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A Ring-Expansion Approach to Roseophilin

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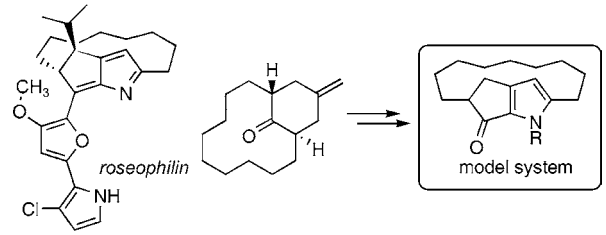
ABSTRACT



Preparation of a cyclopentenone-fused pyrrolophane, which serves as a model for the tricyclic core of roseophilin (1), is described. The synthetic scheme features a palladium-catalyzed annulation and oxidative cleavage sequence to provide a macrocyclic ketoester (17). Modified Paal–Knorr pyrrole synthesis and Friedel–Crafts acylation complete the pyrrolophane model system (20).

The antitumor antibiotic roseophilin (**1**)[1] has stimulated steadily increasing interest from the synthetic community[2−4] since it was first reported in 1992 (Figure 1).[5]

Roseophilin is an ideal target for total synthesis, and synthetic chemistry would play a vital role in capitalizing on its chemotherapeutic potential. Roseophilin displays submicromolar cytotoxicity against human cancer cell lines, which makes it a potential lead compound for cancer research. Furthermore, roseophilin is appealing in that its mechanism of action has not been matched up with any known process,[6] and Boger found that *ent*-roseophilin is up to 10-fold more potent than the natural product.

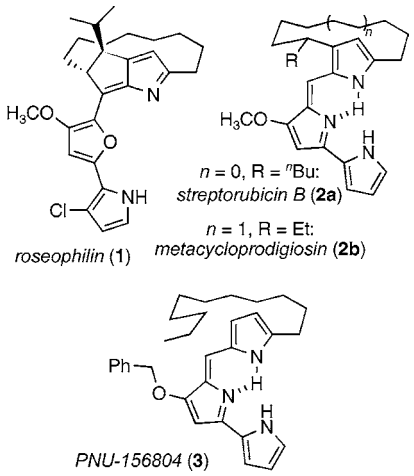


Figure 1. Roseophilin and related prodigiosins.

(1) For a review of the chemistry and biology of roseophilin and related compounds, see: Fürstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582−3603.

(2) Total syntheses: (a) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817−2825. (b) Fürstner, A.; Gastner, T.; Weintritt, H. *J. Org. Chem.* **1999**, *64*, 2361−2366. (c) Harrington, P. E.; Tius, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 8509−8514. (d) Boger, D. L.; Hong, J. *J. Am. Chem. Soc.* **2001**, *123*, 8515−8519.

(3) Formal syntheses: (a) Kim, S. H.; Figueroa, I.; Fuchs, P. L. *Tetrahedron Lett.* **1997**, *38*, 2601−2604. (b) Mochizuki, T.; Itoh, E. Shibata, N.; Nakatani, S.; Katoh, T.; Terashima, S. *Tetrahedron Lett.* **1998**, *39*, 6911−6914. (c) Trost, B. M.; Doherty, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 3801−3810. (d) Bamford, S. J.; Luker, T.; Speckamp, W. N.; Hiemstra, H. *Org. Lett.* **2000**, *2*, 1157−1160. (e) Robertson, J.; Hatley, R. J. D.; Watkin, D. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3389−3396.

(4) Synthethic approaches: (a) Fagan, M. A.; Knight, D. W. *Tetrahedron Lett.* **1999**, *40*, 6117−6120. (b) Viseux, E. M. E.; Parsons, P. J.; Pavey, J. B. J.; Carter, C. M.; Pinto, I. *Synlett* **2003**, 1856−1858. (c) Dyke, C. A.; Bryson, T. A. *Tetrahedron Lett.* **2004**, *45*, 6051−6053. (d) Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A. *J. Org. Chem.* **2005**, *70*, 4542−4545.

(5) Hayakawa, Y.; Kawakami, K.; Seto, H. *Tetrahedron Lett.* **1992**, *33*, 2701−2704.

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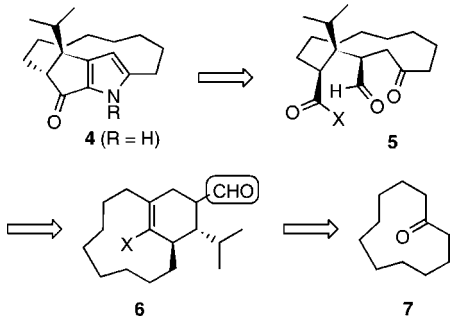
The related prodigiosin compounds (e.g., **2**) also have promising biological activity. The synthetic pyrrole PNU-156804 (**3**) is a clinical candidate that grew out of drug development efforts related to the prodigiosins.[7]

As a synthetic target, roseophilin's most striking challenge is the eight-carbon *ansa* chain that bridges the azafulvene. Such features traditionally have been installed via some form of macrocyclization reaction. Macrocyclization reactions frequently require high dilution conditions that limit their utility on a preparative scale. This is especially true of entropically constrained systems such as tricycle **4**, the pyrrolophane common to all reported approaches to synthetic roseophilin.

