ORGANIC LETTERS

2009
Vol. 11, No. 1
49−52

Formal Synthesis of (±)-Roseophilin

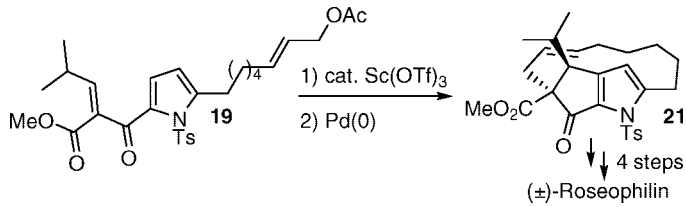
Abdallah Y. Bitar and Alison J. Frontier*

Department of Chemistry, University of Rochester, Rochester, New York 14627

frontier@chem.rochester.edu

Received October 7, 2008

ABSTRACT



A formal synthesis of (±)-roseophilin is described. Scandium(III)-catalyzed Nazarov cyclization of 2,5-disubstituted *N*-tosylpyrrole 19 gives a 5,5′-fused ketopyrrole, and ansa-bridge formation via π-allyl palladium macrocyclization gives 21.

Roseophilin (**1**), isolated from *Streptomyces griseoviridis*, was identified as a potent cytotoxic agent against K562 human erythroid leukemia cells (chronic myeloid leukemia model; IC_{50}, 0.34 μM) and KB human epidermoid carcinoma cells (nasopharyngeal carcinoma model; IC_{50}, 0.88 μM).[1] Unexpectedly, the unnatural enantiomer of **1**, *ent*-roseophilin, was shown to possess 2–10 fold greater potency than the naturally occurring enantiomer.[2]

The structure of **1** contains an ansa-bridged macrocycle that is connected to a pyrrolylfuran moiety via an azafulvene subunit. Its unique chemical structure coupled with its poorly understood mechanism of cytotoxicity[3] has led to the development of several synthetic approaches targeting **1**.[2,4] Herein, we disclose our approach to the formal synthesis of **1** via macrotricycle **2**, using a strategy involving the catalytic Nazarov cyclization of polarized aryl vinyl ketones.[5,6]

Our retrosynthetic analysis of macrotricycle **2** is shown in Scheme 1. Execution of a late-stage macrocyclization to close the strained 13-membered ansa bridge was planned with some trepidation. In most of the published approaches toward this target, the final stages involved closure of either the cyclopentenyl ring or the pyrrole ring within an existing macrocyclic scaffold. In the few cases when a late-stage macrocyclization was performed on the fused 5,5′-fused ring system, bulky substituents on the side chain were needed to conformationally induce ring closure.[4d,h] With greater confidence, we planned to prepare macrocyclization precursor **3** from Nazarov cyclization of pyrrolylvinyl ketone **4**,[6] which

(1) Hayakawa, Y.; Kawakami, K.; Seto, H.; Furihata, K. *Tetrahedron Lett.* **1992**, *33*, 2701.

(2) Boger, D. L.; Hong, J. *J. Am. Chem. Soc.* **2001**, *123*, 8515.

(3) (a) Fürstner, A.; Grabowski, E. J. *ChemBioChem* **2001**, *2*, 706. (b) Fürstner, A.; Reinecke, K.; Prinz, H.; Waldmann, H. *ChemBioChem* **2004**, *5*, 1575. (c) Manger, M.; Scheck, M.; Prinz, H.; von Kries, J. P.; Langer, T.; Saxena, K.; Schwalbe, H.; Fürstner, A.; Rademann, J.; Waldmann, H. *ChemBioChem* **2005**, *6*, 1749.

(4) For a review, see: (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582 . Syntheses of Racemic **1**: (b) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817. (c) Fürstner, A.; Gastner, T.; Weintritt, H. *J. Org. Chem.* **1999**, *64*, 2361. (d) Kim, S. H.; Figueroa, I.; Fuchs, P. L. *Tetrahedron Lett.* **1997**, *38*, 2601. (e) Mochizuki, T.; Itoh, E.; Shibata, N.; Nakatani, S.; Katoh, T.; Terashima, S. *Tetrahedron Lett.* **1998**, *39*, 6911. (f) Harrington, P.; Tius, M. *Org. Lett.* **1999**, *1*, 649. (g) Robertson, J.; Hatley, R. J. D.; Watkin, D. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3389. Asymmetric Syntheses: (h) Bamford, S. J.; Luker, T.; Speckamp, W. N.; Hiemstra, H. *Org. Lett.* **2000**, *2*, 1157. (i) Trost, B. M.; Doherty, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 3801. (j) Harrington, P. E.; Tius, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 8509. (k) Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A. *J. Org. Chem.* **2005**, *70*, 4542. Approaches to the Roseophilin Core: (l) Salamone, S. G.; Dudley, G. B. *Org. Lett.* **2005**, *7*, 4443. (m) Song, C.; Knight, D. W.; Whatton, M. A. *Org. Lett.* **2006**, *8*, 163.

