ORGANIC LETTERS

2006
Vol. 8, No. 16
3481−3483

Total Synthesis of (±)-Mitorubrinic Acid

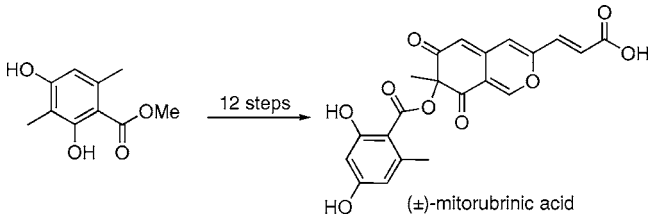
Maurice A. Marsini, Kristoffer M. Gowin, and Thomas R. R. Pettus*

Department of Chemistry and Biochemistry, University of California at Santa Barbara, Santa Barbara, California 93106

pettus@chem.ucsb.edu

Received May 4, 2006

ABSTRACT



(±)-Mitorubrinic acid, a member of the azaphilone family of natural products, has been constructed in 12 steps. Key aspects of the synthesis include elaboration and oxidative dearomatization of an isocoumarin intermediate to provide the azaphilone nucleus with a disubstituted, unsaturated carboxylic acid side chain.

The mitorubrins are a unique subclass of azaphilones isolated from a variety of fungal species (Figure 1).[1] The term

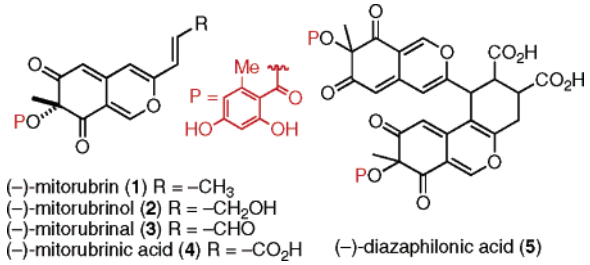


Figure 1. The mitorubrins.

azaphilone arises from the affinity of the 4*H*-pyran nucleus to undergo substitution with primary amines to form the corresponding vinylogous 4-pyridones. The mitorubrin subclass of azaphilones is comprised of (−)-mitorubrin (**1**),[2] (−)-mitorubrinol (**2**),[2] (−)-mitorubrinal (**3**),[1] (−)-mitorubrinic acid (**4**),[3] and its supposed dimer, diazaphilonic acid (**5**).[4] The molecules **1**−**4** only differ by the oxidation state of their accompanying disubstituted *E*-olefinic side chain. They are closely related to the lunatoic acid family of azaphilones, which differ in their ester side chain functionality from the mitorubrins.[1b]

Whalley and co-workers reported an 11-step synthesis of (±)-mitorubrin (**1**) some time ago.[5] However, a resurgence of interest accompanied recognition by the synthetic community of the diverse and distinct biological activities exhibited by the azaphilones. In particular, mitorubrinic acid (**4**) induces formation of chlamydospore-like cells in fungi and inhibits trypsine with an IC_{50} of 41 μmol/L.[3b] On the other hand, its presumed dimer diazaphilonic acid (**5**) inhibits Tth DNA polymerase with an IC_{50} of 2.6 μg/mL and is reported to completely inhibit MTI (human leukemia) telomerase activity at 50 μM.[4]

Porco has reported a concise entry to many azaphilone scaffolds using a gold-mediated cycloisomerization of *o*-

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(3) (a) Locci, R.; Merlini, L.; Nasini, G.; Locci, J. R. *Giornale di Microbiologia* **1967**, *15*, 93. (b) Lesova, K.; Sturdikova, M.; Rosenberg, M. *J. Basic Microbiol.* **2000**, *40*, 365. (c) Steglich, W.; Klaar, M.; Furtner, W. *Phytochemistry* **1984**, *18*, 2874.

