Published in final edited form as:

Angew Chem Int Ed Engl. 2011 April 11; 50(16): 3730–3733. doi:10.1002/anie.201007298.

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 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. This communication describes 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 stereochemistry at C3 of semiviriditoxin was recently confirmed by synthesis,^[26] the axial configuration of viriditoxin was not known unequivocally at the outset of our studies

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 auxiliary- and catalyst-controlled oxidative homo-coupling^[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 or proximal stereogenic centers in the substrate or covalently-

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Supporting information for this article is available on the WWW under <http://www.angewandte.org>.

linked chiral auxiliary. We set out to explore the influence of *remote* stereogenic centers, i.e. 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 perylenequinone natural products.^[44, 45]

Several oxidation catalysts have been employed in the dimerization of naphthols and the vanadium-catalyzed process reported by Uang 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 intermediate **4**. Although the mechanism of this reaction is unclear, several studies suggest that the active catalyst might be bi-metallic,^[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 anti-parallel 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-Dieckman 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 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 through X-ray crystallography (Figure 1).

In order to enhance the atropselectivity of the biaryl bond-formation, we explored the possibility of double diastereo-differentiation^[58] induced by a chiral vanadium catalyst. Gong has previously demonstrated that BINOL-derived bimetallic vanadium catalysts exhibit appreciable levels of 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 pair-wise matched and mismatched selectivity. Specifically, (*S_a*, *R*)-**16** produced the desired isomer of **15** with selectivity that was enhanced to 89:11, (Table 1, entry 4) whereas the catalyst differing only in the amino acid configuration reversed the selectivity to 12:88 (Table 1, entry 5). The isomeric catalysts derived from *R*-BINOL were mis-matched 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). The 7 and 7' hydroxyl groups of **15** were methylated with dimethyl sulfate 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 BCl₃ to yield (–)-viriditoxin. The synthetic material exhibited NMR spectra (¹H and ¹³C) that compared favourably 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.

Supplementary Material

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Acknowledgments

This research was supported by start-up funds from the University of California, Davis, the Petroleum Research Fund (administered by the ACS), and the NIH/NIAID (R56AI080931-01 & R01AI080931-01). This work was initiated at the Broad Institute of Harvard and MIT, where it was supported by the NIH/NIAID (R03 AI062905-01) and the Scientific Planning and Allocation of Resources Committee (SPARC). MGL thanks the Fundación Ramon Areces for a postdoctoral fellowship. The authors thank Prof. Jon Clardy (Harvard Medical School) for helpful discussions, Prof. Dean Tantillo for DFT calculations and Dr. Sheo Singh (Merck Research Laboratories) for providing copies of NMR spectra for viriditoxin.

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- [59]. See supporting information for a copy of the ¹HNMR 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, i.e. 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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Figure 1.
X-ray crystal structure of **15**.

Figure 2.

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

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

Scheme 3.

Stereoselective assembly of core of viriditoxin.

LDA=lithium diisopropylamide; DMPU = N,N'-Dimethylpropyleneurea; DDQ = 2,3-dichloro-5,6-dicyanobenzoquinone; DMS = dimethylsulfide

Scheme 4.

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

Table 1

Double diastereo-differentiating oxidative couplings with chiral bimetallic vanadium catalysts.

entry	substrate (R)	product	catalyst	dr (yield)
1	14 (CH ₂ CH ₂ OTIPS)	15	VO(acac) ₂	76:24 (67%)
2	14	15	(R _a ,S)- 18	19:81
3	14	15	(R _a ,R)- 18	82:18
4	14	15	(S _a ,S)- 18	12:88
5	14	15	(S _a ,R)- 18	89:11 (87%)
6	20 (CH ₃)	23	VO(acac) ₂	60:40 (90%)
7	20	23	(S _a ,R)- 18	90:10 (85%)
8	20	23	(S _a ,S)- 18	18:82 (57%)
9	21 (CH ₂ OTIPS)	24	VO(acac) ₂	61:39 (68%)
10	21	24	(S _a ,R)- 18	96:04 (84%)
11	21	24	(S _a ,S)- 18	30:70 (76%)
12	22 (c-C ₆ H ₁₁)	25	VO(acac) ₂	56:44 (78%)
13	22	25	(S _a ,R)- 18	83:17 (67%)
14	22	25	(S _a ,S)- 18	11:89 (74%)

[a] Diastereomer ratios determined from ¹H 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.

TIPS = triisopropylsilyl