(5) For applications of different Nazarov cyclization strategies toward roseophilin, see refs 4f, j, k, and m.

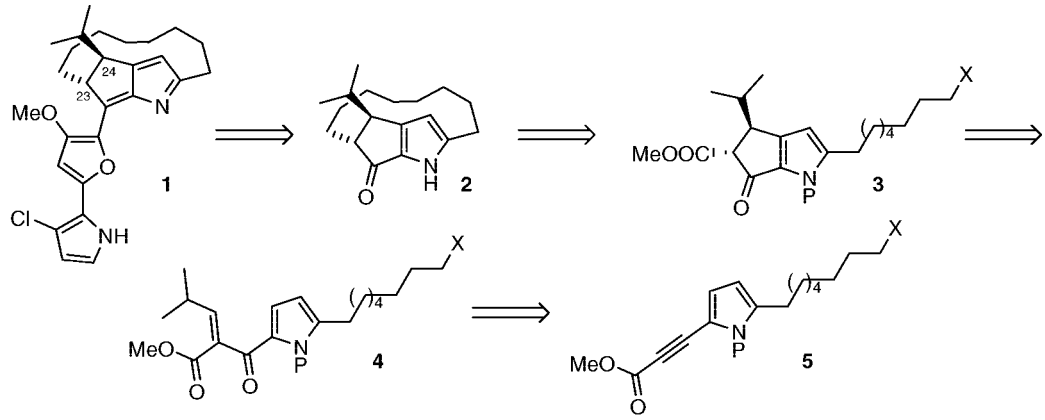
(6) (a) He, W.; Sun, X.; Frontier, A. J. *J. Am. Chem. Soc.* **2003**, *125*, 14728. (b) Malona, J. A.; Colbourne, J. M.; Frontier, A. J. *Org. Lett.* **2006**, *8*, 5661. (c) He, W.; Herrick, I. R.; Atesin, T. A.; Caruana, P. A.; Kellenberger, C. A.; Frontier, A. J. *J. Am. Chem. Soc.* **2008**, *130*, 1003.

(7) (a) Padwa, A.; Kline, D. N.; Perumattam, J. *Tetrahedron Lett.* **1987**, *23*, 913. (b) Padwa, A.; Chiacchio, U.; Kline, D. N.; Perumattam, J. *J. Org. Chem.* **1988**, *53*, 2238.

(8) (a) Canterbury, D. P.; Frontier, A. J.; Um, J. M.; Cheong, P. H.-Y.; Goldfeld, D. A.; Huhn, R. A.; Houk, K. N. *Org. Lett.* **2008**, *10*, 4597. (b) Canterbury, D. P.; Herrick, I. R.; Um, J. M.; Houk, K. N.; Frontier, A. J. *Tetrahedron*, in press.

10.1021/ol802329y CCC: $40.75
Published on Web 11/26/2008

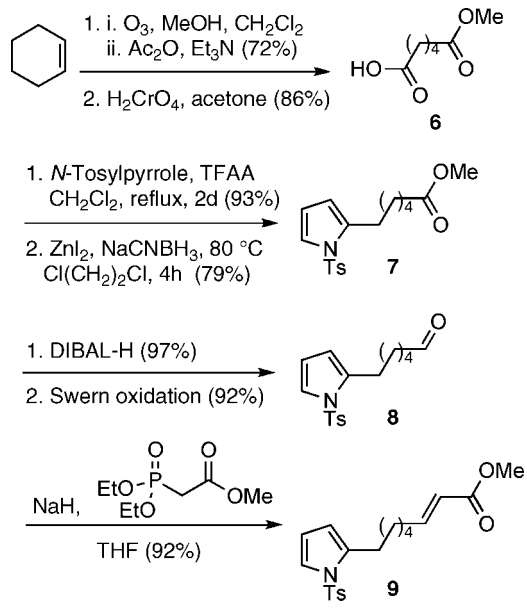
Scheme 1



could in turn be assembled via [3 + 2] cycloaddition/chelotropic extrusion of the alkynyl ester **5**, a sequence discovered by Padwa[7] and investigated further in our laboratory.[8]

The synthesis began with ozonolytic desymmetrization[9] of cyclohexene followed by Jones oxidation of the intermediate aldehyde to provide carboxylic acid **6** in excellent yield (Scheme 2). Under refluxing conditions in the presence of

