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Concise, biomimetic total synthesis of *d,l*-marcfortine C

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We wish to dedicate this paper to Professor Victor Snieckus on the occasion of his 70th birthday

Abstract—A biomimetic total synthesis of the fungal metabolite marcfortine C utilizing an intramolecular Diels–Alder reaction is described. In addition, a key stereoselective oxaziridine-mediated oxidation/pinacol rearrangement of indole **24** was used to complete the total synthesis.

1. Introduction

Fungi produce an exhausting abundance of biologically active natural products possessing complex and diverse ring systems. Prenylated indole alkaloids such as the paraherquamides,[1] brevianamides,[2] stephacidins,[3] and notoamides[4] are fungal metabolites whose synthesis and biogenetic origin have been extensively investigated, in our laboratory and that of others.[5] These fungal metabolites are all believed to arise biogenetically from tryptophan, isoprene, and proline and derivatives of proline.[5] Significantly, a myriad of biological activities are displayed within this family including insecticidal, anti-tumor, anthelminthic, and anti-bacterial, among others. Another sub-class in this family of prenylated indole alkaloids, the marcfortines (**1**–**3**) (Fig. 1), were isolated from *Penicillium roqueforti* in 1980 by Polonsky and co-workers.[6] These metabolites are uniquely derived from pipecolic acid rather than a proline derivative. Like many of the paraherquamides, the marcfortines, as well as several of their derivatives, have proven to possess potent anti-parasitic and anthelminthic activity.[7]

Common structural features of these compounds include a sensitive indolopyran or dioxepin ring system and a tryptophan/proline-derived (or, in the case of the marcfortines, pipecolic acid) bicyclo[2.2.2]diazaoctane embedded in their core. Due to their inherent biological activity and structurally diverse ring systems, this family of prenylated indole alkaloids has become the subject of intense synthetic endeavors. Recent work in this family includes the total synthesis of avrainvillamide and stephacidin B by Myers,[8] and more recently stephacidin A (**4**) enroute to avrainvillamide and stephacidin B by Baran and co-workers.[9] Our laboratory has extensively studied both the synthesis and biosynthesis of prenylated indole alkaloids of this family,[5] and has recently reported the biomimetic total syntheses of

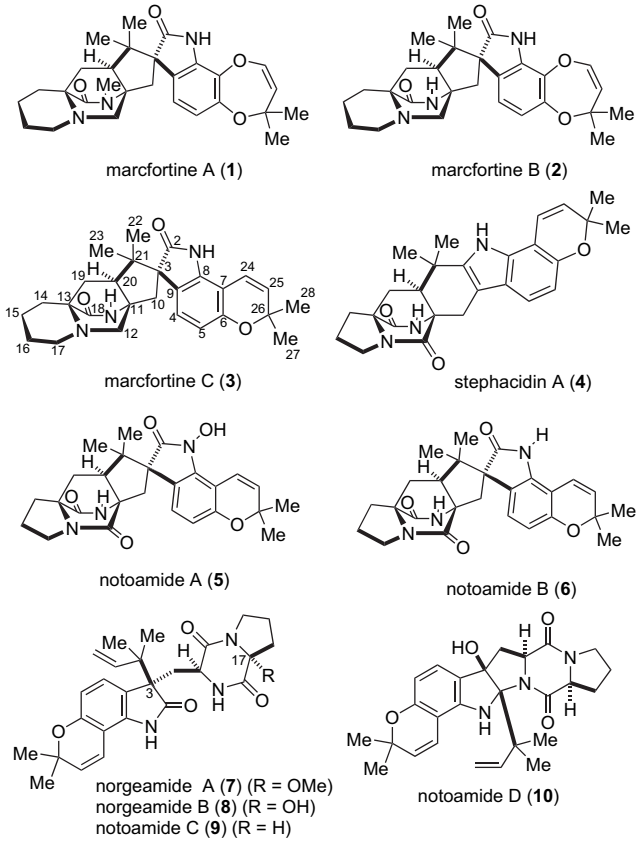

Figure 1. Structures of the marcfortines and various prenylated indole alkaloids.

