

Asymmetric, Stereocontrolled Total Synthesis of Paraherquamide A

Robert M. Williams,* Jianhua Cao, Hidekazu Tsujishima, and Rhona J. Cox

Contribution from the Department of Chemistry, Colorado State University,
Fort Collins, Colorado 80523

Received June 16, 2003; E-mail: rmw@chem.colostate.edu

Abstract: The first total synthesis of paraherquamide A, a potent anthelmintic agent isolated from various *Penicillium* sp. with promising activity against drug-resistant intestinal parasites, is reported. Key steps in this asymmetric, stereocontrolled total synthesis include a new enantioselective synthesis of α -alkylated- β -hydroxyproline derivatives to access the substituted proline nucleus and a highly diastereoselective intramolecular S_N2' cyclization to generate the core bicyclo[2.2.2]diazaoctane ring system.

Introduction

The paraherquamides^{1–4} are an unusual family of fungal natural products which contain a bicyclo[2.2.2]diazaoctane core structure, a *spiro*-oxindole, and a substituted proline moiety. The parent member, paraherquamide A (**1**), was first isolated from cultures of *Penicillium paraherquei* by Yamazaki and co-workers in 1981.¹ Since then, paraherquamides B–G,² VM55595, VM55596, and VM55597,³ SB203105 and SB200437,⁴ and sclerotamide⁵ have been isolated from various *Penicillium* and *Aspergillus* species. Marcfortines A–C are structurally similar, containing a pipercolic acid unit in place of proline.⁶ Also closely related are VM55599,³ aspergamides A and B,⁷ avrainvillamide (CJ-17,665),⁸ and the most recently isolated members of this family, stephacidins A and B.⁹ These last six compounds contain a 2,3-disubstituted indole in place of the *spiro*-oxindole. Brevianamides A and B,¹⁰ which contain a *spiro*-indoxyl rather

than a *spiro*-oxindole, and the asperparalines, which contain a *spiro*-succinimide,¹¹ are also structurally comparable (Figure 1).

The paraherquamides have attracted considerable attention due to their molecular complexity, intriguing biogenesis,^{12,13} and biological activity. Some members, most notably paraherquamide A, display potent anthelmintic activity and antinematodal properties.¹⁴ Due to the appearance of drug resistance developed by helminths, broad spectrum anthelmintic agents such as the macrolide endectocides, benzimidazoles, tetrahydropyrimidines, and imidazothiazoles are beginning to lose efficacy and there has arisen an urgent need to discover new families of antiparasitic agents. The paraherquamides represent an entirely new structural class of anthelmintic compounds, and as such, they hold great potential as drugs for the treatment of intestinal parasites in animals.¹⁵ The mode of action of the paraherquamides is, as yet, incompletely characterized, but recent work suggests that they are selective competitive cholinergic antagonists.¹⁶