Scheme 2



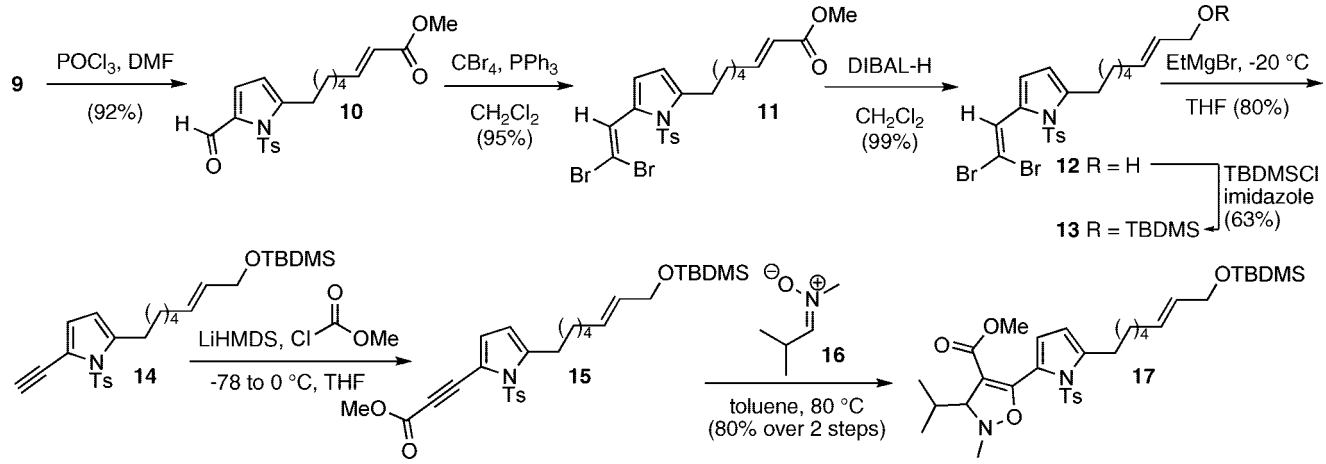
trifluoroacetic anhydride and carboxylic acid **6**, *N*-tosylpyrrole was acylated selectively at the 2-position.[10] Subsequently, the ketopyrrole formed was reductively deoxygenated under mild conditions using zinc iodide and sodium cyanoborohydride to provide ester **7** in good yield.[11] Elaboration upon the alkyl side chain of ester **7** using the high-yielding reduction/oxidation sequence of DIBAL-H and Swern conditions provides aldehyde **8**. Under standard Horner-Wadsworth-Emmons conditions[12] with methyl diethylphosphonoacetate, aldehyde **8** was converted to the α,β-unsaturated ester **9** in excellent yield.

Vilsmeier-Haack formylation[13] of **9** provided pyrrolylcarboxaldehyde **10** which was subjected to the first step of the Corey-Fuchs transformation[14] to arrive at *gem*-dibromoalkene **11** (Scheme 3). Reduction of the α,β-unsaturated ester moiety of **11** with DIBAL-H and subsequent silyl protection of the alcohol **12** yields *gem*-dibromoalkene **13**. The rearrangement step of the Corey-Fuchs sequence provided alkyne **14** in good yield. Selective deprotonation of the acetylenic proton of **14** with lithium hexamethyldisilazide followed by addition of methyl chloroformate yielded alkynyl ester **15**. One-pot formation of the alkynyl ester from **13** using organolithium reagents followed by quenching with methyl chloroformate was problematic due to orthometalation of the *N*-tosyl protecting group.[15] Crude alkynyl ester **15** underwent a [1,3]-dipolar cycloaddition reaction with nitrone **16** at 80 °C in toluene (1.6 M) to provide isoxazoline **17** in excellent yield over two steps.

To unveil the Nazarov cyclization precursor, isoxazoline **17** was exposed to a slight excess of *m*-CPBA at 0 °C, standard conditions for a chelotropic extrusion of this type.[7,8] The desired 2-pyrrolyl vinyl ketone was obtained along with a byproduct resulting from epoxidation of the protected allylic alcohol. If the rate of *N*-oxidation is slightly faster than epoxidation, addition of a sacrificial alkene might minimize unwanted epoxidation of valuable substrate **17**. Indeed, a protocol that involved alternating the addition of

