

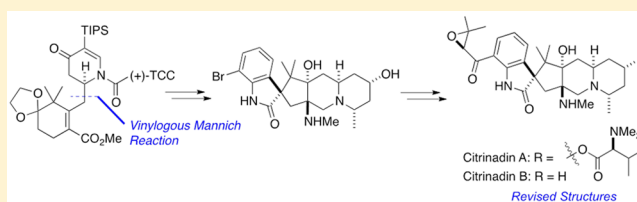
Enantioselective Total Syntheses of Citrinadins A and B. Stereochemical Revision of Their Assigned Structures

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S Supporting Information

ABSTRACT: The concise, enantioselective total syntheses of (–)-citrinadin A and (+)-citrinadin B in a total of only 20 and 21 steps, respectively, from commercially available starting materials are described. Our strategy, which minimizes refunctionalization and protection/deprotection operations, features the highly diastereoselective, vinylogous Mannich addition of a dienolate to a chiral pyridinium salt to set the first chiral center. The absolute stereochemistry of this key center was then relayed by a sequence of substrate-controlled reactions, including a highly stereoselective epoxidation/ring opening sequence and an oxidative rearrangement of an indole to furnish a spirooxindole to establish the remaining stereocenters in the pentacyclic core of the citrinadins. An early stage intermediate in the synthesis of (–)-citrinadin A was deoxygenated to generate a dehydroxy compound that was elaborated into (+)-citrinadin B by a sequence of reaction identical to those used to prepare (–)-citrinadin A. These concise syntheses of (–)-citrinadin A and (+)-citrinadin B led to a revision of their stereochemical structures.



INTRODUCTION

Secondary metabolites of fungi have a long and rich history as an important reservoir of biologically active molecules having unusual structures.¹ The marine-derived fungus *Penicillium citrinum* has been a source of a number different classes of natural products,² and in 2004 and 2005 Kobayashi and co-workers reported the isolation of the two related spirooxindole alkaloids (–)-citrinadin A (**1**) and (+)-citrinadin B (**2**) (Figure 1), which exhibited notable activity against murine leukemia L1210 (**1**, IC₅₀ 6.2 μg/mL; **2**, 10 μg/mL) and human epidermoid carcinoma KB cells (**1**, IC₅₀ 10 μg/mL).³ The absolute and relative stereochemistry of the pentacyclic cores of the citrinadins were assigned based upon a combination of 1D and 2D NMR experiments and electronic circular dichroism (ECD) spectra. Specifically, ROESY correlations between protons on the *N,N*-dimethylvalinyl moiety and protons on the E ring of a chlorohydrin derivative of citrinadin A were used to assign the absolute stereochemical relationships in the E ring relative to (*S*)-valine. Use of the negative first Cotton effect observed in the ECD spectrum of this compound to assign the absolute stereochemistry of the spirocenter as being *S* was consistent with ROESY data observed for (–)-citrinadin A.^{3b} The interpretation of the ROESY data presumed a preferred orientation of the *N,N*-dimethylvalinyl side chain relative to the E-ring. The absolute stereochemistry of the epoxide moiety of citrinadin A was assigned as being (*S*) by comparing its vibrational circular dichroism (VCD) spectrum with those of model α -keto epoxides of known absolute stereochemistry.

A similar group of alkaloids designated as PF1270 A–C (**3**–**5**, Figure 1) were subsequently isolated from *Penicillium waksmanii* strain PF1270 by Kushida in 2007; PF1270 A (**3**),

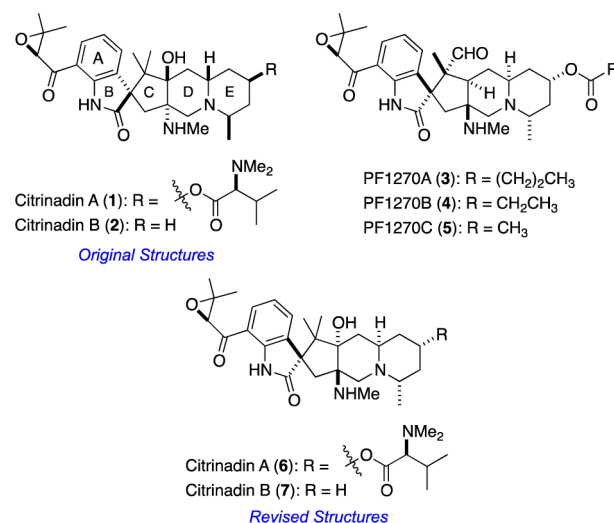


Figure 1. Originally proposed structures for citrinadins A (**1**) and B (**2**), PF1270A–C (**3**–**5**), and revised structures of citrinadins A (**6**) and B (**7**).

B (**4**) and C (**5**) exhibit submicromolar affinities for human H3 histamine receptor (*K_i* 0.047, 0.12, and 0.22 μM, respectively).⁴ Although the absolute stereochemistry of **3**–**5** was not assigned, the relative stereochemical relationships between the pentacyclic core and the epoxy ketone side chain were established by X-ray crystallographic analysis of **3**. A

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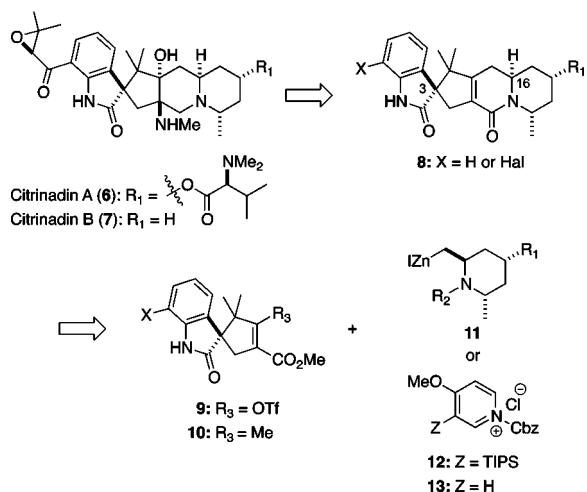
comparison of the structures of 1–5 reveals that the relative stereochemical relationships between the pentacyclic core and the epoxy ketone moieties are opposite.

