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Asymmetric, Stereocontrolled Total Synthesis of Paraherquamide A**

Robert M. Williams,* Jeffrey Cao, and Hidekazu Tsujishima

The paraherquamides (**1**, **2**, **5**, **6**),[1–4] marcfortines (**3**, **4**),[5] brevianamides,[6] VM55599 (**9**),[3b] and, most recently, the sclerotamides (**10**)[7] and aspergimides (**8**)[8] are indolic secondary metabolites isolated from various fungi (Scheme 1). The parent and most potent member, paraher-

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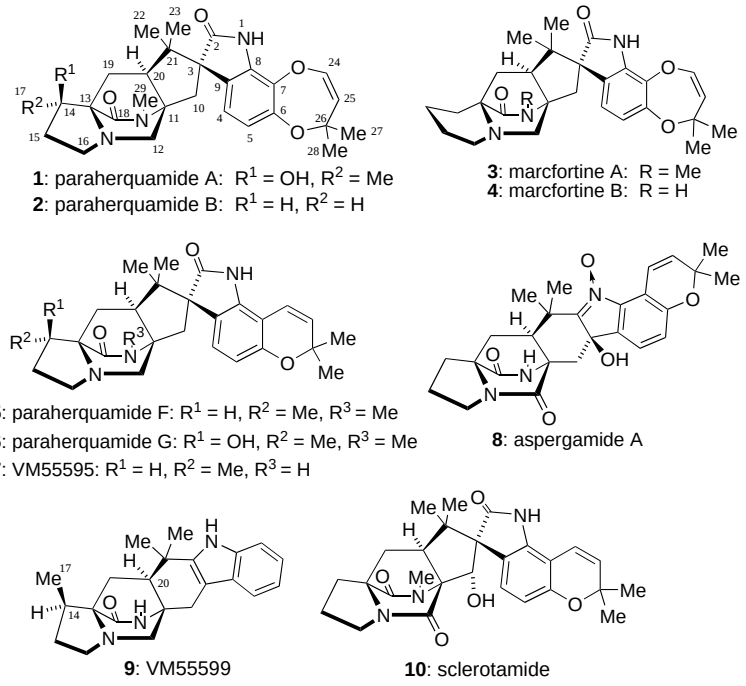

Scheme 1. Structures of the paraherquamides and related metabolites.

quamide A (**1**) was isolated from cultures of *Penicillium paraherquei*, first described by Yamazaki in 1981.[1] The simplest member, paraherquamide B (**2**), plus five other structurally related paraherquamides C–G were isolated from *Penicillium charlesii* (*fellutanum*) (ATCC 20841) in 1990 at Merck & Co.[2] and concomitantly at SmithKline Beecham.[3] Subsequently, three additional related compounds, VM55596, VM55597, and VM55599 (**9**) were discovered by the same group at SmithKline Beecham from *Penicillium* strain IMI 332995.[4] More recently, a Pfizer group[5] reported the isolation of anthelmintic metabolites VM54159, SB203105, and SB200437 along with the non-tryptophan derived metabolites, that possessing the common bicyclo[2.2.2] nucleus, aspergillimide[4] (which is identical to asperparaline A[9]) and 16-keto-aspergillimide from *Aspergillus* strain IMI 337664. This report, and a recent paper by Whyte and Gloer,[7] that described the isolation of sclerotamide (**10**) from *Aspergillus sclerotiorum*, constitute the first examples of paraherquamide derivatives isolated outside of the *Penicillia*. In addition, Zeeck et al. have isolated the interesting paraherquamide-type metabolites aspergamides A (**8**) and B.[8]

