

Asymmetric, Stereocontrolled Total Synthesis of Paraherguamide 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 paraherguamide 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 paraherquamides¹⁻⁴ 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 coworkers 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 pipecolic 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

- (2)(a) Ondeyka, J. G.; Goegelman, R. T.; Schaeffer, J. M.; Kelemen, L.; Zitano, (L) J. Antibiot. 1990, 43, 1375–1379. (b) Liesch, J. M.; Wichmann, C. F. J. Antibiot. 1990, 43, 1380–1386. (c) Blanchflower, S. E.; Banks, R. M.; (3) Blanchflower, S. E.; Banks, R. M.; Everett, J. R.; Reading, C. J. Antibiot. 1991, 44, 492–497.
- **1993**, 46, 1355-1363. (4) Banks, R. M.; Blanchflower, S. E.; Everett, J. R.; Manger, B. R.; Reading,
- C. J. Antibiot. 1997, 50, 840-846. (5) Whyte, A. C.; Gloer, J. B.; Wicklow, D. T.; Dowd, P. F. J. Nat. Prod. 1996, 59, 1093-1095.
- (6) (a) Polonsky, J.; Merrien, M.-A.; Prangé, T.; Pascard, C.; Moreau, S. J. Chem. Soc., Chem. Commun. 1980, 601–602. (b) Prangé, T.; Billion, M.-
- ; Vuilhorgne, M.; Pascard, C.; Polonsky, J.; Moreau, S. Tetrahedron Lett. 1981, 22, 1977-1980. (7) Fuchser, Jens. Beeinflussung der Sekundarstoffbildung bei Aspergillus
- ochraceus durch Variation der Kulturbedingungen sowie Isolierung, Strukturaufklarung und Biosynthese der neuen Naturstoffe. Ph.D. Thesis, University of Göttingen, Germany, 1995. K. Bielefeld Verlag: Friedland, 1996 (Prof. A. Zeeck).
 (8) (a) Fenical, W.; Jensen, P. R.; Cheng, X. C. U.S. Patent 6,066,635, 2000.
- (b) Sugie, Y.; Hirai, H.; Inagaki, T.; Ishiguro, M.; Kim, Y.-J.; Kojima, Y.; Sakakibara, T.; Sakemi, S.; Sugiura, A.; Suzuki, Y.; Brennan, L.; Duignan, J.; Huang, L. H.; Sutcliffe, J.; Kojima, N. J. Antibiot. **2001**, 54, 911–916.
- (9) Qian-Cutrone, J.; Huang, S.; Shu, Y.-Z.; Vyas, D.; Fairchild, C.; Menendez, .; Krampitz, K.; Dalterio, R.; Klohr, S. E.; Gao, Q. J. Am. Chem. Soc. **2002**, 124, 14556-14557.
- (10) (a) Birch, A. J.; Wright, J. J. J. Chem. Soc., Chem. Commun. 1969, 644-(d) Dich, N. J., Wright, J. J. Tetrahedron **1970**, *26*, 2329–2344. (c) Birch, A. J.; Russell, R. A. Tetrahedron **1972**, *28*, 2999–3008.