Interest in the citrinadins by members of the synthetic community has been driven by a combination of their unusual molecular architecture coupled with their biological activity. The pentacyclic framework comprises a spirooxindole that is connected by a cyclopentane ring to a highly substituted quinolizidine ring. The pentacyclic ring system of citrinadin A is punctuated with six stereocenters that include two functionalized tertiary carbon atoms, two contiguous quaternary carbon atoms, and there is an α -epoxy ketone moiety appended to the aromatic ring. Several approaches to the citrinadins have been published,⁵ and the Wood group recently completed the first total synthesis of (+)-citrinadin B using a convergent strategy wherein the spirooxindole ring system and the piperidine ring were joined via a [3 + 2] cycloaddition.⁶ Simultaneous with the report of Wood and co-workers, we disclosed the first total synthesis of (–)-citrinadin A⁷ by a linear approach, in which the first chiral center was created by an enantioselective vinylogous Mannich addition, and the remaining stereocenters on the pentacyclic core were set by substrate based control.⁸ It is notable that these two total syntheses led to revisions of the stereochemical structures of citrinadin A and citrinadin B as being 6 and 7, respectively, thereby demonstrating that the relative stereochemical relationships of the citrinadins in fact correspond to those reported for PF1270A–C (3–5). Herein we provide the details of our synthetic efforts toward the citrinadins that culminated in the enantioselective total syntheses of (–)-citrinadin A (6) and its congener (+)-citrinadin B (7).

RESULTS AND DISCUSSION

First Generation Approach. Our initial retrosynthetic plan toward citrinadins A (6) and B (7) was a convergent one and is outlined in Scheme 1. Because these two alkaloids share

Scheme 1. First Generation Retrosynthesis of Citrinadins

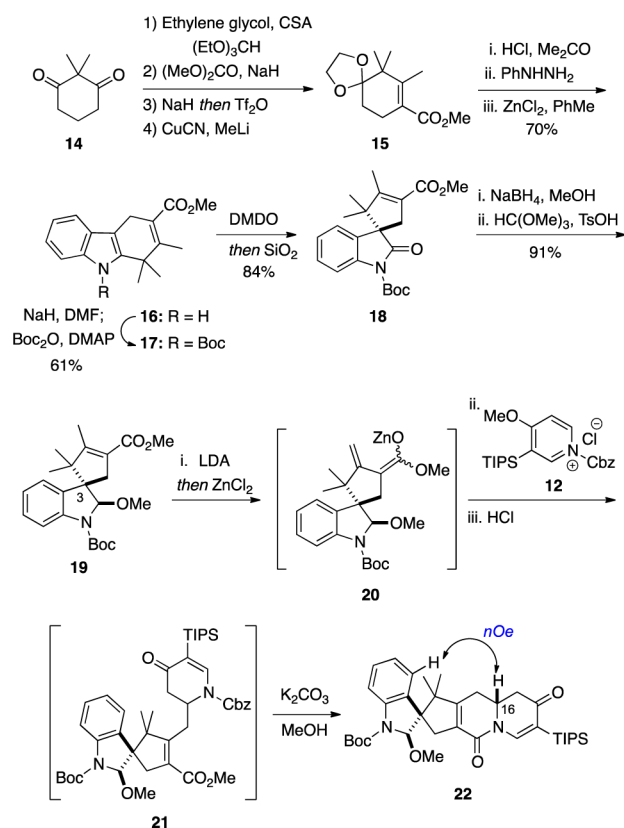


a closely related pentacyclic skeleton, we envisioned a unified route for their synthesis that employed the spirooxindole 9 as a common intermediate. For example, coupling 9 with the organozinc reagent of an appropriately substituted piperidine 11 ($R_1 = \text{H, OR}$) would give adducts that could be transformed into citrinadin A or citrinadin B via the pentacyclic

intermediates 8. Specifically, the 1,2-amino alcohol motif in 6 and 7 would be established by selective epoxidation of 8 from the more accessible face of the carbon–carbon double bond followed by ring-opening, and the epoxy ketone could be introduced via a cross-coupling reaction. In early work directed toward the citrinadins, we developed a novel, oxidation/rearrangement approach for the enantioselective synthesis of spirooxindoles that served as precursors of compounds related to 9,^{5a} but we found that organozinc reagents related to 11 ($R_1 = \text{H}$) were unstable, and attempts to induce their desired coupling with 9 were unsuccessful. Accordingly, we adopted an alternate strategy to generate a precursor of 8. This plan featured a vinylogous Mannich reaction⁹ involving a dienolate generated from 10 and the pyridinium salt 12, the selection of which was inspired by related work of Comins.¹⁰ Implicit in this approach was the hope that the spiro stereocenter in the dienolate derived from 9 would either direct the diastereofacial outcome in the addition to an *achiral* variant of 12 or that this stereocenter would not interfere with directive effects of 12 bearing a chiral carbamate auxiliary.

To evaluate the diastereoselectivity in the addition of a dienolate such as 10 to an achiral pyridinium salt, we synthesized the functionalized spirooxindole 18 from 15 (Scheme 2), which was readily prepared in 64% overall yield

Scheme 2. Addition of a Spirooxindole Dienolate to a Substituted Pyridinium Salt

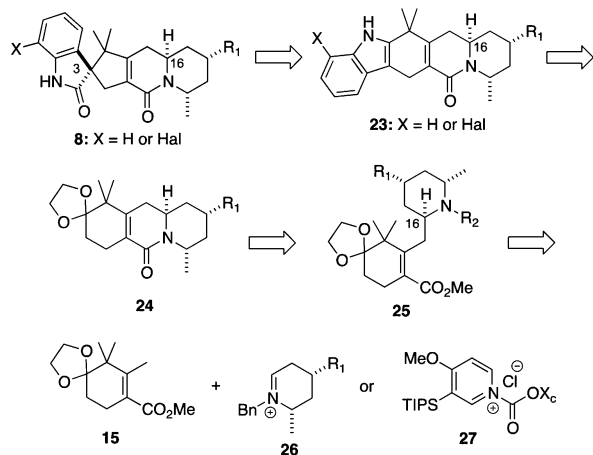


from commercially available 2,2-dimethylcyclohexane-1,3-dione (14) in four straightforward steps that involved protection,¹¹ crossed Claisen condensation, enol triflate formation, and methylation. Hydrolysis of the ketal moiety in 15, followed by phenylhydrazone formation and Fischer indole synthesis, produced the tricyclic indole 16, which was protected to give

