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Modular Access to Complex Prodiginines: Total Synthesis of (+)-Roseophilin via its 2-Azafulvene Prototropisomer

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Supporting Information

ABSTRACT: Ansa-bridged prodiginines are bioactive pigments produced by bacteria. Certain of these structures are reported to be antagonists of protein−protein interactions involved in apoptosis. We describe a new entry to alkaloids of this type, demonstrated with a concise asymmetric synthesis of (+)-roseophilin (**3**). Our route constructs the pyrrolophane motif via phosphoryl transfer-terminated macroaldolization and passes through a previously unexplored prototropic form of the natural product.

Ansa-bridged prodiginines are lipochromophores produced by both terrestrial and marine bacteria.[1] They derive from seco precursors consisting of a prodigiosin heterocycle harboring a long-chain *n*-alkane (e.g., **1** in Figure 1).[2,3] Medium/large rings are formed directly within these materials by way of net dehydrogenation (e.g., **1** → **2**). In the case of streptorubin B (**2**), a specialized non-heme Rieske oxygenase mediates the cyclization, putatively via intermediate alkyl radical addition to the heterocyclic nucleus.[4,5] Metacycloprodigiosin, prodigiosin R1, and nonylprodigiosin are thought to be regioisomeric products of this remarkable chemistry. Polycyclic congeners derived from more extensive oxidation are also known (vide infra).

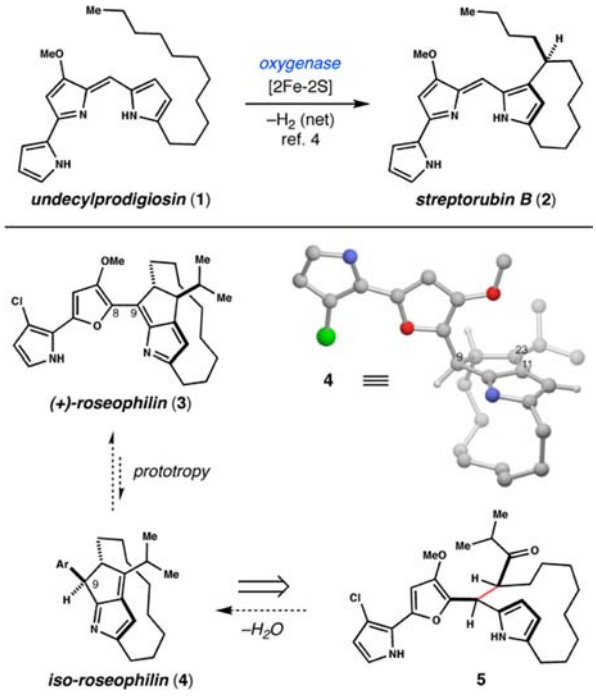

Figure 1. Ansa-bridged prodiginines are biosynthesized from seco hydrocarbons such as **1**. Roseophilin (**3**) and related structures can be approached in an analogous manner by exploiting the intermediacy of azafulvene prototropisomer **4**.

Our interest in these molecules derives from Shore's finding that streptorubin B potentiates apoptotic signaling in cell culture, reportedly through interactions with mitochondrial Bcl-2 proteins.[6,7] This discovery seeded the development of obatoclax, a simplified prodigiosin analogue currently being evaluated in humans as therapy for chronic lymphocytic leukemia.[8,9] To ascertain whether functionalized pyrrolophane variants can more selectively antagonize protein−protein contacts gating mitochondrial membrane permeability,[10] we sought generic access to the group. The goal was a modular synthetic route that would be amenable to varied heterocyclic components and peripheral substitution. An assembly reminiscent of their biosynthesis was attractive, wherein the ansa bridge would be installed late and in such a manner that the extent and position of its connectivity to the chromophore could be altered. We reduced this strategy to practice with a concise total synthesis of (+)-roseophilin (**3**), arguably the most complex member of the group.

