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Total Synthesis of Viridin and Viridiol

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Supporting Information Placeholde

ABSTRACT: The asymmetric total synthesis of (-)-viridin and (-)-viridiol, antifungal metabolite from *Gliocladium virens*, was achieved in 17 and 18 steps from a commercially available starting material. An intramolecular [3+2] cycloaddition was applied to an easily available *L*-ribose derivative in order to construct the highly substituted D ring containing the key chiral *cis*-triol fragment. Co-catalyzed metal-hydride H atom transfer (MHAT) radical cyclization was utilized to form the C-ring and the all-carbon quaternary center at C-10. This convergent strategy provides a scalable approach to prepare viridin and viridiol for biological studies.

The furanosteroids viridin (**1**)[1] from *Gliocladium virens* and wortmannin (**2**)[2] from *Penicillium wortmannii* are biogenetically related to the natural products demethoxyviridin (**3**),[3] viridiol (**4**),[4] demethoxyviridiol (**5**),[3] 9-*epi*-viridiol (**6**)[5], nodulisporiviridin E (**7**)[6] and to dinor-carbon wortmannin derivatives such as wortmannine B (**8**) (Figure 1).[7] Furanosteroids strongly inhibit phosphatidyli-nositol 3-kinase (PI3K),[8] whose overactivity in many cancers is associated with reduced apoptosis and enhanced survival and growth of tumor cells. These compounds therefore show potential as anticancer drugs, but natural furanosteroids such as wortmannin (**2**) are rapidly degraded and highly toxic *in vivo*. Modifying furanosteroids may increase their pharmaceutical potential, as Wipf and coworkers demonstrated when they altered the structure of wortmannin into PX-866 (**9**), which is currently in Phase II clinical trials.[9] Here we report the asymmetric total synthesis of (-)-viridin (**1**) and (-)-viridiol (**4**) through a convergent and scalable approach, which forms part of our larger effort to develop new strategies for the total synthesis of structurally and biogenetically related natural products for medicinal chemistry and biological studies.[10]

Viridin (**1**)[11] features a highly-oxygenated steroid skeleton (A-B-C-D rings) with an extra furan ring (E ring) (Figure 1). The D ring contains three contiguous chiral centers, including a benzylic quaternary carbon center at C-10 and a *cis*-diol unit at C-1,2. Based on this structural analysis, we realized that improving the overall synthetic efficiency would depend on (1) precisely constructing the carbon steroid skeleton, and (2) stereocontrolling the oxidation state. In 2004, the group of Sorensen reported the first total syntheses of viridin (**1**) and viridiol (**4**) involving rhodium-catalyzed cyclotrimerization, ring-closure metathesis and thermal electrocyclic rearrangement.[12,13] Guerrero and co-workers reported an elegant enantioselective synthesis of **1** and **4** through a convergent approach using an asymmetric intramolecular Heck reaction to form the core pentacyclic ring.[14] Based on these pioneer work, we realize that forming the congested *cis*-diol fragment in the D ring is a challenging task. Efforts so far have focused on introducing functional groups and controlling the stereochemistry of late-stage operations (Scheme 1A).

