Synthesis of *ent*-Alantrypinone†

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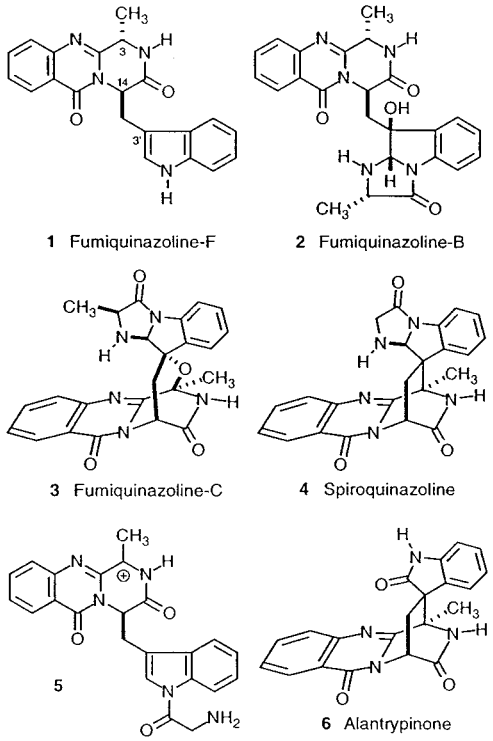
Received January 8, 2001

Abstract: This paper presents a synthesis of *ent*-alantrypinone (*ent*-**6**), the enantiomer of a natural product produced by the fungus *Penicillium thymicola*. The synthesis revolves around the Li[Me_3AlSPh]-promoted isomerization of iminobenzoxazine **33** to quinazolinone **34**, an *N*-acyliminium ion cyclization that converts enamide **9** to bridged indole **35**, and rearrangement of **35** to oxindole *ent*-**6**. Ancillary chemistry that involves thermal fragmentation of an iminobenzoxazine to a nitrile ylide and Me_2AlSPh-mediated cyclization of oxime ether−ester **22** to pyrrolidinone **23** is also described.

Introduction

Fungi belonging to the genera *Aspergillus* and *Penicillium* serve as a rich source of alkaloids clearly derived from amino acids.[1] A number of these alkaloids incorporate anthranilic acid and tryptophan as amino acid components. Some classical examples include the tryptoquivalines,[2] aszonalenins,[3] asperlicins,[4] and ardeemins.[5] More recently a series of alkaloids known as the fumiquinazolines have been reported.[6] These vary in structural complexity, but all seem to be biosynthetically derivable from fumiquinazoline F (**1**) and its C_3-epimer fumiquinazoline G. For example fumiquinazoline B (**2**) has an alanine appended to the indole nitrogen, and oxidative cyclization has occurred onto the indole ring. This structural feature also appears in the tryptoquivalines. One can imagine that fumiquinazoline C (**3**) is derived from **2** via an oxidative cyclization resulting in bridging of C_3 and C_{14} in the pyrazino-[2,1-*b*]quinazoline substructure of fumiquinazoline F. Spiroquinazoline (**4**) is a structurally unique alkaloid, isolated from extracts of *Aspergillus flavipes*.[7] We imagine that Nature might produce spiroquinazoline by an oxidative cyclization of fumiquinazoline F via the formal equivalent of an *N*-acyliminium ion of type **5**. Finally, alantrypinone (**6**) is a structurally simpler relative of spiroquinazoline, recently isolated from *Penicillium thymicola*, that clearly could be produced biosynthetically via a similar oxidative cyclization.[8]



In addition to their interesting structures, a number of the aforementioned compounds are biologically active. For example, spiroquinazoline (**4**) is a competitive inhibitor of substance P binding at the human NK-1 receptor and thus a potential lead

† This paper is dedicated to Professor David A. Evans on the occasion of his 60th birthday.

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(6) Numata, A.; Takahashi, C.; Matsushita, T.; Miyamoto, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Inoue, M.; Ohishi, H.; Shingu, T. *Tetrahedron Lett.* **1992**, *33*, 1621. Takahashi, C.; Matsushita, T.; Doi, M.; Minoura, K.; Shingu, T.; Kumeda, Y.; Numata, A. T. *Chem. Soc., Perkin Trans.* **1995**, 2345.

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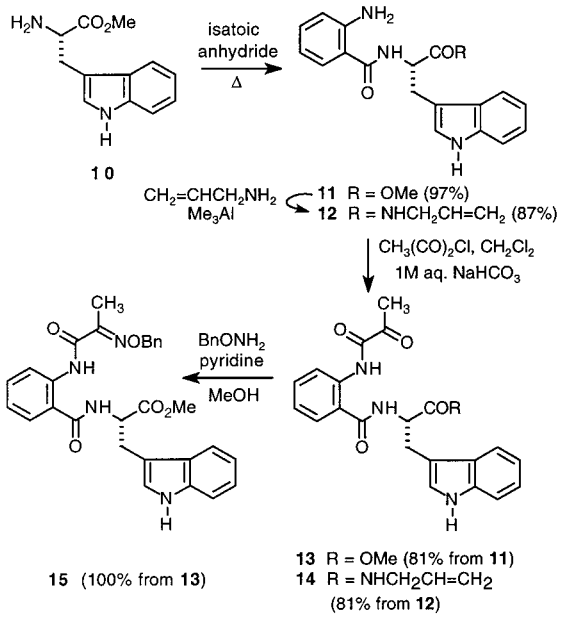
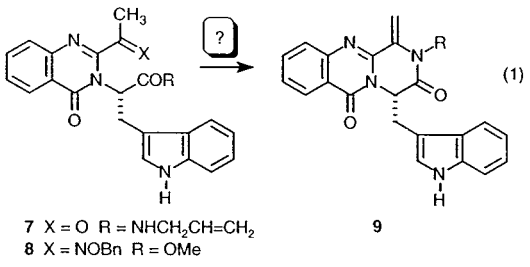
10.1021/ja010066+ CCC: $20.00
Published on Web 05/30/2001

Scheme 1



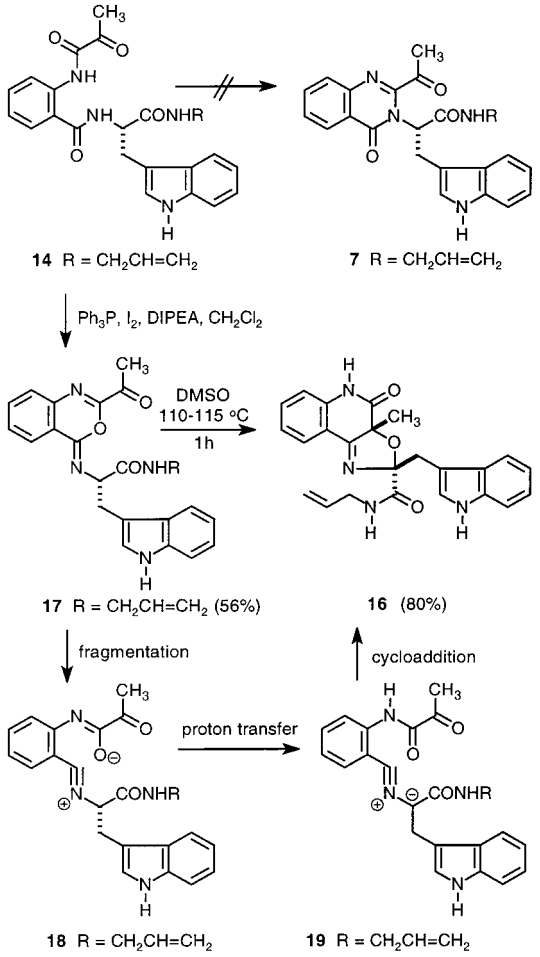
compound for development of analgesics.[7,9] We have initiated a synthetic program with the goal of developing efficient methods for the preparation of spiroquinazoline and related substances.[10,11] Although we have yet to reach spiroquinazoline, a synthesis of the enantiomer of alantrypinone is in hand.[11] This paper presents the details of this synthesis and some of the observations made along the way.

From the start, our studies were guided by the biosynthetic hypotheses described above and thus one of our objectives was to generate *N*-acyliminium ions of type **5** to observe their behavior. Although several routes to such ions were studied, this paper will describe the chemistry of ions derived from protonation of enamides of type **9**, where R represents a hydrogen or an appropriate nitrogen protecting group (eq 1). We initially hoped to prepare **9** via cyclization of quinazolinones **7** and **8**, and thus, these compounds were set as initial targets for synthesis.



Preliminary Studies. It was hoped that **14** and **15** would be the penultimate intermediates en route to **7** and **8**, respectively. It was imagined that cyclodehydration of these intermediates, using known methodology, would provide the desired quinazolinones. Syntheses of **14** and **15** are described in Scheme 1. Thus, reaction of the methyl ester of (*S*)-tryptophan with isatoic anhydride gave amide **11** in 97% yield.[12] Treatment of **11** with the aluminum amide derived from trimethylaluminum and allylamine provided **12** in 87% yield.[13] Acylation of both **11** and **12** with pyruvoyl chloride provided **13** (81%) and **14** (81%).[14] Treatment of **13** with *O*-benzylhydroxylamine gave **15** in quantitative yield.