(4) (a) Tabata, Y.; Ikegami, S.; Yaguchi, T.; Sasaki, T.; Hoshiko, S.; Sakuma, S.; Shin-Ya, K.; Seto, H. *J. Antibiot.* **1999**, *52*, 412. (b) Oikawa, H.; Tokiwano, T. *Nat. Prod. Rep.* **2004**, *21*, 321.

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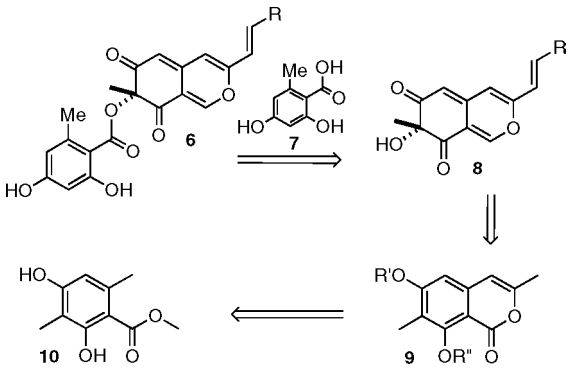
10.1021/ol0610993 CCC: $33.50
Published on Web 07/07/2006

alkynyl benzaldehydes.[6a] More recently, he provided enantioselective access to several azaphilones using stoichiometric copper, O_2, and (−)-sparteine and has applied the method in the synthesis of the azaphilone (−)-S-15183A.[7] However, the gold-mediated cyclization and subsequent copper-mediated enantioselective oxidation may not be amenable to derivatives containing an acrylate or disubstituted olefin, such as that found in the mitorubrins.

Therefore, we set out to devise a racemic route to the mitorubrins, which might be eventually adapted to our enantioselective dearomatization protocol.[8] The fully elaborated skeleton **6** of the mitorubrins arises upon attaching orsellinic acid **7** to the 3° alcohol of **8** (Scheme 1**)**.[9] We

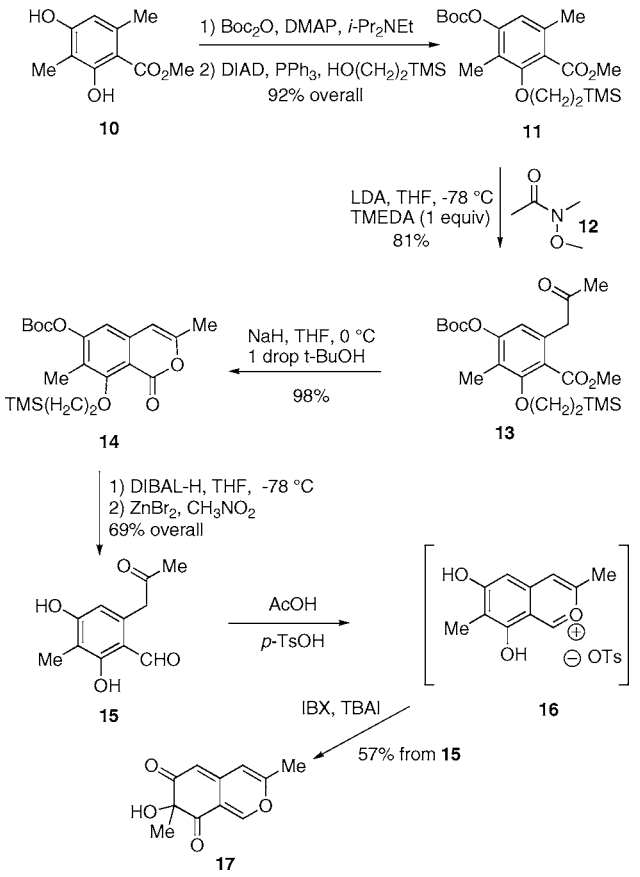
Scheme 1. General Synthetic Strategy to Address the Mitorubrins



imagined that the azaphilone core **8**, in turn, could arise from the isocoumarin **9**. Recognizing that an analogue of isocoumarin **9** had been produced by Staunton's orsellenate enolization protocol some time ago,[10] we chose the methyl benzoate **10** as our starting material.