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

- (13) (a) Stocking, E. M.; Sanz-Cervera, J. F.; Williams, R. M.; Unkefer, C. J. J. Am. Chem. Soc. 1996, 118, 7008-7009. (b) Williams, R. M.; Sanz-Cervera, J. F.; Sancenón, F.; Marco, J. A.; Halligan, K. M. Bioorg. Med. Chem. 1998, 6, 1233-1241. (c) Stocking, E. M.; Williams, R. M.; Sanz-Cervera, J. F. J. Am. Chem. Soc. 2000, 122, 9089-9098. (d) Stocking, E. M.; Williams, R. M.; Sanz-Cervera, J. F. J. Am. Chem. Soc. 2000, 122, 9089-9098. (d) Stocking, E. M.; Williams, R. M.; Sanz-Cervera, J. F. J. Am. Chem. Soc. 2000, 122, 9089-9098. (d) Stocking, E. M.; Sanz-Cervera, J. F. J. Am. Chem. Soc. 2000, 122, 9089-9098. (d) Stocking, E. M.; Sanz-Cervera, J. F. J. Am. Chem. Soc. 2000, 122, 9089-9098. (d) Stocking, E. M.; Sanz-Cervera, J. F. J. Am. Chem. Soc. 2000, 122, 9089-9098. (d) Stocking, E. M.; M.; Sanz-Cervera, J. F. J. Am. Chem. Soc. 2000, 122, 9089-9098. (d) Stocking, E. M.; Sanz-Cervera, J. F. J. Am. Chem. Soc. 2000, 122, 9089-9098. (d) Stocking, E. M.; Sanz-Cervera, J. F. J. Am. Chem. Soc. 2000, 122, 9089-9098. (d) Stocking, E. M.; Sanz-Cervera, J. F. J. Am. Chem. Soc. 2000, 122, 9089-9098. (d) Stocking, E. M.; Sanz-Cervera, J. F. J. Am. Chem. Soc. 2000, 122, 9089-9098. (d) Stocking, E. M.; Sanz-Cervera, J. F. J. Am. Chem. Soc. 2000, 122, 9089-9098. (d) Stocking, E. M.; Sanz-Cervera, J. F. J. Am. Chem. Soc. 2000, 122, 9089-9098. (d) Stocking, E. M.; Sanz-Cervera, J. F. J. Am. Chem. Soc. 2000, 122, 9089-9098. (d) Stocking, E. M.; Sanz-Cervera, J. F. J. Am. Chem. Soc. 2000, 122, 9089-9098. (d) Stocking, E. M.; Sanz-Cervera, J. F. J. Am. Chem. Soc. 2000, 122, 9089-9098. (d) Stocking, E. M.; Sanz-Cervera, J. F. J. Am. Chem. Stocking, E. M.; Sanz-Cervera, J. F. J. Am. Chem. Stocking, E. M.; Sanz-Cervera, J. F. J. Am. Chem. Stocking, E. M.; Sanz-Cervera, J. F. J. Am. Chem. Stocking, E. M.; Sanz-Cervera, J. F. J. Am. Chem. Stocking, E. M.; Sanz-Cervera, J. F. J. Am. Chem. Stocking, E. M.; Sanz-Cervera, J. F. J. Am. Chem. Stocking, E. M.; Sanz-Cervera, J. F. J. Am.; J. F. J. Am.; J. F. J. Am.; J. F. J. Am Cervera, J. F. J. Am. Chem. Soc. 2000, 122, 9089–9096. (d) Stocking, E. M.; Martinez, R. A.; Silks, L. A.; Sanz-Cervera, J. F.; Williams, R. M. J. Am. Chem. Soc. 2001, 123, 3391–3392. (e) Stocking, E. M.; Sanz-Cervera, J. F.; Unkefer, C. J.; Williams, R. M. Tetrahedron 2001, 57, 5303–5320. (f) Stocking, E. M.; Sanz-Cervera, J. F.; Williams, R. M. Angew. Chem., Int. Ed. 2001, 40, 1296–1298.
- Int. Ed. 2001, 40, 1296-1298.
 (14) (a) Ostlind, D. A.; Mickle, W. G.; Ewanciw, D. V.; Andriuli, F. J.; Campbell, W. C.; Hernandez, S.; Mochales, S.; Munguira, E. Res. Vet. Sci. 1990, 48, 260-261. (b) Shoop, W. L.; Egerton, J. R.; Eary, C. H.; Suhayda, D. J. Parasitol. 1990, 76, 349-351. (c) Shoop, W. L.; Eary, C. H.; Michael, H. W.; Haines, H. W.; Seward, R. L. Vet. Parasitol. 1991, 40, 339-341. (d) Shoop, W. L.; Michael, B. F.; Haines, H. W.; Eary, C. H. Vet. Parasitol. 1992, 43, 259-263. (e) Shoop, W. L.; Haines, H. W.; Eary, C. H.; Michael, B. F. Am. J. Vet. Res. 1992, 53, 2032-2034. (f) Schaeffer I. M.; Blizzard, T. A.; Ondevka, J.; Goegelman, B.; Sinclair, P. Schaeffer, J. M.; Blizzard, T. A.; Ondeyka, J.; Goegelman, R.; Sinclair, P. J.; Mrozik, H. Biochem. Pharmacol. 1992, 43, 679-684. For a review, see: (g) Geary, T. G.; Sangster, N. C.; Thompson, D. P. Vet. Parasitol. 1999, 84, 275-295.