These substances have attracted considerable attention due to their molecular complexity, intriguing biogenesis,[10, 11] and some members, most notably paraherquamide A, display potent antiparasitic activity and antinematodal properties.[12] Due to the development of drug resistance by the helminths, the commonly employed broad spectrum antihelmintic agents—such as the benzimidazoles, the levamisoles/morantel, and the avermectins—are beginning to lose efficacy and there has arisen an urgent need for discovering new classes of antiparasitic agents. The paraherquamides represent an entirely new structural class of antiparasitic agents that promise to play a significant role in the near future and the derivatives of paraherquamide A hold potential as drugs for the treatment of intestinal parasites in animals.[13] The relatively low culture yields of paraherquamide A obtained for biological study have slowed the development of these agents. Recently, Lee and Clothier reported the interesting semisynthetic conversion of marcfortine A, a metabolite more readily available by fermentation, into paraherquamide A via paraherquamide B.[13] To date, a total synthesis of paraherquamide A has not been reported in the literature.

We have previously described an asymmetric synthesis of the simplest paraherquamide derivative, paraherquamide B (**2**), from (*S*)-proline.[14] In approaching the synthesis of paraherquamide A, which contains the unusual β-hydroxy-β-methyl proline residue, a new method needed to be developed to generate a suitably functionalized α-alkylated-β-hydroxyproline moiety that could be conscripted for the multistep construction of paraherquamide A. Despite the apparent similarity in the structures of paraherquamide A and B, the synthesis of the former turned out to be a significantly more challenging endeavor. We recently described a potentially general method to construct α-alkylated-β-hydroxyproline residues by the dianion alkylation of the readily available *N*-Boc-β-hydroxyproline ethyl ester derivative **12** with net retention of stereochemistry (Boc = *tert*-butylcarbonyl).[15] We have successfully applied this methodology to a concise asymmetric and stereocontrolled synthesis of paraherquamide A in 27 steps from the racemic β-keto ester **11**, as shown in Scheme 2.

As described previously,[16] β-ketoester **11** was subjected to Baker's yeast reduction to afford the optically active β-hydroxyester **12** (60–80%, *er* ~ 95:5). Dianion alkylation of **12** with (*E*)-3-methyl-4-(*O*-*tert*-butyldimethylsilyl)-2-butene afforded the desired α-alkylated product **13** in 58–70% isolated yield without attendant *O*-alkylation.[15] Protection of the secondary alcohol as the corresponding methoxy methyl (MOM) ether, followed by removal of the Boc group with $ZnBr_2$ in dichloromethane and acylation of the incipient secondary amine with bromoacetyl bromide in the presence of potassium carbonate afforded the bromoacetamide **14** in 86% overall yield from **13**. Treatment of **14** with methanolic ammonia afforded the corresponding glycinamide which was directly subjected to cyclization in the presence of sodium hydride in toluene/HMPA to afford the bicyclic substance **15** in 79% overall yield from **14**. Next, a one-pot double carbomethoxylation reaction was performed by the sequential addition of *n*BuLi in THF followed by addition of methylchloroformate, that carbomethoxylated the amide nitrogen atom. Subsequent addition of four equivalents of methylchloroformate followed by the addition of five equivalents of $LiN(TMS)_2$ afforded **16** as a mixture of diastereomers in 93% yield that were taken on directly without separation.

Somei–Kametani coupling[17] of **16** with the gramine derivative **17**[18] in the presence of tri(*n*-butyl)phosphine gave the tryptophan derivative **18** as a 3:1 mixture of diastereomers (epimeric at the newly created stereogenic center) in 70%

