Asymmetric Total Synthesis of *ent*-(−)-Roseophilin: Assignment of Absolute Configuration

Dale L. Boger* and Jiyong Hong

Contribution from the Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

Received May 23, 2001

Abstract: An asymmetric total synthesis of *ent*-(−)-roseophilin (**1**), the unnatural enantiomer of a novel naturally occurring antitumor antibiotic, is described. The approach enlists a room temperature heterocyclic azadiene inverse electron demand Diels−Alder reaction of dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**7**) with the optically active enol ether **6** bearing the C23 chiral center followed by a reductive ring contraction reaction for formation of an appropriately functionalized pyrrole ring in a key 1,2,4,5-tetrazine → 1,2-diazine → pyrrole reaction sequence. A Grubbs' ring closing metathesis reaction was utilized to close the unusual 13-membered macrocycle prior to a subsequent 5-*exo*-*trig* acyl radical−alkene cyclization that was used to introduce the fused cyclopentanone and complete the preparation of the tricylic *ansa*-bridged azafulvene core **32**. Condensation of **32** with **33** under the modified conditions of Tius and Harrington followed by final deprotection provided (22*S*,23*S*)-**1**. Comparison of synthetic (22*S*,23*S*)-**1** ($[\alpha]^{25}_{D}$, CD) with natural **1** established that they were enantiomers and enabled the assignment of the absolute stereochemistry of the natural product as 22*R*,23*R*. Surprisingly, *ent*-(−)-**1** was found to be 2−10-fold more potent than natural (+)-**1** in cytotoxic assays, providing an unusually rewarding culmination to synthetic efforts that provided the unnatural enantiomer.

Roseophilin (**1**, Figure 1), isolated and characterized by Hayakawa and Seto et al. in 1992[1] from the culture broth of an actinomycete identified as *Streptomyces griseoviridis*, is a novel antitumor antibiotic that possesses a topologically unique pentacyclic skeleton. It was found to consist of a potentially strained macrocycle incorporated in an *ansa*-bridged azafulvene linked to a characteristic conjugated heterocyclic ring system containing a substituted furan and pyrrole. The structure **1** was assigned by spectroscopy, largely NMR,[1] and ultimately confirmed through total synthesis. While the relative stereochemistry of **1** was assigned by NMR spectroscopy, the absolute stereochemistry was not established. It was reported to exhibit promising cytotoxic activity in the submicromolar range (IC_{50}: 0.88 μM against KB human epidermoid carcinoma cells and 0.34 μM against K562 human erythroid leukemia cells).[1] Its unusual structure and this promising biological activity have stimulated substantial synthetic work, culminating in a racemic total synthesis by Fürstner and several subsequent racemic and optically active syntheses of the tricyclic core constituting formal total syntheses of the natural product.[2] Despite these efforts, none have progressed to the stage of establishing the absolute configuration of the natural product. Herein, and in conjunction with the accompanying disclosure of Tius and Harrington,[3] we report an asymmetric total synthesis of *ent*-(−)-roseophilin and the resulting assignment of the absolute configuration of the natural product.

Roseophilin is structurally related to a larger class of important pyrrolylpyrromethene red pigments, of which prodigiosin (**2**) is the parent member, that also exhibit potent antitumor and antibiotic activity. Although their site and mechanism of action have not been established, prodigiosin has been shown to effect double-strand DNA cleavage in the presence of Cu(II) and O_2.[4] The disclosure that members of the prodigiosin class of natural products are also immunosuppressive, acting through a novel mechanism, has generated additional interest in their use in organ transplantation or in the treatment of autoimmune diseases.[5] Undecylprodigiosin[5] and metacycloprodigiosin,[6] as well as prodigiosin,[7] inhibit T-cell proliferation and exert their effects by a mechanism distinct from that of cyclosporin A, FK506, or rapamycin. They appear to inhibit IL-2 signal transduction by inhibiting phosphorylation and activation of JAK-3 at the IL-2 γ-chain.[4] This complementary mechanism

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10.1021/ja011271s CCC: $20.00
Published on Web 08/10/2001

