Synthetic Efforts toward the Isoindolinone Core of Muironolide A

Courtnay E. Shaner, Gregory M. Ferrence, T. Andrew Mitchell*

Department of Chemistry, Illinois State University, Normal, IL 61790-4160, USA
Fax +1(309)4385538 (department); E-mail: tmitche@ilstu.edu

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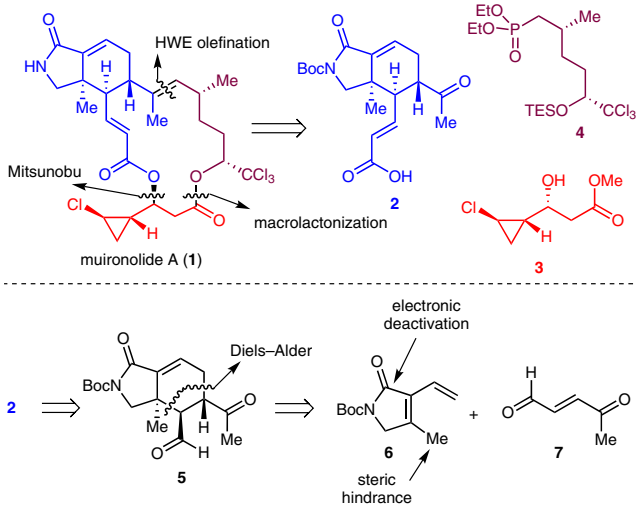
Abstract: Studies directed toward the isoindolinone core of muironolide A are described. An initial plan to implement an intramolecular Diels–Alder cycloaddition was thwarted by an undesired conjugate addition during the attempted preparation of the Diels–Alder substrate. A revised retrosynthetic analysis revealed a direct, albeit challenging, intermolecular Diels–Alder disconnection. Toward this end, a sterically hindered and electronically deactivated diene was utilized with *N*-phenylmaleimide to achieve a Diels–Alder cycloaddition.

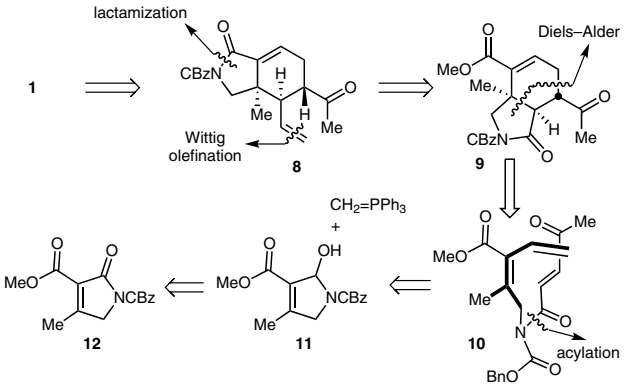
Key words: cycloaddition, Diels–Alder reaction, muironolide A, natural products, total synthesis

Muironolide A was recently isolated by Molinski and coworkers[1] from the same marine sponge that delivered phorboxazole A,[2] which is an extremely potent bioactive natural product with promising anticancer activity.[3] Only 90 μg of muironolide A was isolated, which meant that total synthesis was the only viable means available to undertake a detailed biological evaluation.[4] Molinski disclosed an intramolecular, organocatalytic approach to an isoindolinone core[5] that utilized imidazolidinone precatalysts.[6] Herein, we describe preliminary synthetic efforts toward the isoindolinone, leading to an intermolecular Diels–Alder strategy utilizing a diene that is sterically hindered and electronically deactivated[7] (Scheme 1). Retrosynthetic analysis reveals three key fragments, isoindolinone **2**, chlorocyclopropylcarbinol **3**, and protected trichloromethylcarbinol **4** resulting from Horner–Wadsworth–Emmons (HWE) olefination,[8] Mitsunobu,[9] and macrolactonization[10] disconnections. Isoindolinone **2** can be further disconnected to reveal a second isoindolinone **5**, which could be accessible through Diels–Alder cycloaddition to provide diene **6** and 2-methylfuran-derived dienophile **7**.[11]

Our first-generation strategy centered on an intramolecular Diels–Alder cycloaddition (Scheme 2).[12] Initial retrosynthetic analysis revealed that isoindolinone **8** could be accessed from bicyclic lactam **9**, which, in turn, could be obtained from diene-dienophile **10** through an intramolecular Diels–Alder cycloaddition. Wittig olefination[13] of aminal **11**, which would be achieved through half-reduction[14] of lactam-ester **12**, followed by acylation[15] was proposed for the synthesis of the Diels–Alder cycloaddition precursor **10**. Thus, lactam-ester **12** was viewed as a crucial synthetic intermediate toward this goal.

