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Synthesis of 6,6′-Binaphthopyran-2-one Natural Products: Pigmentosin A, Talaroderxines A and B

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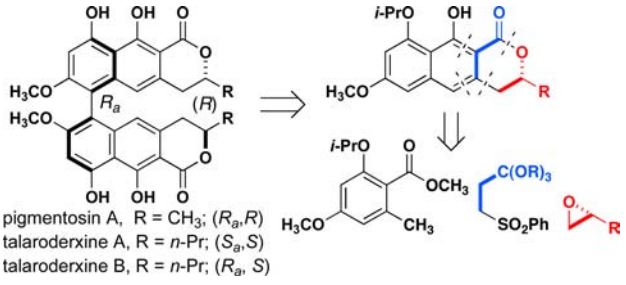
ABSTRACT



Efficient and stereoselective syntheses of pigmentosin A, talaroderxine A, and its diastereomer talaroderxine B are reported. The binaphthyl ring system is assembled by vanadium-catalyzed phenolic coupling of tricyclic precursors. These key intermediates were prepared by Michael–Dieckmann annulation of a protected orsellinate ester, with the requisite pyranones accessed by a new variant of Ghosez's sulfone-epoxide annulation. Preliminary biological experiments are reported for pigmentosin.

6,6′-Binaphthopyranones form a small class of biologically interesting secondary metabolites. Pigmentosin A and talaroderxines A and B (Figure 1) are biosynthetically related natural products isolated from the lichen *Hypotrachyna immaculata*[1] and fungus *Talaromyces derxii*,[2] respectively. These compounds, along with viriditoxin[3] and asteromine,[4] likely result from the oxidative dimerization of condensed polyketide precursors. Our interest in developing general synthetic routes to these compounds stems from their interesting biological activity relevant to fighting bacterial diseases. Specifically, viriditoxin is reported to inhibit the bacterial cell division protein FtsZ,[5] and the talaroderxines were recently reported to inhibit botulinum neurotoxin serotype A (BoNT/A), one of the causative agents in botulism paralysis.[6]

We recently devised an efficient strategy for assembling 6,6′-binaphthopyranones that culminated in the stereoselective synthesis of viriditoxin.[7] The key biaryl bond was formed by an oxidative coupling of an orthogonally protected 7-hydroxy naphthopyranone.[8] The stereochemical outcome of this reaction was subject to complete control by choice of the vanadium catalyst that was employed.[9] We sought to apply this strategy to the synthesis

(1) Elix, J. A.; Wardlaw, J. H. *Aust. J. Chem.* **2004**, *57*, 681–683.
(2) Suzuki, K.; Nozawa, K.; Nakajima, S.; Udagawa, S.; Kawai, K. *Chem. Pharm. Bull.* **1992**, *40*, 1116–1119.
(3) (a) Weisleder, D.; Lillehoj, E. B. *Tetrahedron Lett.* **1971**, *12*, 4705–4706. (b) Suzuki, K.; Nozawa, K.; Nakajima, S.; Kawai, K. *Chem. Pharm. Bull.* **1990**, *38*, 3180–3181.
(4) Arone, A.; Assante, G.; Montorsi, M.; Nasini, G. *Phytochemistry* **1995**, *38*, 595–597.
(5) Wang, J.; Galgoci, A.; Kodali, S.; Herath, K. B.; Jayasuriya, H.; Dorso, K.; Vicente, F.; Gonzalez, A.; Cully, D.; Bramhill, D.; Singh, S. *J. Biol. Chem.* **2003**, *278*, 44424–44428.
(6) Cardellina, J. H., II; Roxas-Duncan, V. I.; Montgomery, V.; Eccard, V.; Campbell, Y.; Hu, X.; Khavrutskii, I.; Tawa, G. J.; Wallqvist, A.; Gloer, J. B.; Phatak, N. L.; Holler, U.; Soman, A. G.; Joshi, B. K.; Hein, S. M.; Wicklow, D. T.; Smith, L. A. *ACS Med. Chem. Lett.* **2012**, *3*, 387–391.
(7) (a) Park, Y. S.; Grove, C. I.; González-López, M.; Urgaonkar, S.; Fettinger, J. C.; Shaw, J. T. *Angew. Chem., Int. Ed.* **2011**, *50*, 3730–3733. (b) Grove, C. I.; Fettinger, J. C.; Shaw, J. T. *Synthesis* **2012**, *44*, 362–371.
(8) For a comprehensive review on strategies for the synthesis of axially chiral compounds, see:Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. *Chem. Rev.* **2011**, *111*, 563–639.
(9) Guo, Q.-X.; Wu, Z.-J.; Luo, Z.-B.; Liu, Q.-Z.; Ye, J.-L.; Luo, S.-W.; Cun, L.-F.; Gong, L.-Z. *J. Am. Chem. Soc.* **2007**, *129*, 13927–13938.