Scheme 2



The cyclodehydration of anthranilic acid derivatives **14** and **15** to quinazolinones **7** and **8** was problematic, but interesting. On the basis of methodology reported by Ganesan during the course of a synthesis of fumiquinazoline G (C_3-*epi*-**1**), it was hoped that treatment of these amides with triphenylphosphine (Ph_3P)−iodine (I_2) in the presence of Hunig's base (DIPEA) would effect the desired transformation.[15] In the event, treatment of **14** ($C_{24}H_{24}N_4O_4$) with this cyclodehydration system provided a product ($C_{24}H_{22}N_4O_3$), initially suspected to be quinazolinone **7**, in 56% yield (Scheme 2). This proved not to be the case. We were initially surprised that this product showed no propensity for intramolecular cyclization of the *N*-allylamide nitrogen onto the carbonyl group of the methyl ketone. In an attempt to effect cyclodehydration of this product (suspected to be **7**) to an enamide of type **9** (R = allyl), this substance was eventually warmed at 110−115 °C in DMSO. A rather clean isomerization was observed in 80% yield. It was difficult to deduce the structure of this rearrangement product solely on the basis of spectral data. Crystallization of the isomerization

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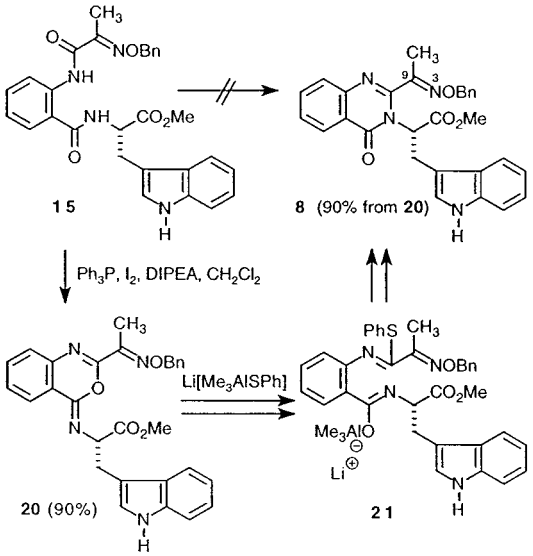
(13) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171.

(14) Ottenheijm, H. C. J.; de Man, J. H. M. *Synthesis* **1975**, 163.

(15) Wang, H.; Ganesan, A. *J. Org. Chem.* **1998**, *63*, 2432.

Scheme 3



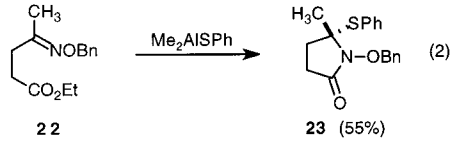
product from acetonitrile, however, provided a suitable single crystal for X-ray crystallographic analysis, which unambiguously determined its structure as **16**.[16] With the structure of **16** established, it was possible to postulate a mechanism for its formation. Given that **16** was racemic, it was felt that the oxazoline substructure might be derived from an intramolecular [3 + 2]-cycloaddition between the nitrile ylide and ketone groups in achiral intermediate **19**. It seemed unlikely that **19** could be derived from **7** but reasonable that it be formed from iminobenzoxazine **17**. For example, fragmentation of **17** would provide **18** and a subsequent proton transfer would then provide **19**. This suggested that the original cyclodehydration of **14** had not provided quinazolinone **7** but had in fact provided iminobenzoxazine **17**.

Concurrent with the studies shown in Scheme 2, we were examining the cyclodehydration of **15** with the intention of preparing quinazolinone **8** (Scheme 3). Thus, treatment of **15** ($C_{29}H_{26}N_4O_5$) with Ph_3P-I_2-DIPEA gave a 90% yield of a product ($C_{29}H_{24}N_4O_4$) originally suspected to be quinazolinone **8**. Once again this was not the case. This product had all the spectroscopic features one might expect to see in **8** but exhibited unexpected chemical behavior. It was sensitive to aqueous acid and could not be induced to undergo cyclodehydration to an enamide of type **9** (R = OBn). In one attempt to accomplish a nucleophile-induced cyclization, this product (suspected to be **8**) was treated with 3 equiv of lithium trimethyl(phenylsulfido)-aluminate (Li[Me_3AlSPh]) for 20 h at room temperature.[17] This reaction provided an isomeric material in 90% yield. The spectroscopic features of this isomerization product were also remarkably consistent with what one would expect for **8**, with the exception that the pyruvate-derived methyl group in this isomer (δ 1.19 in C_6D_6) was significantly more shielded than in the starting isomer (δ 2.02 in C_6D_6). X-ray crystallographic analysis of the rearrangement product unambiguously revealed that the rearrangement product was **8** and, thus, the original cyclodehydration product was something else![16] The crystal structure of **8** also revealed that this compound crystallizes in a conformation with the indolyl group folded over the pyruvate-derived methyl group, explaining the abnormally upfield chemical shift of the methyl group. In addition, **8** crystallizes in a conformation in which the ester carbonyl projects away from the nitrogen of the oxime ether. This could explain the reluctance of **8** to undergo cyclodehydration to a structure of type **9** (vide infra).

The results described above suggest that, once again, the original cyclodehydration conditions (Ph_3P-I_2-DIPEA) had transformed **15** into iminobenzoxazine **20,** rather than quinazolinone **8**, and that the observed isomerization was actually the conversion of **20** into **8**.[18] It was imagined that this might have occurred by Lewis acid assisted nucleophilic opening of **20** to an intermediate such as **21**, followed by cyclization to provide **8**. Whereas the mechanism of this transformation is merely conjecture, the generality of this rearrangement process has been established (vide infra).

Some Comments and Diversions. At this point in our studies, a literature search revealed that the cyclodehydration of *N*-acylanthranilamides to iminobenzoxazines using $Ph_3P-Br_2-Et_3N$ had been reported by Mazurkiewicz, as well as the acid-promoted rearrangement of these iminobenzoxazines to quinazolinones.[19] This report, and the observations noted in Schemes 2 and 3, suggested that the cyclodehydration results reported in Ganesan's elegant fumiquinazoline G synthesis were suspect.[15] Indeed, this was nicely shown to be the case by the Snider group and was later recognized by the authors of the fumiquinazoline G synthesis.[20,21]

We also note that attempts to convert **8** to **9** (R = OBn) were unsuccessful. For example, we were able to develop a nucleophilic addition−ring closure procedure for the cyclization of ethyl levulinate derivative **22** to **23** in 55% yield (eq 2) using

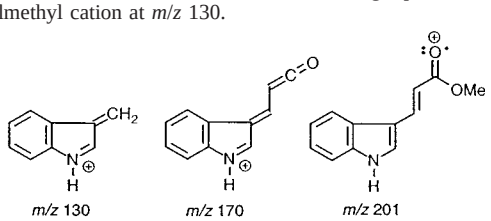


dimethylaluminum thiophenoxide (Me_2AlSPh).[22] Treatment of **8** with Me_2AlSPh under identical conditions, however, returned only starting material. One explanation for the lack of reactivity of **8** evolves from analysis of its crystal structure.[16] The crystal structure of **8** reveals that the dihedral angle between the plane of the quinazolinone ring and the plane of the C=N π-bond is about 45°. This suggests that there is no through-conjugation between the oxime oxygen and the quinazolinone unit. With this in mind, a possible explanation for the failure of Me_2AlSPh to transform **8** to **9** might involve steric congestion inherent in

(16) We thank Dr. Judith C. Gallucci for performing X-ray crystallographic analyses of **8** and **16** at the Ohio State University Department of Chemistry X-ray Crystallography Facility. Details are provided in the Supporting Information.

(17) Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 361.

(18) Mass spectrometry provided another clear method for distinguishing between tryptophan-derived iminobenzoxazines and quinazolinones. For example, quinazolinone **8** undergoes a McLafferty rearrangement and exhibits a peak due to a cation-radical at *m*/*z* 201, which loses a methoxy radical to give a strong peak at *m*/*z* 170. These peaks are absent in iminobenzoxazine **20**. Both **8** and **20** show large peaks due to the 3-indolylmethyl cation at *m*/*z* 130.



(19) Mazurkiewicz, R. *Monatsh. Chem.* **1989**, *120*, 973.

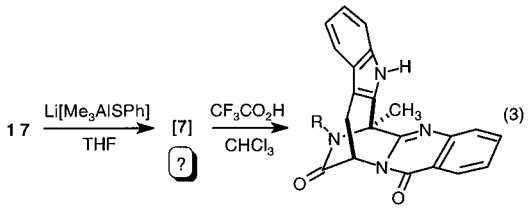
(20) He, F.; Snider, B. B. *J. Org. Chem.* **1999**, *64*, 1397.

(21) Wang, H.; Ganesan, A. *J. Org. Chem.* **2000**, *65*, 1022.