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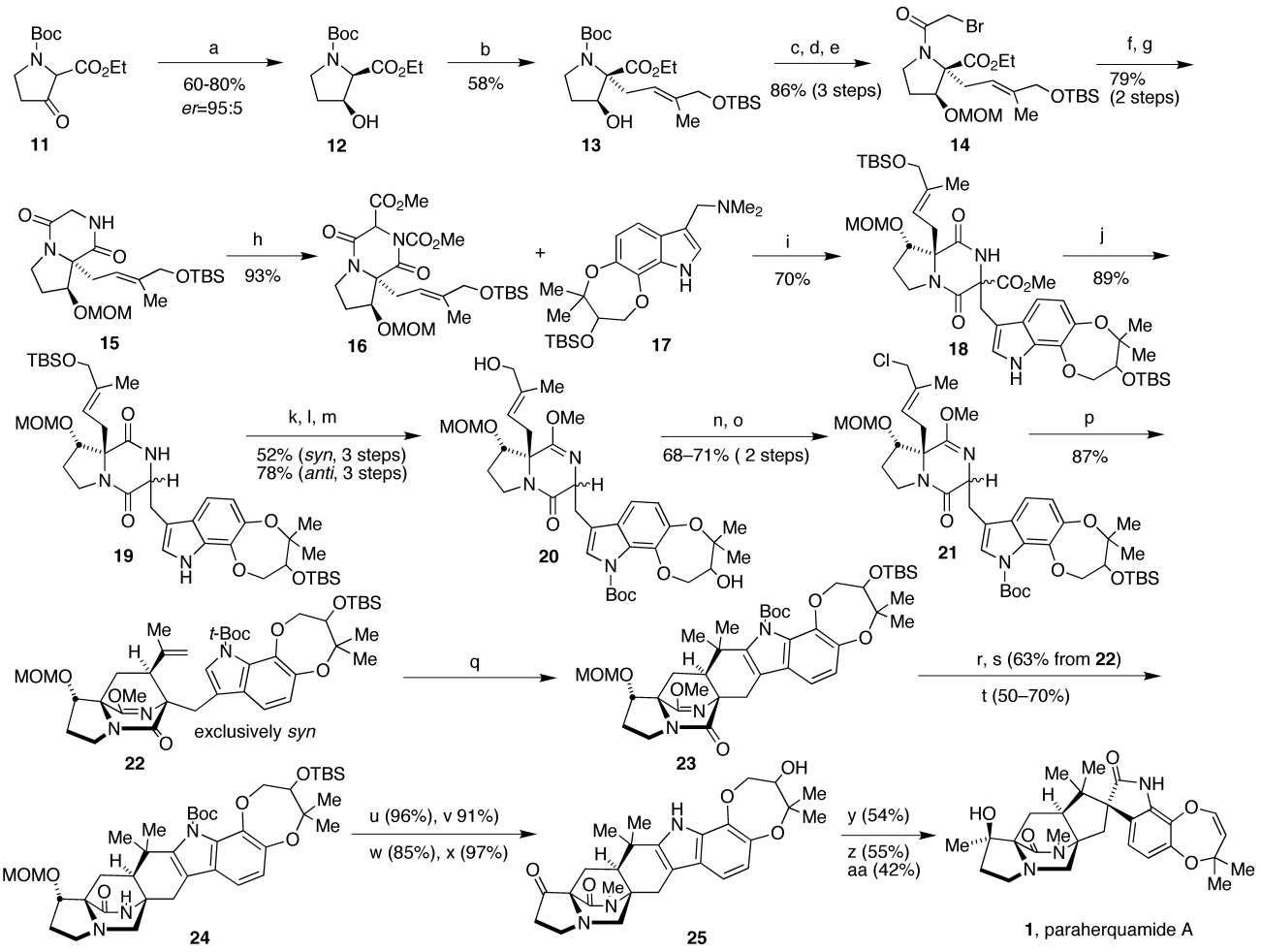