⁽¹⁾ Yamazaki, M.; Okuyama E.; Kobayashi, M.; Inoue, H. Tetrahedron Lett. 1981. 22. 135-136.

^{(11) (}a) Hayashi, H.; Nishimoto, Y.; Nozaki, H. Tetrahedron Lett. 1997, 38, 655-5658. (b) Hayashi, H.; Nishimoto, Y.; Akiyama, K.; Nozaki, H.

^{5655-5658. (}b) Hayashi, H.; Nishimoto, Y.; Akiyama, K.; Nozaki, H. Biosci. Biotechnol. Biochem. 2000, 64, 111-115.
(12) (a) Porter, A. E. A.; Sammes, P. G. J. Chem. Soc., Chem. Commun. 1970, 1103. (b) Baldas, J.; Birch, A. J.; Russell, R. A. J. Chem. Soc., Perkin Trans. 1 1974, 50-52. (c) Birch, A. J. J. Agric. Food Chem. 1971, 19, 1088-1092. (d) Kuo, M. S.; Wiley, V. H.; Cialdella, J. I.; Yurek, D. A.; Whaley, H. A.; Marshall, V. P. J. Antibiot. 1996, 49, 1006-1013.
(12) (a) Stoching E. M.; Song Corners, L. E.; Williams, P. M.; Uklofar, C. J.



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.

- (15) (a) Blizzard, T. A.; Marino, G.; Mrozik, H.; Fisher, M. H.; Hoogsteen, K.; Springer, J. P. J. Org. Chem. **1989**, 54, 2657–2663. (b) Blizzard, T. A.; Mrozik, H.; Fisher, M. H.; Schaeffer, J. M. J. Org. Chem. **1990**, 55, 2256– 2259. (c) Blizzard, T. A.; Margiatto, G.; Mrozik, H.; Schaeffer, J. M.; Fisher, M. H. *Tetrahedron Lett.* **1991**, *32*, 2437–2440. (d) Blizzard, T. A.; Margiatto, G.; Mrozik, H.; Schaeffer, J. M.; Fisher, M. H. Tetrahedron Lett. 1991, 32, 2441-2444. (e) Lee, B. H.; Clothier, M. F.; Johnson, S. S. Bioorg. Med. Chem. Lett. 2001, 11, 553-554. (f) Lee, B. H.; Clothier, M. F.; Dutton, F. E.; Nelson, S. J.; Johnson, S. S.; Thompson, D. P.; Geary, T. G.; Whaley, H. D.; Haber, C. L.; Marshall, V. P.; Kornis, G. I.; McNally, P. L.; Ciadella, J. I.; Martin, D. G.; Bowman, J. W.; Baker, C. A.; Coscarelli, E. M.; Alexander-Bowman, S. J.; Davis, J. P.; Zinser, E. W.; Wiley, V.; Lipton, M. F.; Mauragis, M. A. Curr. Top. Med. Chem. 2002, 2, 779-793. (g) Lee, B. H.; Clothier, M. F. U.S. Patent 5,750,695, 1998
- (16) (a) Robertson, A. P.; Clark, C. L.; Burns, T. A.; Thompson, D. P.; Geary, T. G.; Trailovic, S. M.; Martin, R. J. J. Pharmacol. Exp. Ther. 2002, 302, 853–860. (b) Zinser, E. W.; Wolfe, M. L.; Alexander-Bowman, S. J.; 853-800. (b) ZIBSET, E. W.; WOITE, N. L., ALEXANGE-DOWHAN, S. J., Thomas, E. M.; Davis, J. P.; Groppi, V. E.; Lee, B. H.; Thompson, D. P.; Geary, T. G. J. Vet. Pharmacol. Ther. 2002, 25, 241–250.
 (17) (a) Lee, B. H.; Clothier, M. F. J. Org. Chem. 1997, 62, 1795–1798. (b) Lee, B. H.; Clothier, M. F.; Pickering, D. A. J. Org. Chem. 1997, 62, 7836– 2010.
- 7840
- (18) Williams, R. M.; Glinka, T.; Kwast, E.; Coffman, H.; Stille, J. K. J. Am. Chem. Soc. 1990, 112, 808-821.
- Cushing, T. D.; Sanz-Cervera, J. F.; Williams, R. M. J. Am. Chem. Soc. (19)1996 118 557-579
- (20)Williams, R. M.; Cao, J.; Tsujishima. H. Angew. Chem., Int. Ed. 2000, 39, 2540-2544.