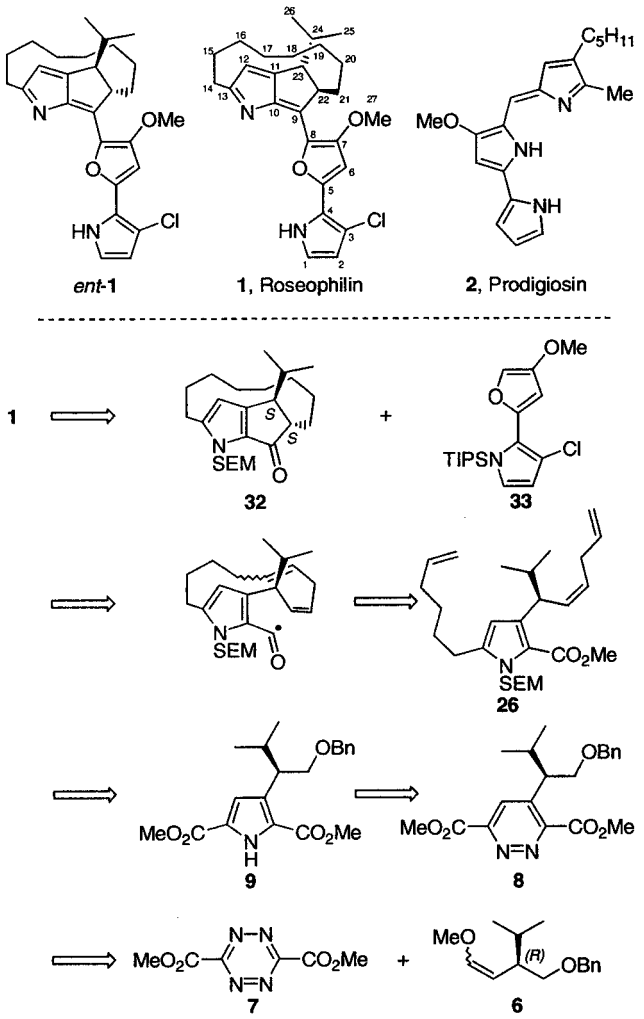
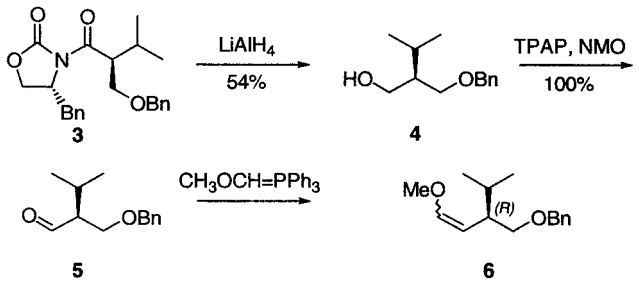


Figure 1.

of action to existing therapies suggests they could be used synergistically in combination with existing drugs as well as in an alternative immunosuppressive therapy on their own and has provided further interest in developing synthetic routes to such compounds.[8] Because of our past studies on prodigiosin and structurally related analogues,[9] roseophilin emerged as a natural and attractive synthetic target for us.

Our approach to roseophilin features both a 1,2,4,5-tetrazine → 1,2-diazine → pyrrole Diels−Alder strategy[10] for construction of an appropriately functionalized pyrrole ring and a 5-*exo-trig* acyl radical−alkene cyclization[11] for formation of the cyclopentanone found in the tricyclic core structure of **1** and is summarized in Figure 1. Following disconnection of **1** into this tricyclic core **32** and the heterocyclic side chain **33** defined in the work of Fürstner et al.,[2e] asymmetric synthesis of **32** would

Scheme 1



not only constitute a formal total synthesis of roseophilin but also permit the absolute configuration assignment of **1** upon condensation with **33**. Thus, inverse electron demand Diels−Alder reaction of the electron-deficient dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**7**) with the optically active electron-rich enol ether **6** was anticipated to provide **8** ideally functionalized for elaboration to the pyrrole **9** for incorporation into the tricyclic core. Formation of the triene **26** followed by Grubbs' ring closing metathesis (RCM)[12] would serve to introduce the 13-membered macrocycle on a nonstrained precursor prior to subsequent 5-*exo-trig* acyl radical−alkene cyclization that was anticipated to provide the strained cyclopentanone, completing the preparation of the tricyclic core.

The starting, optically active electron-rich enol ether **6** was prepared by $LiAlH_4$ reduction of **3**, derived from an Evans aldol reaction of a chelated Ti(IV) enolate with *s*-trioxane[14] followed by *O*-benzyl ether formation, to provide **4** in 54% (Scheme 1). TPAP oxidation[15] of **4** (100%) and Wittig reaction of the aldehyde **5** with $Ph_3P{=}CHOMe$ provided **6**.