(22) Prepared by analogy with the preparation of Et_2AlSPh: Yasuda, A.; Takahashi, M.; Takoya, H. *Tetrahedron Lett.* **1981**, *22*, 2413.

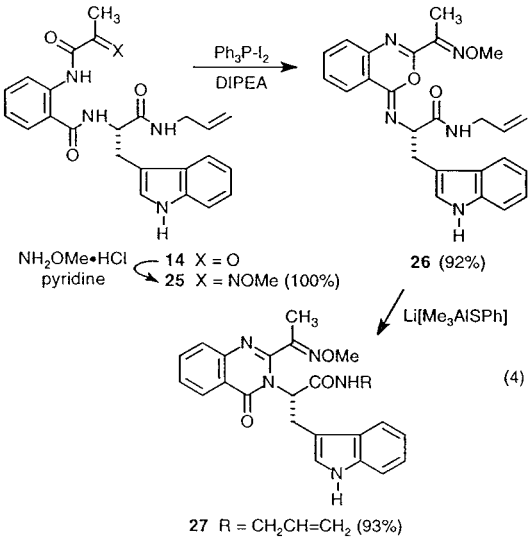
2,3-disubstituted quinazolinones. One can imagine that addition of an external nucleophile across the C_9-N_3 double bond would increase steric congestion in the system upon going from sp^2 to sp^3 hybridization at C_9.[23]

The rearrangement of iminobenzoxazine **17** to quinazolinone **7** was also examined. Treatment of **17** with Li[Me_3AlSPh] provided a complex mixture of products that was not possible to characterize.[24] Whatever the actual composition of this complex mixture, upon treatment with trifluoroacetic acid in chloroform (1:10) at reflux, **24** was obtained in approximately 50% yield (eq 3). The structure of **24** was assigned principally



on the basis of ^{1}H NMR spectroscopy and eventually by a comparison of its ^{1}H NMR spectrum with that of bridged indole **35** (vide infra). We imagine that **24** results from formation of **7**, cyclization to a variety of compounds that could serve as precursors to the carbocation ion derived from enamide **9** (R = allyl),[24] acid-mediated generation of such a carbocation, and an intramolecular electrophilic aromatic substitution reaction. This process, however, was messy and thus a longer, but more controlled reaction sequence was sought.

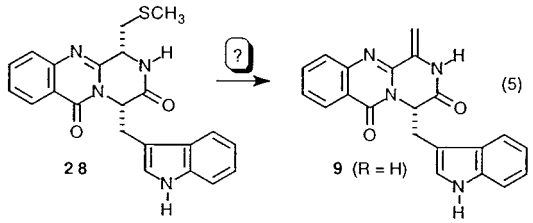
One option that was explored involved conversion of **14** to oxime ether **25**, followed by cyclodehydration to afford benzoxazine **26** in 92% overall yield (eq 4). Application of the



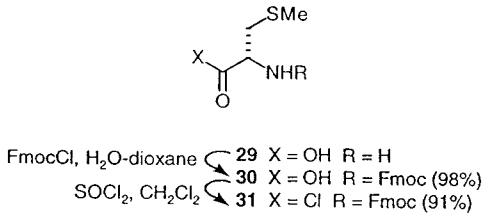
benzoxazine−quinazolinone rearrangement then provided **27** in 93% yield. To our surprise, we were unable to induce **27** to cyclize, even under such drastic conditions as reflux in chloroform−trifluoroacetic acid (10:1). After such treatment, unchanged starting material could be completely recovered.

(23) As noted above **8** was uneffected by Li[Me_3AlSPh] and also by trimethylsilylthiophenoxide in the presence of catalytic amounts of trimethylsilyl triflate. It was possible to convert **8** to the corresponding carboxylic acid using either lithium hydroxide in aqueous tetrahydrofuran (42% with 44% recovery of starting material) or molten imidazole at 160−170 °C (90%). Attempts to convert this acid to **9** by activation of the carboxylic acid were also unsuccessful.

The results described above were both encouraging and discouraging. Whereas we had not been able to develop a reaction sequence that provided isolable enamides of type **9**, a reliable procedure for the synthesis of highly functionalized quinazolinones was in hand, and the observations presented in eq 3 suggested that generation and cyclization of the desired *N*-acyliminium ion was feasible. Thus, we abandoned pyruvic acid derived precursors of enamide **9** and focused on precursors where the oxidation state needed for generation of the *N*-acyliminium ion was displaced by one carbon. Thus, sulfide **28** was set as the next target for synthesis in anticipation that it could be converted to **9** (R = H) using elimination chemistry (eq 5).



***ent*-Alantrypinone (*ent*-6).** The synthesis of **28** required preparation of cysteine-derived acid chloride **31**. This was accomplished in two steps from commercially available *S*-methyl-L-cysteine (**29**) using the standard Carpino protocol.[25] Acylation of **29** with FmocCl in aqueous dioxane provided urethane **30** in 98% yield. Reaction of **30** with excess thionyl



chloride furnished a 91% yield of crystalline acid chloride **31**. Acylation of anthranilic acid derivative **11** (vide supra) with **31** under Schotten−Baumann conditions provided a 96% yield of **32** (Scheme 4). Cyclodehydration of **32** with Ph_3P-I_2−DIPEA in dichloromethane at room temperature gave an 80% yield of iminobenzoxazine **33**. Treatment of **33** with 10 equiv of Li[Me_3AlSPh] in tetrahydrofuran at −78 °C, then at −10 °C for 12 h, and finally at room temperature for 8 h provided a 46% yield of **28**. A better conversion of **33** to **28** was achieved under more selective conditions for the rearrangement. Thus, treatment of **33** with 5 equiv of the aluminum complex at −78 °C for 30 min and then at −10 °C for 36 h provided a 76% yield of quinazolinone **34** in addition to 8% of **28**. Quinazolinone **34** was cleanly transformed into **28** using standard Fmoc removal conditions (piperidine in tetrahydrofuran at 0 °C for 90 min).[26] Oxidation of **28** with *m*-chloroperoxybenzoic acid provided a 3:2 mixture of diastereomeric sulfoxides, and gentle reflux of a suspension of these sulfoxides in benzene containing triphenylphosphine provided enamide **9** (R = H) in 79% yield from **28**.[27] Triphenylphosphine was required to intercept meth-

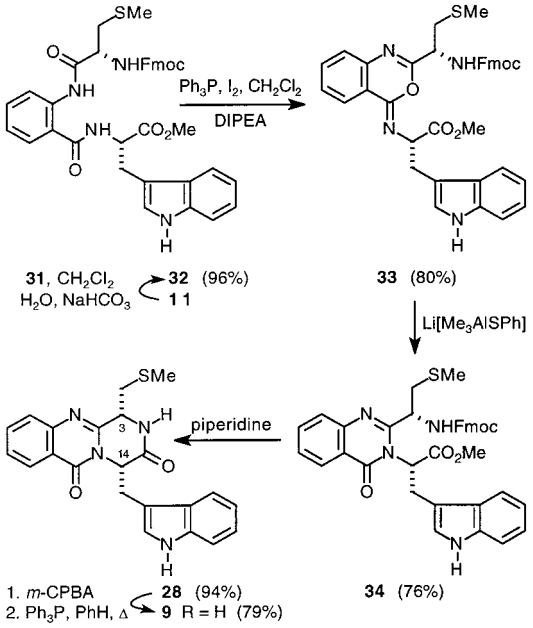
(24) The anticipated quinazolinone (**7**) has keto and amide groups in close proximity and might exist as a pair of diasteromeric cyclols. The ^{1}H NMR of the rearrangement mixture showed that some of the products had incorporated a thiophenoxy group. Such compounds could be derived from the cyclols by exchange of a hydroxyl group with a thiophenoxy group.

(25) Carpino, L. A.; Cohen, B. J.; Stephens Jr., K. E.; Sadat-Aalaee, S. Y.; Tien, J.-H.; Langridge, D. C. *J. Org. Chem.* **1986**, *51*, 3732.

(26) Carpino, L. A. *Acc. Chem. Res.* **1987**, *20*, 401.

(27) Rich, D. H.; Tam, J. P. *J. Org. Chem.* **1977**, *42*, 3815.

Scheme 4

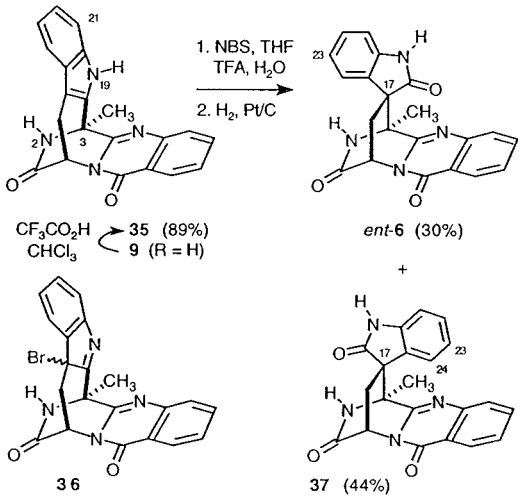


anesulfenic acid, and omission of this reagent reduced the yield of **9** by 20−30%.