Keywords: Marcfortine; Diels–Alder; Indole; Natural product; Azadiene.
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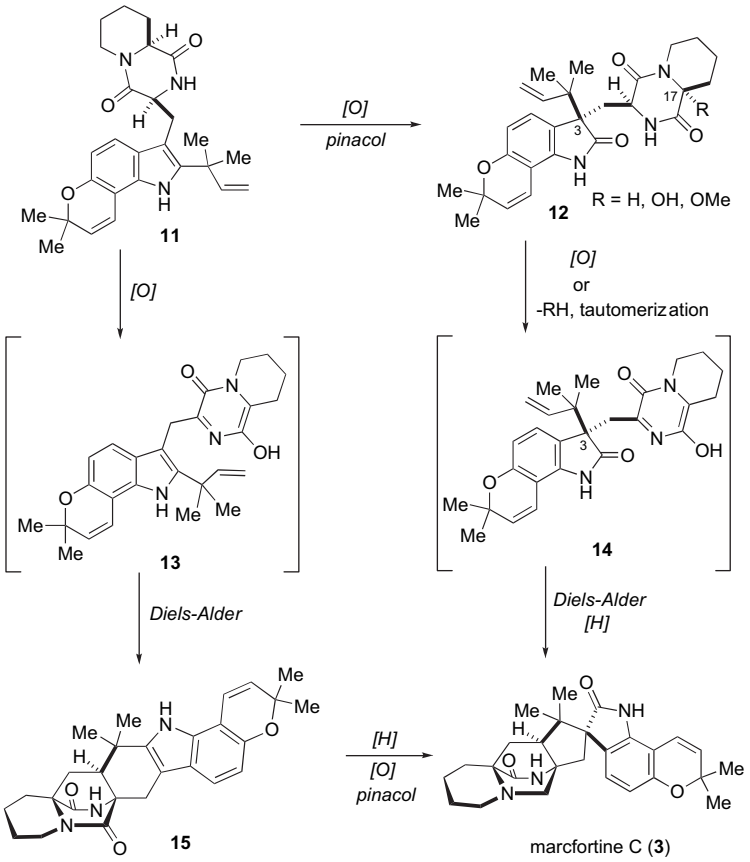
notoamides B (**6**), C (**9**), and D (**10**), as well as stephacidin A (**4**) (Fig. 1).[10] We now wish to report the application of a general biomimetic strategy to the first concise total synthesis of marcfortine C (**3**).

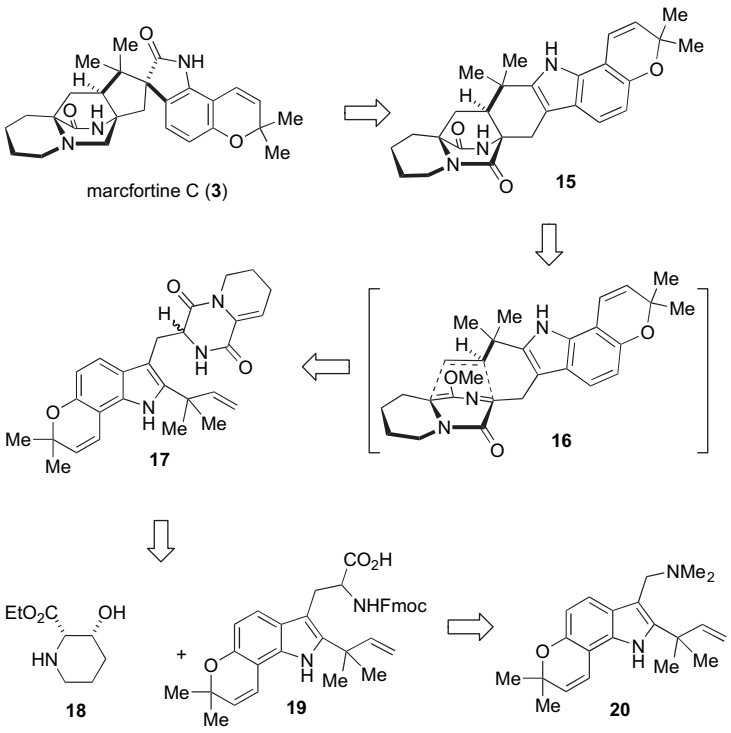
Previous disclosures from our laboratory[5] as well as those of Birch[11] and Sammes[12] have suggested that the core bicyclo[2.2.2]diazaoctane ring system that is characteristic of this family of alkaloids likely arises in Nature via a biosynthetic intramolecular Diels–Alder construction. While [4+2] cycloaddition reactions are perhaps the most powerful tool for rapid construction of highly functionalized six-membered rings in synthetic chemistry, there are relatively few examples of natural products that have been rigorously proven to arise via a biological Diels–Alder reaction, despite a multitude of proposed biogeneses. We have recently proposed some interesting biogenetic relationships between the stephacidins and notoamides[10] in which an intramolecular [4+2] hetero-Diels–Alder cycloaddition is the key transformation in linking natural products such as notoamide C (**9**) and norgeamides A (**7**) and B (**8**) to the core bicyclo-[2.2.2]diazaoctane ring system embodied in notoamides A (**5**) and B (**6**) as well as stephacidin A (**4**) and furthermore avrainvillamide and stephacidin B.

