Natural Product Synthesis

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Synthesis of (−)-Viriditoxin: A 6,6′-Binaphthopyran-2-one that Targets the Bacterial Cell Division Protein FtsZ**

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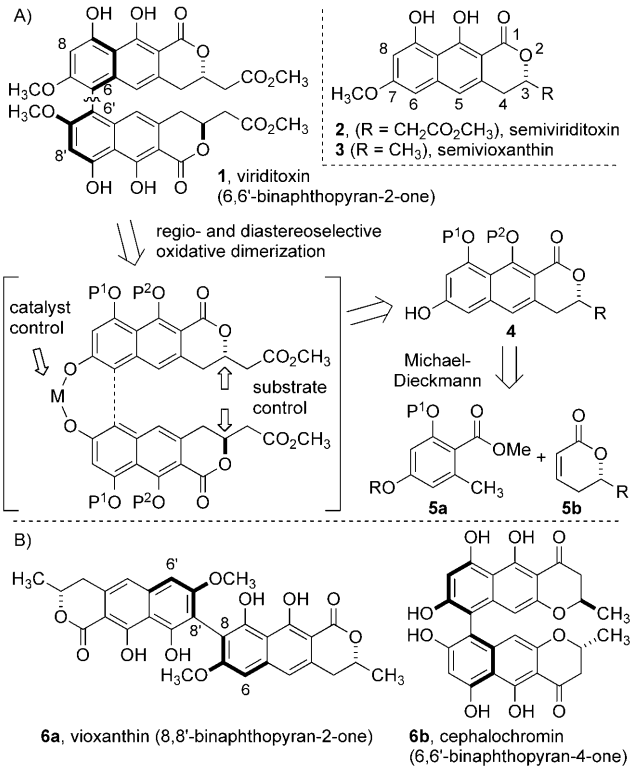
The inhibition of bacterial cell division offers a new approach to controlling resistant bacterial infections.[1,2] FtsZ is a protein of central importance to cell division that is often described as the prokaryotic homolog of tubulin because of the structural similarity of these two proteins, in spite of low sequence homology.[3–5] Both proteins undergo GTP-driven oligomerization and the active sites of both proteins are similar. Tubulin forms microtubules in the bipolar spindle assembly, which mediates chromosome separation in eukaryotes. FtsZ oligomerizes at midcell during bacterial cell division to form the Z-ring, which constricts to induce septation. Inhibition of FtsZ has been validated as a potential new therapeutic strategy for fighting resistant infections, including methicillin-resistant *Staphylococcus aureus* (MRSA).[6–8] In stark contrast to tubulin, few FtsZ-targeting natural products are known and no information regarding the molecular basis of their inhibition of FtsZ has been documented.[9–12] The development of efficient syntheses for FtsZ-targeting natural products will enable elucidation of their mechanisms of inhibition and enable further development of this target. Here, we describe the synthesis of viriditoxin, one the most potent FtsZ-targeting natural products and the first 6,6′-binaphthopyranone to be synthesized.[13]

Viriditoxin was discovered as an FtsZ inhibitor by researchers at Merck in a high-throughput biochemical screen.[14] The 6,6′-binaphthopyranone structure, previously isolated from *Aspergillus viridinutans* (Scheme 1) was originally misassigned as having 8–8′ linkage like that of vioxanthin (**6a**, Scheme 1).[15–17] 6,6′-Binaphthopyran-2-ones are uncommon natural products and so far only four others have been reported.[18–20] A small number of the biosynthetically related binaphthopyran-4-ones, such as cephalochromin (**6b**, Scheme 1), have also been reported.[21–25] Although the absolute configuration at C3 of semivirididitoxin was recently confirmed by synthesis,[26] the axial configuration of viriditoxin was not known unequivocally at the outset of our studies.



Scheme 1. A) Structures of viriditoxin, semiviriditoxin, and semi-vioxanthin; retrosynthesis of viriditoxin. B) Structures of vioxanthin (**6a**), an example of an 8,8′-binaphthopyran-2-one, and cephalochromin (**6b**), an example 6,6′-binaphthopyran-4-one.