Synthesis of an α -Alkylated- β -Hydroxyproline

Despite the apparent similarity in the structures of paraherquamides 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 14oxoparaherquamide 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 $S_N 2'$ 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 mCPBA, 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

⁽²¹⁾ Williams, R. M.; Cao, J. Tetrahedron Lett. 1996, 37, 5441-5444.

⁽²²⁾ (a) Blake, J.; Willson, C. D.; Rapoport, H. J. Am. Chem. Soc. 1964, 86, 5293-5299. For more regioselective methods, see: (b) Yamada, Y.; Ishii, T.; Kimura, M.; Hosaka, K. *Tetrahedron Lett.* **1981**, *22*, 1353–1354. (c) Sibi, M. P.; Christensen, J. W.; Kim, S.-G.; Eggen, M.; Stessman, C.; Oien, L. *Tetrahedron Lett.* **1995**, *36*, 6209–6212.



Figure 2. Assignment of relative stereochemistry of 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.



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

 ^{(23) (}a) Cooper, J.; Gallagher, P. T.; Knight, D. W. J. Chem. Soc., Perkin Trans. *I* 1993, 1313–1317. For alternative baker's yeast reductions, see: (b) Sibi, M. P.; Christensen, J. W. *Tetrahedron Lett.* 1990, *31*, 5689–5692. (c) Bhide, R.; Mortezaei, R.; Scilimati, A.; Sih, C. J. *Tetrahedron Lett.* 1990, *31*, 4827–4830.

⁽²⁴⁾ Seebach, D. Angew. Chem., Int. Ed. Engl. 1988, 27, 1624-1654.

⁽²⁵⁾ Nigam, S. C.; Mann, A.; Taddei, M.; Wermuth, C.-G. Synth. Commun. 1989, 19, 3139–3142.



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 onepot 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 dioxepincontaining 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 $\sim 10:1$ 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

(26) Williams, R. M.; Cushing, T. D. Tetrahedron Lett. 1990, 31, 6325–6328.
 (27) Raiford, L. C.; Stoesser, W. C. J. Am. Chem. Soc. 1928, 50, 2556–2563.

approach circumvents these problems. Instead, we directly used the mixture of nitrobenzaldehydes 39 and 40. After a threestep 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 NH₄Cl²⁹ 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**.

^{(28) (}a) MacDonald, S. F. J. Chem. Soc. 1948, 376–378. (b) Beer, R. J. S.; Clarke, K.; Davenport, H. F.; Robertson, A. J. Chem. Soc. 1951, 2029– 2032.

⁽²⁹⁾ Wissner, A.; Berger, D. M.; Boschelli, D. H.; Floyd, M. B., Jr.; Greenberger, L. M.; Gruber, B. C.; Johnson, B. D.; Mamuya, N.; Nilakantan, R.; Reich, M. F.; Shen, R.; Tsou, H.-R.; Upeslacis, E.; Wang, Y. F.; Wu, B.; Ye, F.; Zhang, N. J. Med. Chem. 2000, 43, 3244–3256.

⁽³⁰⁾ Since this route was developed, McWhorter and Savall have published a route to 45 which is shorter and higher yielding, but the applicability of their synthesis on a large scale has not yet been demonstrated. Savall, B. M.; McWhorter, W. W. J. Org. Chem. 1996, 61, 8696–8697.

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 trimethyloxonium 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

⁽³¹⁾ He, F.; Foxman, B. M.; Snider, B. B. J. Am. Chem. Soc. **1998**, *120*, 6417–6418.

 ^{(32) (}a) Somei, M.; Karasawa, Y.; Kaneko, C. *Heterocycles* 1981, *16*, 941–949. (b) Kametani, T.; Kanaya, N.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* 1981, 959–963.

⁽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.