We have also contemplated a parallel biosynthetic relationship enroute to the fungal metabolite marcfortine C (**3**); two plausible biosynthetic pathways to marcfortine C (**3**) are outlined in Scheme 1. Thus, a [4+2] cycloaddition reaction of compound **11**-derived azadiene **13** with the reverse prenyl group serving as the dienophile, would directly establish the bicyclo[2.2.2]diazaoctane core. Following a selective reduction of the tertiary amide of the diketopiperazine, a subsequent oxidative ring contraction to the spiro-oxindole would give rise to marcfortine C (**3**). Alternatively, initial oxidation and rearrangement of indole **11** would produce the pipecolic acid-derived spiro-oxindole **12**, analogous to the natural proline-derived congener notoamide C (**12**, R=H) or norgeamides A (**12**, R=OMe) and B (**12**, R=OH). Following an oxidation of (R=H) or an elimination/tautomerization (R=OMe, OH) of spiro-oxindole **12**, the resulting azadiene **14** could then be trapped by the proximal isoprenyl group to directly afford marcfortine C (**3**), following reduction of the tertiary amide. We currently prefer the former pathway proceeding through **13** as the spiro-6 IMDA reaction in such systems has intrinsic facial bias favoring the natural *syn*-relative stereochemistry at C-20 although both pathways merit complete experimental evaluation.[5]

Based on our recent successful deployment of a biomimetic Diels–Alder cycloaddition reaction in the total synthesis of stephacidin A enroute to the first biomimetic total synthesis of notoamide B,[10b] we were compelled that a similar strategy could be employed to complete the first total synthesis of the prenylated indole alkaloid marcfortine C. Retrosynthetically, it was envisaged that marcfortine C (**3**) could arise from compound **15** (Scheme 2) via a chemoselective reduction of the tertiary amide over the secondary amide of the diketopiperazine, followed by a well precedented[10]



Scheme 1. Postulated biosyntheses of marcfortine C.



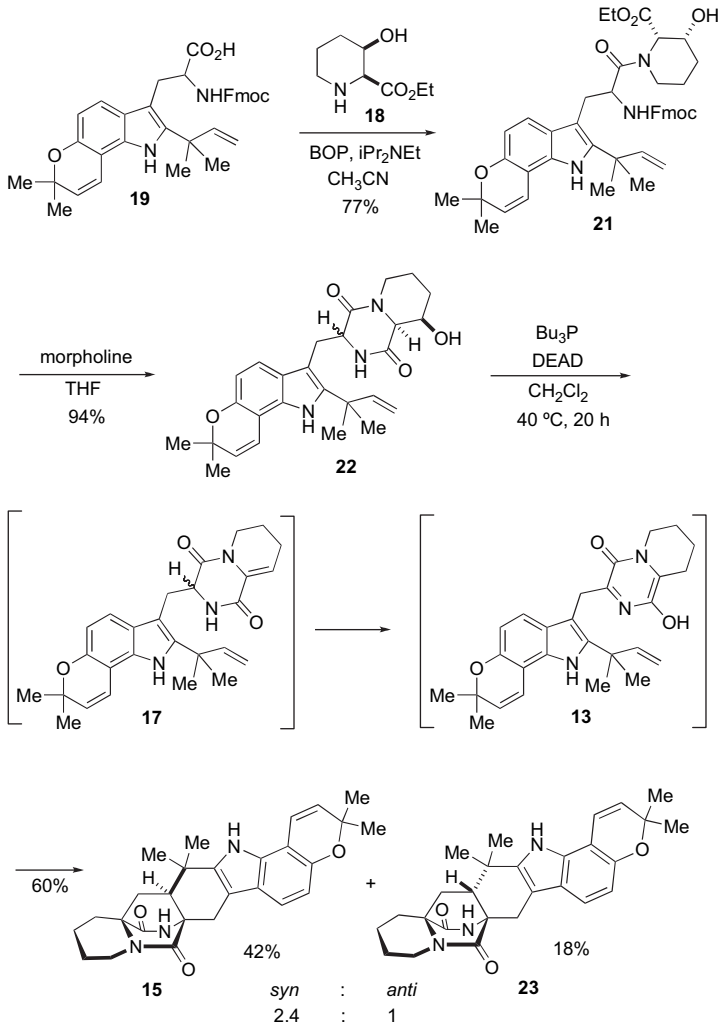
Scheme 2. Biomimetic retrosynthesis of marcfortine C.