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of pigmentosin A and the related talaroderxines with the ultimate goal of accessing natural and synthetic compounds that might also inhibit the bacterial cell division protein FtsZ. Herein we describe a new reagent for the rapid assembly of pyranones related to **6** and their subsequent use in the first syntheses of pigmentosin A, talaroderxine A, and talaroderxine B.

Synthesis of the two tricyclic cores required two key fragments (Figure 1). The orthogonally protected orsellinic methyl ester **5** was used in the viriditoxin synthesis and is available in three steps from methyl acetoacetate. The second fragment is a C-3 chiral α,β-unsaturated lactone, which could be accessed a variety of ways. For pigmentosin A, **6a** could be made by elongation of commercially available hydroxy acid **8** and cyclization. A similar route was not available for the talaroderxines. We anticipated employing a sequence that would start with alcohol **10**, available from enantioselective allylation of *n*-butyraldehyde. An attractive alternative that would provide the most general access to the requisite pyranones involved using

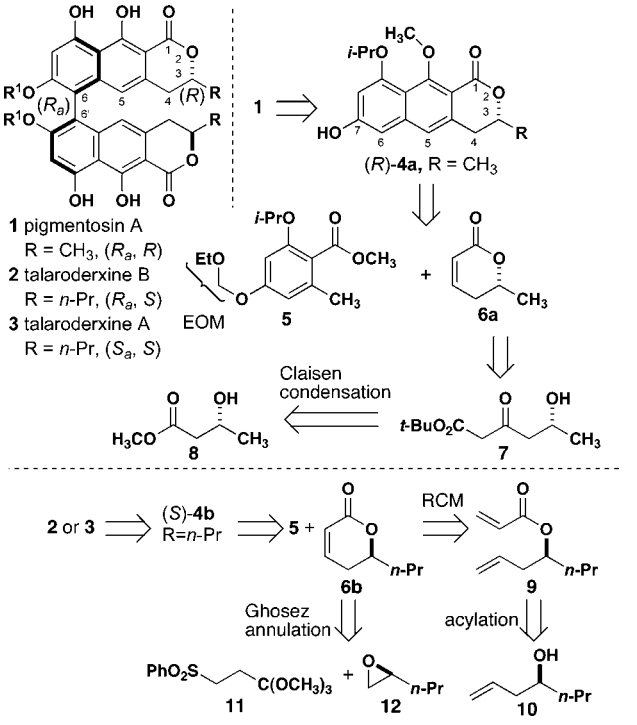


Figure 1. Retrosynthesis of pigmentosin A shown. Compounds **2** and **3** were omitted for clarity.

sulfone **11** in an annulation route reported by Ghosez. We ultimately examined both routes and discovered a general solution to the drawbacks associated with the preparation and handling of **11**.

Lactones **6a** and **6b** were prepared in short sequences. Commercially available methyl-(*R*)-3-hydroxybutyrate **8** was elongated with the lithium enolate of *tert*-butyl acetate,[10] then reduced, and cyclized with concomitant dehydration by acid catalysis (Figure 2). Initially **6b** was accessed via an enantioselective Keck allylation[11] of *n*-butyraldehyde to provide homoallylic alcohol **10** followed by acryloylation and ring closure using Grubbs' second generation catalyst. Although the synthesis of **6b** was concise and stereoselective, we were interested in a sequence avoiding alkyltin reagents that could be generalized for the synthesis of analogs.