Roseophilin's distinct structure has drawn considerable attention.[2] It harbors two C−C σ bonds connecting its hydrocarbon tail to the heterocyclic core, which itself is more highly oxidized relative to **2**. Fürstner's seminal synthesis of **3** constructs the target from two finished segments joined along the C_8−C_9 bond.[11] This blueprint has been influential. Intense activity has since focused on the ansa-bridged azatricyclic component, resulting in many creative contributions and a number of formal syntheses.[12,13]

To place roseophilin within a larger target set, we chose different plans. It was useful to contemplate the stability of **3** relative to its 2-azafulvene prototropisomer **4** (Figure 1). Assuming the former to be lower in energy and a path connecting the two to be available,[14] one might exploit **4** as an intermediate en route to **3**. This was desirable because the synthetic problem simplifies readily from **4**. Net hydration of its azafulvene reveals β-pyrrolyl ketone **5** as a potential precursor. Pyrrolophane **5** resembles simpler *ansa*-prodiginines such as **2**,

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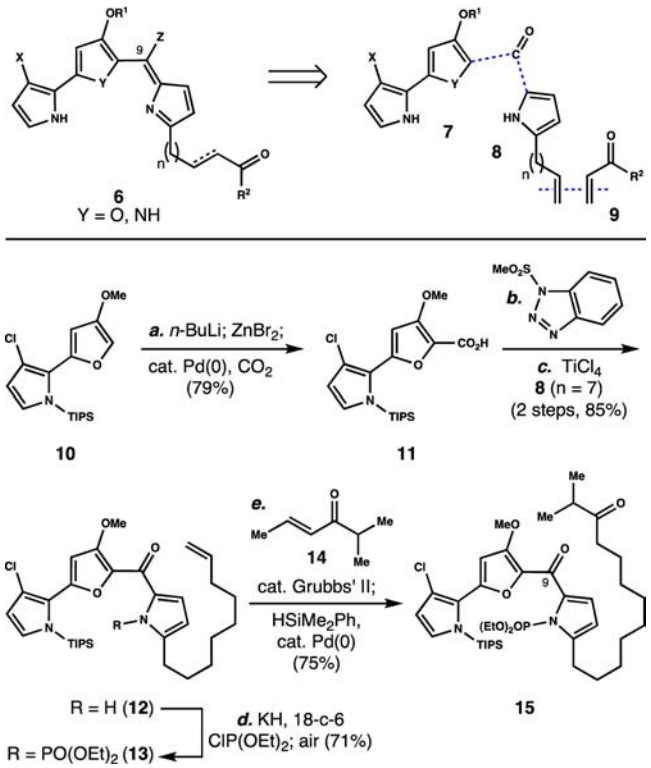
and its carbonyl group is a versatile design handle. Options for large ring formations within keto prodigiosins **6** (Scheme 1) became apparent, as did means to establish absolute stereochemistry late in the sequence via controlled reduction. The question became how best to assemble achiral structures **6** from fragments with an eye toward diversifying the route in subsequent iterations.

We targeted generic components **7** and **8** and sought to link the two in such a way that C_9 in **6** would be at the oxidation state of a ketone (Scheme 1). The α-olefin in **8** would facilitate

Scheme 1. Design and Assembly of Seco Precursors[a]



[a]Reagents and conditions: (a) *n*-BuLi, THF, −78 °C, 30 min; $ZnBr_2$ (1.0 M in THF), −78 to 0 °C, 2 h; $Pd(OAc)_2$ (5 mol %), PCy_3 (10 mol %), CO_2 (1 atm), THF, rt, 24 h, 79%. (b) 1-(Methanesulfonyl)-1*H*-benzotriazole, Et_3N, THF, reflux, 18 h. (c) **8** (n = 7), $TiCl_4$ (2 equiv), CH_2Cl_2, 0 °C, 3 h, 85% from **10**. (d) KH, 18-crown-6, THF, rt; $ClP(OEt)_2$, 0 °C, 1 h; air, 18 h, rt, 71%. (e) **14**, $PCy_3Cl_2(iMes)Ru{=}CHPh$ (5 mol %), CH_2Cl_2, rt, 18 h; $Pd(OAc)_2$ (5 mol %), PCy_3 (10 mol %), $HSiMe_2Ph$, PhMe, 60 °C, 6 h, 75%.

incorporating a third component (i.e., **9**) using alkene cross-metathesis. Toward this end, we developed syntheses of **7**[15] and **8**,[16] each beginning with pyrrole. Our new preparation of **7** requires five steps and permits X, Y, and R^1 to be varied controllably.[15] This route provides facile access to multigram quantities of specific roseophilin segment **10**.[17]