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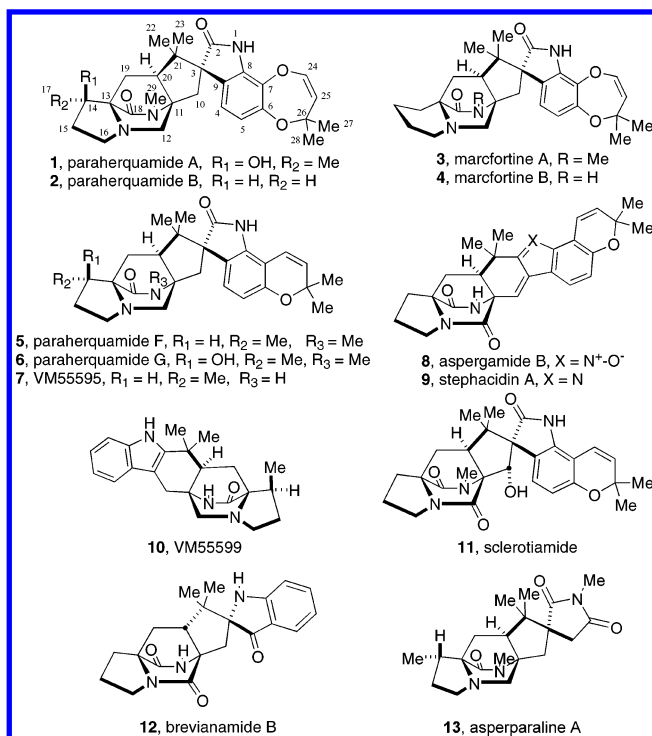
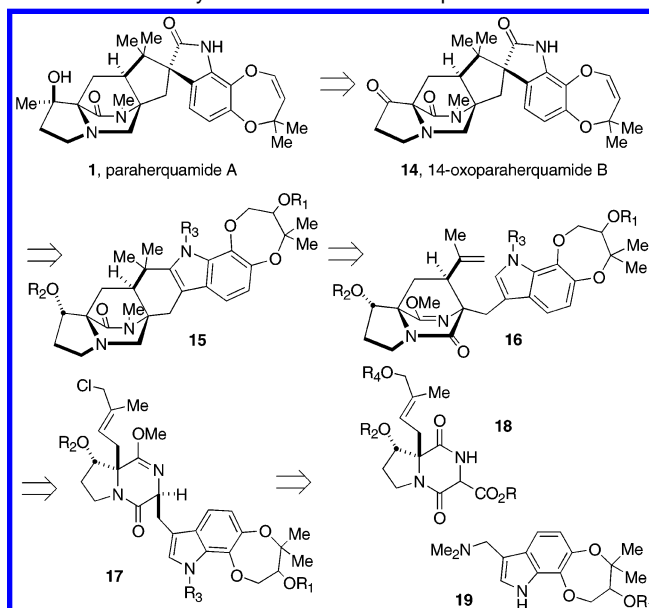


Figure 1. Structures of some paraherquamides and related compounds.

The small quantities of paraherquamide A that can be isolated from cultures for biological study have slowed the development of these agents. Recently, Lee and Clothier reported the interesting semisynthetic conversion of marcfortine A (3), a metabolite more readily available by fermentation, into paraherquamide A via paraherquamide B (2).¹⁷ Following synthetic studies on brevianamide B (12),¹⁸ our laboratory reported the first total synthesis of a member of the paraherquamide family, *ent*-paraherquamide B, in 1993, in which a diastereoselective intramolecular S_N2' cyclization reaction was used to construct the core bicyclo[2.2.2]diazaoctane ring system.¹⁹ We have further exploited this reaction strategy, and we described the first total synthesis of paraherquamide A in 2000.²⁰ Herein, we detail a full account of this work.

Scheme 1. Retrosynthetic Plan for Paraherquamide A



Synthesis of an α -Alkylated- β -Hydroxyproline

Despite the apparent similarity in the structures of paraherquamide A and B, synthesis of the former turned out to be a significantly more challenging endeavor owing to the presence of the unusual β -hydroxy- β -methyl proline residue. In the semisynthesis of paraherquamide A from marcfortine A (3), the final step was addition of methylmagnesium bromide to 14-oxoparaherquamide B (14).¹⁷ We planned to use this same methodology to complete our total synthesis and to construct 14 using a similar strategy to that used for paraherquamide B, that is, coupling of suitably functionalized indole (19) and diketopiperazine (18) units and then an intramolecular S_N2' cyclization followed by palladium-mediated closure of the seventh ring, and finally oxidation and rearrangement of the 2,3-disubstituted indole to the *spiro*-oxindole of 14-oxoparaherquamide B¹⁹ (Scheme 1).

New methodology was now required to prepare a suitably functionalized α -alkylated- β -hydroxyproline residue. A variety of methods were investigated for the asymmetric construction of this class of compound, leading to the development of a potentially general synthetic method which uses dianion alkylation of the readily available *N*-*t*-BOC- β -hydroxyproline ethyl ester derivative 12 with net retention of stereochemistry.²¹ This methodology has now successfully been applied to a concise asymmetric and stereocontrolled total synthesis of paraherquamide A.

