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Spiroaminal Model Systems of the Marineosins with Final Step Pyrrole Incorporation

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Abstract

In this Letter, we describe a short, 6-step enantioselective route to spiroaminal lactam model systems reminiscent of marineosins A and B has been developed starting from either (*R*)- or (*S*)-hydroxysuccinic acid, respectively, in ~9% overall yield. This route enables late stage incorporation of the pyrrole ring at C5 via nucleophilic displacement of an iminium triflate salt.

Keywords

marineosin; iminium triflate; enantioselective; pyrrole; alkaloid

In 2008, Fenical and co-workers reported the discovery of two novel spiroaminals, marineosins A (**1**) and B (**2**), from a marine-derived *Streptomyces*-related actinomycete (Figure 1),[1] and related to the prodigiosin family.[2] Both **1** and **2** displayed inhibition of human colon carcinoma cell growth (HCT-116 IC_{50}s of 0.5 μM and 46 μM, respectively).[1] Fenical also proposed a biosynthesis of **1** and **2** that proceeded through an inverse-electron demand hetero Diels-Alder reaction with **3** to provide **4**, which is then reduced to afford **1** and **2**. We evaluated this biosynthetic proposal, and while **3** was accessible in high yield, we were unable to affect the intramolecular inverse-electron demand hetero Diels-Alder reaction under a variety of conditions. Attempts with multiple substrates for intermolecular variants were equally unsuccessful.[3]

In 2010, Snider and co-workers proposed an alternative biosynthesis of **1** and **2** from undecylprodigiosin that only requires a single two-electron oxidation.[4] Based on this proposal, Snider developed a seven step route to a model system **7** for the spiroiminal moiety from methylvalerolactone **5** (Scheme 1). While an important advance towards the synthesis of **1** and **2**, we aimed to avoid long equilibration times, inseparable equilibrium mixtures, and, importantly, early installation of the pyrrole.[4]

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After the unsuccessful biosynthetic approach,[3] our lab has pursued multiple synthetic strategies en route to a total synthesis of **1** and **2**. Uniformly, routes with early incorporation of the C1-C4 pyrrole moiety, led to reactivity/stability issues that forced abandonment of advanced intermediates and strategies. Based on this outcome, we decided to re-design our routes to install the pyrrole moiety as the final step of the synthesis (Scheme 2). To determine the viability of this new approach, we developed a short, enantioselective synthesis of two spiroiminal model systems of **1** and **2** (highlighted in red). This route enables late stage incorporation of the pyrrole ring at C5 via a novel application of nucleophilic displacement of an iminium triflate salt.

Our model system was inspired by the work of Huang for the construction of aza-spiropyran derivatives by the addition of functionalized Grignard reagents into maleimides.[5] The synthesis of the proposed model system began with the requisite THP-protected bromobutanol **12** (Scheme 3) following a Grieco procedure.[6] Here, tetrahydrofuran is opened with HBr to afford **10** in 75% yield. Protection as the THP ether afforded **12** in 90% yield, which is then converted into Grignard reagent **13**.[6]

With **13** in hand, we prepared the maleimide fragment relevant for a model system of **1**.[7,8] Starting from (*R*)-hydroxy succinic acid **14**, refluxing in *m*-xylenes with *p*-methoxybenzyl amine **15** affords the desired maleimide **16** in 78% yield (Scheme 4). Silver oxide mediated alkylation with MeI in MeCN affords key coupling partner **17** in 78% yield. Addition of **13** into **17** provided hydroxy aminal **18** in 80% yield (Scheme 5).[15]

Treatment with *p*-TsOH cleaves the THP ether and generates iminium salt **19** which is attacked by the free hydroxyl leading to formation of the spiroaminal **20** in 80% yield.[16] Finally, ceric ammonium nitrate (CAN)-mediated removal of the *p*-methoxybenzyl (PMB) group provides lactam **21** in 67% yield.[17] Model system **21** possessed the correct stereochemistry at C7 for **1**, but the opposite absolute stereochemistry at C8. However, **21** is a valuable model from which to develop chemistry for the late stage installation of the pyrrole at C5, and not consume valuable late stage **8**.