To construct a variant of **6** appropriate for the synthesis of **3**, methoxyfuran **10** was lithiated at low temperature, and the resultant organometallic was treated with $ZnBr_2$. Pd-catalyzed carboxylation of the incipient Zn species provided carboxylic acid **11**.[18] Condensation with 1-(methanesulfonyl)-1*H*-benzotriazole then afforded an active amide, which acylates 2-(8-nonenyl)pyrrole (**8**; n = 7) when aided by $TiCl_4$.[19] This Katritsky protocol scaled effectively and gave mixed bis-heteroaryl ketone **12** in high yield.

We originally planned to convert **12** to an azafulvene (e.g., **6**), wherein Z would later participate in an internal cross-coupling reaction en route to **5**. However, converting the ketone in **12** to either an enol sulfonate or a vinyl halide proved difficult. Attempts at the former resulted in N-sulfonylation. Finding means to exploit this outcome led to a new pyrrolophane synthesis.

Consistent with earlier observations, treatment of **12** with potassium hydride and diethyl chlorophosphite gave the *N*-phosphinyl derivative, which oxidized to phosphoramide **13** upon exposure to air.[20] Metathesis of **13** with isopropyl propenyl ketone (**14**)[21] then provided a chain-homologated enone, which was reduced in situ employing Pd-catalyzed hydrosilylation.[22] Hydrolysis of the resultant silyl enol ether during workup afforded diketone **15** as an amber oil.

Analogous to sulfonyl transfer reactions implicated in hydride reductions of *N*-tosyl-2-acylpyrroles,[23] the phosphoramide in **15** was intended as an internal trap for carbon nucleophiles added to the C_9 carbonyl. When **15** was deprotonated with potassium hexamethyldisilazide (KHMDS) at low temperature, quenching the reaction with water returned starting material. The same was true when 1 equiv of 18-crown-6 was added to the medium and the mixture was warmed to room temperature (rt) prior to protonation. However, when the enolate formed from the crown ether/KHMDS combination was brought to 55 °C, we observed gradual formation of pyrrolophane **19** (Scheme 2). Substrate **15** was fully consumed after 18 h, and macrocycle **19** was isolated in 66% yield. We speculate that **19** derives from the minor component in an initial equilibrium, namely, one established between kinetic enolate **16** and hindered internal aldol salt **17**. At low temperature and as unmodified ion pairs, these species regenerate **15** upon protonation. However, given sufficient energy in the presence of a potassium chelator, unimolecular N-to-O phosphoryl transfer can stabilize the aldol adduct as β-phosphoryl ketone **18**. Subsequent elimination of potassium diethylphosphate affords **19**.

Relative to enone **19**, roseophilin (**3**) lies two electrons lower in oxidation state. Samarium diiodide can reduce the $C_9{-}C_{22}$ olefin to provide **21**, albeit as a racemic mixture of diastereomers. Until recently, one may have been content with that outcome. Methods for controllable saturation of electron-rich tetrasubstituted enones are few. Fortunately, we were beneficiaries of a recent study by scientists at Eli Lilly. Through screening they identified a chiral Rh complex/Lewis acid combination that can catalyze the partial hydrogenation of highly substituted chalcones.[24] Adapting this protocol to our system involved hydrogenating **19** (H_2, 100 bar) in the presence of a catalyst generated from $Rh(cod)_2OTf$ and a JosiPhos ligand.[25] Consistent with precedent, turnover required cocatalytic $Zn(OTf)_2$ and MeOH as a cosolvent. Under these conditions, we obtained *cis*-β-pyrrolyl ketone **21** with high diastereoselectivity (>25:1). Furthermore, when the catalyst was formed using enantiopure bisphosphine **20**, the product (+)-**21** was isolated in 92% yield with 67% ee.[26,27]

Compound **21** is an oxygenated structural isomer of prodigiosin R1. It is also a hydrated form of **3**. Among conditions found to dehydrate **21**, catalysis by $[ReBr(CO)_3(thf)]_2$ was most effective.[28,29] A 10 mol % loading of this Lewis acid smoothly induced cyclodehydration, affording unstable 2-azafulvene **22**. It was best not to handle **22** but rather to treat the material in situ with dry HCl and substoichiometric amounts of *t*-BuOH. This provided rose-