The key inverse electron demand Diels−Alder reaction of the electron-deficient methyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**7**) with **6** proceeded effectively at room temperature to provide the optically active 1,2-diazine **8** in excellent yield (Scheme 2). Moreover, the preparation of **8** was found to be most convenient to conduct without purification of the intermediate enol ether **6** and, following the Diels−Alder reaction, provided **8** in yields as high as 91% for the two steps. Thus, the complementary match of the electron-rich dienophile **6** and the electron-deficient 1,2,4,5-tetrazine **7** imparted by the substituents provided a Diels−Alder reaction that proceeds effectively even at room temperature. Reductive ring contraction of **8** effected by treatment with Zn−TFA (25 °C, 1 h) gave the pyrrole **9** in

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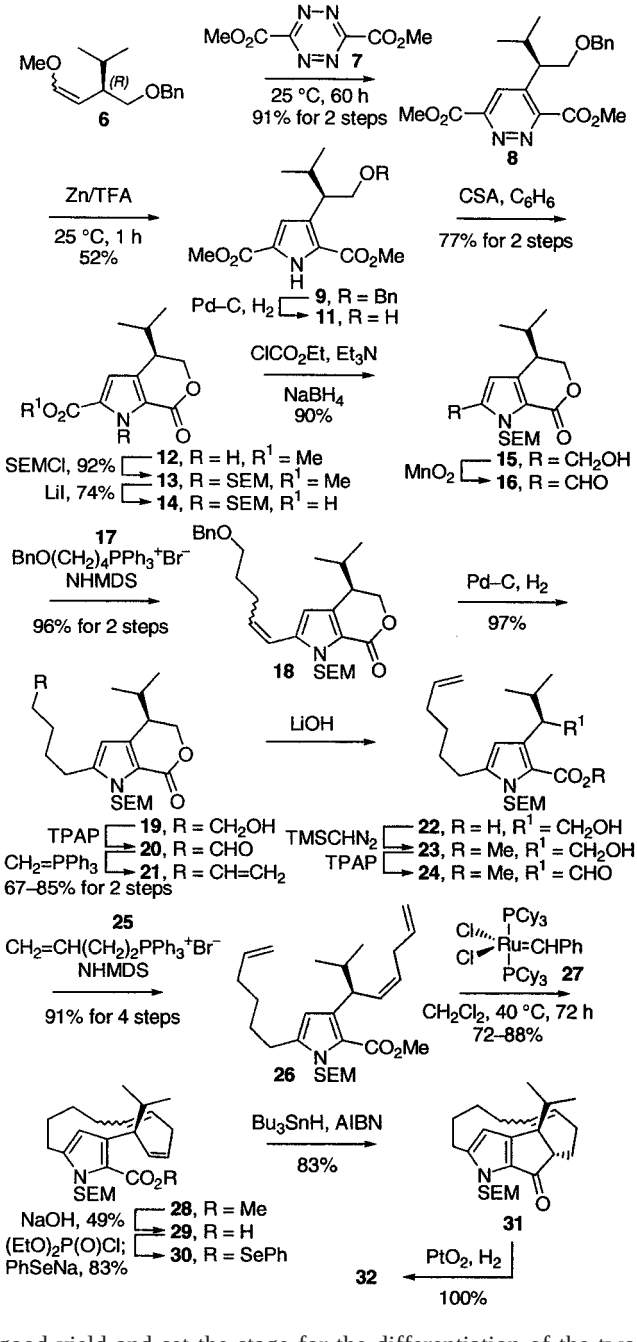
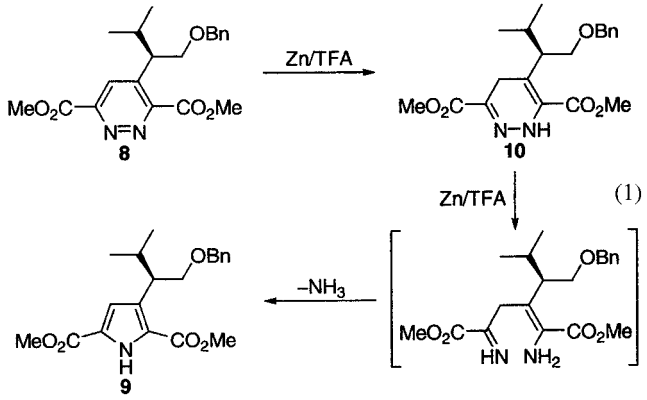
Scheme 2