the Boc carbamate **17**. Treatment of **17** with dimethyldioxirane (DMDO) gave an intermediate epoxide that underwent a facile semipinacol rearrangement upon exposure to SiO₂ to provide the spirooxindole **18**.^{5a,12} Several preliminary experiments to generate the dienolate from **18** suggested that the imide moiety might be unstable to these reaction conditions, so the oxindole was reduced, and the intermediate *N,O*-hemiacetal was converted to the more robust *N,O*-acetal **19**. Deprotonation of **19** with lithium diisopropylamide (LDA), followed by transmetalation with ZnCl₂ and reaction of the enolate thus formed with TIPS-pyridinium salt **12**,^{10b,c} gave the adduct **21**, which was treated with K₂CO₃ in MeOH to induce cyclization. A single diastereoisomeric pentacyclic product **22** was isolated in ~10% yield, but a NOESY experiment suggested the relative stereochemistry at C(16) was opposite that required. It is perhaps noteworthy that addition of **20** to the methoxypyridinium salt **13**, which lacks the TIPS group, gave a mixture (~1:1) of diastereomeric adducts. Based upon these preliminary experiments, it appeared that substrate-control enforced by the stereochemistry at the spirocenter C(3) of **19** was opposite that found in the citrinadins.

Second Generation Approach. To address the undesired stereochemical outcome in the vinylogous Mannich reaction of **19**, we developed an alternate plan in which we envisioned stereochemistry at C(16) of **23** might direct the stereoselectivity of the oxidation/rearrangement to establish the requisite stereochemistry at the C(3) spirocenter of **8** (Scheme 3). We also knew from early work that the stereochemistry of

Scheme 3. Second Generation Approaches to the Citrinadins

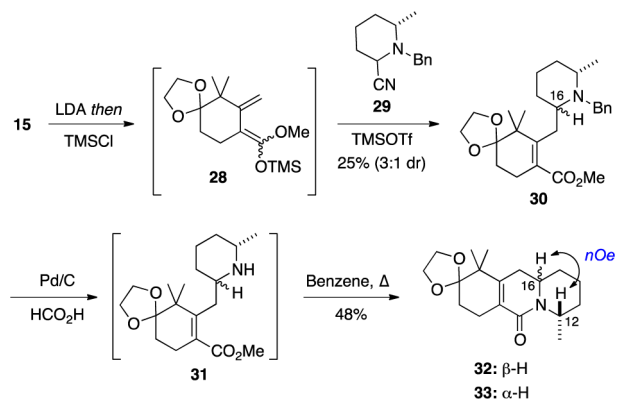


spirooxindole formation could be controlled using a chiral auxiliary on the indole nitrogen atom of **23**,^{5a} which would be accessible from **24** via a Fisher indole reaction. Synthesis of the tricyclic intermediate **24** from its precursor **25** simply required *N*-deprotection and cyclization. A key step in this new approach involves formation of **25** by a stereoselective, vinylogous Mannich reaction between the dienolate derived from **15** and either an iminium ion such as **26** or a pyridinium salt **27** bearing a chiral auxiliary, X_c. Mindful of precedent that additions of small nucleophiles to piperidine-derived iminium salts like **26** proceed to give *cis*-2,6-disubstituted products as a consequence of the combined effects of A^{1,2}-strain and stereoelectronic control,¹³ we hypothesized that a more bulky nucleophile, such as a dienolate derived from **15**, might add to **26** via a boat-like transition state to give a *trans*-2,6-disubstituted piperidine. If this outcome was not observed,

we would then use **27** as the electrophilic partner in the vinylogous Mannich reaction in accord with the work of Comins.¹⁰

Toward probing the diastereoselectivity of vinylogous Mannich reactions with substituted iminium ions **26**, the dienol ether **28** and racemic **29**, which was prepared by a procedure reported by Rychnovsky,¹⁴ were allowed to react in the presence of TMSOTf to give a mixture (3:1) of isomeric adducts **30** (Scheme 4). Because it was impossible to assign the

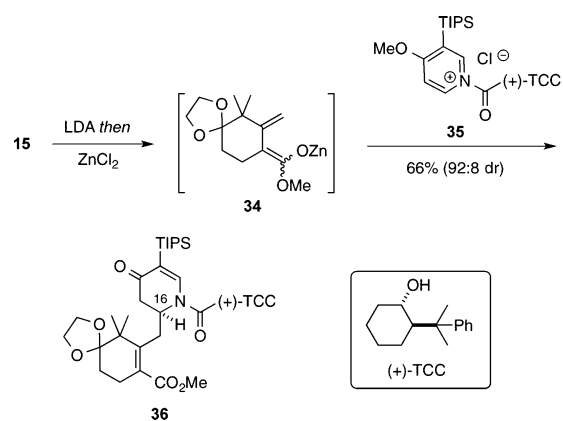
Scheme 4. Vinylogous Mannich Addition to a Substituted 1,2-Dehydropiperidine



structure of the major isomer, this mixture was subjected to *N*-debenzylation using transfer hydrogenation, and the resulting amines **31** were subjected to cyclization by heating in benzene to form lactams **32** and **33**. The major diastereomer of this mixture was purified by chromatography. Unfortunately, a NOESY experiment revealed a *nOe* between the protons at C(12) and C(16) of this compound, suggesting that the major product was **32**. The vinylogous Mannich reaction had thus proceeded preferentially with the undesired diastereofacial selectivity.