A stereochemical aspect of the chemistry presented in Scheme 4 deserves comment. Although Li[Me_3AlSPh] is presumably a nonbasic reagent, the presence of a potentially epimerizable tryptophan-derived methine in **33** led us to look carefully for epimerization products related to **28**. In one experiment, conducted on a large scale, the C_3 epimer of **28** was isolated in 4% yield. ^{1}H NMR spectroscopy could be used to distinguish the two diastereomers. Compound **28** probably exists in a boatlike conformation with the indole unit folded over the pseudoaxial CH_2SMe substituent.[28] As a result, one of the protons of the methylene α to sulfur is highly shielded and appears at δ 0.32 in $CDCl_3$ (the other appears at δ 2.60). In the C_3 epimer of **28**, neither of the protons of the methylene under consideration is shielded (δ 2.37 and 2.67). To establish that the minor product was epimeric to **28** at C_3 rather than C_{14}, this sulfide was oxidized to a mixture of sulfoxides which were converted to **9** in 75% yield upon refluxing in toluene. The optical rotation of this material matched that of **9** derived from sulfide **28**, both in sign and magnitude, providing clear evidence that the epimerization had occurred at C_3.[29,30]

The synthesis of *ent*-alantrypinone was completed as shown in Scheme 5. Treatment of **9** (R = H) with trifluoroacetic acid in chloroform (1:20) under reflux for 2 h effected intramolecular electrophilic attack of a presumed intermediate *N*-acyliminium ion onto the indole to provide **35** in 89% yield. The orientation of the indole nucleus was proven by difference NOE experiments.[31] Irradiation of H_{19} (δ 11.20 in DMSO-d_6) gave enhancements of signals due to H_{21} (δ 7.37) and the C_3 methyl group (δ 2.12). In addition, irradiation of the C_3 methyl group

Scheme 5



resulted in enhancement of the signals due to H_{19} and H_2 (δ 9.55). The downfield chemical shift of the C_3 methyl group was surprising but can be explained by its orientation relative to the deshielding region of the indole nucleus. We note that the ^{1}H NMR spectrum of **24** (vide supra) was a close match with the spectrum of **35**, including the chemical shift of the C_3 methyl group.

To complete the synthesis of alantrypinone, it was necessary to conduct oxidative rearrangement of the indole to an oxindole. A number of procedures for conducting this transformation are known. We settled on *N*-bromosuccinimide (NBS) in aqueous acid as a medium for accomplishing this task.[32] Reaction of **35** with 1.1 equiv of NBS in a mixture of water, acetic acid, and tetrahydrofuran (1:1:1) did not give the desired oxindole but rather provided a 3:2 mixture of diastereomeric bromoindolines **36**. Treatment of the mixture of bromoindolines with strong acids (HBr in DME or TFA in THF) at 0 °C resulted in reversal of the transformation to give starting **35**. Eventually it was found that treatment of **35** with five 1-equiv portions of NBS in a mixture of tetrahydrofuran−trifluoracetic acid−water (5:4:4) at 0 °C accomplished the desired oxidative rearrangement. This reaction, however, was accompanied by polybromination of the indolinone (principally at C_{23}).[33] Thus, the crude reaction product was hydrogenolyzed over platinum on carbon to give, after separation by column chromatography, *ent*-alantrypinone (*ent*-**6**) and *ent*-17-epialantrypinone (**37**) in 30% and 44% yields, respectively.[34,35] The relative configuration of the spiro center (C_{17}) in these stereoisomers was readily assigned on the basis of their ^{1}H NMR spectra. In the spectrum of *ent*-17-epialantrypinone (**37**), H_{23} and H_{24} appeared at abnormally high field (δ 6.66 and 5.87, respectively, in DMSO-d_6), a result of the

(28) For related observations of shielding in diketopiperazines see: Anteunis, M. J. O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 627.

(29) We note that a variation of the conditions used to convert iminobenzoxazines to quinazolinones by others were problematic when applied to **33**. For example, treatment of **33** with a 10% solution of piperidine in acetonitrile at room temperature for 1.5 h provided a crude mixture of materials. Heating these materials in acetonitrile at reflux for 18 h provided enamide **9** (R = H) in 40% yield (from **33**). These conditions, however, resulted in significant racemization as the optical rotation of this material (**9**) was one-fifth of that recorded for material prepared using Li[Me_3AlSPh].

(30) A synthesis of **9** (R = H) that uses a different approach has been reported: He, F.; Snider, B. B. *Synlett* **1997**, 483.

(31) It is possible that this cyclization proceeds mechanistically via initial attack of the electrophile at C_3 of the indole, followed by a Wagner−Meerwein shift. For related cyclizations in substituted diketopiperizines see: Ottenheijm, H. C. J.; Plate, R.; Noordik, J. H.; Herscheid, J. D. M. *J. Org. Chem.* **1982**, *47*, 2147.

(32) Pellegrini, C.; Strassler, C.; Weber, M.; Borschberg, H.-J. *Tetrahedron: Asymmetry* **1994**, *5*, 1979. Stahl, R.; Borschberg, H.-J.; Acklin, P. *Helv. Chim. Acta* **1996**, *79*, 1361.

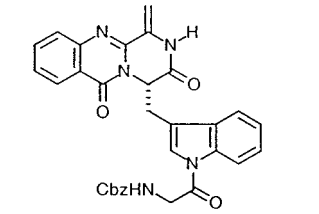
(33) When only 2 equiv of NBS was used, under much the same conditions, bromination of the aromatic ring was limited largely to C_{23}. However, small amounts of unreacted **35** interfered with isolation of pure *ent*-**6** (after debromination), complicating optical rotation measurements due to the large positive specific rotation of **35**. Thus, the polybromination−debromination protocol was preferred.

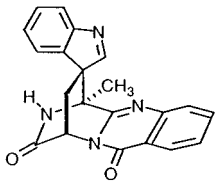
(34) The hydrogenolysis was also conducted using Pd/C, but the rate of the reaction was slower than with Pt/C.

(35) Over a series of experiments, the ratios of **37**:*ent*-**6** ranged from 50:50 to 60:40.

stereochemical relationship of these protons to the π-system of the quinazolinone substructure. In addition, the mobility of **37** on silica gel was much lower than that of *ent*-**6**, presumably a reflection of the greater steric accessibility of the oxindole carbonyl group (in **37**) for binding to the solid support. Finally, we note that the spectral and physical properties of *ent*-**6** were identical to those reported for the natural product with the exception of the sign of the specific rotation.[8,36] This confirms the absolute configuration of the natural product as 3*R*,14*R* as shown in structure **6**.[37] This also means that the biosynthesis of alantrypinone either starts with the less common D-tryptophan or that L-tryptophan is used and an isomerization occurs along the biosynthetic pathway.[38]

As alluded to in the Introduction, one objective of this research yet to be accomplished is a synthesis of spiroquinazoline (**4**). With this objective in mind, enamide **9** (R = H) was converted to *N*-acylindole **38** in 25−34% yield upon treatment





39

with *p*-nitrophenyl *N*-Cbz-glycinate in the presence of KF, 18-C-6, and DIPEA in acetonitrile.[39] We have not yet been able, however, to accomplish the conversion of **38** to spiroquinazoline. For example, treatment of **38** with either TFA−chloroform (1:10) or *p*-toluenesulfonic acid in benzene, at reflux, provided complex mixtures of products. These mixtures were subjected to catalytic hydrogenolysis (Pd/C) to remove Cbz groups, but a comparison of the ^{1}H NMR spectra of the crude products with the reported spectrum of **4** indicated no formation of the target compound. In addition, treatment of enamide **9** with Amberlyst-15 in aqueous acetonitrile, with the hope of intercepting the spiroindoline **39** (expected to be an intermediate en route from **9** to **35**) in a Ritter-type reaction, provided exclusively **35**. Thus, we are currently focusing on the conversion of alantrypinone or **35** to spiroquinazoline.

Conclusions

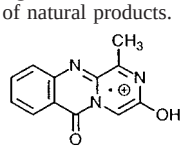
This paper describes a 10-step synthesis of *ent*-alantrypinone (*ent*-**6**) that proceeds in 12% yield and confirms the absolute configuration of the natural product. The studies describe several observations of interest to the field of heterocyclic chemistry including a new method for rearrangement of iminobenzoxazines to quinazolinones that has some advantages over existing methodology, fragmentation of an iminobenzoxazine to a nitrile ylide, and an example of a nucleophile-induced cyclization of an oxime−ester to a highly functionalized lactam.