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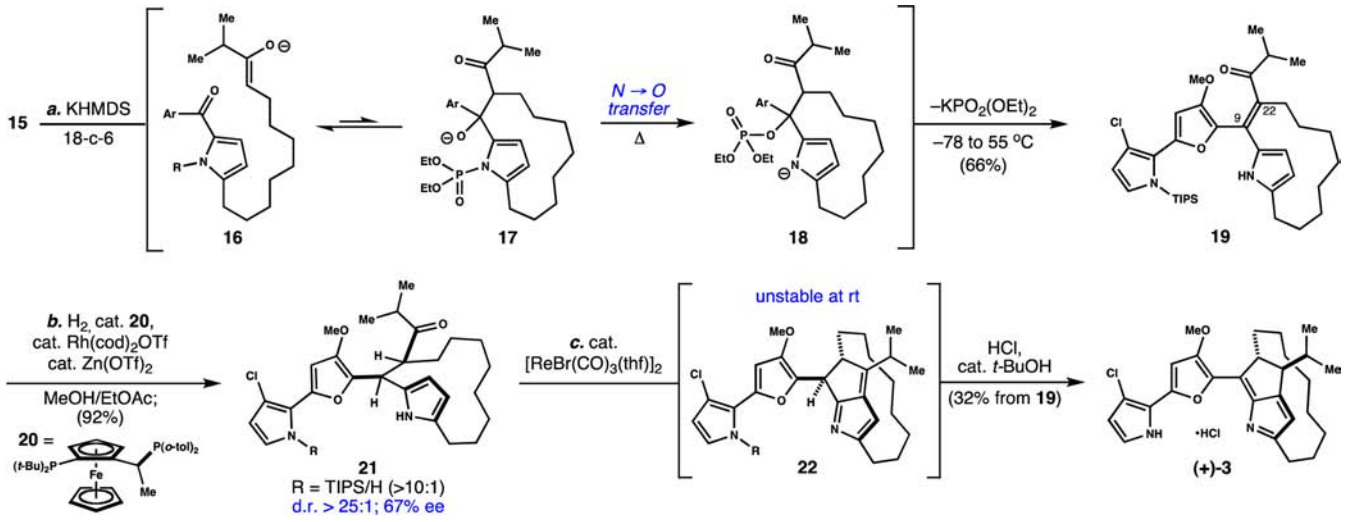
Scheme 2. Total Synthesis of (+)-Roseophilin (3)[a]

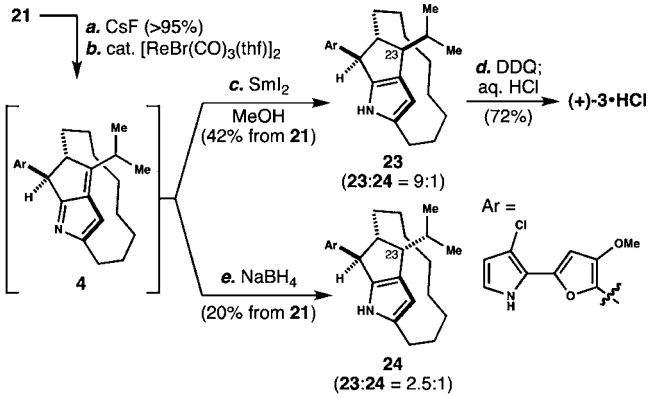


[a]Reagents and conditions: (a) KHMDS (2.2 equiv), 18-crown-6, THF, −78 to 55 °C, 18 h, 66%. Dephosphorylated **15** (5−7%) was also isolated in this experiment. (b) $Rh(cod)_2OTf$ (5 mol %), **20** (5 mol %), $Zn(OTf)_2$ (7.5 mol %), H_2 (100 bar), MeOH/EtOAc (1:1), rt, 24 h. (c) $[ReBr(CO)_3(thf)]_2$ (10 mol %), $(CH_2Cl)_2$, 70 °C, 4 h; *t*-BuOH (25 mol %), HCl, dioxane, −78 °C to rt, 4 h, 32% from **19**.

ophilin hydrochloride directly (Scheme 2). With minimal handling, roseophilin was obtained in 32% overall yield from enone **19**. The ^1H and ^{13}C NMR data for synthetic **3**·HCl were indistinguishable from those reported for the natural product and fully consistent with the structure assignment.