Inspired by the seminal work of Comins and Sahn,^{10d} we then examined the stereoselectivity of the addition of the zinc dienolate **34** to the chiral pyridinium salt **35**, which was generated *in situ* by the reaction of 3-TIPS-4-methoxypyridine and the chloroformate derivative of (+)-*trans*-2-(α -cumyl)-cyclohexanol [(+)-TCC] (Scheme 5). This reaction proceeded successfully to give **36** with high diastereoselectivity (dr =

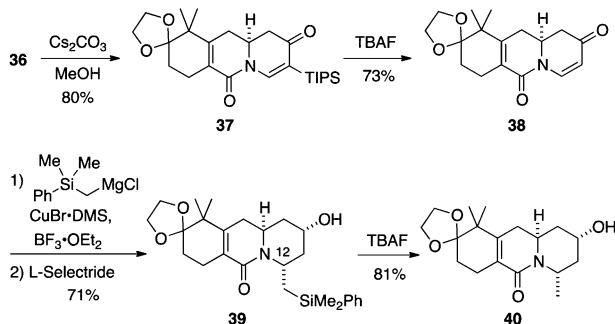
Scheme 5. Vinylogous Mannich Addition of a Dienolate to a Chiral Pyridinium Salt



92:8), and the absolute stereochemistry at the newly created stereocenter at C(16) was initially assigned by analogy with the extensive findings of Comins.¹⁰ This preliminary assignment would later be verified by X-ray crystallography of a derived intermediate (cf. Figure 2).

Having at long last discovered a reliable and efficient strategy to establish the requisite absolute stereochemistry at C(16) of the citrinadins, we turned our attention to forming a suitable CDE tricyclic intermediate (Scheme 6). In the event, exposure

Scheme 6. Preparation of a Key Tricyclic Intermediate



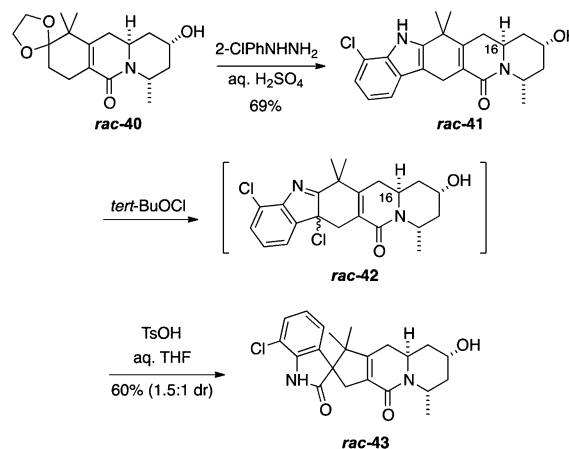
of **36** to Cs_2CO_3 in methanol induced removal of the chiral auxiliary, and spontaneous cyclization ensued to provide the lactam **37** in 84% ee together with about 70% recovered (+)-TCC. Gratifyingly, we found that the optical purity of **37** could be easily improved to 98% ee (chiral HPLC, see Supporting Information) after a recrystallization. Desilylation of the lactam **37** was most efficiently effected employing excess TBAF and microwave heating to afford enone **38**.

The stereoselective 1,4-addition of a methyl group to **38** proved to be more problematic than anticipated, presumably owing to the relatively planar nature of the tricyclic ring system. Additions of simple methyl-derived cuprates and related reagents proceeded with low (<2:1) diastereoselectivity. Similarly, the 1,4-additions of organocopper reagents derived from metalated bis(phenylthio)methane¹⁵ and tris(phenylthio)methane¹⁶ were rather unselective and also low yielding. After extensive experimentation, we eventually discovered that the organocopper reagent generated from (dimethylphenylsilyl)methylmagnesium chloride¹⁷ and CuBr·DMS added smoothly to **38** in the presence of $\text{BF}_3\cdot\text{OEt}_2$ to give a mixture of ketones that were directly reduced with high stereoselectivity using L-selectride to give **39** in 71% yield over two steps; 19% of the C(12) epimer of **39** was also isolated. We resisted the temptation to protect the secondary hydroxyl group and heated **39** with TBAF in a microwave oven to obtain the unsaturated lactam **40**.¹⁸

At this juncture, the challenging tasks associated with stereoselective elaboration of the spirooxindole ring and introduction of the amino alcohol moiety were at hand. We first wanted to ascertain whether the stereocenter at C(16) in a pentacyclic intermediate such as **41** might direct the stereochemical outcome of an oxidation/rearrangement sequence to generate a spirooxindole. Because we wished to conserve the more valuable, enantiomerically pure intermediates in the planned exploratory experiments, we prepared the racemic ketal **rac-40** from the product of the vinylogous Mannich reaction of **13** and **34** in accord with the transformations outlined in Scheme 6. When **rac-40** was heated with *o*-chlorophenylhydrazine hydrochloride in refluxing sulfuric acid (5% v/v), **rac-**

41 was isolated in 69% yield (Scheme 7).¹⁹ Toward converting **rac-41** into the spirooxindole **rac-43**, a number of standard

Scheme 7. Preliminary Experiment To Induce Stereoselective Formation of a Spirooxindole

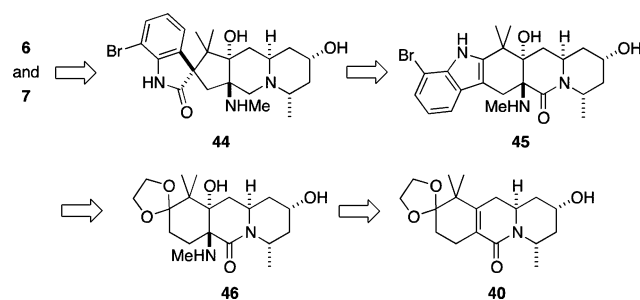


oxidants, including OsO_4 , NBS, and $\text{Pb}(\text{OAc})_4$ were evaluated,²⁰ but mixtures of products were invariably obtained. However, we found that treating **rac-41** with *tert*-BuOCl, followed by exposure of the intermediate chloroindolenines **rac-42** to aqueous acid, provided a mixture (1.5:1 by ¹H NMR) of diastereomeric spirooxindoles **rac-43** as an inseparable mixture.²¹ This result suggested that the resident chirality in **rac-41** is too remote to influence the diastereofacial selectivity of the chlorination of **rac-41** to preferentially give the epimer of **rac-42** that is required for the stereoselective formation of **rac-43**.