Our synthesis begins with *mono*-phenol protection using di-*tert*-butyl dicarbonate, *N*-ethyldiisopropylamine (DIPEA), and 4-(dimethylamino)pyridine (DMAP). Coupling of the more congested phenol proceeds with 2-(trimethylsilyl)-ethanol under Mitsunobu's conditions. This two-pot sequence affords the differentially protected ester **11** in 92% overall yield (Scheme 2). Addition of lithium diisopropylamide (LDA) results in γ-deprotonation and formation of the corresponding dienic enolate, which resembles a dimethide.[10] However, a slight amendment to Staunton's conditions proved necessary. Introduction of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine prior to the Weinreb acetamide **12** provides the keto ester **13** in 81% yield, whereas yields were 40−50% in its absence. Addition of base promotes enolization and cyclization of **13** to afford the isocoumarin **14** in 98%

Scheme 2. A Concise Route to the Azaphilone Core



yield. The four-step sequence from **10** to **14** can easily be carried out on multigram scale.

Selective reduction of the isocoumarin carbonyl moiety in **14** with 1.05 equiv of diisobutylaluminum hydride (DIBAL-H) in tetrahydrofuran followed by global deprotection of the *O*-*tert*-butyl carbonate and *O*-$(CH_2)_2$TMS ethers with zinc bromide in nitromethane provides the keto aldehyde **15** in 69% overall yield. The 2-benzopyrylium salt **16** forms upon addition of acetic acid and *p*-toluenesulfonic acid (*p*-TsOH) to the keto aldehyde **15**.[11] After concentration and evaporation of the solvent, the salt **16** is re-dissolved in 1,2-dichloroethane and stirred with *o*-iodoxybenzoic acid (IBX) and a catalytic amount of tetra-*n*-butylammonium iodide (TBAI) to afford the azaphilone **17** in 57% yield. The delivery of a hydroxy residue *ortho* to both phenols was expected based on our earlier work with IBX.[12] However, an important modification, addition of TBAI as reported by Porco, proved critical for this nucleus.[6]

Having satisfactorily tested the dearomatization protocol, we began the synthesis of (±)-mitorubrinic acid (**4**) in earnest. Starting from isocoumarin **14**, allylic oxidation with

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(10) Lewis, C. N.; Spargo, P. L.; Staunton, J. *Synthesis* **1986**, 944.

(11) For acid-catalyzed formation of benzopyrylium salts, see: (a) Wei, W.; Yao, Z. *J. Org. Chem.* **2005**, *70*, 4585. (b) Suzuki, T.; Okada, C.; Arai, K.; Awaji, A.; Shimizu, T.; Tanemura, K.; Horaguchi, T. *J. Heterocycl. Chem.* **2001**, *38*, 1409. (c) Selenski, C. S.; Pettus, T. R. R. *Tetrahedron* **2006**, *62*, 5298.