Epoxide 20, which is commercially available or made by epoxidation of isoprene with *m*CPBA, was treated with *n*-Bu₄NI and TBSCl to provide iodide 21 as a mixture of geometrical isomers (*E*:*Z* \approx 6:1) in 58% overall yield. Diester 22 was prepared in two steps from ethyl glycinate and ethyl acrylate, and then a Dieckmann cyclization was conducted, using a slight modification of the procedure described by Rapoport,²²

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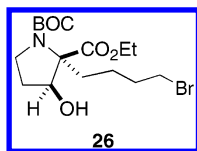
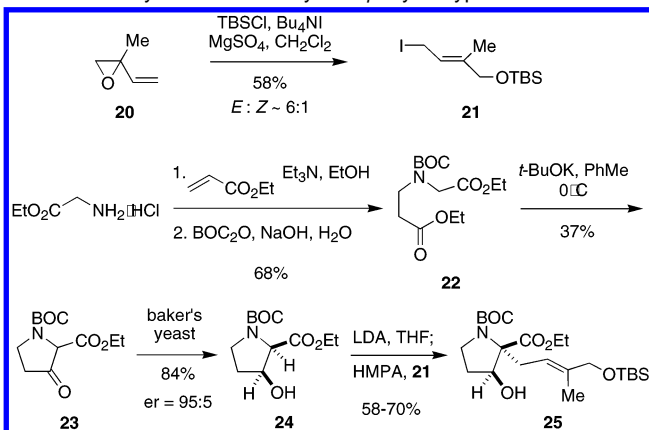


Figure 2. Assignment of relative stereochemistry of **25**.

Scheme 2. Synthesis of α -Alkylated- β -Hydroxyproline **25**



to yield racemic β -ketoester **23** (Scheme 2). Baker's yeast reduction afforded the optically active β -hydroxyester **24** with an enantiomeric ratio of ca. 95:5 as described by Knight et al.²³ Alkylation of the dianion of **24** with substituted allyl iodide **21** proceeded with retention of stereochemistry and excellent diastereoselectivity under the conditions previously developed.²¹ The desired α -alkylated product **25** was obtained in 58–70% isolated yield with little or no *O*-monoalkylation or *O*-,*C*-dialkylation taking place. It was interesting to note during large scale synthesis of **25** that the amount of HMPA required in the alkylation reaction ranged from 1.4 to 13.6 equiv depending on the batch of **24** that was used, despite the batches being apparently identical by ¹H NMR, IR, TLC, and optical rotation. The reasons for this phenomenon are presently unclear.²⁴

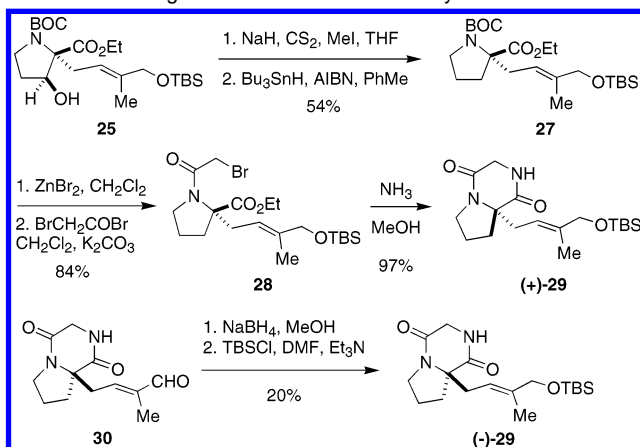
The assignment of the relative stereochemistry of **25** was obtained by comparison of the ¹H NMR and optical rotation data of **25** to those of **26**, which was obtained by alkylation of **24** with 1,4-dibromobutane. The relative stereochemistry of **26** was assigned unambiguously through single-crystal X-ray analysis (Figure 2).²¹ The absolute stereochemistry of **25** was confirmed by Barton deoxygenation and conversion to diketopiperazine (**+**)-**29** as illustrated in Scheme 3. This same diketopiperazine could be obtained, as the enantiomer, from **30**. This compound has previously been converted to (**+**)-paraherquamide B, a substance whose absolute stereochemistry has been confirmed.¹⁹