(9) Claus, R. E.; Schreiber, S. L. *Org. Synth.* **1986**, *Coll. Vol. 7*, 168.
(10) Song, C.; Knight, D. W.; Whatton, M. A. *Tetrahedron Lett.* **2004**, *45*, 9573.
(11) Lau, C. K.; Dufresne, C.; Bélanger, P. C.; Piétré, S.; Scheigetz, J. *J. Org. Chem.* **1986**, *51*, 3038.
(12) Masanori, S.; Mori, K. *Eur. J. Org. Chem.* **2001**, 503.
(13) Xu, R. X.; Anderson, H. J.; Gogan, N. J.; Loader, C. E.; McDonald, R. *Tetrahedron Lett.* **1981**, *22*, 4899.
(14) Tietze, L. F.; Kettschau, G.; Heitmann, K. *Synthesis* **1996**, 851.
(15) For similar difficulties with the *N*-tosyl group, see: Liu, J.; Yang, Q.; Mak, T. C. W.; Wong, H. N. C. *J. Org. Chem.* **2000**, *65*, 3587.

Scheme 3



portions of cyclohexene and oxidant at −30 °C did protect **17** from overoxidation (Scheme 4). Further optimization of this reaction is required. With β-ketoester **18** in hand, we turned our attention to the Nazarov cyclization.

Initial attempts at cyclization of β-ketoester **18** were unsuccessful. The silyl protecting group was cleaved under the reaction conditions, and the exposed alcohol appeared to inhibit catalyst turnover. Further heating resulted in decomposition. After exchanging the silyl protecting group for an acetyl protecting group, the Nazarov substrate **19** was heated in the presence of catalytic amounts of scandium(III) triflate and 1 equiv of lithium perchlorate to provide Nazarov product **20** in good yield (Scheme 4).[6b] Furthermore, the reaction was relatively rapid with complete conversion observed in under 2 h.

Initial attempts to cyclize structures similar to **3** (see Scheme 1) using a mild base in a polar aprotic solvent[16] were unsuccessful. Since intramolecular alkylation of the β-ketoester by S_N2 displacement was not possible, alkylation with the appropriate π-allyl palladium species was explored.[17] We sought to carry out the macrocyclization under

Scheme 4

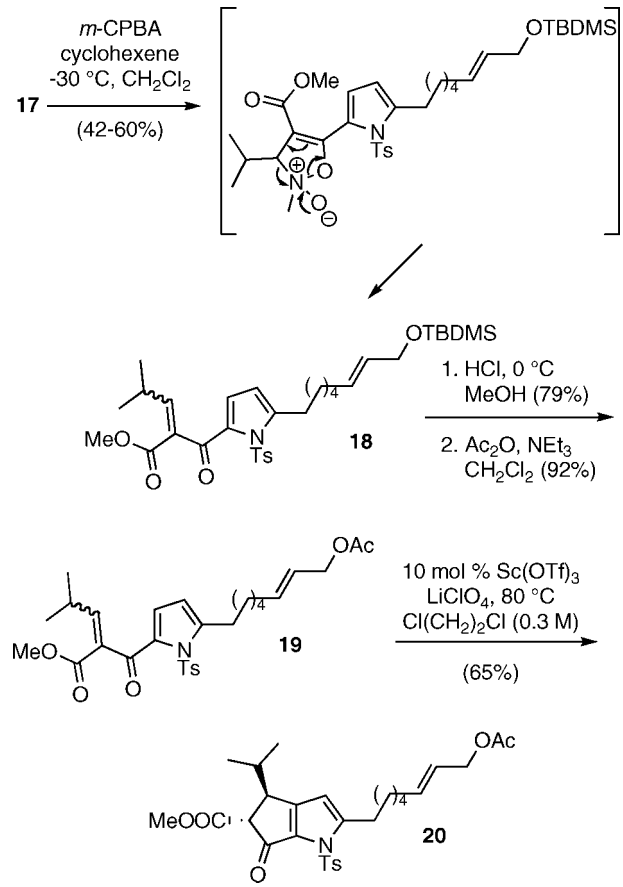
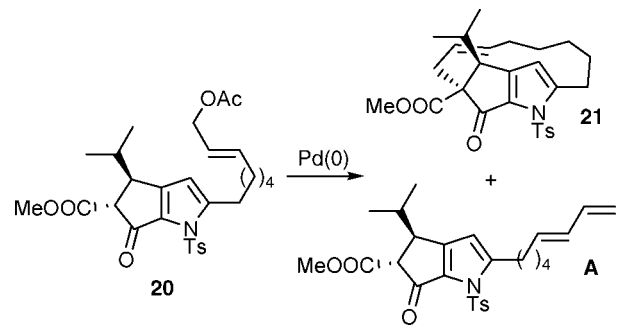