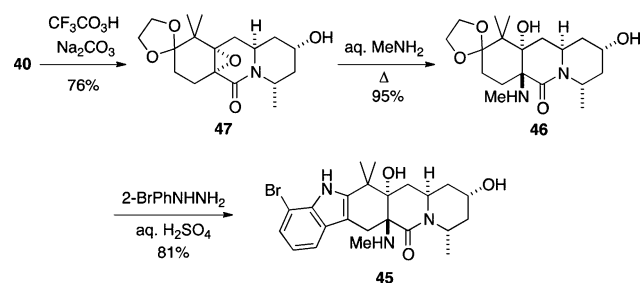
The finding that the oxidation/rearrangement of **41** was not very selective clearly mandated a change in strategy for the end game of the synthesis. We considered the possibility of introducing a chiral carbamate on the indole nitrogen atom because we had previously shown that reactions of such compounds with DMDO followed by rearrangement of the intermediate epoxide could be highly diastereoselective.^{5a} However, such an approach suffered from the need to use a second chiral auxiliary as a stoichiometric reagent, so we considered that plan to be stereochemically inefficient relative to exploiting substrate control to establish relative stereochemistry following the diastereoselective vinylogous Mannich reaction. We were thus intrigued by an alternative approach in which the amino alcohol moiety in **45** was envisioned to direct the stereochemical course of an oxidation/rearrangement sequence to furnish **44** (Scheme 8).

The transformation of enantiomerically pure **40** into **45** was surprisingly straightforward. Epoxidation of **40** with peroxytrifluoroacetic acid in the presence of sodium carbonate was highly diastereoselective, proceeding from the more accessible, slightly convex face to furnish a single epoxide **47** (Scheme 9).²² Although this epoxidation could also be performed in unbuffered media, the ketal moiety suffered hydrolysis under those conditions. The reaction of epoxide **47** with aqueous methylamine in a sealed tube also occurred with high diastereoselectivity to deliver the requisite amino alcohol **46** in 95% yield. Heating **46** with *o*-bromophenylhydrazine hydrochloride in aqueous sulfuric acid provided the indole **45** in 81% yield; trace amounts of the debromo derivative of **45** were observed by LCMS.²³

Scheme 8. Revised Endgame for the Synthesis of the Citrinadins



Scheme 9. Preparation of Pentacyclic Indole Core 45

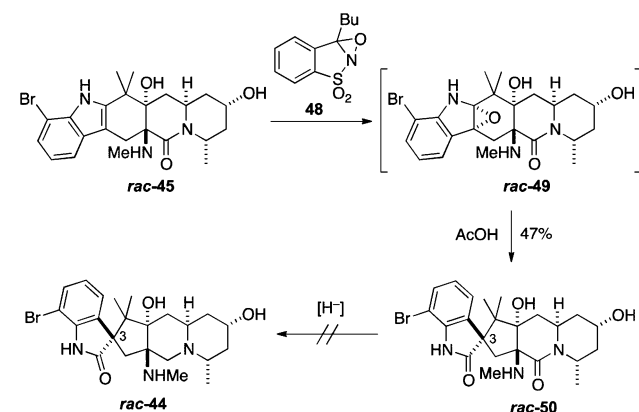


The stage was now set to test the feasibility of creating the critical spirocenter at C(3) by a substrate-controlled oxidation/rearrangement of 45. Anticipating that some of the reactions might be troublesome, we again decided to perform our exploratory experiments using *rac*-45, which was conveniently prepared from *rac*-40 following the sequence of reactions depicted in Scheme 9. As noted previously, creation of spirooxindoles from indoles by oxidation followed by skeletal rearrangement is well documented.^{19,20} However, inducing such a transformation on indole *rac*-45 proved to be much more challenging than anticipated, and many established protocols did not give the desired spirocyclic product. The functionality present in *rac*-45 appeared to conspire against us, but we were reluctant to indulge in a series of unpredictable protecting group maneuvers.

In early studies with model systems, we had examined the possible use of Davis' oxaziridine 48 to induce the oxidation and rearrangement of simple indoles to generate spirooxindoles, but these efforts were unsuccessful. Driven by desperation and inspired by several reports of Williams, who recently used oxaziridines in elegant syntheses of spirooxindole alkaloids related to the notoamides,²⁴ we treated *rac*-45 with an excess of 48 and isolated a moderately stable epoxide that was exposed acetic acid to initiate a facile semipinacol rearrangement (Scheme 10). Gratifyingly, the structure of the product was established by X-ray crystallography to be the desired spirooxindole *rac*-50. The stereochemical outcome of this sequence is consistent with a hydroxyl group-directed delivery of 48 to the bottom face of *rac*-45 to give *rac*-49.

We had thus successfully prepared the pentacyclic core characteristic of citrinadins A and B. The euphoria associated with achieving this milestone was short-lived, however, because all efforts to selectively reduce the tertiary δ -lactam moiety in *rac*-50 in the presence of the secondary γ -lactam to cleanly give *rac*-44 using a variety of hydride reducing agents were uniformly unsuccessful.²⁵ Alane was found to be the best reagent, giving *rac*-44 along with the products from reduction

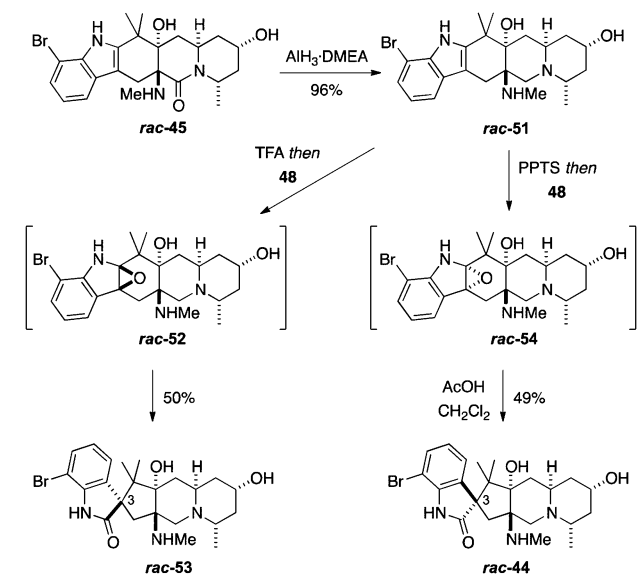
Scheme 10. Synthesis of Racemic Pentacyclic Core of Citrinadin A: The Initial Plan



of the γ -lactam and both lactams in variable yields. Attempts to optimize the reduction by varying reaction temperature and amount of alane failed to improve the chemoselectivity.