good yield and set the stage for the differentiation of the two methyl esters. The reductive ring contraction reaction proceeded with intermediate generation of the isolable 1,4-dihydro-1,2-diazine **10** which in turn could be converted to **9** upon reexposure to treatment with Zn−TFA (eq 1). Notably, this reductive ring contraction reaction was much slower and less effective when conducted in HOAc vs TFA, and attempts to conduct the reaction at a later stage following formation of the fused lactone were not as successful although this was not investigated in detail.[9c]

Debenzylation of **9** with H_2/Pd−C, acid-catalyzed lactonization of **11** (70−83% for two steps) differentiating the two methyl esters, and subsequent protection of **12** with SEMCl gave **13** (92%). This set the stage for the introduction of the first of two pyrrole side chains terminating in a double bond suitable for RCM. Initial attempts to selectively hydrolyze the methyl ester in **13** (1 N LiOH, THF/MeOH/H_2O) resulted in preferential opening of the lactone to give the corresponding hydroxy acid



methyl ester. However, direct dealkylative methyl ester hydrolysis (LiI, DMF, 130 °C) provided the desired carboxylic acid **14** (74%) along with minor amounts of the corresponding SEM-deprotected carboxylic acid (14%). Treatment of **14** with $ClCO_2Et$ and Et_3N followed by immediate $NaBH_4$ reduction of the mixed anhydride gave the corresponding alcohol **15** in 90% yield.[16] Treatment of **14** with BH_3·THF (6 equiv, THF, 25 °C, 6 h) also provided **15**, but in lower conversions (50%). MnO_2 oxidation of the benzylic alcohol **15** and reaction of the aldehyde **16** with the Wittig reagent derived from **17**[17] gave **18** (*E*:*Z* = 1:5, 96% for two steps). Treatment of **18** with H_2/Pd−C served to reduce the double bond and deprotect the benzyl alcohol to give **19** (97%). TPAP oxidation and subsequent Wittig reaction of **20** with $Ph_3P{=}CH_2$ provided **21** in 67−85% overall yield, completing the first side chain introduction.

Hydrolysis of the lactone (LiOH), $TMSCHN_2$ esterification, TPAP oxidation, and reaction of the aldehyde **24** with the Wittig reagent derived from **25**[18] completed the introduction of the second side chain and gave the key triene **26** in 91% overall yield for the four steps (*Z*:*E* >20:1). Ring closing metathesis of **26** with 20 mol % of Grubbs' catalyst (**27**, 0.25 mM, CH_2Cl_2, 40 °C, 72 h) gave **28** as a 1:1 mixture of *E* and *Z* olefin isomers in yields as high as 88% (72−88%), completing the introduction of *ansa*-bridged macrocycle. This olefin metathesis closure of the *ansa* macrocycle prior to formation of the fused cyclopentanone, itself introducing a large part of the strain associated with the tricyclic core, does not require the use of specialized substrates incorporating conformational constraints favoring cyclization as required in the Fuchs and Speckamp RCM approach. In this regard, our observations are analogous but complementary to those of Fürstner[2h] and especially Tius[2j,3] who employed substrates that contained acyclic precursors to both the pyrrole and cyclopentanone ring systems or that lacked the pyrrole vs cyclopentanone, respectively.

Because of the hindered nature of the methyl ester in **28**, its conversion to the corresponding carboxylic acid **29** proved challenging. Only NaOH in refluxing EtOH−H_2O (49%) was successful in providing the carboxylic acid **29**,[19] whereas a range of more standard conditions failed to react with **28**. The conversion of **29** to the key tricyclic core required formation of the cyclopentanone and removal of the *ansa* chain internal double bond. This was accomplished through use of an acyl radical−alkene 5-*exo*-*trig* cyclization for closure of the five-