As an alternative approach, we planned to introduce the chiral

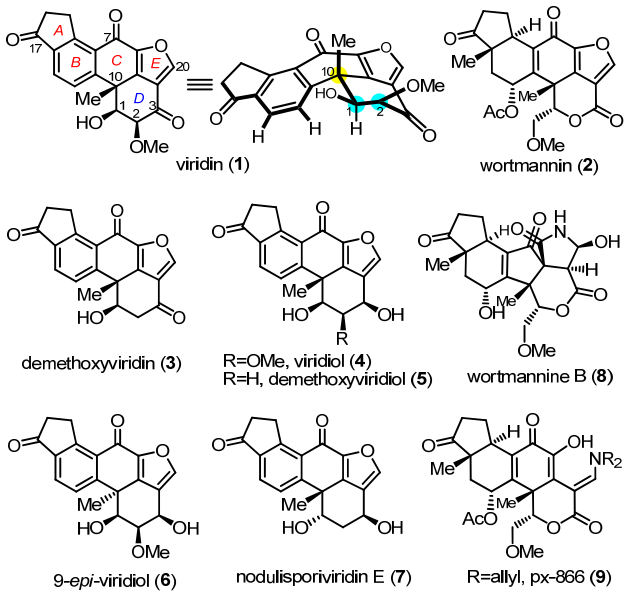
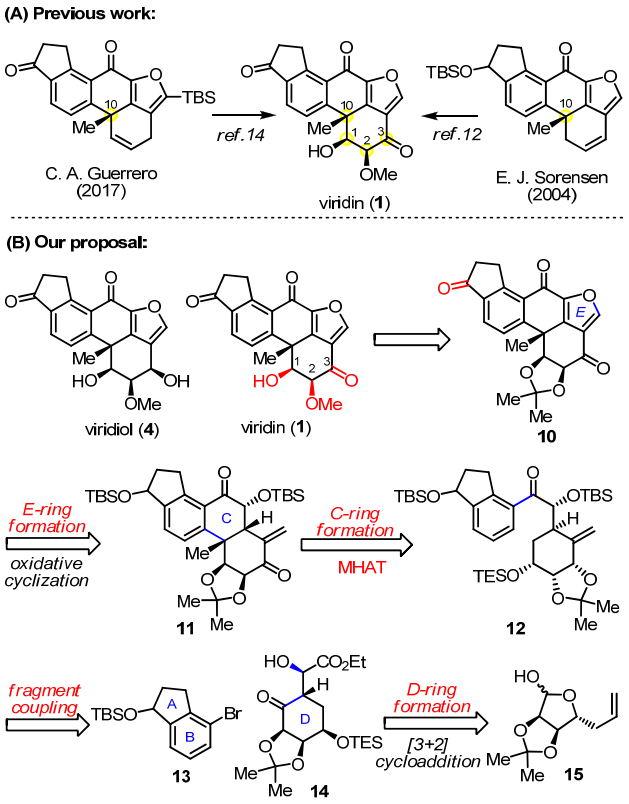


Figure 1. Structures of furanosteroids.

cis-diol unit at the very beginning of the synthesis using the easily available chiral starting material *L*-ribose (Scheme 1B). Intramolecular [3+2] cycloaddition would be used to construct **14** containing the highly substituted D ring with the key chiral *cis*-triol fragment. Coupling **14** with the dihydroindenol fragment **13** would furnish intermediate **12**, which would undergo a Co-catalyzed metal-hydride H atom transfer (MHAT) radical reaction to cyclize and thereby close the C-ring with an all-carbon quaternary center at C-10.[15] We predicted that the stereochemistry of MHAT cyclization would be substrate-controlled, giving the desired tetracyclic compound **11**. Installing the furan E ring and changing the oxidation state of the D ring would produce viridin (**1**) and viridiol (**4**). We reasoned that the MHAT radical reaction would not only allow the scalable preparation of viridin (**1**), but also serve as a useful methodology in the retrosynthetic disconnection.