The key bond construction in viriditoxin is the stereoselective formation of the 6–6′ biaryl linkage. Strategies for achieving atropselectivity in the construction of complex molecules have been recently reviewed.[27,28] Subsequent recent examples for asymmetric biaryl construction often employ auxillary- and catalyst-controlled oxidative homocoupling[29–31] and cross-coupling reactions.[32–35] In two complementary approaches, atropselectivity can also be realized by the asymmetric de novo assembly of aromatic rings in cycloadditions[36–41] and by dynamic kinetic resolution polycyclic lactones through aminolysis[42] or reduction.[43] Most of these strategies rely on either the influence of chiral catalysts

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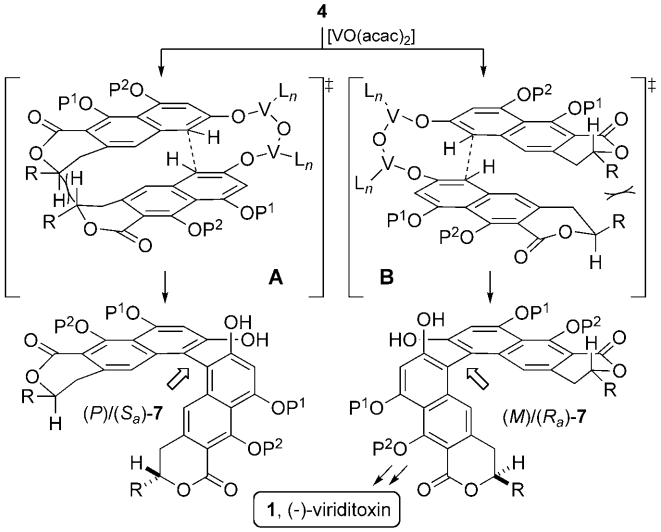
or proximal stereogenic centers in the substrate or covalently linked chiral auxiliary. We set out to explore the influence of remote stereogenic centers, that is, those located more than three bonds from the reacting aromatic carbon center, in the catalytic oxidative dimerization of naphthols. Two previous examples of similarly remote influence in the oxidative dimerization of arylcuprate intermediates have been reported in studies leading to the synthesis of phleichrome and related perylenequnione natural products.[44,45]

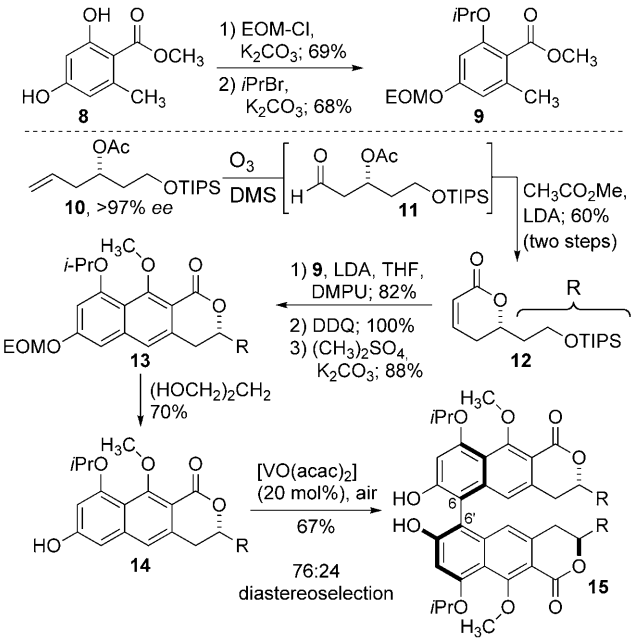
Several oxidation catalysts have been employed in the dimerization of naphthols and the vanadium-catalyzed process reported by Uang et al. was best suited to the substitution pattern of **4**.[46] Two diastereomeric transition states (**A** and **B**, Scheme 2) could lead to the two possible isomers of biaryl



Scheme 2. Remote asymmetric induction in the dimerization of **4**.

intermediate **4**. Although the mechanism of this reaction is unclear, several studies suggest that the active catalyst might be bimetallic,[47] possibly a μ-oxo dimer,[48] albeit of undefined oxidation state and ligation. Under this assumption, the naphthopyranone rings could be expected to react in an antiparallel fashion in which the stereogenic centers of the pyranone ring would be forced into proximity. This ring system favors the equatorial conformation (shown), which forces an interaction between either the axial hydrogen atoms (**A**) or the equatorial alkyl substituents (**B**). These two transition structures lead to the (*M*)/(*R*$_a$) or (*P*)/(*S*$_a$) isomers of binaphthopyranone **7**, the latter of which leads to the proposed configuration of viriditoxin.