Experimental Section[40]

(±)-1-(Benzyloxy)-5-methyl-5-(phenylthio)-2-pyrrolidinone (23). To a stirred solution of 115 μL of PhSH in 1 mL of dry CH_2Cl_2 was added dropwise 0.56 mL of a 2 M solution of $AlMe_3$ in toluene over a period of 3 min at room temperature under an argon atmosphere. The solution was stirred at room temperature for 10 min, then cooled to −78 °C, and transferred via cannula into a cooled (−78 °C) solution of 200 mg (0.80 mmol) of **22** in 1 mL of dry CH_2Cl_2. The cooling bath was removed and the reaction mixture was stirred for 1 h 20 min. After that time, the reaction mixture was quenched with 1 mL of 1 N aqueous HCl and partitioned between 100 mL of CH_2Cl_2 and 10 mL of water. The organic layer was washed with 10 mL of water, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 20 g of flash silica gel (gradient elution with Et_2O:hexanes, 1:3, then 1:1, then neat Et_2O) to yield 138 mg (55%) of pyrrolidone **23** as a thick colorless oil: IR (neat) 3060, 2975, 2938, 2880, 1726, 1453, 1374, 1062 cm^{-1}; ^{1}H NMR (acetone-d_6, 300 MHz) δ 1.27 (ddd, J = 17.0 Hz, 10.0 Hz, 9.0 Hz, 1H, C*H*HCS), 1.63 (s, 3H, CH_3), 1.97 (ddd, J = 17.0 Hz, 9.8 Hz, 2.1 Hz, 1H, CH*H*CS), 2.21 (ddd, J = 13.6 Hz, 9.8 Hz, 9.0 Hz, 1H, COC*H*H), 2.43 (ddd, J = 13.6 Hz, 10.0 Hz, 2.1 Hz, 1H, COCH*H*), 5.05 (d, J = 9.9 Hz, 1H, C*H*HO), 5.29 (d, J = 9.9 Hz, 1H, CH*H*O), 7.34−7.48 (m, 6H, ArH), 7.52−7.55 (m, 2H, ArH), 7.58−7.61 (m, 2H, ArH); ^{13}C NMR (acetone-d_6, 75.5 MHz) δ 26.7 (t), 27.2 (q), 32.9 (t), 75.4 (s), 78.9 (t), 129.3 (d), 129.3 (d), 129.5 (d), 130.0 (d), 130.0 (d), 130.2 (d), 130.2 (d), 130.4 (d), 131.9 (s), 136.6 (s), 138.1 (d), 138.1 (d), 170.6 (s); mass spectrum (EI), *m*/*z* (relative intensity) 314 (M + 1$^+$, 0.03), 204 (14), 179 (10), 110 (25), 109 (11), 92 (10), 91 (100), 77 (14), 65 (13), 51 (8), 43 (11); exact mass calcd for $C_{18}H_{20}NO_2S$ (M + 1$^+$) *m*/*z* 314.1215, found *m*/*z* 314.1261.

***N*-[*N*-[(*R*)-2-Carboxyamino-3-(methylthio)propionyl]anthraniloyl]-L-tryptophan, *N*-(Fluoren-9-ylmethyl) Methyl Ester (32).** To a vigorously stirred two-phase system consisting of a solution of 432 mg (1.28 mmol) of aniline **11** in 12 mL of CH_2Cl_2 and 12 mL of 10% aqueous $NaHCO_3$ was added dropwise a solution of 529 mg (1.41 mmol) of acid chloride **31** in 10 mL of CH_2Cl_2 over a period of 5 min at room temperature. The resulting mixture was stirred for 15 min, after which time TLC (silica, EtOAc/Hex, 2:1) indicated complete consumption of starting material. The organic layer was separated and the aqueous layer was extracted with 50 mL of CH_2Cl_2. The combined organic solutions were dried ($MgSO_4$) and concentrated in vacuo to give about 1 g of light-yellow foam which was fairly clean by ^{1}H NMR. Flash chromatography over 65 g of silica gel (gradient elution with EtOAc/Hex 1:1, then 2:1) gave 887 mg of tripeptide **32** as a white foam: $[\alpha]^{17}_D$ +16.2 (*c* 0.585, $CHCl_3$); IR (KBr) 3370, 3055, 2951, 1732, 1714, 1696, 1683, 1651, 1644, 1600, 1587, 1537, 1519, 1503, 1447 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, 60 °C) δ 2.14 (s, 3H, CH_3S), 2.99−3.11 (m, 2H, C*H*$_2$SCH$_3$), 3.31 (dd, J = 15.2 Hz, 6.0 Hz, 1H, C*H*HCHCOO), 3.39 (dd, J = 15.2 Hz, 5.5 Hz, 1H, CH*H*CHCOO), 3.71 (s, 3H, CH_3O), 4.29 (t, J = 7.2 Hz, 1H, C*H*CH$_2$O), 4.42 (dd, J = 10.6 Hz, 7.2 Hz, 1H, OC*H*H), 4.50 (dd, J = 10.7 Hz, 7.2 Hz, 1H, OCH*H*), 4.49−4.57 (m, 1H, C*H*CH$_2$S), 5.05 (ddd, J = 7.6 Hz, 6.0 Hz,

(36) It is interesting that the major fragmentation pathway in the mass spectra of both *ent*-**6** and **37** involves a retro-Diels−Alder reaction (loss of 3-methylideneoxindole) to give an ion at *m*/*z* 227, suggesting alternate approaches to this family of natural products.



m/z 227

(37) We note that Larsen had assigned absolute stereochemistry to **6** on the basis of X-ray crystallographic studies and this research supports that assignment.[8]

(38) We note the absolute configuration of fumiquinazoline G also requires that its biosynthesis employ D-tryptophan or involve an isomerization along the way.[15,30]

(39) Nakagawa, M.; Ito, M.; Hasegawa, Y.; Akashi, S.; Hino, T. *Tetrahedron Lett.* **1984**, *25*, 3865. Klausner, Y. S.; Chorev, M. *J. Chem. Soc., Perkin Trans. 1* **1977**, 627.

(40) See spectra in supporting information for numbering scheme used in ^{1}H NMR assignments.

5.5 Hz, 1H, C*H*COOCH$_3$), 5.72 (bd, J = 7.0 Hz, 1H, NHCOO), 6.65 (bd, J = 7.6 Hz, 1H, N*H*CHCOO), 6.94 (d, J = 1.8 Hz, 1H, N_{ind}-HC*H*), 7.00 (tm, J = 7.8 Hz, 1H, ArH), 7.05 (tm, J = 7.9 Hz, 1H, ArH), 7.16 (tm, J = 7.8 Hz, 1H, ArH), 7.26−7.32 (m, 4H, ArH), 7.35−7.41 (m, 2H, ArH), 7.47 (t, J = 7.8 Hz, 2H, ArH), 7.61 (d, J = 7.4 Hz, 1H, ArH), 7.66 (d, J = 7.4 Hz, 1H, ArH), 7.75 (d, J = 7.4 Hz, 2H, ArH), 8.04 (bs, 1H, N_{ind}H), 8.59 (d, J = 8.3 Hz, 1H, ArH), 11.6 (bs, 1H, N*H*COCH); ^{13}C NMR ($CDCl_3$, 75.5 MHz, 60 °C) δ 16.0 (q), 27.6 (t), 37.1 (t), 47.6 (d), 52.5 (q), 53.6 (d), 55.8 (d), 67.7 (t), 109.9 (s), 111.5 (d), 118.5 (d), 119.9 (d), 120.1 (d), 120.8 (s), 121.7 (d), 122.4 (d), 123.0 (d), 123.5 (d), 125.4 (d), 127.0 (d), 127.2 (d), 127.8 (d), 132.8 (d), 136.5 (s), 139.1 (s), 141.5 (s), 144.0 (s), 144.3 (s), 156.2 (s), 168.4 (s), 169.4 (s), 172.2 (s); mass spectrum (EI), *m*/*z* (relative intensity) 605 (1), 432 (2), 303 (3), 201 (71), 170 (11), 131 (12), 130 (100), 47 (10); mass spectrum (FAB), *m*/*z* (relative intensity) 677 (M + 1$^+$). Anal. Calcd. for $C_{38}H_{36}N_4O_6S$: C, 67.49; H, 5.37. Found: C, 67.22; H, 5.28.