⁽³⁴⁾ Corey, E. J.; Kim, C. U.; Takeda, M. *Tetrahedron Lett.* **1972**, *13*, 4339–4342.

in the synthesis of paraherquamide B for conversion of an allylic alcohol to the corresponding chloride, proved unreliable when applied to the paraherquamide A system. Under the conditions used previously, cleavage of the lactim ether and chlorination at the 2-position of the indole were observed. Extensive investigation into suitable conditions was carried out, and it was eventually found that selective conversion of the primary alcohols 58 and 59 to the corresponding mesylates was possible in the presence of the hindered base collidine. Displacement of mesylate by a chloride ion under these reaction conditions was very slow so Bu₃BnNCl (as an external chloride source) and a polar solvent were added to accelerate the reaction, allowing formation of the allylic chlorides (60 and 61) in up to 90% yield. This is a simple, practical, and reproducible method for preparing allylic chlorides in molecules bearing labile functional groups. Finally, careful reprotection of the secondary alcohols with tert-butyldimethylsilyl triflate in the presence of 2,6-lutidine afforded the key allylic chlorides 62 and 63.

$S_N 2^\prime$ Cyclization and Closure of the Seventh Ring

The stage was now set for the critical intramolecular $S_N 2'$ cyclization, that sets the relative stereochemistry at C-20 during formation of the bicyclo[2.2.2]diazaoctane ring nucleus. Based on precedent from the paraherquamide B synthesis,19 63E was treated with NaH in refluxing benzene. However, the reaction was very slow and gave the desired cyclization product 64 in only 25% yield, accompanied by products from competing pathways. The acidic proton in 63E is more sterically hindered than in the corresponding substrate for the paraherquamide B synthesis, due to the presence of the MOM ether. Since NaH likely exists as heterogeneous clusters in benzene, it was expected that use of a more coordinating solvent may break up the clusters and render deprotonation more facile. Conveniently, use of NaH in refluxing THF afforded the desired S_N2' cyclization product 64 in 87% yield from 63E exclusively as the desired syn-isomer.35 This remarkably diastereoselective intramolecular S_N2' cyclization reaction proceeds, in a nonpolar solvent like THF, via a tight, intramolecular ion-pair driven cyclization ("closed" transition state)³⁶ as shown in Scheme 7. Compound 62E also underwent the same transformation to give 64 in 82% yield. In both cases, the product was sometimes accompanied by a small amount of Boc-deprotected cyclized product which could be reprotected under standard conditions. In addition, it was interesting to note that the Z-isomer, 63Z, provides the same cyclization product, again with exclusive syn selectivity, in 50% yield.

Closure of the seventh ring was attempted using PdCl₂ and AgBF₄ in acetonitrile followed by NaBH₄ to reduce the incipient heptacyclic σ -palladium adduct,³⁷ reaction conditions which had

(35) The syn/anti relationship in this case refers to the relative stereochemistry between the C-20 stereogenic center (see paraherquamide numbering) and the proline residue.



(36) (a) Denmark, S. E.; Henke, B. R. J. Am. Chem. Soc. 1989, 111, 8032– 8034. (b) Denmark, S. E.; Henke, B. R. J. Am. Chem. Soc. 1991, 113, 2177–2194.

Scheme 7. Formation of the Heptacycle



been successful in the paraherquamide B synthesis.¹⁹ However, the only products isolated under the same conditions with **64** were those appearing to arise from removal of the *N*-*t*-BOC, MOM and lactim ether protecting groups, presumably by HBF₄ generated in situ. To buffer the reaction mixture, propylene oxide was added as an acid scavenger and the reaction now proceeded to give the desired 2,3-disubstituted indole (**65**) in 85% yield.

Completion of the Synthesis

Conditions could not be found which would allow direct and high-yielding conversion of the lactim ether (65) to the amide. However, use of 0.1 M aqueous HCl in THF gave the corresponding ring-opened amine methyl ester (66) which was recyclized to the bicyclo[2.2.2]diazaoctane (67) by treatment of 66 with catalytic 2-hydroxypyridine in hot toluene. Chemoselective reduction of the tertiary amide in the presence of the secondary amide to give 68 could be effected by treatment of the diamide 67 with the AlH₃-Me₂NEt complex followed by quenching with sodium cyanoborohydride, methanol, and acetic acid, as used in the synthesis of paraherquamide B. However, use of excess diisobutylaluminum hydride (DIBAL-H) in dichloromethane was a simpler experimental procedure and gave improved yields of 68.38 N-Methylation of the secondary amide proceeded smoothly and was followed by cleavage of the MOM ether with bromocatecholborane.³⁹ Oxidation of the secondary alcohol with Dess-Martin periodinane40 and concomitant removal of the N-t-BOC group and TBS ether with TFA gave ketone 70 (Scheme 8).

The final critical oxidative spirocyclization of the 2,3disubstituted indole was effected by a two-step procedure.