stereoselective oxidative ring contraction of the 2,3-disubstituted indole. A biomimetic intramolecular Diels–Alder reaction of the azadiene **16** with the isoprene residue should proceed preferentially to produce the desired *syn*-relative stereochemistry at the C11–C20 ring fusion required to access marcfortine C (**3**). In addition to the stephacidin A/notoamide B synthesis, our laboratory has previously reported related biomimetic Diels–Alder cyclizations,[5a,13] which culminated in the total synthesis of the fungal metabolites VM55599[13b] and brevianamide B.[13c] Based on our experiences with similar substrates, it seemed unlikely that azadiene **13** would be stable, and therefore a functional equivalent (**16**) would be generated from enamide **17** via lactim ether formation, followed by a base-induced tautomerization. Herein, we detail implementation of this strategy to the biomimetic total synthesis of marcfortine C, which has not hitherto succumbed to total synthesis.

2. Results and discussion

Our plan mandated the construction of the key enamide **17**, which should be available through coupling of tryptophan derivative **19** with *cis*-3-hydroxypipecolic acid ethyl ester (**18**), followed by Fmoc removal, concomitant diketopiperazine formation, and dehydration. Tryptophan derivative **19** is readily available from the corresponding gramine **20** and has been recently synthesized in our group on gram-scale.[10a,14]

Our synthesis commenced with a coupling of *cis*-3-hydroxypipecolic acid ethyl ester (**18**)[15] and *d,l*-acid **19** in the presence of BOP and *i*-Pr_2NEt to afford amide **21** (Scheme 3) as an inseparable mixture of diastereomers in 77% yield. Subjecting peptide **21** to a solution of morpholine in THF at room temperature effected removal of the *N*-Fmoc group and a concomitant cyclization of the resultant amine onto the ethyl ester to provide diketopiperazine **22**, once again produced as an inseparable and inconsequential mixture of diastereomers. As previously described in our stephacidin A synthesis,[10b] we had planned to eliminate the alcohol of compound **22** under Mitsunobu conditions to afford enamide **17** (Scheme 3). Following lactim ether formation and a KOH-induced tautomerization, azadiene **16** (see Scheme 2) would then undergo the desired cycloaddition reaction to construct the desired bicyclo[2.2.2]diazaoctane core. However, upon subjection of alcohol **22** to our standard elimination conditions (PBu_3, DEAD, CH_2Cl_2, room temperature), only a small amount of enamide **17** (~15%) was obtained, along with large amounts of recovered starting material. In an effort to thermally force the Mitsunobu reaction to completion, we were surprisingly pleased to find that heating alcohol **22** with excess PBu_3 and DEAD to 40 °C for 20 h, not only effected the anticipated dehydration, but the incipient enamide **17** spontaneously underwent enolization and tautomerization directly furnishing the desired intramolecular [4+2] aza-Diels–Alder reaction that smoothly provided cycloadducts **15** and **23** as a 2.4:1 mixture of diastereomers favoring the desired *syn*-stereoisomer. This amazing one-pot transformation must produce azadiene **13** in situ, which then undergoes the subsequent cycloaddition reaction to produce cycloadducts **15** and **23**. We currently have no experimental data with which to speculate about the possible roles the tributylphosphine, DEAD, or the diethyl 1,2-hydrazinedicarboxylate by-product may have in this fortuitous sequence. It was found, however, that re-subjecting enamide **17** (isolated from a room temperature Mitsunobu reaction) to the same reaction conditions (PBu_3, DEAD, CH_2Cl_2) at 40 °C did produce varying amounts of cycloadducts **15** and **23** albeit in diminished yields (25–45%). To our knowledge, this is the very first example of