Synthesis of a Functionalized Diketopiperazine

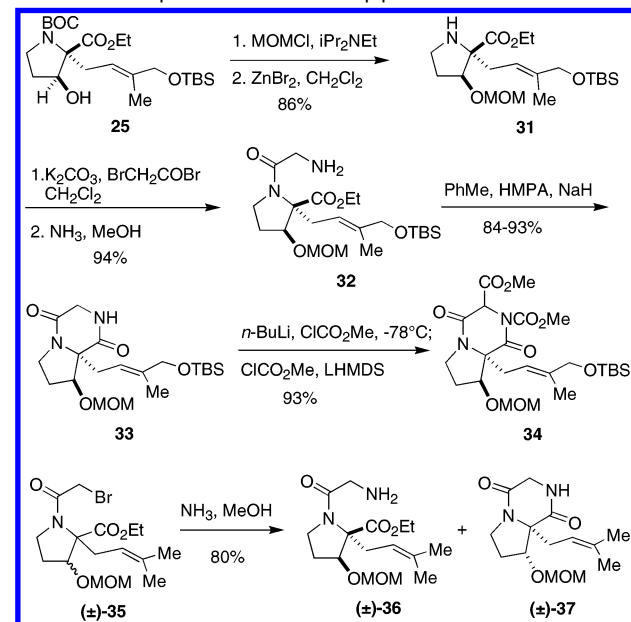
It was necessary to convert the substituted proline (**25**) into a suitably functionalized diketopiperazine for a similar Somei–Kametani coupling reaction to that used in our total synthesis of paraherquamide B. Initial studies on this system were carried out with the secondary alcohol protected as a benzyl ether.

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Scheme 3. Assignment of Absolute Chemistry of **25**



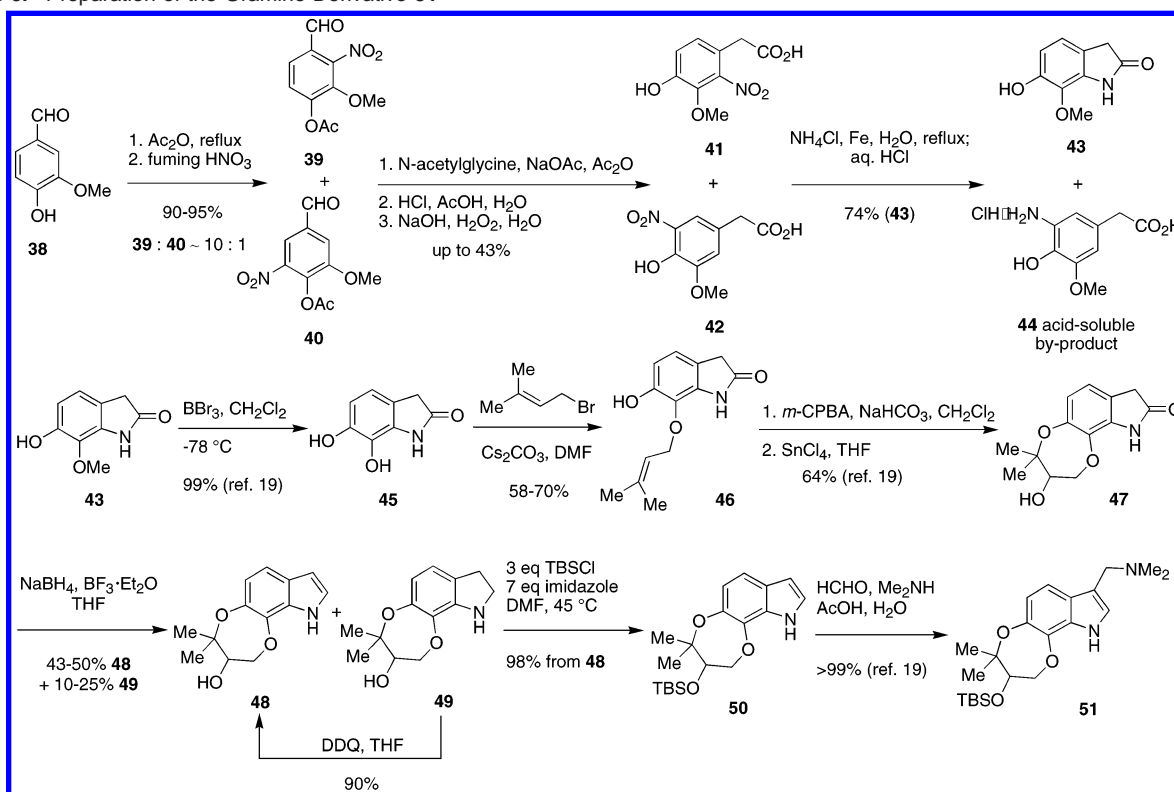
Scheme 4. Preparation of the Diketopiperazine **34**



