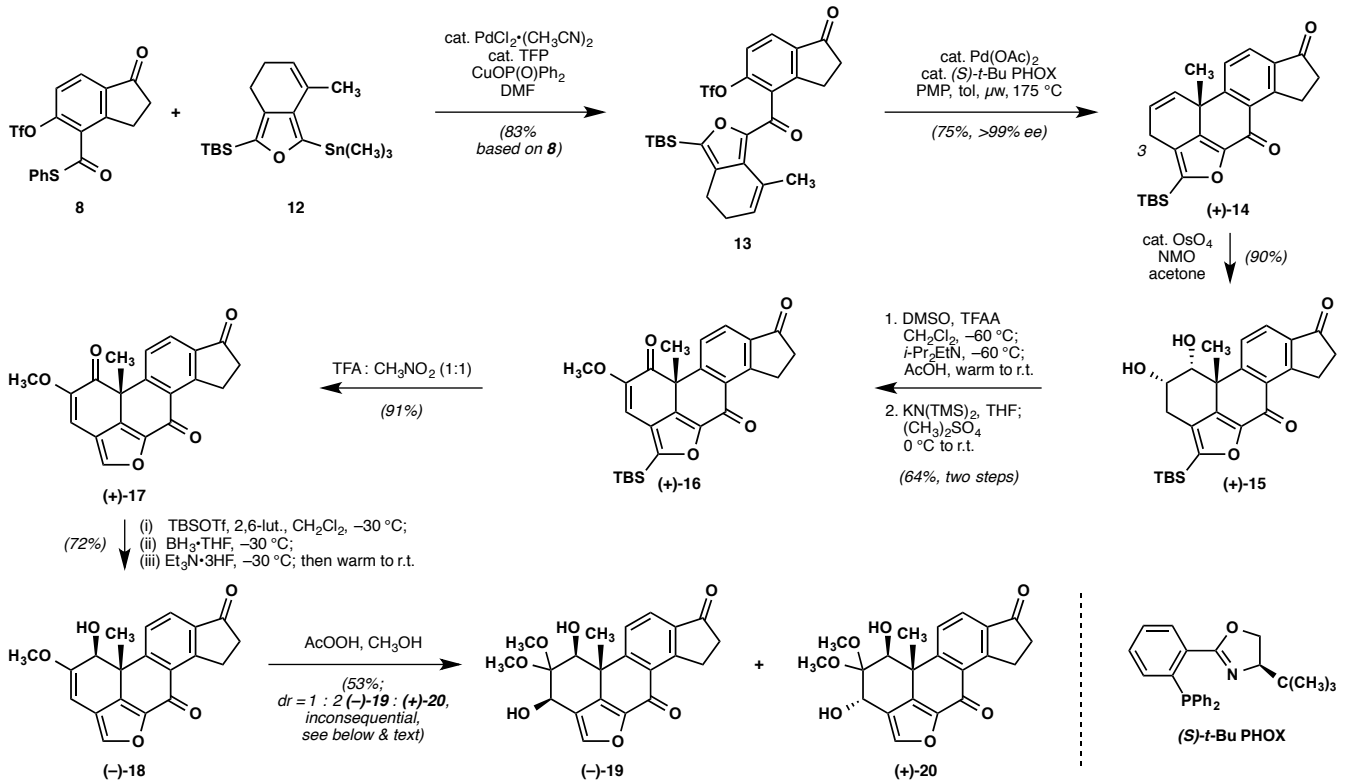
Although we were initially interested in using lithiated **9** in a ketone synthesis with indanone **8**, the superiority of a Liebeskind stannane-thioester coupling[16] quickly became evident (see Scheme 2). At first, the site of oxidative addition on indanone **8** was uncertain (aryl triflate versus thioester), though in practice only reaction of the thioester was observed, furnishing diketone **13** in high yield (83% based on **8**) on a multi-gram scale. In the stereochemically-defining event of our synthesis, ketone **13** undergoes highly enantioselective intramolecular Heck reaction catalyzed by a *t*-Bu-PHOX-ligated Pd(0) complex.[17] In line with previous observations, the use of this ligand with 1,2,2,6,6-pentamethylpiperidine is crucial in achieving complete reactant consumption and in minimizing alkene isomerization (observed with diphosphine ligands; see the Supporting Information for additional discussion of this reaction).[17a,b] Heck cyclization thus furnishes **14** in 75% yield and high enantioselectivity (>99% *ee*).

Unconjugated alkene **14** bears the complete carbon skeleton of viridin, but resides at a much lower oxidation state. We believe this dichotomy of complexity, manifest in the work of others as well, is why no synthesis of viridin has followed Sorensen's work.[9,12] The first step to ameliorate this oxidation state difference is a diastereoselective Upjohn dihydroxylation, furnishing diol **15**; the relative flatness of the A-, B-, and C-rings[7] ensures that the angular methyl group biases reactions to occur on the α-face in this and several ensuing reactions. Next, double Swern oxidation and *O*-methylation gives methoxy enone **16** in 65% isolated yield over two steps. Of strategic importance, taking advantage of the propensity of 1,2-diketones to exist as their tautomeric forms is an indirect way to oxidize at C3, an essential transformation given that we were unable to oxidize at this position of intermediate **14** by other means in other, unsuccessful approaches. Additionally, the acidity of the diosphenol unit permitted site-selective deprotonation and alkylation, sparing the D-ring.