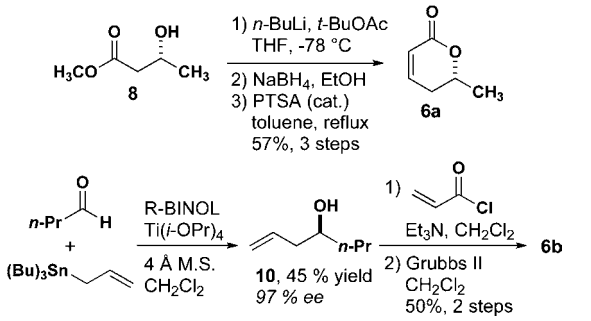
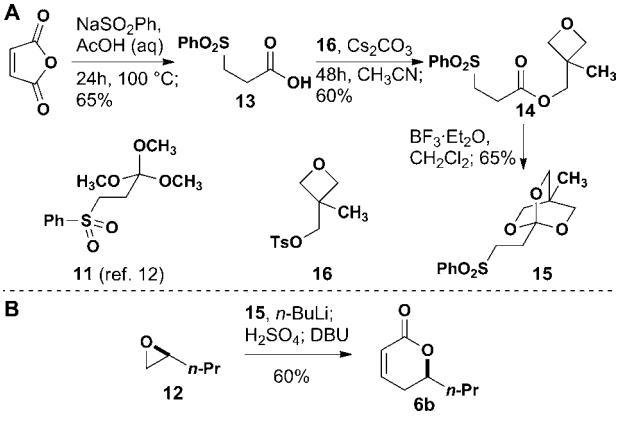


Figure 2. Synthesis of lactones **6a** and **6b**.

We envisioned using trimethyl-3-phenylsulfonyl orthopropionate **11** employed by Ghosez to access lactones from enantiopure epoxides.[12] This attractive route can, in theory, provide a one-pot synthesis of unsaturated lactones related to **6** from any epoxide. That said, we experienced extreme difficulty in the preparation of sulfone **11**, consistent with other studies of this compound subsequent to the original report.[13] In order to circumvent the liabilities of the original route, we designed a new reagent, namely 2,6,7-trioxabicyclo[2.2.2]octane (OBO) sulfone ester **15**. Treatment of maleic anhydride with benzene sulfinic acid sodium salt in refluxing aqueous acetic acid provided **13** in good yield.[14] Esterification of the free acid with **16** followed by Lewis acid catalyzed rearrangement provided **15** (Scheme 1A) in good yield. Sulfone **15** is a white, crystalline

Scheme 1. Synthesis of OBO-Sulfone **14** and Assembly of **6b**

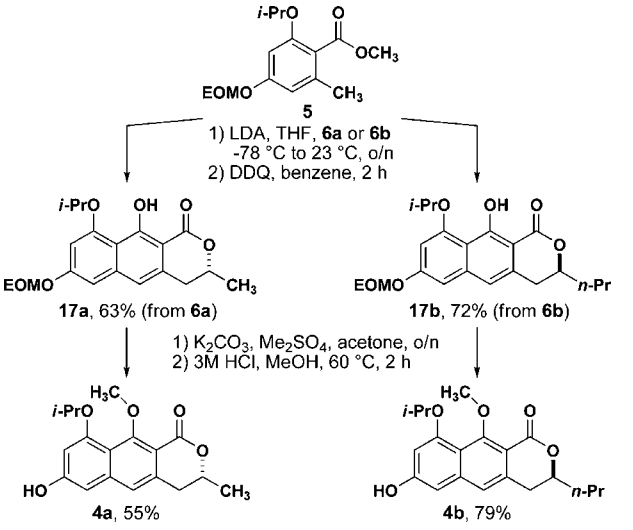


(10) Drochner, D.; Muller, M. *Eur. J. Org. Chem.* **2001**, 211–215.

solid that is bench-stable and easily prepared in multigram quantities. Treatment of epoxide **12**[15,16] with the lithium anion of **15** produced **6b** (Scheme 1B) in 60% overall yield after hydrolysis, lactonization, and elimination. Under optimal conditions, 1.3 equiv of **15** was employed whereas 3 equiv of **11** were often employed in related transformations.