Stereochemical assignments of **20**, with *anti* O-1,O-7 geometry, was made based on literature precedent and from extensive nOe studies (Figure 2).[9]

With **21** in hand, we were poised to evaluate conditions to install the pyrrole moiety at C5 to validate our retrosynthetic approach aimed at accessing **8**. Our initial thought was to install the pyrrole through classical Vilsmeier-type chemistry ($POCl_3$/pyrrole);[9] however, this failed to provide the desired **22**. We surveyed a number of known strategies to convert the lactam carbonyl into a suitable electrophile, followed by treatment with pyrrole under a variety of reaction conditions, but none proved successful. The lactam was converted into the corresponding triflate **23** through treatment with Tf_2O or $PhNTf_2$, followed by a Suzuki coupling with various forms of *N*-protected, 2-pyrrole boronic acid. Unfortunately, all attempts with multiple Pd(0) and Ni(0) sources, bases, and solvents afforded either no product or only trace amounts of **22** (Scheme 6).

A deeper perusal of the literature led us to consider the chemistry of triflic anhydride/amide adducts, and the opportunity to potentially intercept the *in situ* generated triflate with the pyrrole nucleophile in a single pot reaction.[10,11] It has been demonstrated that treatment of an indolin-2-one with Tf_2O, to generate the iminium triflate salt, followed immediately by the additon of a functionalized indole affords the *bis*-indole product.[11] With this lone precedent, we treated **21** with 2.0 equivalents of Tf_2O, to generate the iminium triflate salt, followed by the addition of 5.0 equivalents of pyrrole in CH_2Cl_2 at 0 °C. Unfortunately, these conditions afforded only a trace (<5%) of the desired **22**. Evaluation and refinement of

the reaction conditions identified that employing 1.0 equivalent of Tf_2O, to generate the iminium triflate salt, followed by the addition of 5.0 equivalents of pyrrole in CH_2Cl_2 at 0 °C did provide the desired model system **22** of marineosin A, **1**, in 36% yield (Scheme 7).[19] The stereochemistry was further confirmed at this stage by nOe studies on **22**. Irradiation of H-7 supported the 6*R*,7*S* stereochemical assignment of **22**; no equilibration to the *syn* O-1,O-7 isomer had occurred after installation of the pyrrole, even after a period of two weeks in $CDCl_3$.[4,9] Identical nOe data was seen in model system **22**. Although the configuration of the spirocenter in model **22** is opposite to marineosins A, we envision that a *syn* O-1,O-7 isomer can be obtained by increasing the steric demands of the pyran ring through stereoselective functionalization of a carbon fragment similar to Grignard **13**. Repetition of this sequence, starting from the (*S*)-hydroxy succinic acid, afforded the model system **24** reminiscent of marineosin B in ~9% overall yield. Once again, literature preceent and extensive nOe data confimred the sterochemcial assignment.

As both **1** and **2** displayed inhibition of human colon carcinoma (HCT-116 IC_{50}s of 0.5 μM and 46 μM, resectively), and due to the fact that many related, bi- and tricyclic prodigiosin natural products have potent cytotoxicity,[13,14] we evaluated **22** and **24** in our HCT-116 cytotoxicity assay in order to ascertain if the model systems represented a minimum pharmacophore for **1** and **2**, respectively. Interestingly, both model systems were inactive in this assay, suggesting the larger construct, and/or stereochemical conformation, of **1** and **2** are important for the observed biological activity, thus warranting completion of the total synthesis of **1** and **2**.

In summary, we have developed chemistry to enable late stage introduction of the pyrrole moiety at C5 in marineosin A (**1**) and B (**2**) via a novel application of the nucleophilic displacement of an iminium triflate salt by pyrrole. Moreover, we have performed an enantioselective synthesis of two spiroaminal model systems reminiscent of **1** and **2** starting from chiral pool molecules. Overall yields for both **22** and **24** averaged ~9% from commercial tetrahydrofuran. This synthetic approach is currently being applied to the total synthesis of **1**, and results will be presented in due course.