To avoid the problems associated with the unselective lactam reduction, we decided to reverse the steps and reduce the lactam in *rac*-45 prior to the oxidation/rearrangement sequence (Scheme 11). In the event, reduction of *rac*-45 with the

Scheme 11. Successful Synthesis of Racemic Pentacyclic Core of Citrinadin A



complex of alane and dimethylethylamine (DMEA)^{20b,25b} delivered *rac*-51 in excellent yield. We found it was necessary to protonate the basic amino groups in *rac*-51 to protect them from oxidation under the conditions of the next step. Accordingly, sequential treatment of *rac*-51 with trifluoroacetic acid (TFA) and then an excess of Davis' oxaziridine 48 directly delivered the spirooxindole *rac*-53 as a single diastereoisomer, presumably via the intermediate epoxide *rac*-52. To our dismay, however, X-ray crystallographic analysis revealed that the product was *rac*-53, wherein the relative stereochemistry at C(3) is opposite that present in the citrinadins. The aberrant stereochemical outcome of this oxidation relative to that of *rac*-45 can be rationalized if the protonated, axial *N*-methylammonium group in *rac*-51 directs the oxidation by

Davis' oxaziridine **48** from the top face to give *rac*-**52**, which then undergoes rearrangement leading to the formation of the undesired spirooxindole *rac*-**53**.

This analysis suggested that a bulky Lewis or Brønsted acid might associate with the axial secondary amine group, thereby blocking the top face of *rac*-**51** and enforcing approach of Davis' oxaziridine **48** from the bottom face. Indeed, we had utilized this tactic to direct the stereochemistry of chlorination of an indole ring in our successful syntheses of the *Strychnos* alkaloids akuammicine and strychnine.²⁶ A variety of Brønsted acids (e.g., AcOH, camphorsulfonic acid, and TsOH) and Lewis acids (e.g., AlEt₃, SnCl₄, ZnCl₂ and BF₃·OEt₂) were screened, but none of these led to the desired spirooxindole *rac*-**44**. We eventually discovered that treating *rac*-**51** sequentially with pyridinium *p*-toluenesulfonate (PPTS), excess of Davis' oxaziridine **48**, and then acetic acid provided the spirooxindole *rac*-**44** as a single stereoisomer, the structure of which was unambiguously determined by X-ray analysis. The apparently unique role that PPTS plays in controlling the stereochemical outcome of this oxidation is not understood, but we tentatively surmise that ion-pairing effects may be involved that render oxidation from the top face of *rac*-**51** sterically unfavorable.

Having thus validated our approach to the stereoselective synthesis of the pentacyclic core of the citrinadins, it was necessary to prepare **44** in enantiomerically pure form and to install the dimethyl valine side chain on the hydroxyl group at C(14) and the epoxy ketone side chain on the aromatic ring to complete the synthesis of citrinadin A (**6**). In the event, following the procedures outlined in Scheme 11, enantiomerically pure **45** was readily transformed into enantiomerically pure **44** (Scheme 12). After unsuccessfully investigating the

possibility of converting the aryl bromide group in **44** directly into an α,β -unsaturated ketone using a carbonylative cross-coupling reaction we had previously developed,²⁷ we turned to a stepwise procedure that commenced with the Sonogashira coupling between **44** and 3-methylbut-1-yne to furnish the alkyne **55**.²⁸ *O*-Acylation of the hydroxyl group at C(14) with *N,N*-dimethyl-*L*-valine in the presence of 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide (EDCI) and 4-*N,N*-dimethylaminopyridine (DMAP) provided **56** in excellent yield.²⁹ The absolute and relative stereochemistry of **56** was established unequivocally by X-ray crystallography (Figure 2).

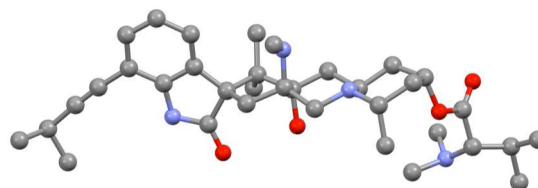


Figure 2. X-ray structure of **56**.

The gold-promoted oxidation of **56** using 2-bromopyridine *N*-oxide according to a method reported by Zhang gave the enone **57**.³⁰ Finally, diastereoselective epoxidation of **57** to deliver a mixture (5:1) of **6** and **58**, respectively, was achieved by applying an Enders protocol for the enantioselective synthesis of (*S*)-epoxides from α,β -unsaturated ketones using (*S,S*)-*N*-methylpseudoephedrine as the chiral ligand.³¹

The CD spectrum of the synthetic **6** thus obtained as the free base is identical with that reported by Kobayashi for (–)-citrinadin A,^{3b} whereas the CD spectrum for **58** is very different (Figure 3). The ¹H and ¹³C NMR data of the free base forms of **6** and **58** are wholly consistent with their assigned structures, and the ¹H and ¹³C NMR data of **6** as its putative bis-hydrochloride salt, which was formed upon standing in CDCl₃, are also in good agreement with those reported for a bis-salt of (–)-citrinadin A (see Supporting Information).³

Scheme 12. First Total Synthesis of (–)-Citrinadin A (**6**)