***N*-[2-[(*R*)-1-Carboxyamino-2-(methylthio)ethyl]-4*H*-3,1-benzoxazin-4-ylidene]-L-tryptophan, *N*-(Fluoren-9-ylmethyl) Methyl Ester (33).** To a solution of 5.11 g (19.50 mmol) of triphenylphosphine and 4.95 g (19.50 mmol) of iodine in 100 mL of dry CH_2Cl_2 was added, via cannula, a solution of 2.63 g (3.90 mmol) of tripeptide **32** in 20 mL of CH_2Cl_2 (plus a 10 mL portion of CH_2Cl_2 to rinse), followed by addition of 6.83 mL of Hunig's base in one portion. The reaction mixture was stirred for 5 h at room temperature under an argon atmosphere, after which time TLC (silica, EtOAc/Hex, 2:1) indicated complete consumption of starting material. The reaction mixture was directly deposited to the top of a 250-g flash silica gel column. Gradient elution with EtOAc/Hex 1:1, then with 2:1, and finally with neat EtOAc (eluent contained 2% of triethylamine) provided 2.05 g (80%) of iminobenzoxazine **33** as a yellow foam: $[\alpha]^{16}_D$ −124.3 (*c* 0.53, EtOAc); IR (KBr) 3392, 3055, 2951, 2919, 1718, 1684, 1648 cm^{-1}; ^{1}H NMR (MeCN-d_3, 300 MHz) δ 2.02 (s, 3H, SCH_3), 2.75 (dd, J = 14.1 Hz, 7.7 Hz, 1H, C*H*HSCH$_3$), 2.87 (dd, J = 14.1 Hz, 5.9 Hz, 1H, CH*H*SCH$_3$), 3.26 (dd, J = 14.4 Hz, 7.5 Hz, 1H, C*H*HCHCO), 3.41 (dd, J = 14.4 Hz, 5.6 Hz, 1H, CH*H*CHCO), 3.64 (s, 3H, OCH_3), 4.23 (t, J = 6.5 Hz, 1H, OCH_2C*H*), 4.43 (d, J = 6.5 Hz, 2H, OCH_2), 4.43−4.51 (m, 1H, C*H*CH$_2$S) 4.92 (dd, J = 7.5 Hz, 5.6 Hz, 1H, NCHCO), 5.81 (bs, 1H, NHCO), 7.00 (ddd, J = 7.9 Hz, 7.0 Hz, 1.0 Hz, 1H, ArH), 7.09 (ddd, J = 8.2 Hz, 7.0 Hz, 1.2 Hz, 1H, ArH), 7.12 (d, J = 2.3 Hz, 1H, N_{ind}HC*H*), 7.23−7.41 (m, 6H, ArH), 7.44 (ddd, J = 7.7 Hz, 7.7 Hz, 1.2 Hz, 1H, ArH), 7.59−7.65 (m, 4H, ArH), 7.80 (d, J = 7.5 Hz, 2H, ArH), 8.09 (dd, J = 7.9 Hz, 1.5 Hz, 1H, H$_a$), 8.88 (bs, 1H, N_{ind}H); ^{13}C NMR (MeCN-d_3, 75.5 MHz) δ 16.4 (q), 30.6 (t), 37.3 (t), 48.6 (d), 52.7 (q), 54.8 (d), 61.3 (d), 67.9 (t), 112.5 (d), 112.9 (s), 120.2 (d), 120.7 (s), 121.2 (d), 122.7 (d), 124.8 (d), 126.4 (d), 126.4 (d), 127.2 (d), 127.5 (d), 128.4 (d), 129.0 (d), 129.2 (s), 129.8 (d), 134.8 (d), 137.8 (s), 142.6 (s), 145.4 (s), 145.5 (s), 148.5 (s), 157.0 (s), 159.3 (s), 173.6 (s); mass spectrum (EI), *m*/*z* (relative intensity) 655 (0.4), 375 (3), 346 (19), 286 (8), 179 (14), 178 (100), 177 (11), 176 (12), 160 (6), 152 (9), 130 (42), 90 (14), no molecular ion peak was detected; mass spectrum (FAB), *m*/*z* 659 (M + 1$^+$). Anal. Calcd. for $C_{38}H_{34}N_4O_5S$: C, 69.34; H, 5.21. Found: C, 69.14; H, 5.10.

(*S*)-2-[(*R*)-1-Carboxyamino)-2-(methylthio)ethyl]-α-(indol-3-ylmethyl)-4-oxo-3(4*H*)-quinazolineacetic Acid, *N*-(Fluoren-9-ylmethyl) Methyl Ester (34). To a stirred solution of 1.01 mL (9.88 mmol) of thiophenol in 50 mL of dry THF, cooled to −78 °C, was added dropwise 6.17 mL of a 1.6 M solution of *n*-BuLi in hexanes over a period of 10 min under an argon atmosphere. The solution was stirred at −78 °C for 5 min, the mixture was warmed to 0 °C, and $AlMe_3$ (4.9 mL of 2 M solution in toluene, 9.88 mmol) was added dropwise over a period of 2 min. To the resulting solution of the lithium trimethyl-(phenylsulfido)aluminate, cooled to −78 °C, was added by cannula a solution of 1.30 g (1.98 mmol) of iminobenzoxazine **33** in 10 mL of THF (plus two 5 mL portions of THF to rinse). The reaction mixture was stirred for 12 h at −25 °C. TLC (silica, EtOAc/Hex, 1:1) indicated that reaction was slow at this temperature and that the reaction mixture contained more starting material than the presumed product. The reaction temperature was increased to −10 °C and the mixture was stirred for additional 36 h. The mixture was partitioned between 50 mL of 0.5 N aqueous HCl (caution: brisk gas evolution during the acid−base reaction) and 200 mL of EtOAc, the organic layer was separated, and the aqueous layer was extracted with two 80 mL portions of EtOAc. The combined organic extracts were washed with 50 mL of water, dried ($MgSO_4$), and concentrated in vacuo to give a thick yellow oil. The oil was flash chromatographed over 120 g of silica gel (gradient elution with EtOAc:Hex, 1:3, 1:2, 1:1, 2:1, neat EtOAc) to give 1.0 g (76%) of quinazolinone **34** as a yellow foam and 67 mg (8%) of **28** as a white amorphous solid. Quinazolinone **34**: $[\alpha]^{18}_D$ −295.8 (*c* 0.36, EtOAc); IR (KBr) 3395, 3064, 2950, 2917, 1743, 1718, 1679, 1596, 1508, 1262, 1229 cm^{-1}; ^{1}H NMR (Me_2CO-d_6, 300 MHz, 57 °C) δ 1.59 (s, 3H, SCH_3), 2.15 (dd, J = 14.1 Hz, 4.7 Hz, 1H, C*H*HSCH$_3$), 2.85 (dd, J = 14.1 Hz, 9.4 Hz, 1H, CH*H*SCH$_3$), 3.58 (s, 3H, OCH_3), 3.76−3.86 (m, 2H, C*H*$_2$CHCO), 4.21 (dd, J = 7.4 Hz, 6.9 Hz, 1H, OCH_2C*H*), 4.31 (dd, J = 10.3 Hz, 6.9 Hz, 1H, OC*H*H), 4.39 (dd, J = 10.3 Hz, 7.4 Hz, 1H, OCH*H*), 4.52 (ddd, J = 9.7 Hz, 9.4 Hz, 4.7 Hz, 1H, SCH_2C*H*), 5.67 (bm, 1H, NCHCO), 6.71 (bd, J = 9.7 Hz, 1H, CHN*H*CO), 6.82 (tm, J = 7.8 Hz, 1H, ArH), 6.95 (d, J = 1.9 Hz, 1H, C*H*N$_{ind}$H), 7.04 (ddd, J = 8.0 Hz, 7.2 Hz, 1.1 Hz, 1H, ArH), 7.25−7.30 (m, 2H, ArH), 7.34−7.40 (m, 4H, ArH), 7.53−7.58 (m, 2H, ArH), 7.69 (d, J = 7.5 Hz, 2H, ArH), 7.77−7.82 (m, 3H, ArH), 8.27−8.30 (m, 1H, H$_a$), 9.86 (bs, 1H, N_{ind}H); ^{13}C NMR (Me_2CO-d_6, 100 MHz) δ 15.3 (q), 24.7 (t), 37.9 (t), 47.9 (d), 51.5 (d), 52.6 (q), 60.5 (d), 67.9 (t), 111.1 (s), 112.4 (d), 118.8 (d), 120.1 (d), 120.8 (d), 122.1 (s), 122.5 (d), 124.8 (d), 126.3 (d), 127.3 (d), 128.0 (d), 128.2 (d), 128.3 (d), 128.6 (d), 135.4 (d), 137.6 (s), 142.1 (s), 142.1 (s), 144.9 (s), 147.5 (s), 156.1 (s), 157.4 (s), 162.5 (s), 170.2 (s); mass spectrum (EI), *m*/*z* (relative intensity) 658 (M$^+$, 0.01), 629 (2), 458 (3), 356 (5), 214 (6), 201 (21), 196 (8), 179 (11), 178 (60), 176 (13), 170 (17), 166 (25), 165 (35), 131 (11), 130 (100), 76 (10), 43 (10); exact mass calcd for $C_{38}H_{34}N_4O_5S$ *m*/*z* 658.2250, found *m*/*z* 658.2296. Anal. Calcd for $C_{38}H_{34}N_4O_5S$: C, 69.34; H, 5.21. Found: C, 69.01, 69.07; H, 5.21, 5.26.