Scheme 2. Synthesis of paraherquamide A. a) Baker's yeast; b) $Li(NiPr)_2$, THF, HMPA, (*E*)-$ICH_2CH{=}C(Me)CH_2OTBS$; c) 5.7 equiv MOMCl, $(iPr)_2NEt$, CH_2Cl_2; d) 2.7 equiv $ZnBr_2$, CH_2Cl_2; e) K_2CO_3, 2 equiv $BrCH_2COBr$, CH_2Cl_2, 0 °C; f) NH_3 in MeOH (5.7 M solution), 25 °C; g) 3 equiv NaH, toluene, HMPA, 25 °C; h) 1.3 equiv *n*BuLi, THF, 1.1 equiv $ClCO_2Me$, −78 °C; then 4 equiv $ClCO_2Me$, 5 equiv $LiN(TMS)_2$, −78 °C; i) 0.7 equiv $(nBu)_3P$, MeCN; j) 5 equiv LiCl, H_2O, HMPA, 105 °C, 5 h; k) 2.5 equiv Me_3OBF_4, CH_2Cl_2, Cs_2CO_3, 25 °C; l) DMAP, 3 equiv $(Boc)_2O$, CH_2Cl_2, 0 °C; m) 3.3 equiv TBAF, THF, 25 °C; n) 1.1 equiv MsCl, collidine, CH_2Cl_2, 0 °C; o) 2 equiv TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; p) 20 equiv NaH, THF, reflux, 30 h; q) 3.1 equiv $AgBF_4$, 4.68 equiv $PdCl_2$, MeCN, propylene oxide; then $NaBH_4$, EtOH; r) 0.1 M HCl, THF; s) 2-hydroxypyridine, toluene, 120 °C, 2 h; t) 5 equiv $(iBu)_2AlH$, CH_2Cl_2, 0 °C; u) NaH, MeI, DMF, 0 °C; v) 6 equiv *B*-bromocatechol borane, CH_2Cl_2, 0 °C; w) 5 equiv Dess–Martin periodinane, CH_2Cl_2, 25 °C; x) TFA, CH_2Cl_2, 25 °C; y) 1.5 equiv *t*BuOCl, py; then 5 equiv *p*-TsOH, THF, H_2O, reflux; z) 5 equiv $(PhO)_3PMeI$, DMPU; aa) MeMgBr, THF. Abbreviations: HMPA = hexamethylphosphoramide; TBS = *tert*-butyldimethylsilyl; MOMCl = chloromethyl methyl ether; TMS = trimethylsilane; DMAP = 4-(dimethylamino)pyridine; $(Boc)_2O$ = dicarbonic acid bis(*tert*-butyl) ester; TBAF = tetrabutylammonium fluoride; MsCl = methanesulfonyl chloride; TBSOTf = *tert*-butyldimethylsilyl trifluoromethanesulfonate; Dess–Martin periodinane = 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one; TFA = trifluoroacetic acid; *t*BuOCl = *tert*-butyl hypochlorite; py = pyridine; *p*-TsOH = *para*-toluenesulfonic acid; DMPU = *N*,*N*′-dimethylpropyleneurea.

yield. Decarbomethoxylation of **18** was effected by treatment of **18** with LiCl in hot, aqueous HMPA at 105 °C providing **19** as a mixture of diastereomers that were separated and carried forward individually. Protection of the secondary amide group as the corresponding methyl lactim ether was accomplished by treating **19** with trimethyloxonium tetrafluoroborate in dichloromethane that contained cesium carbonate. Next, the indole nitrogen atom was protected as the corresponding Boc derivative by treatment with dicarbonic acid bis(*tert*-butyl) ester in the presence of DMAP and the silyl ether was removed with tetrabutylammonium fluoride to provide diol **20** in 52–78% overall yield from **19**. Selective conversion of the allylic alcohol to the corresponding allylic chloride was accomplished by mesylation in the presence of collidine. Silylation of the secondary alcohol with *tert*-butyldimethylsilyl triflate in the presence of 2,6-lutidine afforded the key allylic chloride **21** in 68–71% yield over the two steps.