Acknowledgments

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15. A flame-dried flask was charged with magnesium powder (447 mg, 18.4 mmol) and placed under an inert argon atmosphere. The magnesium was suspended in anhydrous THF (21 mL). To this mixture was added pyran **12** (1.4 mL, 7.5 mmol). After warming to 50 °C, pyran **12** (2.0 mL, 10.7 mmol) was added dropwise. The reaction mixture was heated periodically until it sustained reflux. A separate flame-dried flask was charged with ether **17** (1.5 g, 6.0 mmol) and THF (30 mL). After cooling to −20 °C, the solution of Grignard **13** was added dropwise via syringe. The reaction mixture was kept between −10 °C and −15 °C. After 2.5 h, water (5 mL) was added and the reaction was allowed to reach rt. The product was extracted with diethyl ether (3 × 20 mL). The combined organics were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified on silica gel (30:70 EtOAc:hexanes) to provide 6.61 g (80%) of tertiary alcohol **18**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48-1.59 (m, 5H), 1.61-1.75 (m, 2H), 1.77-1.90 (m, 1H), 2.12-2.24 (m, 2H), 2.57 (d, *J* = 17.9 Hz, 1H), 2.71 (dddd, *J* = 1.9, 7.2, 17.8 Hz, 1H), 3.27 (s, 3H), 3.29-3.34 (m, 1H), 3.45-3.50 (m, 1H), 3.63-3.71 (m, 1H), 3.77 (s, 3H), 3.80-3.85 (m, 1H), 4.49-4.52 (m, 1H), 4.55-4.66 (m, 3H), 4.85 (q, *J* = 6.8 Hz, 1H), 6.81 (d, *J* = 8.6 Hz, 2H), 7.13 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.6, 19.8, 23.4, 23.5, 25.4 (2C), 30.1, 30.2, 30.7, 30.8, 36.0 (2C), 42.9 (2C), 55.1, 55.2, 62.3, 62.6, 66.5, 66.7, 72.0 (2C), 98.9, 99.0, 107.0, 107.1, 113.9 (2C), 127.9, 128.3, 128.4, 139.2, 139.3, 158.8 (2C), 173.0, 173.1. HRMS (TOF ES+): $C_{22}H_{33}NO_6Na$ $[M+Na]^+$ calcd 430.2206, found 430.2210. $[\alpha]^{22}_D$= −15.0 (c 0.6, $CHCl_3$).
16. To a stirred solution of tertiary alcohol **18** (390 mg, 1.0 mmol) in CH_2Cl_2 (6 mL) at 0 °C was added *p*-toluenesulfonic acid monohydrate (41 mg, 0.2 mmol). After 30 minutes the solvent was removed. The residue was purified on silica gel (30:70 EtOAc:hexanes) to provide 244 mg (80%) of spiroaminal **20**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.39-1.51 (m, 4H), 1.63-1.70 (m, 1H), 1.85-1.92 (m, 1H), 2.47 (d, *J* = 17.4 Hz, 1H), 2.65 (dd, *J* = 5.5, 17.4 Hz, 1H), 3.32 (s, 3H), 3.61 (m, 1H), 3.73 (s, 3H), 3.84 (dd, *J* = 2.4, 11.2 Hz, 1H), 3.95 (d, *J* = 5.5 Hz, 1H), 4.11 (d, *J* = 16.0 Hz, 1H), 4.70 (d, *J* = 16.0 Hz, 1H), 6.78 (d, *J* = 8.7 Hz, 2H), 7.14 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.0, 24.6, 27.9, 34.3, 41.8, 55.0, 56.6, 64.7, 74.9, 94.9, 113.5, 127.9, 130.5, 158.2, 174.5. HRMS (TOF, ES+): $C_{17}H_{24}NO_4$ $[M+H]^+$ calcd 306.1705, found 306.1702. $[\alpha]^{22}_D$ = −50.6 (c 1, $CHCl_3$).
17. To a stirred solution of spiroaminal **20** (258 mg, 0.85 mmol) in acetonitrile (27 mL) and water (3.5 mL) was added ceric ammonium nitrate (1.4 g, 2.5 mmol). After 1.5 h, a second portion of ceric ammonium nitrate (467 mg, 0.8 mmol) was added. After 1 h, the acetonitrile was removed under reduced pressure. The product was extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified on silica gel (30:70 EtOAc/hexanes) to provide 105 mg (67%) of amide **21**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.54-1.63 (m, 2H), 1.63-1.73 (m, 1H), 1.73-1.83 (m, 3H), 2.29 (dd, *J* = 1.7, 17.2 Hz, 1H), 2.70 (dd, *J* = 5.6, 17.2 Hz, 1H), 3.34 (s, 3H), 3.66-3.72 (m, 3H), 8.64 (bs, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.4, 25.2, 29.3, 35.7, 57.3, 62.7, 82.4, 91.8, 177.3. HRMS (TOF, ES+): $C_9H_{16}NO_3[M+H]^+$ calcd 186.1130, found 186.1131. $[\alpha]^{22}_D$ = −97.1 (c 1.1, $CHCl_3$).
18. A flame-dried flask was charged with amide **21** (64 mg, 0.3 mmol) and placed under an inert argon atmosphere. After cooling to 0° C, CH_2Cl_2 (4 mL) and trifluoromethanesulfonic anhydride (58.2 μL, 0.3 mmol) were added. After 2 minutes, pyrrole (119.8 μL, 1.7 mmol) was added. After 10 minutes, the reaction was quenched with saturated $NaHCO_3$ and allowed to reach rt. The product was extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were dried over Na_2SO_4 and concentrated. The residue was purified on silica gel (30:70 EtOAc/hexanes) to provide 29 mg (36%) of pyrrole **22**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.54-1.78 (m, 5H), 1.86-1.99 (m, 2H), 2.78 (dd, *J* = 5.3, 16.5 Hz, 1H), 3.21 (dd, *J* = 6.8, 16.5 Hz, 1H), 3.44 (s, 3H), 3.72 (d, *J* = 10.8 Hz, 1H), 3.84 (t, *J* = 6.2 Hz, 1H), 4.15 (dt, *J* = 2.8, 11.1 Hz, 1H), 6.21 (t, *J* = 3.2 Hz, 1H), 6.57 (d, *J* = 3.5 Hz, 1H), 6.90 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.6, 25.8, 29.2, 38.7, 58.2, 64.2, 85.3, 102.8, 110.7, 112.8, 121.1, 126.3, 164.6. HRMS (TOF, ES+): $C_{13}H_{19}N_2O_2$ $[M+H]^+$ calcd 235.1447, found 235.1447. $[\alpha]^{22}_D$ = −65.2 (c 1.6, $CHCl_3$).