The naphthopyranones needed for the key phenolic coupling reaction were prepared in short sequences from **6a** and **6b** (Scheme 2). Michael–Dieckmann annulation with the lithium enolate of **5**[7a] proceeded smoothly with **6a**

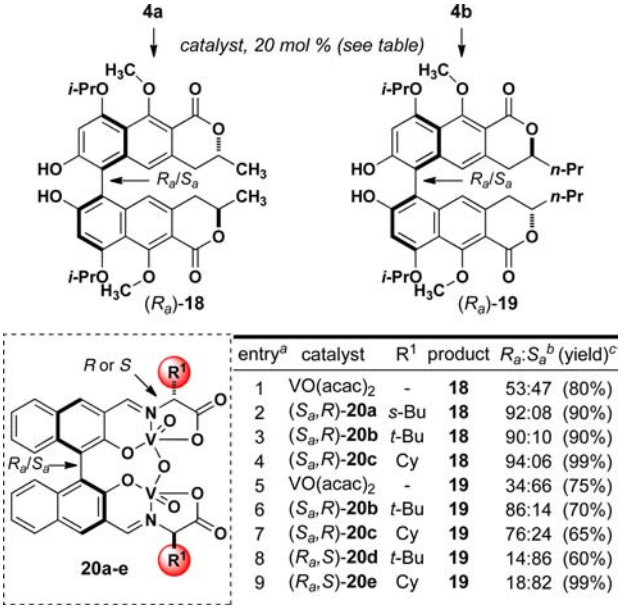
Scheme 2. Synthesis of Naphthopyranones **4a** and **4b**



and **6b** to furnish **17a** and **17b**, respectively after oxidation. We have previously observed higher yields from this two-step process when compared to the one-step Staunton–Weinreb conditions employing β-alkoxy pyranones.[17]

Naphthopyranones **4a** and **4b** underwent atrop-selective phenolic coupling reactions that were controlled by the structure of the catalyst. $VO(acac)_2$ catalyzed coupling of **4a** proceeded in good yield and with little diastereoselectivity. Use of Gong-type[9] catalysts produced (R_a)-**19** with high atrop-selectivity that topped out at 94:6 with catalyst (S_a,*R*)-**20c**, which is derived from cyclohexylglycine. The couplings of **4b** were generally less selective. Treatment of **4b** with the optimal catalyst for **4a** resulted in a disappointingly low ratio of 76:24 selectivity (entry 6) favoring (R_a)-**19**, i.e. the isomer that would eventually lead to talaroderxine B. Changing the catalyst substituent from *cyclo*-hexyl to *tert*-butyl boosted the selectivity up to 86:14. A similar trend was observed for the production of (S_a)-**19**, with the enantiomeric catalyst (R_a,*S*)-**20d** producing a nearly complete reversal of selectivity (14:86). The configuration of the products is assigned based on analogy to our previous studies.

Table 1. Oxidative Coupling of Naphthopyranones Stereochemistry at C-3 Shown as R for Clarity



entry[a]	catalyst	R^1	product	R_a:S_a[b] (yield)[c]
1	$VO(acac)_2$	-	**18**	53:47 (80%)
2	(S_a,*R*)-**20a**	*s*-Bu	**18**	92:08 (90%)
3	(S_a,*R*)-**20b**	*t*-Bu	**18**	90:10 (90%)
4	(S_a,*R*)-**20c**	Cy	**18**	94:06 (99%)
5	$VO(acac)_2$	-	**19**	34:66 (75%)
6	(S_a,*R*)-**20b**	*t*-Bu	**19**	86:14 (70%)
7	(S_a,*R*)-**20c**	Cy	**19**	76:24 (65%)
8	(R_a,*S*)-**20d**	*t*-Bu	**19**	14:86 (60%)
9	(R_a,*S*)-**20e**	Cy	**19**	18:82 (99%)