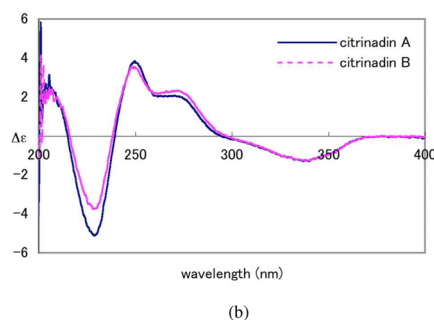
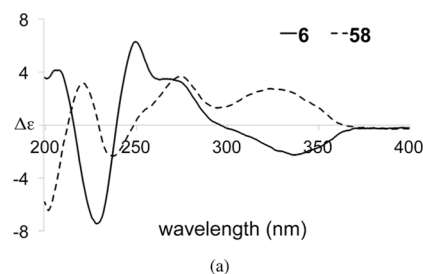
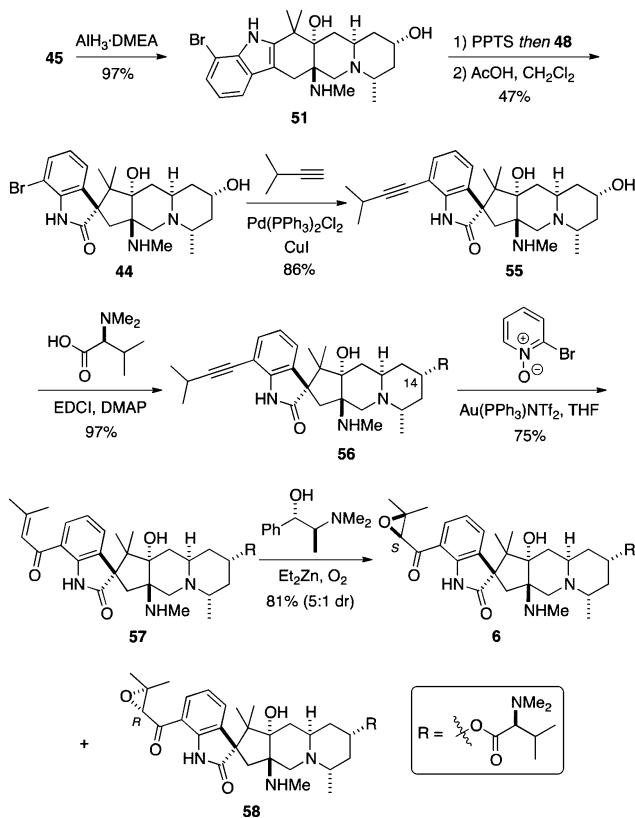
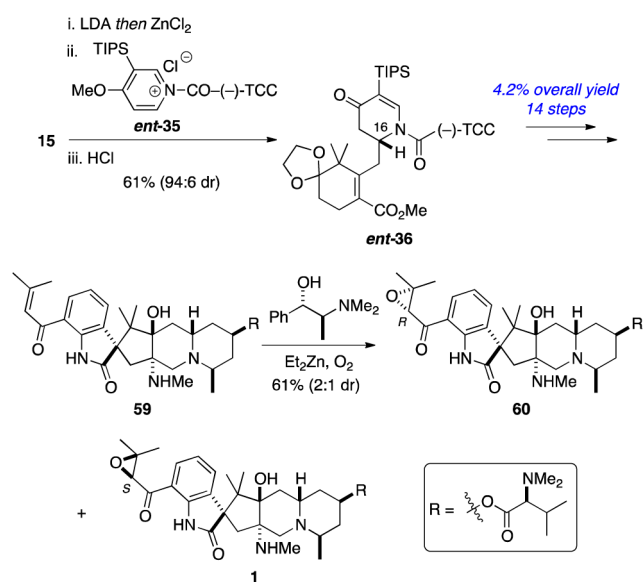


Figure 3. (a) CD Spectra of **6** and **58**. (b) CD spectra of citrinadins A and B. Adapted with permission from 3b. Copyright 2005 American Chemical Society.

Because we were unable to obtain an authentic sample of (–)-citrinadin A or its bis-salt, a direct comparison of natural material with the synthetic sample was not possible. Nevertheless, the CD spectrum of synthetic **1** coupled with the crystallographic data for **56** strongly suggests that the correct stereochemical structure of (–)-citrinadin A is **6**, so the absolute stereochemistry of the pentacyclic core of the citrinadins is *opposite* that assigned by Kobayashi.³ Notably, this revised structure is in agreement with the findings of Wood and co-workers, who completed the first total synthesis of (+)-citrinadin B.⁶

Further corroboration of the correctness of the stereochemical assignment of (–)-citrinadin A as being that shown in **6** was obtained by the independent synthesis of **1**, the compound that Kobayashi had assigned as being (–)-citrinadin A (Scheme 13).³ In the event, the vinylogous Mannich reaction

Scheme 13. Synthesis of (–)-Citrinadin A Isomer **1**



of the zinc dienolate of **15** with the chiral pyridinium salt *ent*-**35**, which has (–)-TCC as the chiral auxiliary, provided the adduct *ent*-**36** in 61% yield (dr = 94:6). Following the same sequence of reactions described for the conversion of **36** into **57** (Schemes 6, 9, and 12), *ent*-**36** was transformed into **59** in 4.2% overall yield over 14 steps. It is significant that en route to **59**, the absolute configuration of *ent*-**44** was unambiguously established by X-ray crystallography (Figure 4). Diastereoselective epoxidation of enone **59** with (*S,S*)-*N*-methylpseudoephedrine according to the Enders protocol afforded a separable

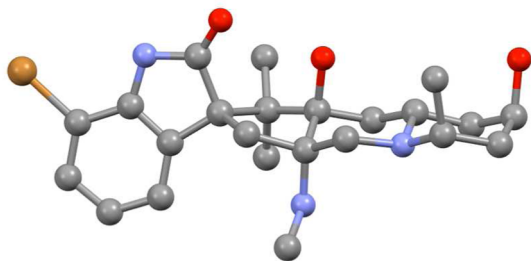


Figure 4. X-ray structure of *ent*-**44**. A molecule of CHCl₃ and AcOH was removed for clarity.

mixture (2:1) of **60** and **1**.³¹ The CD spectra of neither the major isomer **60** nor **1** matches the CD spectrum for (–)-citrinadin A reported by Kobayashi (Figure 5).^{3b} On the

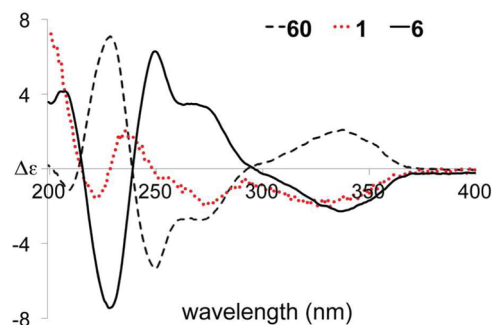


Figure 5. CD Spectra of **60**, **1**, and **6**.