The TBS group in **16** is removed by stirring this intermediate in 1:1 TFA:CH_3NO_2 for two days; all fluoride-based desilylations lead to decomposition. Site- and diastereoselective reduction of **17** is then accomplished using a three-stage, single-flask operation wherein: (1) the D-ring ketone is temporarily protected as an enol silyl ether, (2) the A-ring ketone is selectively reduced with BH_3•THF; and (3) the intermediate reduction product is desilylated with Et_3N•3HF, delivering keto alcohol **18** in 72% isolated yield.

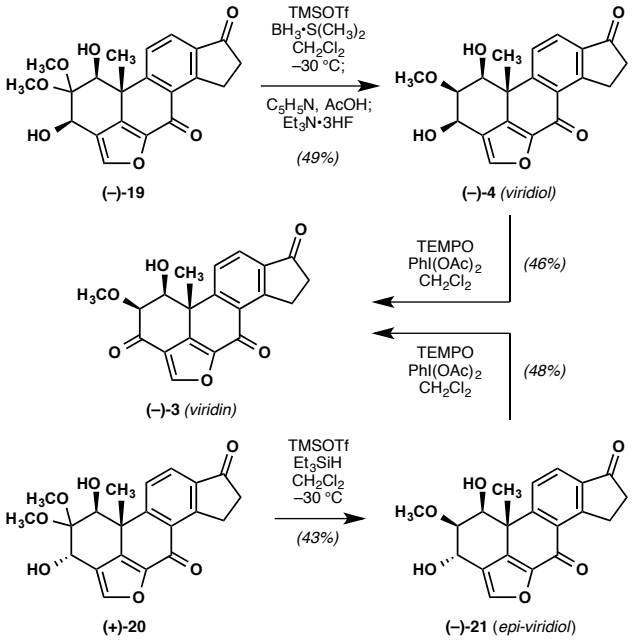
At first glance, allylic alcohol **20** is only two steps away from viridin, namely hydroboration–oxidation and selective alcohol oxidation. However, we were unable to perform the former process, despite strong precedent.[18] Instead, we executed an alkene epoxidation–reduction sequence. Thus, treating enol **18** with AcOOH in methanol delivers an inconsequential 1:2 mixture of hydroxy ketal diastereomers, where methanol was incorporated by design, mirroring chemistry reported in Myers's dynemicin synthesis.[19] This trapping event was incorporated deliberately, for experiments which aimed to generated a C2-ketone failed due to the extreme instability of the desired product, a compound that we were never able to observe in pure form.

Scheme 2. Synthesis of advanced, diastereomeric hydroxy ketals **19** and **20**



Although alkene epoxidation seemed to solve our alkene reactivity problem, ketals **19** and **20** presented a new, stern challenge: diastereoselective demethoxylation, given that their C2 ketone counterparts were intractable. Despite ample precedent for monodealkoxylation of ketals, particularly in the chemical literature on (–)-oseltamivir,[20] the complexity of our intermediates cast a dark shadow over the planned ketal reduction, especially given the possibility for hydride shifts. Nevertheless, as shown in Scheme 3, isolated diastereomers **19** and **20** are demethoxylated using TMSOTf and a hydride donor. The low efficiency of these reactions is due to decomposition of either reactants or products, and not to poor diastereoselectivity.[21] Moreover, both reducing agents, Et_3SiH and BH_3•$S(CH_3)_2$, are effective in the conversion of **19** to **4** (viridiol) and of **20** to **21** (*epi*-viridiol), and the use of each merely reflects the most detailed procedure available at the time these studies were brought to a close. Finally, each isolated diastereomer **4** and **21** is converted to viridin itself using TEMPO-catalyzed oxidation, though a molar excess of each catalyst and terminal oxidant, $PhI(OAc)_2$, were used to force the reaction to proceed at an acceptable rate. Synthetic viridin independently produced from diastereomers **4** and **21** was spectroscopically indistinguishable from each other as well as from the natural product, although we noted a difference in specific optical rotation: synthetic (–)-**3**: $[\alpha]_D = -145°$ (c = 0.23, $CHCl_3$); natural (–)-**3**[2a]: $[\alpha]_D = -222°$ (c = 1.00, $CHCl_3$); see the Supporting Information for a discussion of this discrepancy.

Scheme 3. Completion of the synthesis of viridin (**3**): convergence of alcohols **19** and **20** via viridiol (**4**) and *epi*-viridiol (**23**)



In summary, our synthesis of (–)-viridin up to fragments **8** and **12** is direct and efficient, permitting rapid assembly and late-stage functionalization of the A-ring. Thereafter, several novel and strategic maneuvers are executed including: (1) an intramolecular, highly enantioselective Heck reaction to set the absolute stereochemical course of the synthesis; (2) double Swern oxidation to indirectly oxidize C3; (3) an epoxidation-trapping

sequence to install a hydroxyl group at C3; and (4) highly diastereoselective demethoxylation to address functionality at C2. We emphasize that although our syntheses are built on the edifice of a highly enantioselective, intramolecular Heck reaction, the uncertainty of the path forward loomed large, especially in light of other studies where the viridin skeleton was secured but the natural product itself remained elusive.[9] Our syntheses of (–)-viridiol and (–)-viridin generate these targets as single enantiomers for the first time and proceed in 17 and 18 steps, respectively, from commercially-available materials, and thus compare favorably to prior art (for complete disclosure regarding step counting methodology, see the Supporting Information). More generally, by demonstrating the feasibility of a fragment coupling approach to access the viridin core, we enable the synthesis of analogs with deep-seated modifications to the C,D-ring system for medicinal chemistry investigations.

ASSOCIATED CONTENT

Experimental procedures and spectroscopic data for all isolated intermediates, as well as additional references and discussion. The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interest.

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