However, because of problems with selectivity and purification later in the synthesis, the less bulky and more polar methoxymethyl (MOM) protecting group was used in the final synthetic route. After MOM protection of the alcohol, the *N*-*t*-BOC group was smoothly removed with ZnBr₂ in dichloromethane²⁵ and the exposed secondary amine (**31**) was acetylated with bromoacetyl bromide under Schotten–Baumann conditions (Scheme 4). Treatment of the bromoacetamide with methanolic ammonia afforded the corresponding glycinamide (**32**) which was directly subjected to cyclization in the presence of sodium hydride in toluene/HMPA to afford the bicyclic compound **33** in 75% overall yield from **25**. An interesting observation about the ease of closure of hydroxylated diketopiperazines was made during this study. When there is no hydroxyl substituent (e.g., in **28**) or the protected hydroxyl group is *trans* to the ester, the diketopiperazine typically forms spontaneously from the aminoester in methanol at room temperature. On the other hand, a *cis*-isomer such as **31** can be isolated as the aminoester from the amination reaction, and formation of the diketopiperazine requires much more forcing conditions. On amination of a

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Scheme 5. Preparation of the Gramine Derivative 51



mixture of diastereomeric bromoacetamides **35**, the aminoester **36** and the diketopiperazine **37** are produced. This is presumably because the *cis*-diketopiperazine is significantly more sterically hindered. After diketopiperazine formation, a one-pot double carbomethoxylation reaction was performed by the sequential addition of *n*-BuLi in THF followed by addition of methylchloroformate, which carbomethoxylates the amide nitrogen. Subsequent addition of more methylchloroformate followed by LHMDs afforded **34** in 93% yield as an ~6:1 mixture of *E* and *Z* isomers, with the newly created stereogenic center as a single stereoisomer (relative configuration was not assigned).

Improved Synthesis of the Gramine Derivative

With this functionalized diketopiperazine in hand, we turned our attention to improvement of the synthesis of the dioxepin-containing indole fragment that we originally described in 1990.²⁶ The original route provides compound **51** in 14 steps with no chromatography required until the ninth step. However, further optimization was necessary to achieve a more rapid and efficient large-scale synthesis. The route we have developed is illustrated in Scheme 5. Vanillin (**38**) was acetylated with acetic anhydride and then treated with fuming nitric acid to afford **39**, the desired regioisomer, and **40**, the undesired isomer, in an ~10:1 ratio. Initially, these regioisomers were separated by hydrolysis of the acetate group and isolation of the desired phenol isomer by crystallization.²⁷ Analysis of the product mixture by TLC revealed that **39** had a lower R_f and **40** had exactly the same R_f as that of the starting material, and it was possible to isolate **39** by flash chromatography. However, neither purification method proved optimal for a large-scale protocol. The new