The stage was now set for the critical intramolecular S_N2' cyclization that sets the relative stereochemistry at C-20 during formation of the bicyclo[2.2.2]octane ring nucleus. Based on a solid precedent from the paraherquamide B synthesis,[14] it was found that treatment of **21** with NaH in refluxing THF afforded the desired S_N2' cyclization product **22** in 87% exclusively as the desired *syn*-isomer.[19] This remarkably *syn*-selective intramolecular S_N2' cyclization reaction proceeds through a tight, intramolecular, ion-pair driven cyclization ("closed" transition state),[20] as shown in Scheme 3. Closure of the seventh ring was effected by treatment of **22** with 4.68 equivalents of $PdCl_2$ and 3.1 equivalents of $AgBF_4$[21] in acetonitrile containing propylene oxide

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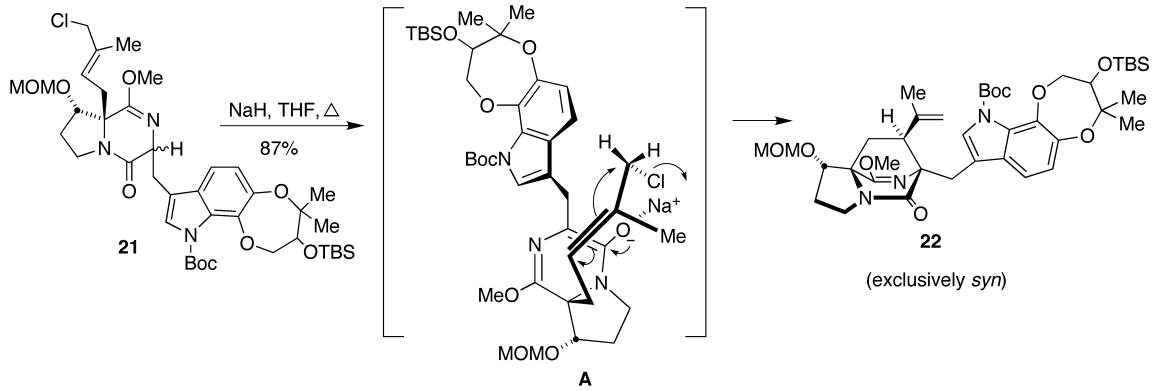


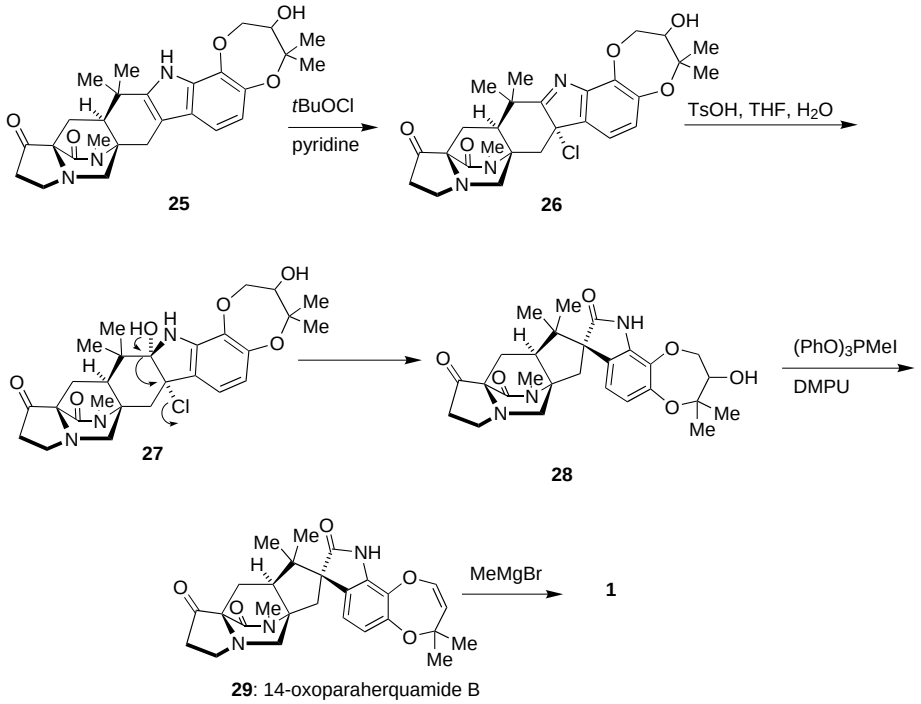
Scheme 3. Diastereoselective, intramolecular S_N2' cyclization.

as an acid scavenger. It was found that without propylene oxide to buffer this reaction, the MOM ether suffered extensive cleavage. The incipient heptacyclic σ-palladium adduct was worked up immediately by the addition of ethanol and sodium borohydride to afford the desired 2,3-disubstituted indole **23**.

