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 regiosomeric products of this remarkable chemistry. Polycyclic congeners derived from more extensive oxidation are also known (vide infra).

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 C₈–C₉ 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-pyryrol ketone 5 as a potential precursor. Pyrrolophane 5 resembles simpler ansa-prodiginines such as 2.

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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 intermediary of azafulvene prototropisomer 4.
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 C9 in 6 would be at the oxidation state of a ketone (Scheme 1). The C-O olefin in 8 would facilitate controllably.15 This route provides facile access to multigram quantities of speciﬁc reagent (incipient Zn species) provided carboxylic acid combination that can catalyze the partial hydrogenation of electron-rich tetrasubstituted enones are few. Fortunately, we found an oxygenated structural isomer of N-tosyl-2-acylpyrroles,23 the phosphoramidate in 21 was isolated as an amber oil. Metathesis of 21 was intended as an internal trap for carbon nucleophiles added to the C9 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 19 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 aldo 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, roseophenil (3) lies two electrons lower in oxidation state. Samarium diiodide can reduce the C9–C12 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 (H2, 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-pyrryl 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 dehydrat 21, catalysis by [ReBr2(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 r-BuOH. This provided rose-

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**Scheme 1. Design and Assembly of Seco Precursors**

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| a | n-BuLi, ZnBr2 | cat. Pd(0), CO2 | 79% |
| b | 1-(Methanesulfonyl)-1H-benzo triazole, Et3N, THF, reflux | 18 | 8 (n = 7), TiCl4 (2 equiv), CH2Cl2, 0 °C, 1 h | 71% |
| c | KH, 18-crown-6, THF | 18 h, rt | 71% |
| d | PCy3 (10 mol %), Pd(OAc)2 (5 mol %) | 60 °C, 18 h | 85% |
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Incorporating a third component (i.e., 9) using alkene cross-metathesis. Toward this end, we developed syntheses of 715 and 8,16 each beginning with pyrrole. Our new preparation of 7 requires five steps and permits X, Y, and R to be varied controllably.17 This route provides facile access to multigram quantities of speciﬁc roseophenil 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 ZnBr2. Pd-catalyzed carboxylation of the incipient Zn species provided carboxylic acid 11.18 Condensation with 1-(methanesulfonyl)-1H-benzotriazole then activated an active amide, which acylates 2-(8-nonenyl)pyrrole (8; n = 7) when aided by TiCl4.19 This Katritsky protocol scaled effectively and gave mixed bis-heteroaryl ketone 12 in high yield.

We originally planned to convert 12 to an azafulene (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 selenolate 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 phosphoramidate 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 phosphoramidate in 15 was intended as an internal trap for carbon nucleophiles added to the C9 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 aldo 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.

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ophelin hydrochloride directly (Scheme 2). With minimal handling, roseophilin was obtained in 32% overall yield from enone 19. The $^1$H 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 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 $\alpha$-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

S Supporting Information

Experimental details, characterization data, copies of $^1$H 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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REFERENCES


(9) Phase I/II of obatoclax (GX15-070) in untreated chronic lymphocytic leukemia: ClinicalTrials.gov, Identifier NCT00600964.


(14) A concerted sigmatropic shift of C22−H to C23 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) Isoxazolopyrrole 25 was assembled in three steps from commercial dibromoformaldoxime, benzy 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.

(16) Pyrrole 8 (n = 7) has been reported previously. See: Aldrich, L. N.; Dawson, E. S.; Lindley, C. W. Org. Lett. 2010, 12, 1048. We describe a shortened synthesis in the Supporting Information (SI).


(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. >2S:1) enriched in the cis isomer epimerized at C12 to afford largely the corresponding trans diastereomer (1:4 cis:trans) upon exposure to DBU (0.5 M, THF, rt, 48 h).


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