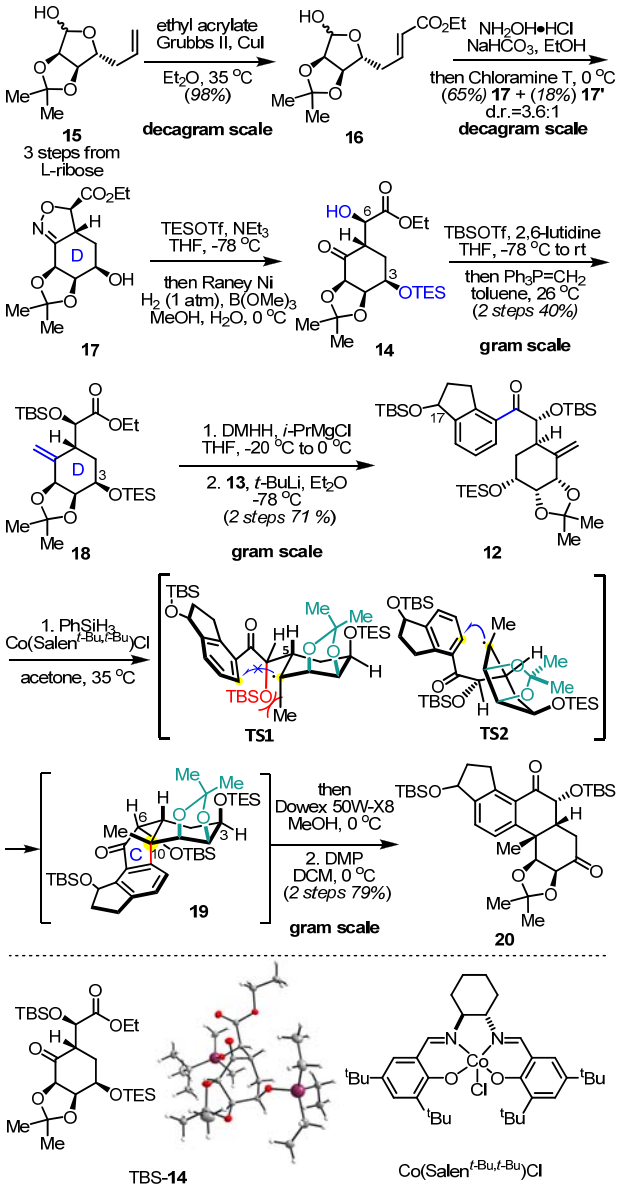


Scheme 1. Retrosynthetic analysis of viridin

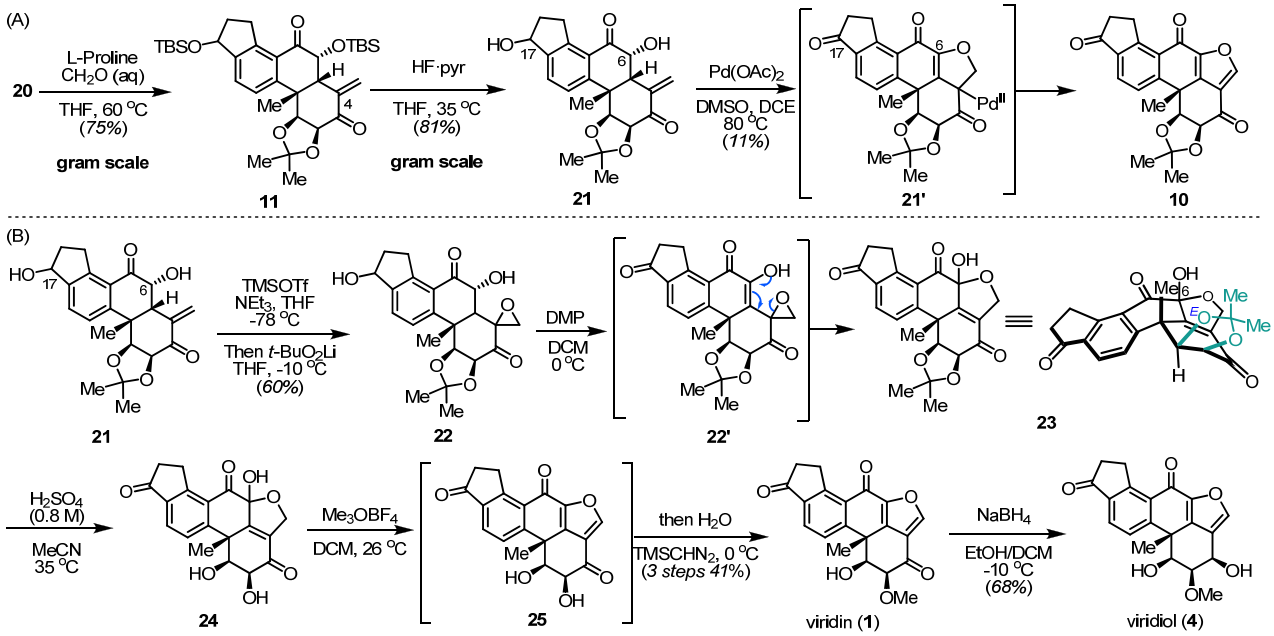
Our synthesis commenced with the preparation of the highly oxygenated D-ring **18** (Scheme 2). The known sugar derivative **15**, easily prepared in large quantities (>30 g) in 3 steps from *L*-ribose,[16] was transformed via Ru-catalyzed cross metathesis to unsaturated ester **16** in 98% yield. Hydroxylamine treatment of **16** gave the oxime intermediate, which was used directly in subsequent [3+2] cycloaddition. Chloramine-T oxidation of the crude oxime[17] generated a nitrile oxide, which was intramolecularly trapped by the unsaturated ester, thereby affording the desired isoxazoline **17** on the >25 g scale in 65% yield and diastereoisomer product **17'** in 18% yield (d.r. = 3.6:1). Silyl protection of the C-3 hydroxyl group, followed by reductive cleavage of the isoxazoline ring in a one-pot operation, gave rise to **14** containing multiple sensitive functional groups, including α- and β-hydroxyl carbonyl fragments. Enolization of the carbonyl group facilitated epimerization of the side chain on C-5 under acidic or basic conditions. Therefore, **14** was used directly in the next transformation without further purification. The hydroxyl group on C-6 was masked as a TBS ether, and the structure and stereochemistry of **TBS-14** was confirmed using x-ray diffraction. The carbonyl group was methylenated with triphenyl phosphonium ylide via Wittig reaction to afford the desired terminal olefin **18** in 40% yield over 2 steps.