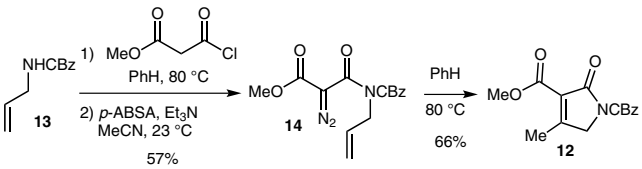


Scheme 1



Scheme 2

Toward this end, CBz-allylamine **13**[16] was subjected to acylation with methyl malonyl chloride followed by diazo transfer[17] with *p*-acetamidobenzenesulfonyl azide (*p*-ABSA)[18] to provide diazo ester **14** (Scheme 3). Upon heating in benzene, cyclization provided α,β-unsaturated lactam-ester **12** in moderate yield.[19]



Scheme 3

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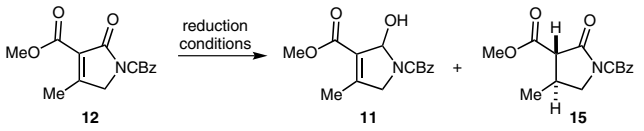
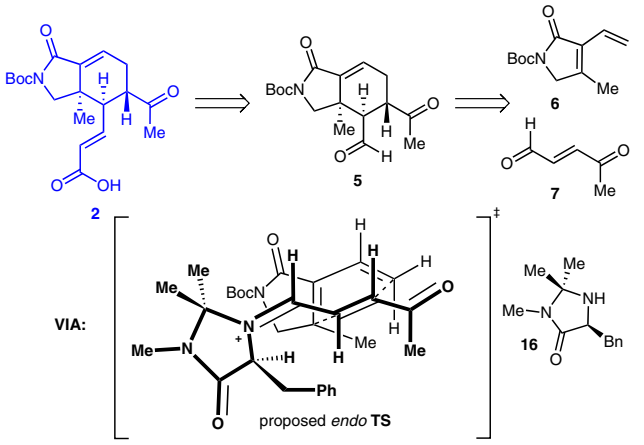
In pursuit of aminal **11**, α,β-unsaturated lactam-ester **12** was subjected to a variety of reduction conditions (Table 1).[14] Aminal **11** was not detected, but saturated amide-ester **15** was observed as a result of conjugate addition.[20] Reduction with Li(*t*-BuO)$_3$AlH (entry 4) provided the best, albeit unoptimized, isolated yield of **15** (38%) as a mixture of diastereomers. Treatment of **12** with $NaBH_4$ and $CeCl_3$ provided a complex mixture (analyzed by ^1H NMR spectroscopy) in which aminal **11** was not detected.

Table 1 Reduction of Lactam **12** to Lactam **15**



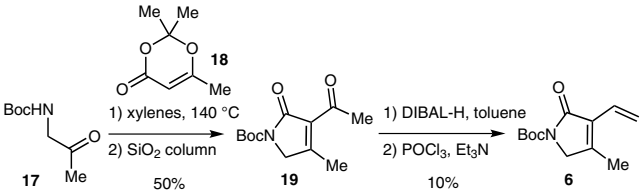
Entry	Reductant	Conv. **11** (%)	Conv. **15** (%)	dr **15**
1	DIBAL-H	ND	77	2.0:1
2	$LiAlH_4$	ND	74	2.3:1
3	$LiEt_3BH$	ND	>95	6.8:1
4	Li(*t*-BuO)$_3$AlH	ND	>95	6.0:1

In light of our retrosynthetic analysis for isoindolinone **5**, which was further disconnected to reveal diene **6** and dienophile **7** (cf. Scheme 1), we envisioned an organocatalytic, intermolecular Diels–Alder cycloaddition[6a] catalyzed by imidazolidinone **16** as an attractive strategy with which to construct the highly functionalized isoindolinone **5** with high diastereo- and enantioselectivity (Scheme 4).



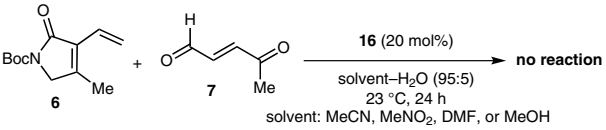
Scheme 4

Toward this end, Boc-protected amino acetone **17**[21] was treated with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**18**)[22] in xylenes at reflux to provide a β-ketoamide (not shown) that underwent intramolecular aldol cyclization when subjected to silica gel column chromatography[23] to provide lactam **19** in moderate yield (Scheme 5). Unoptimized reduction and elimination delivered the requisite diene **6**.



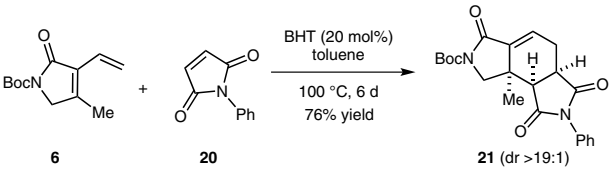
Scheme 5

Initial investigation toward intermolecular Diels–Alder cycloaddition between diene **6** and 2-methylfuran-derived dienophile **7** catalyzed by imidazolidinone **16** was unsuccessful (Scheme 6). Several solvents were screened under ambient conditions, however, these did not lead to any reaction; increased temperature resulted in decomposition.