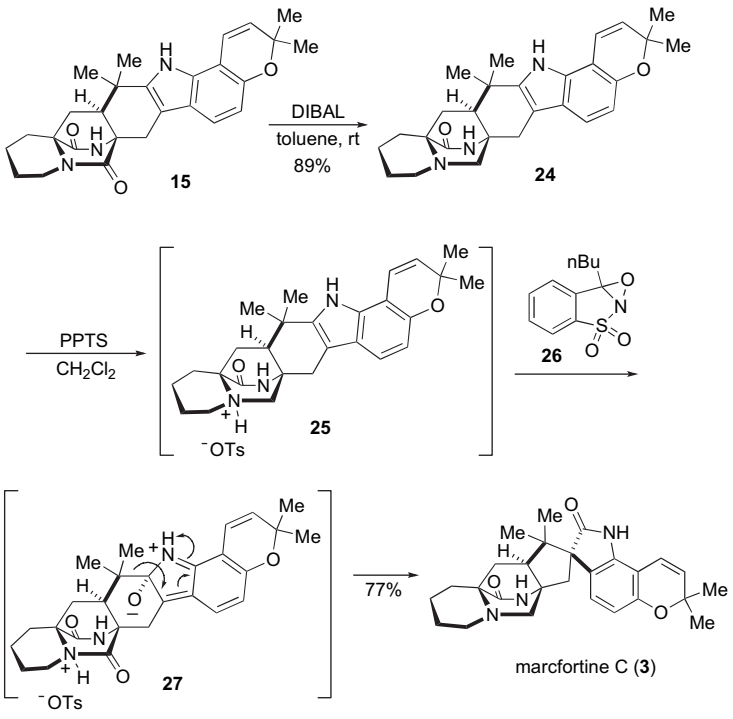


Scheme 3. Construction of the marcfortine C ring system via an intramolecular Diels–Alder cycloaddition.

such a cycloaddition reaction wherein the putative azadiene species (**13**) is generated with a free hydroxyl residue. The facility with which putative azadiene species **13** was generated under these conditions was striking and provides provocative support for the possible intermediacy of such a species in the biological construction of this ring system within this family of secondary metabolites.

The tentative stereochemical assignment for *syn*-cycloadduct **15** was confirmed by its transformation to racemic marcfortine C (**3**). Thus, selective reduction of the tertiary amide over the secondary amide was accomplished by treatment of **15** with excess DIBAL-H (20 equiv) to provide amine **24** in 89% yield (Scheme 4). We have previously been successful in effecting the desired oxidation/pinacol rearrangement in the total synthesis of notoamide B (**6**)[10b] by employing oxaziridine **26**.[16] In the case at hand, however, **24** contains a tertiary amine that can be easily oxidized by the oxaziridine, an incompatibility issue borne out experimentally in this specific case. To circumvent this inherent problem, we surveyed a variety of acids that would be acidic enough to protonate the tertiary amine and render it unreactive toward oxidizing agents, but still be compatible with the sensitive oxaziridine reagent. We were pleased to find that pyridinium *para*-toluene sulfonate (PPTS) met both criteria. Thus, treatment of amine **24** with 1.25 equiv of PPTS for 15 min at room temperature allowed for protonation to the amine salt **25**, which was then treated with excess oxaziridine **26** in CH_2Cl_2 to effect the desired stereoselective oxidation and pinacol rearrangement to produce marcfortine C (**3**) as a single diastereomer in 77% yield. The stereochemical result can be rationalized by epoxidation of the 2,3-disubstituted indole from the less hindered α-face, followed by ring opening of the incipient epoxide to the 2-alkoxyindole intermediate **27**. A subsequent α-face ring contraction by a [1,5]-sigmatropic shift successfully furnishes **3** as a single diastereomer.

The ^1H and ^{13}C NMR spectral properties of the synthetic material were identical to those published by Polonsky and co-workers.[6b] In addition, the synthetic material was identical by mobility on TLC and ^1H NMR to an authentic specimen kindly provided by Prof. David Miller of Carleton University, Canada. Once again, the deployment of oxaziridine **26** for the one-step conversion of a 2,3-disubstituted indole to the corresponding spiro-oxindole has proven to be a highly useful transformation that provides a mild alternative to the standard methods that have been utilized over the years for effecting such a transformation.[17,18]



Scheme 4. Conversion of **15** to marcfortine C.

3. Conclusion

In conclusion, we have completed a concise biomimetic total synthesis of marcfortine C (**3**) via an intramolecular azadiene Diels–Alder reaction in 15 steps and 3.7% overall yield from commercially available 6-hydroxyindole and constitutes the first total synthesis of this alkaloid.[19] This work underscores the low activation barriers inherent in this specific class of azadiene IMDA reactions that have been strongly implicated in the construction of the bicyclo-[2.2.2]diazaoctane core ring system common to the paraherquamide/stephacidin/marcfortine family of prenylated indole alkaloids. Significantly, enamide species such as **17**, provide a provocative new venue for generating the hitherto elusive azadiene species **13**, which have been strongly implicated as biosynthetic intermediates. Further studies to experimentally corroborate the biosynthesis of this family of fungal metabolites are under investigation and will be reported in due course.

4. Experimental

4.1. General methods

Unless otherwise noted, all materials were obtained from commercial sources and used without purification. All reactions requiring anhydrous conditions were performed under a positive pressure of argon using flame-dried glassware. Dichloromethane, acetonitrile, and tetrahydrofuran were degassed with argon and dried through a solvent purification system (J.C. Meyer of Glass Contour) prior to use. Flash chromatography was performed on Merck silica gel Kieselgel 60 (230–400 mesh) from EM science with the indicated solvent. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 300 or 400 MHz spectrometer as indicated. For all NMR spectra, δ values are given in parts per million and J values are given in hertz. Infrared spectra were recorded on a Nicolet Avatar 320-FTIR spectrometer. Mass spectra were obtained at the Colorado State University CIF on a Fisons VG Autospec.