Compound **18,** which bears all the necessary functional groups and stereocenters required for the D ring of viridin and related furanosteroids, was converted to its Weinreb amide.[18] This amide then interacted with the anion of dihydroindenol fragment (±)-**13** to furnish **12**, as an inconsequential mixture of diastereomers at C-17, the precursor for radical cyclization. Inspired by the pioneering work of the Shenvi[15a-d] and Baran[15e-f] groups, we planned to close the C ring and build the all-carbon quaternary center at C-10 via a MHAT radical reaction. To our satisfaction, reaction of **12** with catalytic Co(Salen^{tBu,tBu})Cl in the presence of $PhSiH_3$ in anhydrous acetone gave the desired tetracyclic core **19** as a single diastereomer at C-10 in excellent yield.[15b] To the best of our knowledge, this is the first use of the MHAT reaction to synthesize aromatic steroids. This strategy provides an alternative approach to rapidly generate the core structure of a large family of terpenoids, such as aromatic abietane diterpenoids.[19]

We reasoned that the stereochemistry of MHAT cyclization was precisely controlled due the configuration of the radical intermediate **TS-1** and **TS-2** (Scheme 2), wherein the side chain on the C-5 located on the equatorial bond of the cyclohexane D ring.[20] Structural analysis suggests that the D ring of **TS-1** switches to the chair conformation to avoid ring strain due to the additional acetonide ring which results a 1,3-interaction between the OTBS and the methyl group. While intermediate **TS-2** maintains a twisted boat conformation and no such steric effect occurs. These considerations lead us to hypothesize that the intermediate **TS-2** is a favorable transition state for the radical cyclization to generate tetracyclic core **19** despite greater ring strain. Then, we selectively deprotected the TES group, producing a free hydroxyl group on C-3, which we oxidized with Dess–Martin periodinane to yield dicarbonyl compound **20** in 79% yield over 2 steps.[21]



Scheme 2. MHAT radical cyclization to construct the tetracyclic ring



Scheme 3. Total synthesis of viridin and viridiol.