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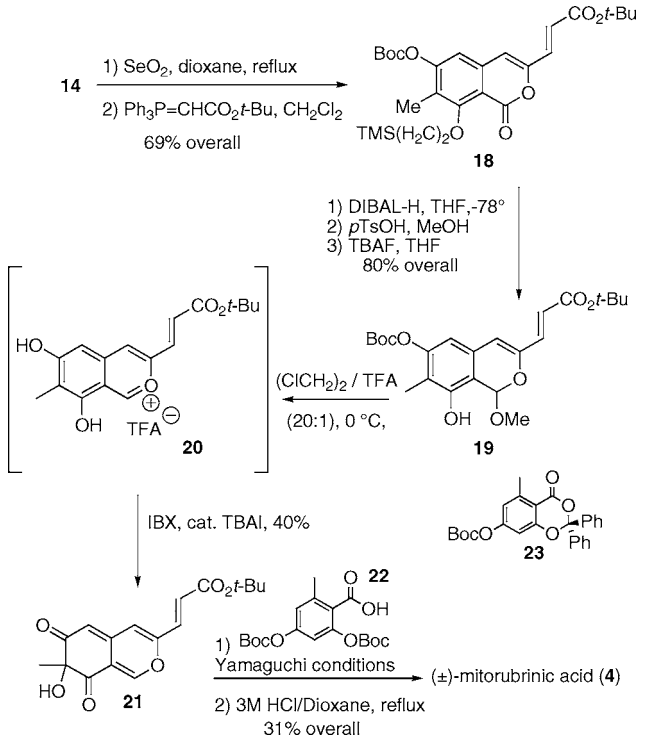
selenium dioxide in anhydrous dioxane affords the corresponding 3-formyl isocoumarin intermediate.[13] Homologation using (*t*-butoxycarbonylmethylene)triphenylphosphorane in methylene chloride gives a 69% overall yield of *E*-*tert*-butyl ester **18**, along with a small amount of its corresponding *Z*-isomer that is easily removed by chromatography. DIBAL-H in THF selectively reduces the lactone moiety, and the *tert*-butyl ester emerges unscathed. Addition of acidic methanol to the hemi-ketal intermediate followed by desilylation with tetra-*n*-butylammonium fluoride (TBAF) yields the mono-O-Boc phenol **19** in 80% over the three steps. Because of a

Scheme 3. Completion of (±)-Mitorubrinic Acid (**4**)



problematic selective O-Boc cleavage in the presence of the *tert*-butyl ester, we decided to oxidize **19**. Given our previous finding shown in Scheme 2, the oxidative dearomatization of **19** proved surprisingly difficult. This problem stems from competitive *tert*-butylation of the azaphilone by acidic cleavage of the O-Boc moiety. After considerable experimentation, we find that the ketal **19** converts to the benzopyrylium salt **20** when dissolved in a 20:1 mixture of 1,2-dichloroethane and trifluoroacetic acid at 0 °C. Upon subsequent exposure to IBX/TBAI,[6a,12] the azaphilone **21** is produced in a modest yet reproducible 40% yield. The azaphilone **23** also directly arises from reaction of ketal **19** with iodosylbenzene and Lewis acids, such as trimethylsilyl trifluoromethanesulfonate or BF_3•OEt_2. However, these conditions prove capricious (5−54%) and in some instances result in accompanying *tert*-butylation of the azaphilone nucleus.

Nevertheless, with a modest amount of the fully functionalized azaphilone core in hand, our attentions turned toward esterification. Several protocols were examined. Most conditions failed in our hands. In particular, photolysis of **21** with an orsellenate-derived benzodioxin (**23**) using De Brabander's[14] protocol proved ineffective due to decomposition of the azaphilone. However, Yamaguchi's lactonization conditions using 2,4,6-trichlorobenzoyl chloride, acid **22**, and NEt_3 produces the desired ester in a 35% yield.[15] Subsequent global cleavage of the *tert*-butyl ester and *tert*-butyl carbonates proceeds with 3 M HCl in refluxing dioxane over 4 h to afford (±)-mitorubrinic acid (**4**) in a 31% yield over the two steps.

In conclusion, the first total synthesis of (±)-mitorubrinic acid (**4**) has been completed. The target is obtained in 12 steps in 5% overall yield. The core **21** is accessible in 16% yield after 10 steps. Although the congested esterification with the acid **22** needs further optimization (35% yield), the final deprotection proceeds in nearly quantitative fashion. We are currently examining the intramolecular cycloaddition of the symmetric anhydride derived from **4** to address diazaphilonic acid (**5**), as well as an enantioselective synthesis of (−)-**4**. Our findings will be reported shortly.

Acknowledgment. We are thankful for financial support provided by the NIH GM-64831 and U.S. Army Medical Research and Material Command (M.A.M.) (DAMD17-02-1-0334). M.A.M. thanks the University of California at Santa Barbara for a Graduate Mentor Fellowship.

Supporting Information Available: Full experimental details and compound characterization (^{1}H NMR, ^{13}C NMR, HRMS, FT-IR). This material is available free of charge via the Internet at http://pubs.acs.org.

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