4.1.1. Amide (21). To a solution of acid **19**[10a,14] (230 mg, 0.40 mmol) in CH_3CN was added HATU (228 mg, 0.60 mmol), *i*-Pr_2NEt (209 μL, 1.20 mmol), and *cis*-3-hydroxypipecolic acid ethyl ester (**18**)[15] successively at rt. The mixture was stirred at rt for 3 h. The resulting solution was quenched with 1 M aqueous HCl and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated. Purification by silica gel chromatography (ethyl acetate–hexane, 2:3) afforded amide **21** as a mixture of diastereomers and amide rotamers (225 mg, 77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12–1.24 (m, 3H), 1.40 (s, 3H), 1.45 (s, 3H), 1.64 (s, 3H), 1.66 (s, 3H), 1.70–1.77 (m, 2H), 2.20 (m, 1H), 2.75 (m, 1H), 3.08–3.47 (m, 4H), 3.72 (m, 1H), 4.05–4.29 (m, 3H), 4.33–4.49 (m, 3H), 5.05 (m, 1H), 5.21 (d, J=10.4 Hz, 1H), 5.27 (d, J=17.4 Hz, 1H), 5.65 (d, J=9.7 Hz, 1H), 6.00 (d, J=8.1 Hz, 1H), 6.26 (dd, J=10.4, 17.4 Hz, 1H), 6.58 (d, J=9.7 Hz, 1H), 6.67 (m, 1H), 7.25–7.45 (m, 5H), 7.60–7.65 (m, 2H), 7.70–7.80 (m, 2H), 7.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 14.1, 14.2, 21.9, 22.3, 26.6, 27.4, 27.5, 27.6, 27.8, 29.3, 29.5, 29.6, 30.8, 30.9, 38.9, 39.2, 42.8, 43.1, 47.2, 50.8, 51.2, 53.9, 55.6, 59.1, 61.7, 62.0, 67.9, 68.0, 68.4, 75.6, 104.7, 105.5, 105.8, 110.7, 110.8, 112.5, 112.8, 117.0, 117.2, 118.7, 120.0, 125.0, 125.1, 125.2, 127.1, 127.8, 129.8, 130.0, 130.2, 130.3, 139.1, 139.6, 141.3, 143.82, 143.88, 143.9, 145.6, 146.4, 148.8, 155.4, 155.6, 170.4, 170.8, 172.2, 172.7; IR (neat) 3370, 2972, 1720, 1638 cm^{-1}; FAB-HRMS (MH^+) calcd for $C_{44}H_{50}N_3O_7$ 732.3649, found 732.3622.

4.1.2. Diketopiperazine (22). To a solution of amide **21** (225 mg, 0.31 mmol) in THF (12 mL) at rt was added morpholine (3 mL). The mixture was stirred at rt for 2 h. The resulting solution was concentrated to afford the crude diketopiperazine **22** as a mixture of diastereomers. The inseparable mixture of diastereomers was purified by silica gel chromatography (ethyl acetate) to afford diketopiperazines **22a** and **b** as a yellow gum (134 mg, 94%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 3H), 1.41 (s, 3H), 1.47 (s, 3H), 1.50 (s, 3H), 1.68 (m, 1H), 1.85–1.96 (m, 2H), 2.50 (m, 1H), 2.63 (m, 1H), 3.06 (**a**) (dd, J=11.4, 14.4 Hz, 1H), 3.25 (**b**) (dd, J=11.4, 14.4 Hz, 1H), 3.66 (dd, J=2.9, 14.4 Hz, 1H), 3.80 (**a**) (s, 1H), 3.85 (**b**) (s, 1H), 4.25 (m, 1H), 4.39 (m, 1H), 4.67 (m, 1H), 5.09–5.15 (m, 2H), 5.62 (**b**) (d, J=9.7 Hz, 1H), 5.63 (**a**) (d, J=9.7 Hz, 1H), 5.80 (**a**) (s, 1H), 5.90 (**b**) (s, 1H), 6.07 (**a**) (dd, J=10.4, 17.4 Hz, 1H), 6.09 (**b**) (dd, J=10.4, 17.4 Hz, 1H), 6.58 (d, J=9.7 Hz, 1H), 6.61 (d, J=8.5 Hz, 1H), 7.18 (**a**) (d, J=8.5 Hz, 1H), 7.30 (**b**) (d, J=8.5 Hz, 1H), 7.95 (**b**) (s, 1H), 8.00 (**a**) (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6 (**a**), 18.8 (**b**), 27.4, 27.5, 27.9, 28.0, 30.0 (**a**), 31.2 (**a**), 31.4 (**b**), 31.6 (**b**), 39.1 (**a**), 39.2 (**b**), 42.6 (**b**), 42.9 (**a**), 54.3 (**a**), 55.9 (**b**), 62.9 (**b**), 63.6 (**a**), 66.1 (**b**), 66.8 (**a**), 75.7, 104.7 (**b**), 104.9 (**a**), 105.2 (**a**), 105.9 (**b**), 110.7 (**a**), 110.8 (**b**), 112.2 (**a**), 112.4 (**b**), 117.0, 118.5 (**a**), 118.9 (**b**), 123.6 (**a**), 124.2 (**b**), 129.7 (**b**), 129.9 (**a**), 130.8 (**b**), 130.9 (**a**), 139.9 (**b**), 140.4 (**a**), 146.0 (**a**), 146.1 (**b**), 148.7 (**b**), 148.8 (**a**), 165.4 (**a**), 165.5 (**b**), 166.1 (**a**), 166.3 (**b**); IR (neat) 3365, 2971, 2930, 1674, 1641 cm^{-1}; FAB-HRMS (M^+) calcd for $C_{27}H_{33}N_3O_4$ 463.2471, found 463.2474.