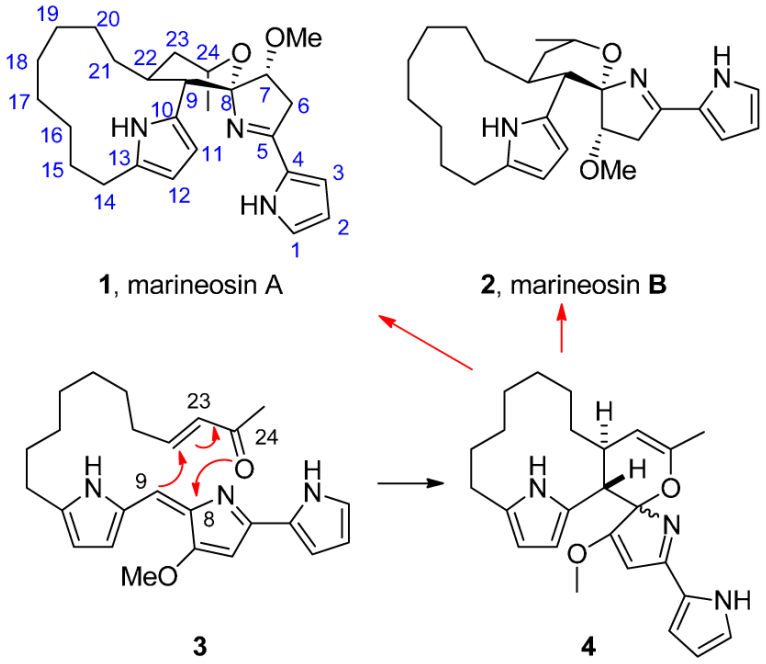
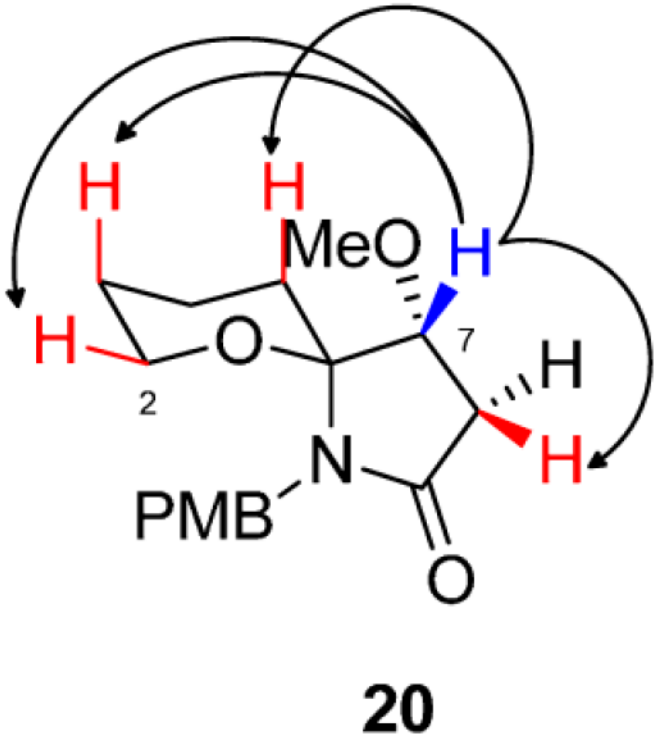
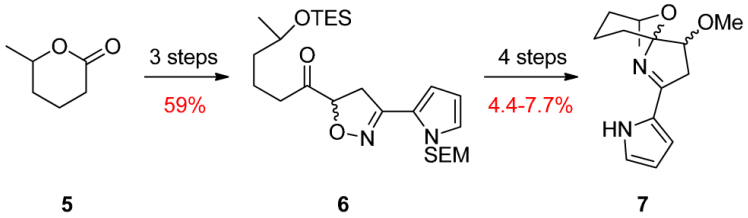