approach circumvents these problems. Instead, we directly used the mixture of nitrobenzaldehydes **39** and **40**. After a three-step transformation,²⁸ **39** provided the desired acid **41**, and **40** provided the undesired acid **42**. Reduction of the nitro group was originally carried out in 95% yield by hydrogenation over palladium on carbon at 40 psi and 80 °C. However, this protocol could prove awkward on a large scale, so an alternative approach was developed using iron and NH_4Cl ²⁹ which, while the yield (74%) is more moderate, proved easier to scale-up. On reduction to the corresponding amines, the amine intermediate from **41** cyclized to oxindole **43**, but **42** was simply reduced to amino acid **44**, which cannot undergo an intramolecular cyclization reaction due to geometric restriction. On extraction of the reaction mixture, the amino acid (**44**) was removed with aqueous acid leaving the oxindole (**43**) in the organic phase. Demethylation then proceeded smoothly as already described to give **45**.³⁰

Prenylation of **45** is partially selective for the 7-hydroxy position due to the greater acidity of this hydroxyl group. However, under the prenylation conditions originally developed for paraherquamide B, small amounts of the 6-prenyloxy and 6,7-diprenyloxy isomers were also formed, and the three compounds are difficult to separate by flash chromatography. In this modification of our original route, replacement of the base with Cs_2CO_3 improves the selectivity and yield of **46**.

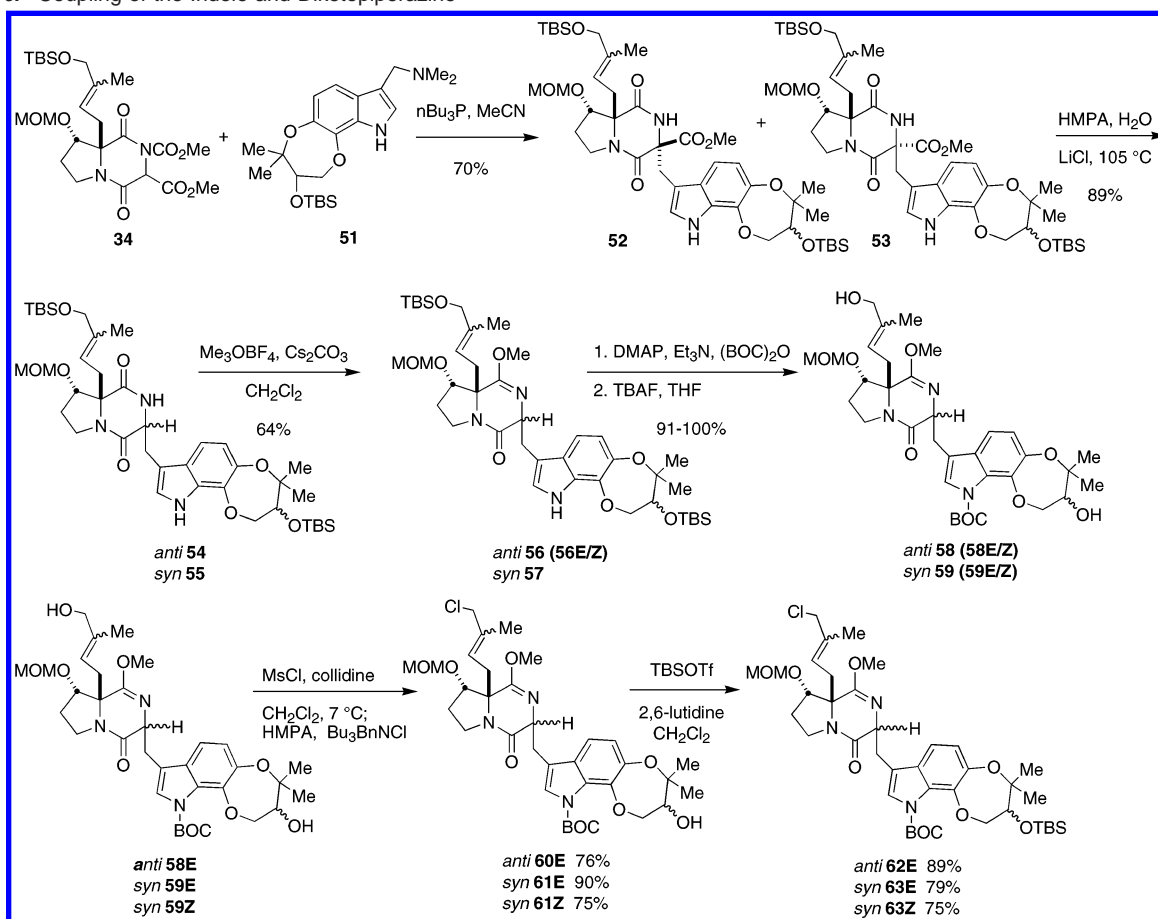
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Scheme 6. Coupling of the Indole and Diketopiperazine