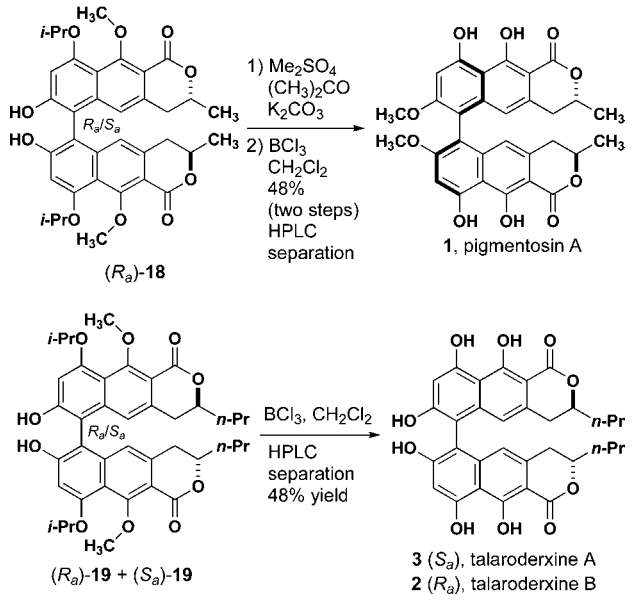
[a] Reactions conducted in DCM at 0.03 M for 16 h. [b] Diasteromeric ratios were determined by HPLC, and the product configuration (R_a or S_a) is based on previous studies and assigned by CD. [c] Yields of isolated product.

Completion of the syntheses of **1**–**3** from **18** and **19** was straightforward. Methylation of **18** followed by global deprotection with BCl_3 produced pigmentosin A (**1**) in 48% yield over two steps (Scheme 3). Talaroderxines A and B were completed by a global deprotection of (R_a)-**19** and (S_a)-**19**, which provided the two atropisomers in 34% and 14% yield, respectively, after HPLC separation.

Synthetic pigmentosin A exhibits physical properties that are in good agreement when compared to a natural sample. The ^1H and ^{13}C NMR spectra for synthetic pigmentosin A were identical to what was reported for the natural sample. The optical rotation values for natural pigmentosin A is surprisingly small at −7.1, and the value recorded for the synthetic sample −20.8 compared favorably. Finally, a sample was sent to Prof. Elix who demonstrated that coinjected samples of natural extract and synthetic pigmentosin A had identical retention times by HPLC analysis.[18]

(11) Keck, G. E.; Krishnamurthy, D. *Org. Synth.* **1998**, *75*, 12–18.
(12) De Lombaert, S.; Nemery, I.; Roekens, B.; Carretero, J. C.; Kimmel, T.; Ghosez, L. *Tetrahedron Lett.* **1986**, *27*, 5099–5102.
(13) Craig, D.; Lu, P.; Mathie, T.; Tholen, N. T. H. *Tetrahedron* **2010**, *66*, 6376–6382.
(14) This reaction was observed during the study of conjugate addition reactions of maleic anhydrides for a different project in the laboratory. For a related base-mediated process, see: Wunderlich, K.; Harms, W. ; Herd, K. J.; Jager, H. Triphendioxazine Dyestuffs. U.S. Patent 4,665,179, May 12, 1987.
(15) Prepared in three steps from D-norvaline. Margot, C.; Simmons, D. P.; Reichlin, D.; Skuy, D. *Helv. Chim. Acta* **2004**, *87*, 2662–2684.
(16) Epoxide **12** can also be prepared from (*S*)-epichlorohydrin. See: Holub, N.; Neidhoefer, J.; Blechert, S. *Org. Lett.* **2005**, *7*, 1227–1229.
(17) (a) Evans, G. E.; Leeper, F. J.; Murphy, J. A.; Staunton, J. *Chem. Commun.* **1979**, 205–206. (b) Dodd, J. H.; Weinreb, S. M. *Tetrahedron Lett.* **1979**, *20*, 3593–3596. (c) Tan, N. P. H.; Donner, C. D. *Tetrahedron* **2009**, *65*, 4007–4012.
(18) See Supporting Information.