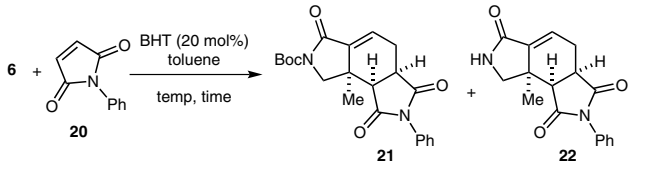
Scheme 6

To demonstrate reactivity in a more fundamental way, diene **6** was subjected to a thermal Diels–Alder cycloaddition with *N*-phenylmaleimide (**20**; Table 2). Ambient conditions provided no reaction, as anticipated (entry 1). Upon heating in the presence of a radical scavenger (BHT), Diels–Alder adduct **21** was observed with significant amounts of starting diene **6** remaining (entry 2). Prolonged heating at 100 °C for six days provided complete conversion into the desired adduct **21** (entry 4). Heating to 120 °C did not improve the rate of conversion to any appreciable degree (entry 5) and heating to 150 °C resulted in significant Boc-deprotection (entry 6). Fortuitously, deprotected isoindolinone **22** was amenable to single crystal X-ray crystallographic analysis,[24] which confirmed both the expected *endo* adduct and the crucial α,β-unsaturated lactam moiety (Figure 1). Not only does the stereochemical outcome demonstrate the feasibility of this direct intermolecular Diels–Alder cycloaddition with diene **6**, but construction of the α,β-unsaturated lactam embedded within the isoindolinone allows access to a critical structural feature that have proven difficult to obtain by using the approach developed by Flores and Molinski.[5] Finally, the optimized conditions were utilized for the synthesis of isoindolinone **21**, providing 76% yield of the desired product as a single diastereomer (Scheme 7).[25]



Scheme 7

Table 2 Optimization of Diels–Alder Cycloaddition with Diene **6**



Entry	Temp (°C)	Time (d)	Conv. **21** (%)	Conv. **22** (%)
1	23	1	ND	ND
2	100	1	38	ND
3	100	4	78	ND
4	100	6	>95	ND
5	120	3	73	ND
6	150	1	38	58

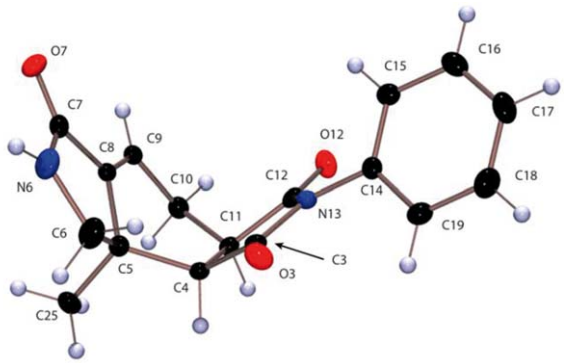


Figure 1 ORTEP of Boc-deprotected Diels–Alder adduct **22**

In conclusion, this investigation toward the natural product muironolide A initially focused on an intramolecular Diels–Alder cycloaddition as a key step. Undesired conjugate reduction of a precursor within the proposed intramolecular approach led to a revised retrosynthetic analysis that entailed a more direct intermolecular Diels–Alder cycloaddition utilizing a sterically hindered and electronically deactivated diene. Initial investigation toward an enantioselective, organocatalytic synthesis of the isoindolinone core was unsuccessful, but a challenging Diels–Alder addition reaction was accomplished, which gives credence to the viability of this novel diene for participation in Diels–Alder cycloaddition processes. Future studies utilizing this diene and others for the construction of the isoindolinone core of muironolide A will be reported in due course.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html.

(25) **Experimental Procedure for the Synthesis of Isoindolinone 21:** *N*-Phenylmaleimide **20** (89 mg, 0.51 mmol), BHT (11 mg, 0.05 mmol), and diene **6** (56 mg, 0.25 mmol) were dissolved in toluene (1.0 mL). The solution was sealed in a Teflon-capped vial, heated to 100 °C for 6 d, cooled to 23 °C, and then concentrated under reduced pressure. Purification by flash column chromatography (hexanes–EtOAc, 60:40) delivered isoindolinone **21** (75 mg, 76%) as a white solid; mp 80–82 °C; R_f = 0.13 (hexanes–EtOAc, 60:40). IR (neat): 1769, 1705, 1147, 727, 691 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.39 (s, 3 H), 1.54 (s, 9 H), 2.71 (ddd, *J* = 2.8, 9.0, 17.8 Hz, 1 H), 3.10 (ddd, *J* = 1.3, 7.5, 17.8 Hz, 1 H), 3.36 (d, *J* = 8.9 Hz, 1 H), 3.49 (ddd, *J* = 1.3, 8.9, 9.0 Hz, 1 H), 3.63 (d, *J* = 11.6 Hz, 1 H), 4.73 (d, *J* = 11.6 Hz, 1 H), 6.97 (dd, *J* = 2.8, 7.5 Hz, 1 H), 7.18–7.20 (m, 2 H), 7.38–7.48 (m, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.5, 26.7, 28.1 (3), 35.8, 39.1, 47.8, 53.9, 83.3, 126.5 (2), 129.0, 129.3 (2), 131.4, 131.6, 139.9, 150.4, 163.7, 175.5, 177.5. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{25}N_2O_5$: 397.1763; found: 397.1769.