We aim to prepare roseophilin and other cyclophanoid natural products using annulation and ring expansion strategies that are amenable to large-scale production of synthetic material.

Scheme 1 outlines our retrosynthetic analysis of roseophilin, which features, as the key strategic maneuver, oxidative cleavage of a bridged bicyclic system to reveal an appropriately functionalized precursor to the *ansa*-bridged ketopyrrole. At the design stage, we were confident that a simple Diels–Alder-based sequence would provide tetrahydrometacyclophane **5** in three steps from cycloundecanone.[8]

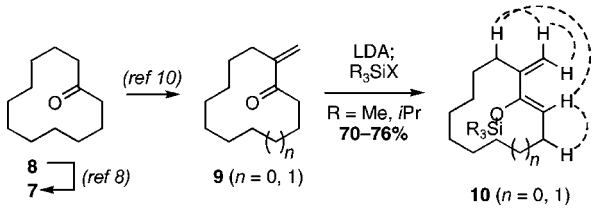
Scheme 1. Retrosynthetic Analysis of Roseophilin



For our initial (model) investigations, we chose to employ cyclododecanone (**8**) in lieu of **7**.[9] This material would ultimately provide a homologated analogue of roseophilin.

Elaboration of **8** and **7** into silyloxy dienes **10** proved to be straightforward. At the outset, we did not know what to expect with regard to kinetic enolization of ketones **9**.[10] Silylation of the *Z*-(O)-enolate (to yield *E*-diene **10**) would afford the highest probability of success in Diels–Alder cycloadditions. In fact, we obtained silyloxydienes **10** as single stereoisomers, which were assigned as shown in Scheme 2 on the basis of spectroscopic analysis.

Scheme 2. Synthesis of Bridged Macrocyclic Dienes[a]

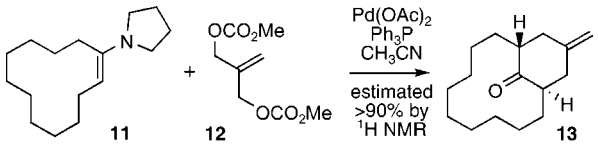


[a] Dashed lines indicate NOE cross-peaks for **10** (R = Me, $n = 0$)

Attempted cycloadditions of dienes **10** with appropriate dienophiles were unsuccessful under thermal or Lewis acidic conditions. The *ansa*-bridge is a complicating factor, but we speculate that a more subtle effect is undermining this reaction: acyclic dienes with an oxygen substituent flanked by alkyl groups (e.g., **10**) may be less reactive in Diels–Alder chemistry than a cursory analysis would predict.[11] Ongoing studies in our laboratory aim to verify and address this hypothesis, but in the meantime we explored alternative methods for formation of the model bicyclo[9.3.1]pentadecanone system.

We assembled the requisite bridged bicycle **13**, albeit without the isopropyl substituent, using Buono's enamine bis-allylation protocol (Scheme 3).[12] The in/out[13] (trans) stereoisomer is obtained almost exclusively. Bicycle **13** can be purified by chromatography or recrystallization from MeOH, but simple aqueous workup provides material of sufficient purity for subsequent reactions.[14] This palladium-catalyzed annulation provides significantly improved access to crystalline **13**, which was obtained previously in low yield as an oily mixture of cis and trans isomers.[15]

Scheme 3. Annulation of Bicyclic Ketone **13**



(6) (a) Fürstner, A.; Grabowski, E. J. *ChemBioChem* **2001**, 706–709. (b) Fürstner, A.; Reinecke, K.; Prinz, H.; Waldmann, H. *ChemBioChem* **2004**, 1575–1579.

(7) D'Alessio, R.; Bargiotti, A.; Carlini, O.; Colotta, F.; Ferrari, M.; Gnocchi, P.; Isetta, A.; Mongelli, N.; Motta, P.; Rossi, A.; Rossi, M.; Tibolla, M.; Vanotti, E. *J. Med. Chem.* **2000**, *43*, 2557–2565.

(8) Cycloundecanone (**7**) is available commercially or by ring contraction of cyclododecanone (**8**): Wohllebe, J.; Garbisch, E. W., Jr. *Organic Syntheses*; Wiley and Sons: New York, 1990; Collect. Vol. VI, pp 368–371.

(9) We purchased 100 g of **8** from Aldrich for $27. The catalog price of **7** is $63 for 1 g.

(10) (a) Gras, J.-L. *Tetrahedron Lett.* **1978**, 2111–2114. (b) Kruizinga, W. H.; Kellogg, R. M. *J. Am. Chem. Soc.* **1981**, *103*, 5183–5189. (c) Ohta, T.; Miyake, T.; Seido, N.; Kumobayashi, H.; Takaya, H. *J. Org. Chem.* **1995**, *60*, 357–363.

(11) Literature searches revealed only a single example, which employed a highly reactive quinone dienophile: Barrish, J. C.; Lee, H. L.; Baggiolini, E.; Uskokovic, M. *J. Org. Chem.* **1987**, *52*, 1375–1378.