Figure 1.
Structures and proposed biosynthesis of marineosins A (**1**) and B (**2**).



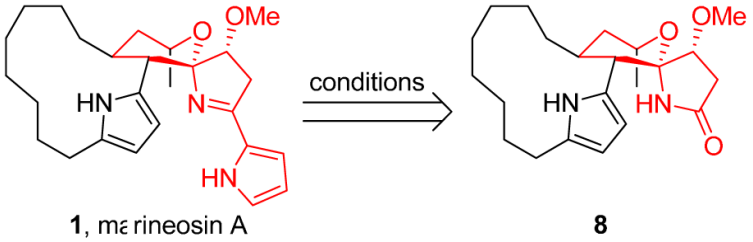
20

Figure 2.
Diagnostic nOe correlations in the (6*S*,7*R*)-spiroaminal **20** model system reminiscent of **1**.



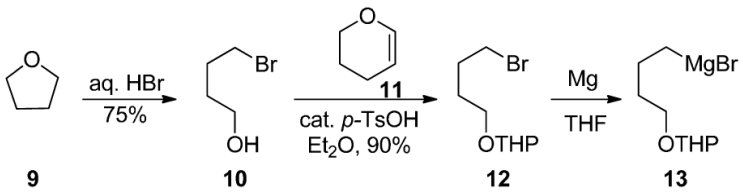
5 **6** **7**

Scheme 1.
Snider's Spiroiminal Model System.

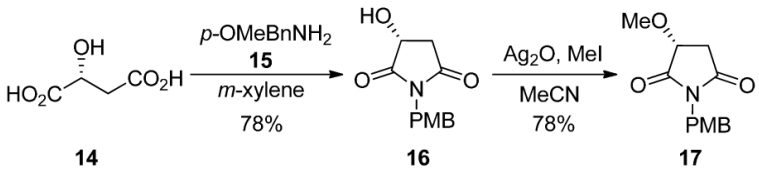


1, marineosin A **8**

Scheme 2.
Envisioned Disconnection for the Synthesis of **1**.