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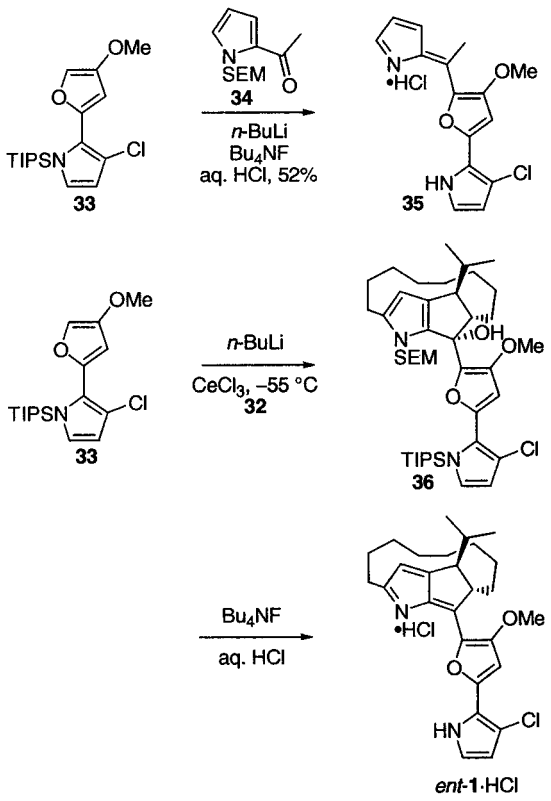
Scheme 3



membered ring followed by hydrogenation of the remaining double bond. Thus, treatment of **29** with $(EtO)_2P(O)Cl$ and Et_3N followed by addition of PhSeNa, generated in situ from NaH and PhSeH, provided the phenyl selenoester **30** (83%), the key acyl radical precursor.[11g] Notably, the conversions of **29** to **30** were low unless a respectable excess of reagents was employed and alternative methods for formation of phenyl selenoesters (*N*-phenylselenophthalimide, *n*-Bu_3P; $(PhSe)_2$, *n*-Bu_3P; $(COCl)_2$, NaSePh) failed to react with this hindered substrate. 5-*exo*-*trig* acyl radical−alkene cyclization (Bu_3SnH, AIBN, C_6H_6, 90 °C, 3 h)[11] smoothly and cleanly formed the strained cyclopentanone and provided **31** as a single diastereomer (*trans*) in 83% yield. Not only is this the thermodynamically most stable isomer, but its preferential kinetic formation would be consistent with cyclization through a chairlike allylic H-eclipsed conformation with the olefin occupying an equatorial orientation[20] and the relative stereochemistry of **31** was confirmed by ^1H NMR. The coupling pattern of H-23 (δ 2.56, d, $J = 6.5$ Hz) in the ^1H NMR spectrum showed no coupling to H-22. This same pattern is observed in roseophilin[1] and the tricyclic core[2e] and confirmed the *trans* stereochemical relationship between the two chiral centers. Catalytic hydrogenation (H_2/PtO_2, EtOAc, 2 h) of the remaining double bond in **31**[2l] provided the tricyclic core **32**, identical in all aspects with that reported for authentic **32**.[2e,m,3]

The heterocyclic side chain **33** was prepared by the method of Kim and Fuchs,[21] lithiated upon treatment with *n*-BuLi (1 equiv, THF, −57 °C, 5 h), and condensed with the model pyrrole substrate **34**, providing **35** in good yield (52%) comparable with the report of Fürstner,[2h] Scheme 3. However, all attempts to follow the protocol described in detail by Fürstner for conversion of **33** to the corresponding cerium reagent and condensation with **32** failed to provide **36**, leading instead to recovered starting materials. Considerable effort over several months was expended to ensure that the quality and dispersion of our $CeCl_3$ preparation were satisfactory including drying the reagent according to the procedure of Imamoto[22] and the removal of residual water with *t*-BuLi.[23] Despite these efforts, not even a trace of the desired adduct **36** was detected in our reaction mixtures. However, following the modified protocol detailed in the accompanying article of Tius and Harrington,[3] when this reaction was run with the $CeCl_3$ transmetalation conducted at −55 °C (2 h) before recooling the solution to −78 °C for addition of **32**, the elusive labile adduct **36** was obtained in good conversions, Scheme 3. Subsequent removal of the SEM and TIPS protecting groups (Bu_4NF) followed by brief treatment with aqueous HCl provided roseophilin hydrochloride as a red solid. The remarkable optical rotation of our synthetic (22*S*,23*S*)-**1** ($[\alpha]^{25}_D$ −5100 (*c* 0.3 × 10^{-4}, CH_3OH)) was nearly identical, but of an opposite sign to that of natural roseophilin ($[\alpha]^{25}_D$ +5500 (*c* 0.8 × 10^{-4}, CH_3OH)), indicating that we prepared the unnatural enantiomer and that natural **1** possesses the 22*R*,23*R* absolute stereochemistry. Similarly, the CD spectra of our synthetic *ent*-**1** and natural **1** exhibited identical but opposite curves, further establishing that they were enantiomers, Figure 2.