To continue our synthesis towards (-)-viridin and (-)-viridiol, we planned to perform one-carbon homologation on C-4 as a first step towards building the mutiply-substituted furan ring. However, this approach did not work because of the heavily oxygenated carbocycle D ring. After extensive studies, we found that enamine chemistry was effective (Scheme 3A). Treating **20** with *L*-proline in the presence of formaldehyde afforded the unsaturated ketone in 81% yield. We then investigated Pd-promoted dehydrogenation and Wacker-type cyclization[22] to adjust the oxidation state and construct the furan E ring. After careful optimization of (see Table 1 in Supporting Information), we found that allowing **21** to stand in 1,2-dichloroethane containing palladium (II) acetate gave rise to the desired product **10** in only 11% yield. We propose that **10** forms through a cascade of dehydrogenation of the hydroxyl groups on C-17 and C-6, intramolecular enol-palladation, and reductive elimination of intermediate **21'**. We attribute the low reaction yield to formation of an unstable tetracarbonyl intermediate that is more likely to undergo oxidative cleavage and decomposition. Deprotection of the acetonide in **10** followed by methylation generated viridin (**1**). The high oxidation state of **10** made it unstable under acidic conditions (BCl_3), such that addition of the methylation reagent trimethyloxonium tetrafluoroborate (Me_3OBF_4) produced viridin (**1**) in trace amounts.

Changing strategy, we performed epoxidation of the terminal olefin of **21** using *t*-BuO_2Li,[23] yielding unstable epoxide **22** (Scheme 3B). Oxidation of the C-6 hydroxyl group with Dess–Martin periodinane[20] efficiently converted **22** to the desired pentacyclic product **23**. We propose that the active tetracarbonyl intermediate **22'** exists in an enol form that promotes epoxide opening and hemiacetylation, thereby affording the furan E ring. H_2SO_4-mediated removal of the acetonide moiety of compound **23** gave the *cis*-diol **24**. Given the extreme instability of **24** under basic conditions, we quenched the reaction over an ion-exchange resin and then filtered the eluate to obtain crude **24**. We originally predicted the dehydration and selective methylation of **24** could be realized by means of trimethyloxonium tetrafluoroborate (Me_3OBF_4). Indeed, reaction of **24** with Me_3OBF_4 afforded the dehydration product **25**, but the rate of methylation was slow due to the newly produced fluoroboric acid. Then we added trimethylsilyldiazomethane ($TMSCHN_2$) to the one-pot reaction to accelerate methylation, and yielded the target natural product (**1**) in 41% yield over 3 steps. Selective reduction of the carbonyl group at C-3 with sodium borohydride generated viridiol (**4**) in 68% yield.[13] The synthetic compounds **1** and **4** showed the same spectra of ^1H and ^{13}C NMR and high-resolution mass spectrometry as the data reported by Sorensen[12-13] and Guerrero.[14]

In summary, the asymmetric total syntheses of furanosteroids viridin and viridiol were achieved in 17 and 18 steps from the commercially available *L*-ribose, respectively. An intramolecular nitrile oxide-alkene cycloaddition was used to construct the highly substituted D ring with the key chiral *cis*-triol fragment, while Co-catalyzed MHAT radical cyclization was applied to form the C-ring and the all-carbon quaternary center at C-10. We are currently using MHAT cyclization in the total synthesis structurally related natural products which will be reported in the due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

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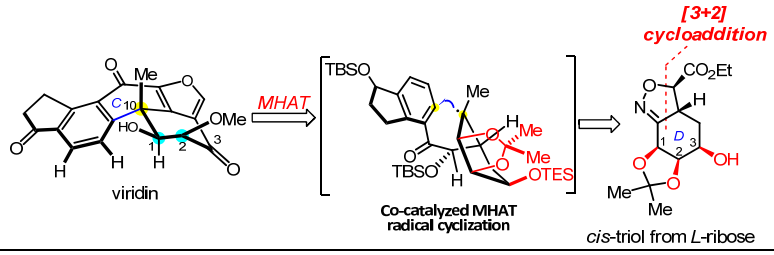
[3+2]
cycloaddition
MHAT
viridin
TBSO
Me
H
Me
Me
OTES
TBSO
H
Co-catalyzed MHAT
radical cyclization
CO2Et
H
OH
Me
Me
cis-triol from L-ribose