A suitable tricyclic precursor for viriditoxin was prepared from orsellinic acid derivative **9** and pyranone **12**, each of which was available in two steps from known compounds (Scheme 3).[49–52] A Michael addition–Dieckmann condensation sequence was employed to yield naphthopyranone **13** after subsequent oxidation and methylation. Although this route is ostensibly less efficient than the Staunton–Weinreb condensation of the corresponding β-alkoxy pyranone,[17,53,54] we observed significantly higher yields in the two-step



Scheme 3. Stereoselective assembly of core of viriditoxin. LDA = lithium diisopropylamide; DMPU = *N*,*N*′-Dimethylpropyleneurea; DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone; DMS = dimethylsulfide; TIPS = triisopropylsilyl; EOM = ethoxymethyl.

process.[55,56] The ethoxymethyl (EOM) ether was readily cleaved by propylene glycol providing the dimerization precursor **14**.[57] When **14** was treated with 20 mol% of [VO(acac)$_2$], a rapid reaction ensued, producing a single regioisomer of desired product **15** with respectable diastereoselection favoring proposed transition state **B** (Scheme 2). This is one of the few cases of biaryl bond formation in which appreciable levels of stereocontrol are induced by a distal stereogenic center of the substrate without concomitant ring-formation.[44,45] The stereochemistry of **15** was established though X-ray crystallography (Figure 1).

In order to enhance the atropselectivity of the biaryl bond formation, we explored the possibility of double diastereodifferentiation[58] induced by a chiral vanadium catalyst. Gong et al. have previously demonstrated that BINOL-derived bimetallic vanadium catalysts exhibit appreciable levels of

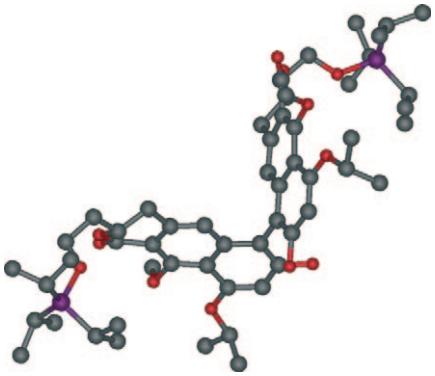
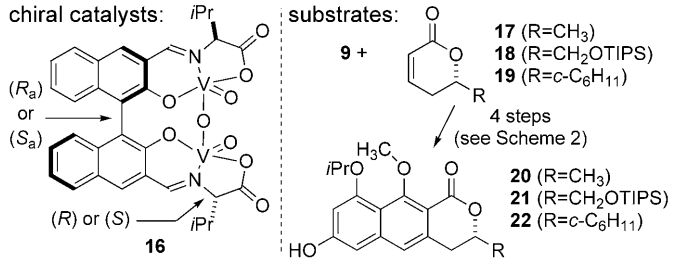


Figure 1. X-ray crystal structure of **15**. Red O, purple Si, gray C.

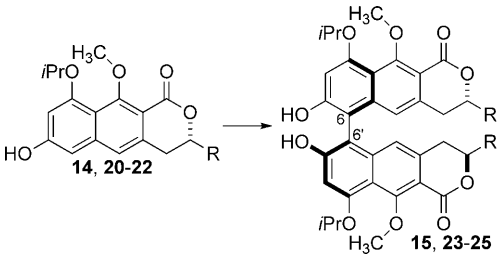


Scheme 4. Chiral vanadium catalysts and variously substituted naphthopyranones for evaluating substrate scope.

enantioselectivity in the oxidative dimerization of naphthols.[48] We prepared four catalysts derived from *R*- and *S*-BINOL and D- and L-valine (Scheme 4).

Although substrate **14** is central to the goal of preparing viriditoxin, we wanted to explore the scope of diastereoselectivity enabled by this new remotely induced axial chirality. Pyranones **17**–**19**, prepared in three steps from the requisite chiral epoxides, were converted to naphthopyranones **20**–**22** in analogy to **14** (Scheme 4).