4.1.3. Cycloadduct (15). To a solution of alcohols **22** (55 mg, 0.12 mmol) in CH_2Cl_2 (12 mL) at rt was added DEAD (112 μL, 0.71 mmol). The mixture was stirred at rt for 5 min and PBu_3 (178 μL, 0.71 mmol) was then added. The solution was heated to 40 °C for 20 h. The resulting mixture was concentrated. Purification by silica gel chromatography (ethyl acetate–hexane, 1:1) afforded cycloadducts **15** and **23** as a 2.4:1 crude mixture of diastereomers. This mixture was further separated by preparative TLC (MeOH–CH_2Cl_2, 3:97) to afford *syn*-cycloadduct **15** as a colorless oil (22.4 mg, 42%) along with *anti*-cycloadduct **23** as a colorless oil (9.4 mg, 18%); *syn*-cycloadduct **15**: ^{1}H NMR (400 MHz, $CDCl_3$–CD_3OD, 10:1) δ 1.00 (s, 3H), 1.25 (s, 3H), 1.37 (s, 6H), 1.58–1.69 (m, 5H), 1.92 (dd, J=10.3, 13.8 Hz, 1H), 2.02 (dd, J=5.0, 13.8 Hz, 1H), 2.38 (m, 1H), 2.43 (dd, J=5.0, 10.3 Hz, 1H), 2.59 (d, J=15.5 Hz, 1H), 3.30–3.37 (m, 2H), 3.64 (d, J=15.5 Hz, 1H), 5.57 (d, J=9.8 Hz, 1H), 6.54 (d, J=8.4 Hz, 1H), 6.64 (d, J=9.8 Hz, 1H), 7.15 (d, J=8.4 Hz, 1H), 8.99 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$–CD_3OD, 10:1) δ 17.4, 21.4, 21.9, 24.7, 26.1, 26.98, 27.00, 28.0, 32.0, 34.7, 39.0, 48.3, 58.8, 59.7, 75.5, 104.1, 105.3, 109.3, 117.7, 117.9, 121.8, 129.1, 133.2, 138.8, 148.1, 172.4, 174.1; IR (neat) 3300, 2917, 1685 cm^{-1}; FAB-HRMS (MH^+) calcd for $C_{27}H_{32}N_3O_3$ 446.2438, found 446.2433. *anti*-Cycloadduct **23**: ^{1}H NMR (400 MHz, $CDCl_3$–CD_3OD, 10:1) δ 1.17 (s, 3H), 1.25 (s, 3H), 1.37 (s, 3H), 1.38 (s, 3H), 1.55–1.70 (m, 5H), 1.75 (dd, J=3.3, 13.5 Hz, 1H), 2.12 (dd, J=3.3, 10.3 Hz, 1H), 2.21 (dd, J=10.3, 13.5 Hz, 1H), 2.37 (m, 1H), 2.79 (d, J=17.7 Hz, 1H), 3.45 (m, 1H), 3.73 (d, J=17.7 Hz, 1H), 4.11 (m, 1H), 5.59 (d, J=9.8 Hz, 1H), 6.56 (d, J=8.4 Hz, 1H), 6.68 (d, J=9.8 Hz, 1H), 7.16 (d, J=8.4 Hz, 1H), 9.12 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$–CD_3OD, 10:1) δ 17.7, 21.6, 23.7, 24.5, 26.3, 27.1, 27.4, 28.7, 33.6, 34.6, 39.6, 44.8, 59.9, 60.3, 75.6, 103.4, 105.3, 109.8, 117.5, 118.0, 122.1, 129.5, 133.2, 138.9, 148.4, 171.1, 173.3; IR (neat) 3300, 2917, 1686 cm^{-1}; FAB-HRMS (MH^+) calcd for $C_{27}H_{32}N_3O_3$ 446.2438, found 446.2437.