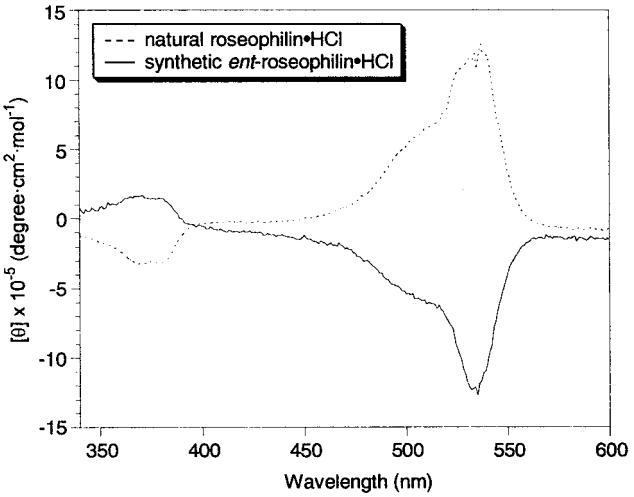


Figure 2. CD spectrum of (+)-**1**·HCl and *ent*-(−)-**1**·HCl in MeOH.

By testing both natural and *ent*-**1** alongside prodigiosin (**2**), we were able to establish that neither enantiomer of **1** cleaves DNA effectively under conditions that have been disclosed for **2** and related compounds (Cu(II), O_2).[4,24] Although other structural features may also contribute to these distinctions, the comparisons suggest the methoxypyrrole ring of **2**, vs the methoxyfuran found in **1**, is central to this activity, presumably affecting metal chelation and the subsequent steps leading to DNA cleavage. More importantly, and although the prodigiosins may derive their cytotoxic activity through this metal mediated ss or ds DNA cleavage, roseophilin most likely expresses its activity through other mechanisms.

Remarkably, a side-by-side comparison of **35** and natural and *ent*-(−)-roseophilin in a range of cytotoxic assays revealed not only that natural roseophilin was more potent than the simplified

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(24) Trace amounts of DNA cleavage were observed with natural (+)-roseophilin (<1% at 25 °C, 8% at 37 °C, 90 min) versus prodigiosin (44% at 25 °C, 80% at 37 °C, 90 min). Synthetic *ent*-(−)-roseophilin (10% at 25 °C, 16% at 37 °C, 90 min) was more effective than the natural enantiomer, but still less effective than prodigiosin (**2**).

Table 1. In Vitro Cytotoxic Activity

	IC_{50} (μM)[a]	
compound	L1210	CCRF-CEM
ent-(−)-**1**	0.1	0.1
(+)-**1**	0.2	1.5
35	2.5	3.3

[a] Average of triplicate determination.

model **35** as expected from the work of Terashima[2a] but also that *ent*-(−)-roseophilin was approximately 2−10-fold *more* potent than the natural enantiomer (Table 1). Although we are aware of instances where the unnatural enantiomer of a naturally occurring antitumor agent is comparably or equally potent,[25] we are not aware of an example where the unnatural enantiomer exceeds the natural enantiomer potency by as much as 10-fold. As such, this unanticipated behavior of *ent*-(−)-**1** provided an unusually rewarding culmination to synthetic efforts that by chance provided the unnatural enantiomer.

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Experimental Section

Full experimental details and compound characterizations are provided in the Supporting Information.

Acknowledgment. We gratefully acknowledge the financial support of the National Institutes of Health (CA42056) and the award of a Bristol-Myers Squibb Fellowship to J.H. (2000-2001). We are especially grateful to Professor M. A. Tius for sharing his results prior to publication, especially those required for condensation of **32** with **33** allowing our joint publication, to Winston Tse for assistance with the DNA cleavage assays, to Michael P. Hedrick for conducting the cytotoxic assays, to Alan Saghatelian for the CD measurements, to Professor Fürstner for helpful discussions, and to Professor Y. Hayakawa for a sample of authentic, naturally occurring roseophilin.

Supporting Information Available: Full experimental details and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

JA011271S