Extraction into base during the workup procedure also removes the diprenylated byproduct which allowed for easier purification.

A major problem in our first generation synthesis of the gramine derivative was during reduction of the oxindole to the indole, when over-reduction to the indoline occurred in variable quantities giving a ratio of 4:1 to 2:1 of indole/indoline. Attempts were made, without success, to effect a more selective reduction of the oxindole. However, the problem was solved in an indirect fashion as it proved possible to oxidize the indoline byproduct to the indole with DDQ³¹ in greater than 90% yield.

Formation of TBS ethers on hindered alcohols is known to be very sensitive to the concentration of the reaction mixture. The silylation reaction was optimized by concentrating the reaction mixture to give an improved yield of 95% from 82%. Finally indole **50** was converted to the gramine derivative **51** under standard conditions. The advantages of this new approach are significant in terms of increased yield, lower cost, and faster synthesis on a large scale.

Coupling of the Indole and Diketopiperazine

Somei–Kametani coupling³² of diketopiperazine **34** with the gramine derivative **51** in the presence of tri-*n*-butylphosphine gave a separable mixture of two diastereomers **52** and **53** in a

3:1 ratio, each as a mixture of four diastereomers (Scheme 6).³³ Decarbomethoxylation was effected by treatment of **52** and **53** individually with LiCl in hot, aqueous HMPA to provide, in both cases, a mixture of **54** (*anti*-isomer) and **55** (*syn*-isomer), which could now be separated into the *E* and *Z* isomers, each of which as a mixture of two diastereomers (epimeric at the dioxepin secondary alcohol). However, as separation of the geometric isomers proved to be difficult, the compounds were usually carried through the synthetic sequence as a mixture and separated only for analytical purposes. Protection of the secondary amide as the corresponding methyl lactim ether was accomplished by treating **54** and **55** with trimethylxonium tetrafluoroborate and Cs₂CO₃ in dichloromethane. Model studies had shown that Cs₂CO₃ was a more efficient base than Na₂CO₃ for this reaction, as it leads to a lower incidence of TBS cleavage and *N*-methylation. Next, the indole nitrogen was protected as the corresponding *N*-*t*-BOC derivative by treatment with di-*tert*-butyl dicarbonate in the presence of DMAP, and then the silyl ethers were removed with tetrabutylammonium fluoride (TBAF) to provide **58** (*anti*) and **59** (*syn*). From this point onward, the *E* and *Z* isomers were utilized separately. Unfortunately, the Corey procedure,³⁴ which had been successful

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(33) The stereochemistry at the newly formed stereogenic centers in **52** and **53**, and in all subsequent compounds, was assigned on the basis of ¹H NMR data. In compounds where the indole substituent is on the same face of the diketopiperazine as the MOM ether, the signal for the methoxy group is at significantly higher field than in the situation where these two substituents are on opposite faces. This is due to the proximity of the methoxy group to the shielding effects of the aromatic system.

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