4.1.4. Amine (24). To a solution of lactam **15** (11.8 mg, 0.027 mmol) in toluene (5.3 mL) at 0 °C was added DIBAL (1.0 M in toluene, 530 μL, 0.53 mmol). The mixture was slowly warmed to rt and stirred at rt for 3 h. The resulting solution was quenched by the slow addition of solid $Na_2SO_4\cdot 10H_2O$ (500 mg). The mixture was stirred for an additional hour at rt. The resulting mixture was filtered through a fritted glass funnel to remove the solid and subsequently washed with ethyl acetate and concentrated. Purification by silica gel chromatography (MeOH–CH_2Cl_2, 5:95) afforded amine **24** as a colorless oil (10.1 mg, 89%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.44 (s, 3H), 1.45 (s, 6H), 1.49–1.64 (m, 3H), 1.75–1.90 (m, 4H), 2.05 (d, J=11.0 Hz, 1H), 2.07 (m, 1H), 2.19 (m, 1H), 2.25 (dd, J=3.0, 11.8 Hz, 1H), 2.67 (m, 1H), 2.70 (d, J=15.4 Hz, 1H), 2.87 (d, J=15.4 Hz, 1H), 3.54 (d, J=11.0 Hz, 1H), 5.67 (d, J=9.7 Hz, 1H), 6.25 (s, 1H), 6.61 (d, J=9.7 Hz, 1H), 6.64 (d, J=8.4 Hz, 1H), 7.14 (d, J=8.4 Hz, 1H), 7.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1, 21.5, 24.5, 26.0, 27.5, 30.7, 30.9, 31.4, 34.1, 34.5, 46.8, 55.4, 55.7, 58.3, 60.9, 75.7, 104.9, 105.2, 110.2, 117.2, 118.0, 121.7, 130.0, 132.9, 139.4, 148.9, 175.0; IR (neat) 3311, 2931, 1673 cm^{-1}; FAB-HRMS (MH^+) calcd for $C_{27}H_{34}N_3O_2$ 432.2646, found 432.2643.

4.1.5. Marcfortine C (3). To a solution of amine **24** (14.0 mg, 0.032 mmol) in CH_2Cl_2 (3.2 mL) at rt was added PPTS (10.2 mg, 0.041 mmol). The mixture was stirred at rt for 20 min. To the resulting solution was added oxaziridine **26** (31.1 mg, 0.13 mmol) and the reaction mixture was stirred at rt for 18 h. The resulting solution was placed directly on a column of silica gel and eluted with CH_2Cl_2, followed by MeOH–CH_2Cl_2 (5:95, then 10:90) to afford marcfortine C (**3**) (R_f=0.4, MeOH–CH_2Cl_2, 10:90) as a white solid (11.2 mg, 77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (s, 3H), 1.12 (s, 3H), 1.44 (s, 3H), 1.45 (s, 3H), 1.55–1.85 (m, 7H), 1.93 (d, J=15.3 Hz, 1H), 2.13 (br d, J=11.2 Hz, 1H), 2.26 (d, J=15.3 Hz, 1H), 2.42 (m, 1H), 2.45 (d, J=11.2 Hz, 1H), 2.68 (br d, J=11.2 Hz, 1H), 3.11 (t, J=10.1 Hz, 1H), 3.70 (d, J=11.2 Hz, 1H), 5.72 (d, J=9.9 Hz, 1H), 6.40 (d, J=9.9 Hz, 1H), 6.42 (d, J=8.2 Hz, 1H), 6.90 (d, J=8.2 Hz, 1H), 7.40 (s, 1H), 9.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, three drops CD_3OD) δ 20.6, 20.7, 24.0, 25.7, 27.8, 28.0, 30.9, 31.4, 39.9, 46.3, 54.2, 54.6, 61.0, 61.1, 61.3, 62.4, 76.3, 105.4, 109.4, 116.4, 121.5, 125.6, 130.9, 137.7, 152.9, 177.2, 184.5; IR (neat) 3298, 2923, 1672, 1601 cm^{-1}; FAB-HRMS (MH^+) calcd for $C_{27}H_{34}N_3O_3$ 448.2600, found 448.2608.

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