(12) Buono, F.; Tenaglia, A. *J. Org. Chem.* **2000**, *65*, 3869–3874.

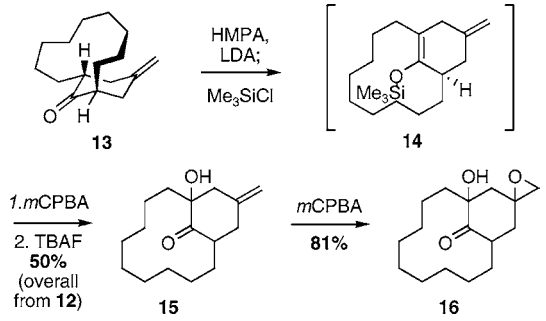
(13) For use of this term, see: Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J.; Jeon, Y. T. *J. Am. Chem. Soc.* **2002**, *124*, 9726–9728.

(14) See the Supporting Information for details.

(15) Hiyama, T.; Ozaki, Y.; Nozaki, H. *Tetrahedron* **1974**, *30*, 2661–2668.

Bicycle **13** comprises the full complement of carbon atoms needed for model system **20**, so we then focused on the oxidative manipulations needed to access a more suitable keto-pyrrole precursor (Schemes 4 and 5).

Scheme 4. Double Epoxidation of Ketone **13**

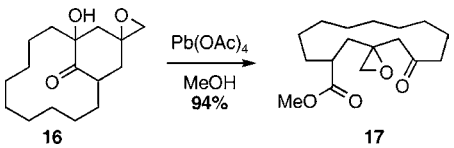


Our initial attempts at forming silyl enol ether **14** were frustrated by poor reactivity of the *ansa*-bridged cyclohexanone (**13**) toward LDA. We assume that at least one of the α-hydrogens occupies an axial position and is electronically activated by the carbonyl, and so we hypothesize that steric congestion is responsible for this sluggish reactivity. Considering a potential closed transition state for deprotonation,[16] perhaps LDA coordinates selectively to the less hindered lone pair of the ketone carbonyl, which happens to be the side of the nonacidic equatorial hydrogen. Addition of HMPA may disrupt the closed transition state; enolization with LDA in the presence of HMPA proceeded efficiently, and silyl enol ether **14** is obtained in good yield upon trapping with TMSCl.

Rubottom oxidation[17] of **14** provided α-hydroxy ketone **15** after fluoride workup. The *exo*-methylene was subsequently epoxidized; a one-pot bis-epoxidation using excess *m*-CPBA also afforded **16**, but the two-step approach provided higher yields of **16** with easier purification. The epoxidations are diastereoselective, providing **16** as a single isomer to the limits of detection by ^{1}H NMR spectroscopy. Although we made no effort to assign the relative stereochemistry of **16** (it is lost in the pyrrole formation), as a procedural matter it was convenient to be working with a single diastereomer.

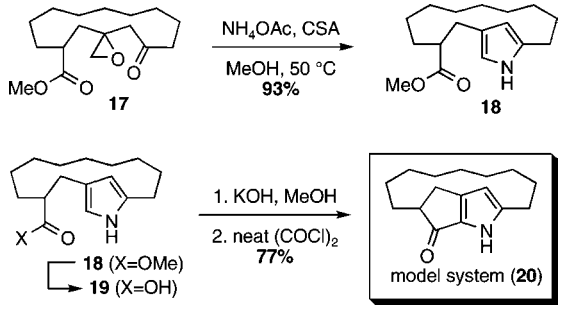
Oxidative cleavage using lead tetraacetate in MeOH afforded ketoester **17**. This is the key step from a strategic standpoint, and it reduces to practice in a highly satisfactory manner (Scheme 5).

Scheme 5. Strategic Oxidative Cleavage Reaction



With the epoxidized keto-ester (**17**) in hand, the final stages of the model study required crafting the ketopyrrole unit. The epoxide of **17** serves as an aldehyde equivalent for the pyrrole condensation. Treatment of **17** with ammonium acetate under Paal−Knorr conditions afforded **18** in high yield. Saponification of the methyl ester and intramolecular Friedel−Crafts acylation completed the assembly of ketopyrrole **20** (Scheme 6). Note that cyclization

Scheme 6. Formation of the Ketopyrrole Unit



(to **20**) occurred spontaneously under conditions intended to convert **19** into the corresponding acid chloride.

With this model study, we lay the groundwork for an eventual synthesis of roseophilin, its enantiomer, and a diverse set of analogues. It may be possible to derivatize **20** with the requisite isopropyl group, but we are currently interested in revisiting the Diels−Alder reaction and introducing the isopropyl group at an earlier stage.

In conclusion, the synthesis of ketopyrrole **20** described herein provides insight necessary to the development of our ring expansion approach to ketopyrrole **4**. By avoiding macrocyclization reactions, we aim to facilitate large-scale production of synthetic roseophilin and analogues. Future efforts will be directed toward the total synthesis of roseophilin, beginning with cycloundecanone (or a suitable substitute) in place of cyclododecanone.

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Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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