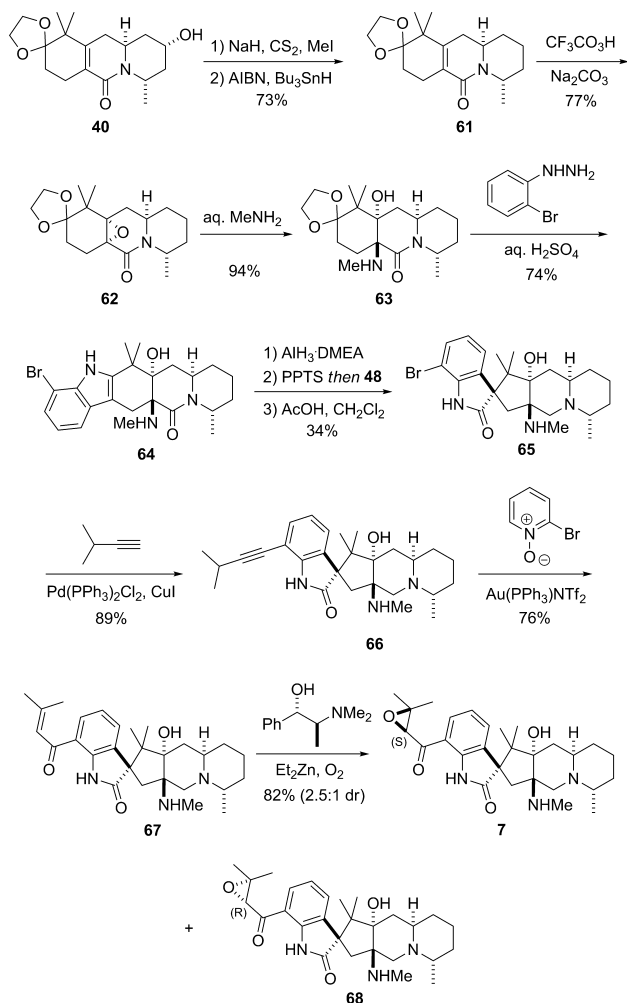
contrary, the CD spectrum of **60** is clearly opposite to that of naturally occurring (–)-citrinadin A. This observation is consistent with the absolute stereochemistry of the pentacyclic core of **60** being enantiomeric to that of (–)-citrinadin A, which must therefore have the stereochemical structure depicted in **6**.

Total Synthesis of (+)-Citrinadin B. The difference between citrinadin A (**6**) and citrinadin B (**7**) is the presence of a dimethyl valine ester at C(14). Accordingly, one may envisage that deoxygenation at C(14) of a late stage intermediate in the synthesis of citrinadin A would give a precursor of citrinadin B. In several exploratory experiments, we examined the feasibility of deoxygenating *rac*-**50** and *rac*-**44** using procedures reported by Barton³² and Myers,³³ but because mixtures of products were obtained, we turned to the removal of the C(14) hydroxyl group an earlier stage. Thus, Barton deoxygenation of **40** afforded **61** in 73% yield (Scheme 14). Epoxidation of **61** using buffered peroxytrifluoroacetic acid gave epoxide **62** (77% yield) as a single stereoisomer, and when **62** was heated with aqueous methylamine, the desired amino alcohol **63** was isolated in 94% yield. The Fisher indole reaction of **63** with *o*-bromophenylhydrazine hydrochloride furnished the pentacyclic indole **64**, which was then converted into the spirooxindole **65** in 34% overall yield by sequential hydride reduction of the tertiary lactam, indole oxidation with Davis' oxaziridine **48**, and acid-catalyzed rearrangement of the intermediate epoxide. The aryl bromide moiety of **65** was then elaborated via a Sonogashira coupling with 3-methylbut-1-yne to furnish the alkyne **66** that was processed to the enone **67** in 68% overall yield from **65** by reaction with 2-bromopyridine *N*-oxide in the presence of gold.³⁰ Finally, epoxidation of enone **67** using the Enders procedure³¹ afforded a separable mixture of **7** and **68** (dr = 2.5:1). The CD spectrum of major isomer **7** was in agreement with CD data obtained for natural (+)-citrinadin (B), and the spectral data (¹H and ¹³C NMR) of the synthetic **7** thus isolated were consistent with those reported by Wood.⁶

■ SUMMARY AND CONCLUSIONS

In summary, we completed the enantioselective total syntheses of (–)-citrinadin A (**6**) and (+)-citrinadin B (**7**) by concise sequences of reactions involving only 20 and 21 steps, respectively, from commercially available starting materials. The brevity of the approach was enabled by minimizing protecting group operations and unproductive refunctionaliza-

Scheme 14. Total Synthesis of (+)-Citrinadin B



tion. The syntheses of **6** and **7** feature a highly diastereoselective, vinylogous Mannich reaction of a dienolate with a chiral pyridinium salt to establish the first stereogenic center. The stereochemical efficiency of the syntheses was then possible because the chirality of this carbon atom was exploited to introduce the remaining stereocenters of the pentacyclic core in a linear sequence of reactions that were subject to substrate-control. Notable stereoselective transformations include an epoxidation/ring opening sequence and an oxidation/rearrangement of an indole to furnish a spirooxindole. Our completion of the syntheses of **6** and **7** coupled with the corroborative findings of Wood⁶ led to the revision of the stereochemical structures from those that were originally proposed as being **1** and **2**, respectively, by Kobayashi,³⁵ who relied upon ROESY and ECD data to assign absolute and relative stereochemical relationships in the pentacyclic cores of the citrinadins. The misassignment of the absolute stereochemistry of the citrinadin structures by Kobayashi serves as a reminder of the potential pitfalls associated with using ROESY, as well as ECD, when assigning stereochemistry, especially when other stereoisomers are not available for comparison.

■ ASSOCIATED CONTENT

S Supporting Information

Complete experimental procedures, full characterization of new compounds, X-ray crystallographic data for *ent*-**36**, *ent*-**46**, *ent*-

47, *rac*-**50**, *rac*-**53**, *rac*-**44**, *ent*-**44**, **56**, comparison of CD spectra of **7** and **68** compared with those published for citrinadins A and B, comparison of ¹H and ¹³C NMR data for **6** as its free base and as a bis-salt with those published for a bis-salt of (–)-citrinadin A, and a comparison of ¹H and ¹³C NMR data for **7** with those obtained by Wood. 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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