(1*R*,4*S*)-4-(Indol-3-ylmethyl)-1-[(methylthio)methyl]-2*H*-pyrazino-[2,1-*b*]quinazoline-3,6(1*H*,4*H*)-dione (28). To a solution of 2.07 g (3.146 mmol) of **34** in 100 mL of THF, cooled to 0 °C, was added 15 mL of piperidine in one portion. The reaction mixture was stirred at ice bath temperature for 2 h 30 min. To the reaction mixture was added 100 mL of toluene, and the solution was concentrated on a rotary evaporator to an approximate volume of 100 mL. The resulting solution was partitioned between 30 mL of 1 N aqueous HCl and 200 mL of EtOAc. The organic layer was sequentially washed with two 50 mL portions of 0.5 N aqueous HCl and two 30 mL portions of water and concentrated in vacuo. The residue was flash chromatographed over 65 g of silica gel (EtOAc) to provide 1.20 g (94%) of **28** as a light yellow foam: $[\alpha]^{18}_D$ +465.0 (*c* 0.795, EtOAc); IR (KBr) 3339, 3061, 2918, 1681, 1610, 1593, 1568, 1473, 1405, 1334 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.32 (dd, J = 13.8 Hz, 11.7 Hz, 1H, C*H*HSCH$_3$), 1.75 (s, 3H, CH_3), 2.60 (dd, J = 13.8 Hz, 3.0 Hz, 1H, CH*H*SCH$_3$), 3.74 (dd, J = 15.1 Hz, 3.2 Hz, 1H, COCHC*H*H), 3.83 (dd, J = 15.1 Hz, 4.7 Hz, 1H, COCHCH*H*), 4.24 (ddd, J = 11.7 Hz, 3.0 Hz, 2.4 Hz, 1H, C*H*CH$_2$S), 5.56 (dd, J = 4.7 Hz, 3.2 Hz, 1H, NCHCO), 6.60 (bs, 1H, NHCO), 6.67 (d, J = 2.4 Hz, 1H, N_{ind}HC*H*), 6.85 (ddd, J = 8.0 Hz, 7.0 Hz, 0.9 Hz, 1H, ArH), 7.09 (ddd, J = 8.0 Hz, 7.0 Hz, 1.0 Hz, 1H, ArH), 7.24 (dm, J = 8.0 Hz, 1H, ArH), 7.28 (dm, J = 8.0 Hz, 1H, ArH), 7.52−7.57 (m, 2H, ArH), 7.76−7.81 (m, 1H, ArH), 8.12 (bs, 1H, NH), 8.40 (dd, J = 8.2 Hz, 1.4 Hz, 1H, H$_a$); ^{13}C NMR (Me_2CO-d_6, 75.5 MHz) δ 15.2 (q), 27.1 (t), 41.8 (t), 55.6 (d), 57.9 (d), 109.5 (s), 112.3 (d), 119.1 (d), 120.0 (d), 121.0 (s), 122.5 (d), 125.2 (d), 127.2 (d), 127.4 (d), 128.7 (s), 135.4 (d), 136.9 (s), 147.9 (s), 151.1 (s), 161.4 (s), 167.5 (s), one doublet was not seen due to overlap with other peaks; mass spectrum (EI), *m*/*z* (relative intensity) 404 (M$^+$, 4), 356 (6), 170 (15), 143 (9), 131 (17), 130 (100), 129 (5), 115 (5), 103 (12), 102 (5), 77 (10), 48 (11), 47 (13), 45 (8); exact mass calcd for $C_{22}H_{20}N_4O_2S$ *m*/*z* 404.1307, found *m*/*z* 404.1304. Anal. Calcd for $C_{22}H_{20}N_4O_2S$: C, 65.39; H, 4.99. Found C, 64.75; H, 5.13.

(*S*)-4-(Indol-3-ylmethyl)-1-methylene-2*H*-pyrazino[2,1-*b*]quinazoline-3,6(1*H*,4*H*)-dione (9, R = H). To a solution of 150 mg (0.37 mmol) of sulfide **28** in 10 mL of EtOAc was added a solution of 97 mg (0.48 mmol, 80% content) of *m*-CPBA in 1 mL of EtOAc in one portion at −78 °C. The reaction mixture was stirred at −78 °C for 1

h, after which time TLC (silica gel, EtOAc) indicated complete consumption of starting material. The cold reaction mixture was partitioned between 150 mL of EtOAc and 10 mL of a 1:1 mixture of water and saturated aqueous Na_2SO_3. The organic layer was sequentially washed with two 15 mL portions of sodium carbonate and three 30 mL portions of water and concentrated in vacuo without drying. During one experiment, attempted drying over $MgSO_4$ resulted in substantial loss of the product, which appeared to have very strong affinity for the surface of the drying agent. The residual moisture was removed by addition of 30 mL of benzene to the mixture of sulfoxides followed by concentration in vacuo, the procedure being repeated twice. The ^{1}H NMR spectrum of the crude product (143 mg, 92%) showed the presence of a mixture of diastereomeric sulfoxides (3:2) in addition to trace amounts of **9**. The mixture of sulfoxides was suspended in 100 mL of benzene. Triphenylphosphine (205 mg, 0.78 mmol) was added, and the resulting mixture was gently refluxed for 18 h under an argon atmosphere. The reaction mixture was cooled to room temperature and concentrated in vacuo, and the residue was chromatographed over 12 g of flash silica gel (Et_2O) to give 104 mg (79% from **28**) of **9** as a white amorphous solid: $[\alpha]^{18}_D$ +472.3 (*c* 0.419, EtOAc); IR (KBr) 3409, 3224, 2926, 1702, 1686, 1658, 1642, 1579, 1561, 1470, 1458, 1398, 1332 cm^{-1}; ^{1}H NMR (Me_2CO-d_6, 300 MHz) δ 3.49−3.61 (m, 2H, CHC*H*$_2$), 4.36 (s, 1H, H$_f$), 5.24 (s, 1H, H$_e$), 5.57 (dd, J = 4.6 Hz, 3.7 Hz, 1H, NCHCO), 6.70 (d, J = 2.5 Hz, 1H, N_{ind}HC*H*), 6.73 (ddd, J = 8.1 Hz, 7.1 Hz, 1.0 Hz, 1H, ArH), 6.97 (ddd, J = 8.1 Hz, 7.1 Hz, 1.1 Hz, 1H, ArH), 7.22 (dm, J = 8.1 Hz, 1H, ArH), 7.27 (dm, J = 8.1 Hz, 1H, ArH), 7.54−7.59 (m, 2H, ArH), 7.82 (m, 1H, H$_c$), 8.29 (ddd, J = 8.4 Hz, 1.6 Hz, 0.5 Hz, 1H, H$_a$), 9.43 (bs, 1H, NHCO), 10.03 (bs, 1H, N_{ind}H); ^{13}C NMR (DMSO-d_6, 75.5 MHz) δ 27.3 (t), 56.3 (d), 98.3 (t), 106.6 (s), 111.1 (d), 117.5 (d), 118.4 (d), 120.0 (s), 120.9 (d), 124.5 (d), 126.2 (d), 126.9 (d), 127.2 (d), 127.5 (s), 134.0 (s), 134.7 (d), 136.0 (s), 144.0 (s), 146.7 (s), 159.9 (s), 164.9 (s); mass spectrum (EI), *m*/*z* (relative intensity) 356 (M$^+$, 10), 341 (5), 227 (9), 170 (8), 143 (11), 131 (11), 130 (100), 129 (19), 103 (12), 102 (16), 77 (10); exact mass calcd for $C_{21}H_{16}N_4O_2$ *m*/*z* 356.1273, found *m*/*z* 356.1273.