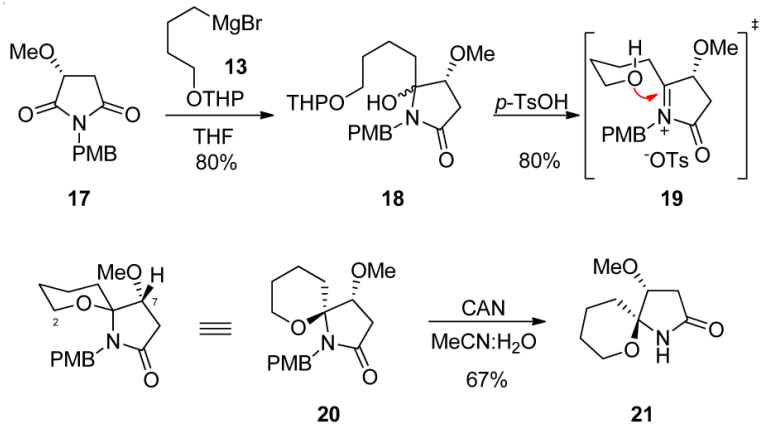


Scheme 3.
Synthesis of the Key Gringard Reagent **13**.

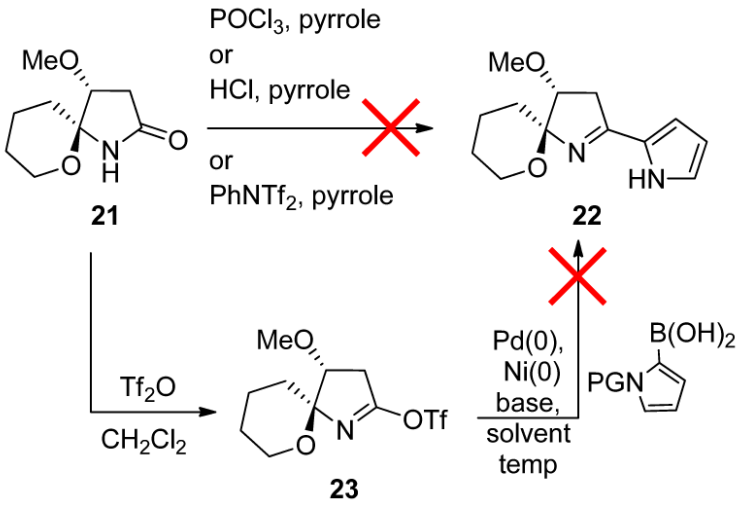


14 16 17

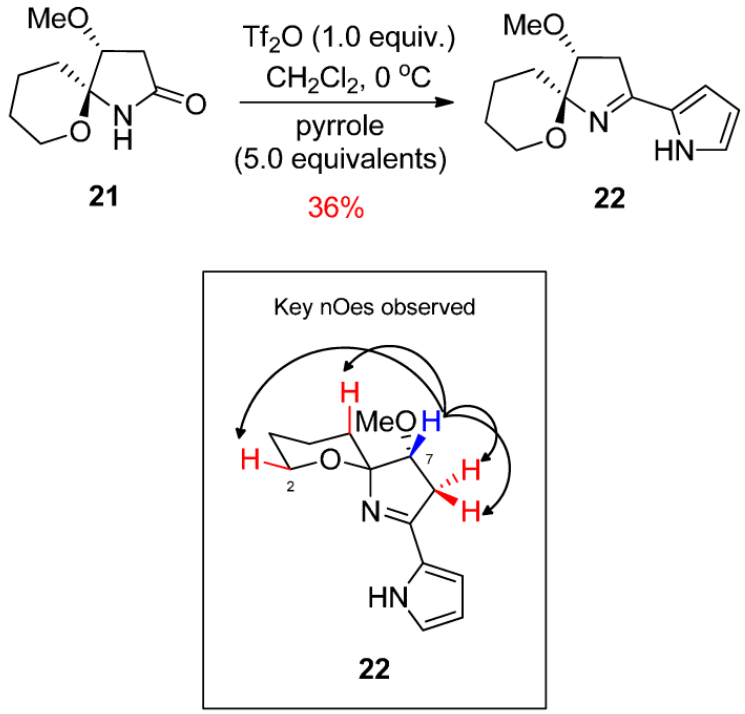
Scheme 4.
Synthesis of the Key Malimide **17**.



Scheme 5.
Synthesis of the Spiroaminal Moiety of **1**.



Scheme 6.
Attempts to Install the Pyrrole Moiety at C5.



Scheme 7.
Late Stage Installation of the Pyrrole and Completion of the Model Systems of **1**.