The chiral bimetallic vanadium catalysts exhibited superior diastereoselectivity and reactivity [Eq. (1), Table 1]. Naphthopyranone **14** was treated with all four isomers of Gong-type catalyst **16** and showed pairwise matched and mismatched selectivity. Specifically, (S_a,*R*)-**16** produced the



(1)

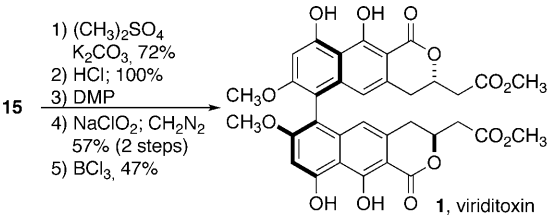
Table 1: Double diastereodifferentiating oxidative couplings with chiral bimetallic vanadium catalysts.

Entry	Substrate, R	Product	Catalyst	d.r. (yield)
1	**14**, $(CH_2)_2$OTIPS	**15**	$[VO(acac)_2]$	76:24 (67%)
2	**14**	**15**	(R_a,*S*)-**16**	19:81
3	**14**	**15**	(R_a,*R*)-**16**	82:18
4	**14**	**15**	(S_a,*S*)-**16**	12:88
5	**14**	**15**	(S_a,*R*)-**16**	**89:11 (87%)**
6	**20**, CH_3	**23**	$[VO(acac)_2]$	60:40 (90%)
7	**20**	**23**	(S_a,*R*)-**16**	90:10 (85%)
8	**20**	**23**	(S_a,*S*)-**16**	18:82 (57%)
9	**21**, CH_2OTIPS	**24**	$[VO(acac)_2]$	61:39 (68%)
10	**21**	**24**	(S_a,*R*)-**16**	96:4 (84%)
11	**21**	**24**	(S_a,*S*)-**16**	30:70 (76%)
12	**22**, *c*-C_6H_{11}	**25**	$[VO(acac)_2]$	56:44 (78%)
13	**22**	**25**	(S_a,*R*)-**16**	83:17 (67%)
14	**22**	**25**	(S_a,*S*)-**16**	11:89 (74%)

[a] Diastereomer ratios determined from ^{1}H NMR spectra of crude reaction mixtures. [b] Axial configuration determined by X-ray crystallography (**15**) and chemical shift comparison (**23**–**25**), see Supporting Information. [c] All reactions performed on a 10 mg scale. A larger scale run (70 mg) for entry 7 proceeded in identical isolated yield.

desired isomer of **15** with selectivity that was enhanced to 89:11 (Table 1, entry 5) whereas the catalyst differing only in the amino acid configuration reversed the selectivity to 12:88 (Table 1, entry 4). The isomeric catalysts derived from *R*-BINOL were mismatched and showed the same sense of induction controlled by the amino acid with lesser degrees of induction. A similar trend was observed for the other substrates for which the selectivity of $[VO(acac)_2]$ was modest and the choice of Gong-type catalysts could produce either isomer as the major product. In addition, the bimetallic catalysts generally provided higher yields than $[VO(acac)_2]$.

The synthesis of viriditoxin was completed in five steps [Eq. (2); DMP = Dess–Martin periodinane]. The 7 and 7′ hydroxy groups of **15** were methylated with dimethyl sulfate



(2)

followed by removal of the TIPS protecting groups. The resultant diol was oxidized to the corresponding diacid and converted to the requisite diester in 57% overall yield. The 9,9′-isopropyl and 10,10′-methyl ethers were cleaved readily with BCl_3 to yield (−)-viriditoxin. The synthetic material exhibited NMR spectra (^{1}H and ^{13}C) that compared favorably with reported values.[59] Synthetic viriditoxin was thus produced in a longest linear sequence of 12 steps from the alkene precursor of **10**.[60]

In conclusion, we have described the first synthesis of a 6,6′-binaphthopyranone natural product and, in so doing, established the relative configuration of viriditoxin. This synthesis represents a general route to related natural products[18,20] and it will enable the exploration of the interactions that result in inhibition of the bacterial cell division protein FtsZ.

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[59] See Supporting Information for a copy of the ^{1}H NMR spectrum supplied by Dr. Singh (Merck). Our observed optical rotation for viriditoxin (−118° and −110°, two different batches) is significantly lower than the original reported value of −202° (see reference [15]) for which no experimental details are given. The high yield observed in the coupling step, that is, the lack of heterodimer formation and a chiral HPLC trace of **28** (see Supporting Information) are both consistent with high optical purity.
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