Scheme 3. Completion of Natural Products



Synthetic samples of talaroderxines A and B agreed with most of the analytical data for the natural materials. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) matched closely with those reported by Suzuki (d_6-DMSO) and with spectra from a more recent isolation by the Gloer group, also recorded in $CDCl_3$.[6] That said, the chemical shifts in both experiments are very similar for the diastereomeric natural products. A mixed sample of synthetic and natural talaroderxine B produced no additional peaks among the key aromatic and hydroxyl signals in the ^{1}H NMR spectrum. Furthermore, HPLC analysis showed that the retention times were identical when injected separately or analyzed as a coinjection. CD spectra are nearly equal and opposite in their shape and compare favorably with data reported by Suzuki. The only discrepancy arises in the optical rotation values. Suzuki reports optical rotations of -75.4 and -86.8 for talaroderxines A and B, respectively. Synthetic samples showed $+67.1$ and -71.8, which is consistent with many examples of atrop-diastereomers that have opposite axial chirality and the same configuration of a distal stereogenic center.[19] Following this trend, freshly isolated talaroderxines A and B were found to have rotations of $+117.8$ and -215.0, suggesting that Suzuki's material was not isomerically pure or that the sign of the rotation of talaroderxine A was reported incorrectly.[20] We did observe that rotation values for the talaroderxines varied significantly in magnitude, but not in sign, based on the source of the methanol used to prepare the solutions. The convincing NMR, CD, and HPLC data all support the identical structures of natural and synthetic talaroderxines A and B.[18]

Preliminary biological studies of pigmentosin A are encouraging. This compound inhibits the growth of *Bacillus subtilis* with an MIC of 20 μM, which is slightly higher than that of a 1:1 mixture of talaroderxines A and B, as reported by Suzuki.[3b] Given that our original interest in these molecules stemmed from its structural similarity to viriditoxin, the mammalian toxicity was evaluated. Viriditoxin, whose structure differs from pigmentosin only by replacement of the methyl groups on the heterocycle with $CH_2CO_2CH_3$, exhibits a low LD_{50} of 2.8 mg/kg. Pigmentosin was administered to mice in increasing doses with no significant difference from control groups based on body weight and behavior up to 30 mg/kg. Although a true LD_{50} was not measured for pigmentosin A, this compound is safely described as significantly less toxic to mice than viriditoxin.

In summary we have completed the first syntheses of pigmentosin A, talaroderxine A, and talaroderxine B. Central to the success of the latter two compounds was the development of a new annulation reagent that enables rapid assembly of unsaturated pyranones from epoxides. Preliminary biological data are encouraging in that the low mammalian toxicity of pigmentosin A suggests that these structures may warrant further investigation as biological probes.

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Supporting Information Available. Characterization of all new compounds, ^{1}H and ^{13}C NMR spectra, and comparative analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

Note Added after ASAP Publication. This manuscript was published ASAP on August 13, 2012. Scheme 2 has been updated. The corrected version was reposted on August 15, 2012.

The authors declare no competing financial interest.

(19) (a) Kuyama, S.; Tamura, T. *J. Am. Chem. Soc.* **1957**, *79*, 5725–5726. (b) Bringmann, G.; Günther, C.; Saeb, W.; Mies, J.; Wickramasinghe, A. Mudogo, V.; Brun, R. *J. Nat. Prod.* **2000**, *63*, 1333–1337. (c) Bringmann, G.; Messer, K.; Brun, R.; Mudogo, V. *J. Nat. Prod.* **2002**, *65*, 1096–1101. (d) Mitchell, T. K.; Alejos-Gonzalez, F.; Gracz, H. S.; Danehower, D. A.; Daub, M. E.; Chilton, W. S. *Phytochemistry* **2003**, *62*, 723–732. (e) Watanabe, T.; Tanaka, Y.; Shoda, R.; Sakamoto, R.; Kamikawa, K.; Uemura, M. *J. Org. Chem.* **2004**, *69*, 4152–4158. (f) Talele, H. R.; Sahoo, S.; Bedekar, A. V. *Org. Lett.* **2012**, *14*, 3166–3169.

(20) Extract from a liquid fungal culture (*Delitschia* sp.) containing talaroderxines A and B was prepared by the Gloer group (U. Iowa) according to ref 2 and transferred to UC Davis for HPLC purification and analysis. See Supporting Information.