Cleavage of the lactim ether of **23** was effected with 0.1M HCl to give the corresponding ring-opened amine methyl ester that was recyclized by treatment of this material with 2-hydroxypyridine in hot toluene (63% overall from **22**). Chemoselective reduction of the secondary amide in the presence of the tertiary amide was effected by treatment of the product obtained in the previous step with excess diisobutylaluminum hydride in dichloromethane (50–72%) to furnish **24**.[22] Methylation of the secondary amide of **24** proceeded in 96% yield. Cleavage of the MOM ether with bromocatecholborane[23] (91% yield) followed by oxidation of the secondary alcohol with Dess–Martin periodinane[24] (85% yield) and cleavage of the Boc group and TBS ether with TFA (97% yield) gave ketone **25**.

The final, critical oxidative spirocyclization of the 2,3-disubstituted indole to the *spiro* oxindole was effected by treatment of **25** with *tert*-butyl hypochlorite in pyridine, which provided a labile 3-chloroindolenine. It was necessary to rigorously remove all of the pyridine solvent prior to the Pinacol-type rearrangement, that was conducted by treating the incipient 3-chloroindolenine with *para*-toluenesulfonic acid in THF/H_2O. It is assumed that the chlorination of **25** proceeds from the least hindered face of the indole, to give the α-chloroindolenine **26**. The hydration of the imine functionality must, interestingly, also occur from the same α-face that is *syn* to the relatively large chlorine atom furnishing the *syn*-chlorohydrin **27**, that subsequently rearranges stereospecifically to the desired *spiro* oxindole **28** (Scheme 4).

The dioxepin ring was then formed by dehydration of the secondary alcohol of **28** with methyl triphenoxyphosphonium iodide (MTPI) in DMPU to afford 14-oxoparaherquamide B **29**, (55%).[13] This intermediate has been previously described by a Pharmacia–Upjohn group (obtained semi-synthetically from marcfortine A) and comparison of the authentic and synthetic materials (^1H and ^{13}C NMR, IR, exact mass, mobility on thin-layer chromatography (TLC)) confirmed the identity of this substance. The final step, a methyl Grignard addition to the ketone group of **29** has been previously described to give paraherquamide A along with a trace of the corresponding C-14 epimer in ~50% yield when MeMgBr was employed.[13a] 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 that was identical in all respects (^1H and ^{13}C NMR,



Scheme 4. Formation of the *spiro* oxindole.

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IR, exact mass, mobility on TLC, m.p. (250 °C (decomp.)), $[\alpha]_D^{25} = -22$ ($c = 0.2$ MeOH)) to natural paraherquamide A.[25]

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, which may have significant biological properties. The application of this methodology to the asymmetric, stereocontrolled, total synthesis of other members of the paraherquamide family and the evaluation of their properties is currently under study in these laboratories.

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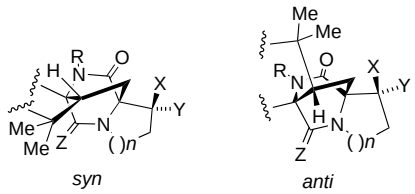

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[25] The synthetic sample was recrystallized from ether. A sample of natural paraherquamide A recrystallized from ether under the same conditions rendered a sample with a m.p. = 250 °C (decomp.) and $[\alpha]_D^{25} = -21$ ($c = 0.2$ in MeOH), lit. [1] $[\alpha] = -28$ ($c = 0.43$ in MeOH). All intermediates up to the final product have an ~97.5:2.5 *er*; the final synthetic paraherquamide A upon recrystallization from ether is optically pure.

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