(6*S*,14*S*)-14,15-Dihydro-6-methyl-6,14-(iminomethano)-5*H*-indolo-[2′,3′:4,5]azepino[2,1-*b*]quinazoline-12,15(6*H*)-dione (35). To a solution of 130 mg (0.37 mmol) of **9** (R = H) in 50 mL of chloroform was added 2.6 mL of TFA in one portion at room temperature. The resulting mixture was refluxed for 1 h, cooled to room temperature, and concentrated in vacuo, and the residue was flash chromatographed over 12 g of silica gel (Et_2O) to give 116 mg (89%) of bridged indole **35** as a white amorphous solid: $[\alpha]^{18}_D$ +267.1 (*c* 0.243, EtOAc); IR (KBr) 3343, 3269, 2903, 1692, 1672, 1609, 1569, 1470, 1452, 1385, 1332, 1305, 1242, 1188, 1160 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.12 (s, 3H, CH$_3$), 3.23 (dd, J = 17.4 Hz, 4.5 Hz, 1H, CHC*H*H), 3.43 (dd, J = 17.4 Hz, 2.8 Hz, 1H, CHCH*H*), 5.70−5.72 (m, 1H, C*H*CH$_2$), 6.99 (ddd, J = 7.9 Hz, 7.1 Hz, 0.9 Hz, 1H, ArH), 7.12 (ddd, J = 8.1 Hz, 7.1 Hz, 1.1 Hz, 1H, ArH), 7.36−7.42 (m, 2H, ArH), 7.53 (tm, J = 8.0 Hz, 1H, ArH), 7.64 (d, J = 7.9 Hz, 1H, ArH), 7.81 (ddd, J = 8.3 Hz, 7.3 Hz, 1.4 Hz, 1H, ArH), 8.14 (dd, J = 8.0 Hz, 1.4 Hz, 1H, H$_a$), 9.55 (s, 1H, NHCO), 11.20 (s, 1H, N_{ind}H); ^{1}H NMR (THF-d_8, 300 MHz) δ 2.18 (s, 3H, CH$_3$), 3.29 (dd, J = 17.2 Hz, 4.6 Hz, 1H, CHC*H*H), 3.46 (dd, J = 17.2 Hz, 2.8 Hz, 1H, CHCH*H*), 5.87 (ddd, J = 4.6 Hz, 2.7 Hz, 1.5 Hz, 1H, C*H*CH$_2$), 6.96 (ddd, J = 8.0 Hz, 7.1 Hz, 1.1 Hz, 1H, ArH), 7.06 (ddd, J = 8.2 Hz, 7.1 Hz, 1.2 Hz, 1H, ArH), 7.27 (dm, J = 8.2 Hz, 1H, ArH), 7.38 (d, J = 7.7 Hz, 1H, ArH), 7.41 (ddd, J = 8.0 Hz, 7.1 Hz, 1.2 Hz, 1H, H$_b$), 7.57 (ddd, J = 8.2 Hz, 1.2 Hz, 0.5 Hz, 1H, H$_d$), 7.67 (ddd, J = 8.2 Hz, 7.1 Hz, 1.6 Hz, 1H, H$_c$), 8.19 (ddd, J = 8.0 Hz, 1.6 Hz, 0.5 Hz, 1H, H$_a$), 8.48 (bs, 1H, NHCO), 10.20 (bs, 1H, N_{ind}H); ^{13}C NMR (DMSO-d_6, 75.5 MHz) δ 18.3 (q), 25.6 (t), 54.1 (d), 54.6 (s), 105.5 (s), 111.7 (d), 118.0 (d), 119.3 (d), 120.1 (s), 122.2 (d), 126.3 (d), 127.1 (d), 127.3 (d), 127.4 (s), 134.0 (s), 134.6 (d), 134.8 (s), 146.6 (s), 154.3 (s), 159.3 (s), 169.2 (s); mass spectrum (EI), *m*/*z* (relative intensity) 357 (12), 356 (M$^+$, 52), 342 (23), 341 (100), 317 (7), 313 (17), 312 (9), 299 (12), 286 (23), 267 (10), 212 (9), 211 (28), 183 (12), 163 (11), 162 (21), 151 (13), 113 (17), 70 (11), 51 (59); exact mass calcd for $C_{21}H_{16}N_4O_2$ *m*/*z* 356.1273, found *m*/*z* 356.1287.

(−)-Alantrypinone (*ent*-6); (1*S*,3′*R*,4*S*)-1-Methylspiro[1,4-ethano-2*H*-pyrazino[2,1-*b*]quinazoline-13,3′-indoline]-2′,3,6(1*H*,4*H*)-trione (37). To a stirred solution of 132 mg (0.371 mmol) of **35** in 13 mL of a mixture of THF:TFA:H_2O (5:4:4), cooled to 0 °C, was added 66 mg (0.371 mmol) of solid NBS in one portion. After 1 h of stirring at ice bath temperature, an additional 66 mg (0.371 mmol) of solid NBS was added to the reaction mixture. A total of 5 equiv of NBS was added to the reaction mixture over a period of 8 h. The reaction mixture was partitioned between 200 mL of EtOAc and 50 mL of saturated aqueous $NaHCO_3$. The organic layer was washed with two 30 mL portions of water and concentrated in vacuo. The residue, representing a fairly complex mixture of polybrominated spiro oxindoles (^{1}H NMR), was dissolved in 50 mL of MeOH. The solution was charged with 200 mg of 5% Pt/C, 400 mg of NaOAc, and 0.80 mL of AcOH and then hydrogenolyzed for 30 min under 1 atm of H_2 at room temperature. The reaction mixture was filtered through a 1 cm pad of Celite followed by concentration in vacuo. The residue was dissolved in 200 mL of EtOAc and washed with six 30 mL portions of water to remove sodium acetate. Concentration in vacuo provided a fairly clean mixture of *ent*-**6** and **37**, which was separated by preparative TLC (silica gel, EtOAc) to give 42 mg (30%) of *ent*-**6** and 61 mg (44%) of **37**, both as white amorphous solids. (−)-Alantrypinone (*ent*-**6**): mp >300 °C; $[\alpha]^{18}_D$ −40.3 (*c* 0.265, EtOH); IR (KBr) 3434, 3248, 1708, 1661, 1620, 1470, 1382, 1334 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.19 (s, 3H, CH$_3$), 2.36−2.47 (m, 2H, H$_{15}$), 5.59 (m, 1H, H$_{14}$), 6.93 (d, J = 7.6 Hz, 1H, ArH), 7.11 (t, J = 7.6 Hz, 1H, ArH), 7.20 (d, J = 7.2 Hz, 1H, ArH), 7.32 (ddd, J = 7.6 Hz, 7.6 Hz, 1.2 Hz, 1H, ArH), 7.60 (tm, J = 8.0 Hz, 1H, ArH), 7.70 (d, J = 8.0 Hz, 1H, ArH), 7.86 (ddd, J = 8.2 Hz, 7.4 Hz, 1.3 Hz, 1H, ArH), 8.21 (dd, J = 8.0 Hz, 1.1 Hz, 1H, H$_{10}$), 9.55 (d, J = 1.7 Hz, 1H, H$_2$), 10.63 (s, 1H, H$_{19}$); ^{13}C NMR (DMSO-d_6, 75.5 MHz) δ 13.4 (q), 35.9 (t), 52.0 (d), 54.7 (s), 61.8 (s), 109.9 (d), 120.0 (s), 122.3 (d), 123.8 (d), 126.3 (d), 127.2 (d), 127.7 (d), 129.1 (d), 129.9 (s), 134.7 (d), 142.6 (s), 146.8 (s), 152.9 (s), 158.3 (s), 169.7 (s), 176.6 (s); mass spectrum (EI), *m*/*z* (relative intensity) 372 (M$^+$, 6), 228 (14), 227 (100), 199 (33), 198 (8), 170 (6), 145 (16), 144 (5), 130 (5), 117 (13), 103 (7), 90 (11), 89 (6); exact mass calcd for $C_{21}H_{16}N_4O_3$ *m*/*z* 372.1222, found *m*/*z* 372.1211.

Compound **37**: mp >300 °C; $[\alpha]^{18}_D$ +84.3 (*c* 0.115, THF); IR (KBr) 3435, 3196, 2926, 1723, 1684, 1622, 1608, 1470, 1383, 1332 cm^{-1}; ^{1}H NMR (THF-d_8, 300 MHz) δ 1.35 (s, 3H, CH$_3$), 2.29 (dd, J = 14.0 Hz, 3.9 Hz, 1H, H$_{15}$), 2.66 (dd, J = 14.0 Hz, 1.9 Hz, 1H, H$_{15}$), 5.67 (ddd, J = 3.9 Hz, 3.2 Hz, 1.9 Hz, 1H, H$_{14}$), 5.95 (dm, J = 7.6 Hz, 1H, H$_{24}$), 6.62 (ddd, J = 7.6 Hz, 7.6 Hz, 1.0 Hz, 1H, H$_{23}$), 6.82 (dm, J = 7.6 Hz, 1H, H$_{21}$), 7.10 (ddd, J = 7.6 Hz, 7.6 Hz, 1.2 Hz, 1H, H$_{22}$), 7.53 (ddd, J = 7.9 Hz, 7.1 Hz, 1.2 Hz, 1H, H$_9$), 7.62 (ddd, J = 8.2 Hz, 1.2 Hz, 0.5 Hz, 1H, H$_7$), 7.76 (ddd, J = 8.2 Hz, 7.1 Hz, 1.6 Hz, 1H, H$_8$), 8.28 (bs, 1H, H$_2$), 8.31 (ddd, J = 7.9 Hz, 1.6 Hz, 0.5 Hz, 1H, H$_{10}$), 9.64 (bs, 1H, H$_{19}$); ^{13}C NMR (DMSO-d_6, 75.5 MHz) δ 13.3 (q), 35.2 (t), 52.2 (d), 52.6 (s), 61.9 (s), 109.5 (d), 120.1 (s), 121.6 (d), 123.3 (d), 126.5 (d), 127.6 (d), 127.8 (d), 128.9 (d), 129.2 (s), 134.9 (d), 142.4 (s), 146.3 (s), 152.4 (s), 158.1 (s), 168.9 (s), 177.1 (s); mass spectrum (EI), *m*/*z* (relative intensity) 372 (M$^+$, 4), 317 (2), 267 (2), 228 (14), 227 (100), 199 (43), 198 (11), 172 (5), 171 (7), 170 (7), 146 (6), 145 (33), 144 (8), 130 (9), 117 (28), 116 (6), 103 (11), 90 (24), 89 (15), 63 (6); exact mass calcd for $C_{21}H_{16}N_4O_3$ *m*/*z* 372.1222, found *m*/*z* 372.1208.

Acknowledgment. We thank the National Institutes of Health for support of this research and the Campus Chemical Instrumentation Center at the Ohio State University for technical support.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for most compounds, crystallographic data for **8** and **16**, experimental procedures and spectral data for all compounds not presented in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

JA010066+