Table 1. Optimization of the π-Allyl Palladium Macrocyclization[a]



entry	catalyst	ligand (mol %)	overall yield (%)	ratio **21**:**A**[b]
1	$Pd(PPh_3)_4$	-	56	4:1
2	$Pd(OAc)_2$	dppp[c] (48 mol %)	73	3:1
3	$Pd(OAc)_2$	dppe[d] (48 mol %)	82	4:1
4	$Pd(OAc)_2$	dppb[e] (48 mol %)	[f]	-

[a] Reaction conditions: 20 mol % catalyst, ligand, NaH (1.1 equiv), reflux, THF (0.001 M). [b] Based on ^{1}H NMR integration. [c] dppp = 1,3-bis(diphenylphosphino)propane. [d] dppe = 1,2-bis(diphenylphosphino)ethane. [e] dppb = 1,4-bis(diphenylphosphino)butane. [f] Decomposition was observed.

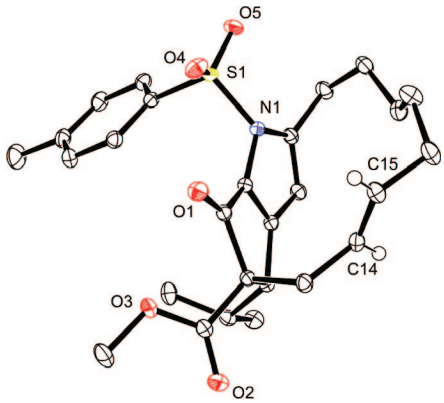


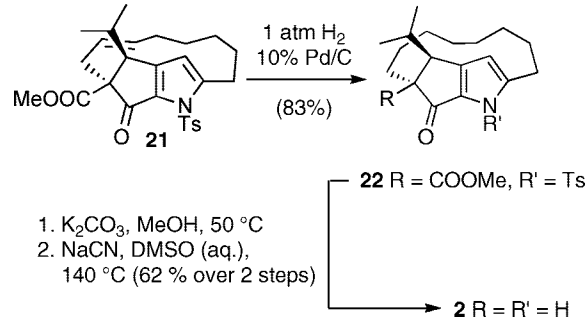
Figure 1. ORTEP drawing of macrocycle **21**.

dilute and controlled conditions using a suitable palladium (0) catalyst system (Table 1). Our initial attempt relied upon slow addition of the sodium enolate of **20** to a refluxing THF solution of tetrakis(triphenylphosphine)palladium (entry 1).[18] The reaction provided a 4:1 mixture of macrocycle **21** to a product resulting from β-hydride elimination (**A**). The two products were difficult to separate via flash chromatography. Fortunately, macrocycle **21** could be recrystallized, and an X-ray crystal structure was obtained as shown in Figure 1. By preforming the Pd(0) catalyst using palladium acetate in the presence of dppp, we were pleased to find the overall yield increased to 73% (entry 2). The ratio was improved to 4:1 with the use of dppe (entry 3). Decomposition was observed when dppb was employed (entry 4).

Functional group modification was required to complete the formal synthesis of **1** (Scheme 5). Hydrogenation followed by deprotection of the pyrrolyl nitrogen under basic conditions furnished macrocyclic β-ketoester **22**. Krapcho dealkoxycarbonylation of **22** delivered **2** in good yield.

Future work will focus on developing a more efficient synthesis of Nazarov cyclization precursor **19**, optimizing

Scheme 5



the macrocyclization and adapting the strategy to the asymmetric synthesis of **2**.

Acknowledgment. We are grateful to the NSF (CAREER: CHE-0349045), the NIH (NIGMS R01 GM079364), and the University of Rochester for generous financial support. We thank Prof. Robert K. Boeckman, Jr. (University of Rochester) and Prof. David W. C. MacMillan (Princeton University) for helpful discussions. We are also grateful to Dr. William Brennessel (University of Rochester) for solving the structure of **21** by X-ray crystallography and Dr. Alice Bergmann (University of Buffalo) for carrying out high-resolution mass spectroscopy.

Supporting Information Available: Experimental procedures, characterization data, X-ray crystal structure coordinates, and files for compound **21** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802329Y

(16) (a) Casadei, M. A.; Galli, C.; Mandolini, L. *J. Am. Chem. Soc.* **1984**, *106*, 1051. (b) Brillon, D.; Deslongchamps, P. *Can. J. Chem.* **1987**, *65*, 56.

(17) For a review, see: Trost, B. M. *Angew. Chem., Int. Ed.* **1989**, *28*, 1173.

(18) Kitagawa, Y.; Itoh, A.; Hashimoto, S.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3864.