- (38) Fukuyama, T.; Liu, G. Pure Appl. Chem. 1997, 69, 501-505.
- (39) Boeckman, R. K., Jr.; Potenza, J. C. Tetrahedron Lett. 1985, 26, 1411–1414.
 (40) (a) Dess D B: Martin J C J Org. Chem 1983 48 4155-4156 (b)
- (40) (a) Dess, D. B.; Martin, J. C. J. Org. Chem. 1983, 48, 4155–4156. (b) Dess, D. B.; Martin, J. C. J. Am. Chem. Soc. 1991, 113, 7277–7287.

⁽³⁷⁾ Trost, B. M.; Fortunak, J. M. D. Organometallics 1982, 1, 7-13.



Scheme 9. Spirocyclization and Completion of the Synthesis



Treatment of **70** with *tert*-butyl hypochlorite in pyridine provided a labile 3-chloroindolenine, from which it was found necessary to rigorously remove, by azeotroping with benzene, all of the pyridine prior to the next step. Pinacol-type rearrangement with TsOH in aqueous THF then generated the desired *spiro*-oxindole (**73**). From our investigations during the paraherquamide B synthesis, it was found that use of a sterically demanding amine such as pyridine gives the best stereoselectivity during the chlorination reaction. It is assumed that addition of chlorine to **70** proceeds from the least hindered face of the indole giving the α -chloroindolenine **71**. Hydration of the imine functionality, interestingly, must also occur from the same α -face, that is, *syn*-to the relatively large chlorine atom, to furnish the *syn*-chlorohydrin **72** which subsequently rearranges stereospecifically to the desired *spiro*-oxindole **73** (Scheme 9).

Dehydration of the seven-membered ring in **73** with methyl triphenoxyphosphonium iodide (MTPI) in DMPU afforded 14-oxoparaherquamide B (**14**) in moderate yield.¹⁷ This intermediate has been previously obtained semisynthetically from marcfortine A by a group from Pharmacia–Upjohn, and comparison of the authentic and synthetic materials confirmed the identity of this substance. Addition of methylmagnesium bromide to the ketone group of **14** has been previously described to give paraherquamide A along with the corresponding C-14 epimer in around 50% yield.^{17a} Employment of this protocol using

MeMgBr with our synthetic ketone gave (–)-paraherquamide A (1) as the exclusive product (the C-14 epimer was not detected) in 42% yield. This product was identical to a natural sample of paraherquamide A by ¹H NMR, ¹³C NMR, IR, exact mass, and mobility on TLC (R_j). A synthetic sample was recrystallized from ether and had mp 250 °C (dec), $[\alpha]_D^{25} = -22 (c = 0.2, MeOH)$. Natural paraherquamide A recrystallized from ether under the same conditions yielded a sample with mp 250 °C (dec) and $[\alpha]_D^{25} = -21 (c = 0.2, MeOH)$. All intermediates up to the final product have an enantiomeric ratio of approximately 97.5:2.5; the final synthetic paraherquamide A upon recrystallization from ether is approximately optically pure.

We have reported here the first total synthesis of paraherquamide A, the most biologically potent member of this family of compounds. This asymmetric synthesis proceeds in 46 steps from commercially available materials, with the longest linear sequence being 34 steps.

The approach developed in this study makes it feasible to examine the design and synthesis of other members of the paraherquamide family and should also permit access to structurally unique paraherquamides that may have significant biological properties. The application of this methodology to the asymmetric, stereocontrolled total synthesis of other members of the paraherquamide family, and evaluation of their properties is currently under study in these laboratories.

Acknowledgment. This work was supported by the NIH (Grant CA 70375). The Japanese Society for the Promotion of Science (JSPS) is acknowledged for providing fellowship support to H.T. Mass spectra were obtained on instruments supported by the NIH Shared Instrumentation Grant GM49631. We also wish to thank Dr. Timothy Blizzard of Merck & Co. for providing an authentic sample of natural paraherquamide A. We also wish to acknowledge Dr. Byung H. Lee of the Pharmacia–Upjohn Co. (now Pfizer) for providing NMR spectra and an authentic specimen of 14-oxoparaherquamide B. We also wish to thank Dr. Alfredo Vazquez for assistance with purification and characterization of synthetic paraherquamide A.

Supporting Information Available: Complete experimental procedures and spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JA036713+