Intermediate **21** could also be desilylated with CsF. Dehydration of the product with catalytic $[ReBr(CO)_3(thf)]_2$ afforded *iso*-roseophilin (**4**) (Scheme 3). This reactive

Scheme 3. Reductions of *iso*-Roseophilin (4)[a]



[a]Reagents and conditions: (a) CsF, THF, rt, 3 h, >95%. (b) $[ReBr(CO)_3(thf)]_2$ (10 mol %), $(CH_2Cl)_2$, 70 °C, 4 h. (c) SmI_2, MeOH, THF, −78 °C to rt, 42% from **21**. (d) DDQ, CH_2Cl_2, rt, 5 h, 72%. (e) $NaBH_4$, THF, 50 °C, 3 h, 20% from **21**.

substance could be characterized, although loss during isolation was significant. It degrades intractably on standing ($t_{1/2}$ < 1 h at rt). Reduction of crude **4** with SmI_2 in MeOH afforded dihydro-roseophilin (**23**), an air-sensitive molecule that can be converted cleanly to **3** using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). When $NaBH_4$ was used to reduce **4**, epimer **24** was formed in significant amounts. Upon standing in air (0.1 M $CHCl_3$ solution, rt, 18 h), a mixture of **23** and **24** converted only to roseophilin. Epimer **23** was oxidized, while **24** remained largely unchanged. DDQ treatment degraded **24** rather than form a diastereomer of **3**. Additional studies on these fascinating structures are ongoing.

In conclusion, we have completed the shortest synthesis of roseophilin to date. Phosphoryl-transfer terminated macroaldolization uniquely installs the ansa bridge. It does so at an oxidation state where saturated asymmetry can be introduced via reduction late in the sequence. We expect the route to accommodate changes in ring sizes and substitution patterns, providing analogues that would be otherwise difficult to prepare. Since the C_{23} substituent follows from the choice of metathesis partner **9** and our synthesis of heterocycle **10** tolerates varying halogen and alkoxy groups,[15] design flexibility exists at multiple points along the angled periphery of the polyheterocycle. We can test whether roseophilin and its relatives are ligands for antiapoptotic Bcl-2 proteins and probe in detail whether the heterocyclic backbone is a scaffold upon which new α-helix mimetics can be developed. Work along these lines is ongoing, as are attempts to adapt the route to syntheses of other members of this important group of natural products.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, copies of ^1H and ^{13}C NMR spectra for new compounds, and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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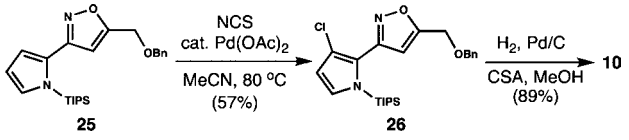
(14) A concerted sigmatropic shift of C_9−H to C_{23} within structure **4** is improbable. However, successive bimolecular protonation/deprotonation events appeared to be a viable path to **3** from **4**. The 3D structure of conformer **4** shown in Figure 1 (Spartan; B3LYP) was rendered with CYLview 1.0b (www.cylview.org).

(15) Isoxazolylpyrrole **25** was assembled in three steps from commercial dibromoformaldoxime, benzyl propargyl ether, and pyrrole. Substrate-directed, Pd-catalyzed chlorination provided a single isomer of **26**. Hydrogenolysis of **26** and treatment of the resultant enaminone with CSA/MeOH in situ afforded **10**. Full details of this route (five steps, 19% overall yield) and application of related methods in syntheses of congeners **7** will be reported separately.



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(25) Refinements are ongoing. For catalyst screening to date, see the SI.

(26) The same reaction employing the antipode of **20** provided scalemic **5** enriched in the opposite enantiomer (70% yield, 65% ee).

(27) A diastereomeric mixture of **5** (d.r. >25:1) enriched in the cis isomer epimerized at C_{22} to afford largely the corresponding trans diastereomer (1:4 cis:trans) upon exposure to DBU (0.5 M, THF, rt, 48 h).

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(29) The cyclodehydration protocol was optimized in a model system. For details, see the SI.