Synthesis C. A. Olson et al. Special Topic

Hexahydro-1*H*-Isoindolinone-Like Scaffolds from Electronically Deactivated and Sterically Hindered Dienes: Synthesis in the Context of Muironolide A

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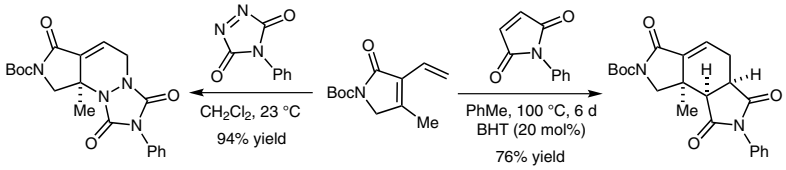

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Abstract Initial synthetic efforts toward muironolide A based upon an intramolecular Diels–Alder strategy were hampered by a conjugate reduction rather than the desired half-reduction. An intermolecular Diels–Alder strategy was initiated that utilized electronically deactivated and sterically hindered dienes. The [4+2] cycloadditions were successful, but only with highly reactive dipolarophiles such as *N*-phenylmaleimide and 4-phenyl-1,2,4-triazoline-3,5-dione thus establishing the scope of these dienes. Although limited, installation of the α,β-unsaturated lactam embedded in the hexahydro-1*H*-isoindolinone is noteworthy.

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

Muironolide A is a novel marine natural product with very intriguing structural features.[1] Molinski isolated muironolide A from the same specimen of *Phorbas*[1a] that afforded the phorbasides[2] and the phorboxazoles,[3] which have become prominent targets of recent total synthesis endeavors (Figure 1).[4] Exquisite structural elucidation was accomplished with just 90 μg of muironolide A,[1a] but only minimal biological activity could be ascertained.[5] Thus, total synthesis represents the sole access point toward biological investigation of muironolide A. Molinksi[1b] and Zakarian[1c] have both disclosed elegant approaches based on intramolecular Diels–Alder cycloadditions.[6] Recently, Zakarian accomplished the total synthesis[7] of the originally proposed structure of muironolide A only to discover that it was in fact the epimer of the natural product. He subsequently proposed a revised structure based on a hypothesis that this inconsistency arose from the degradation studies performed on very small scale.[1a] Upon completion of the enantioselective total synthesis in which 25 mg was obtained, data for the revised structural assignment was in complete agreement with the isolated natural product (Figure 2).[8] In addition to the unknown biological potential, unique structural features make this an exciting synthetic target: 1) a hexahydro-1*H*-isoindolinone core with three contiguous stereocenters (including one all-carbon quaternary); 2) a macrocyclic diester fused to the hexahydro-1*H*-isoindolinone; 3) a trisubstituted alkene flanked with stereocenters on either side; 4) a trichloromethylcarbinol ester; 5) a chlorocyclopropylcarbinol ester possessing three contiguous stereocenters; and 6) remote arrangement of these eight total stereocenters.

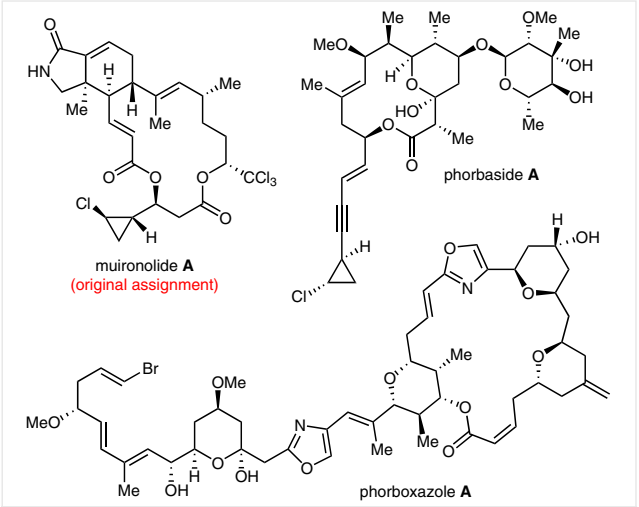


Figure 1 Natural products isolated from the marine sponge *Phorbas*

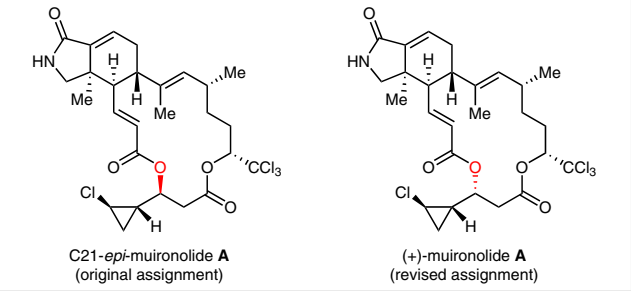
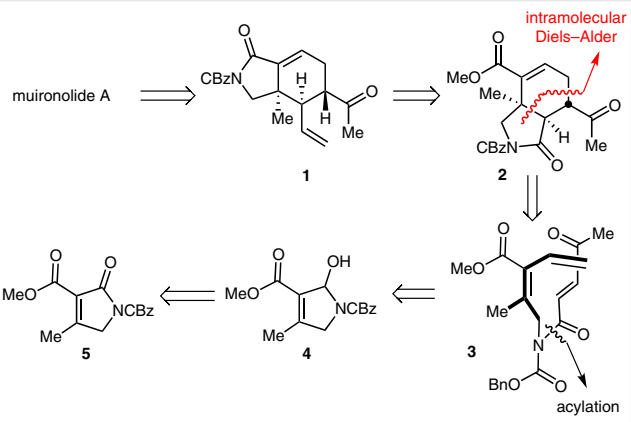


Figure 2 Original and revised assignments of muironolide A

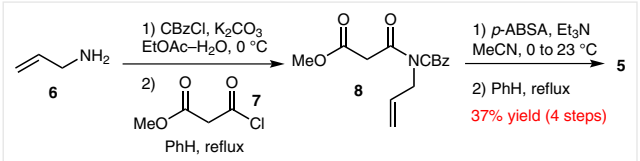
Our original synthetic strategy also focused on an intramolecular Diels–Alder cycloaddition,[6] but was altered in order to investigate an intermolecular variant. Previously, we showed proof of principle within the intermolecular context demonstrating that an electronically deactivated and sterically hindered diene was capable of undergoing Diels–Alder cycloaddition with *N*-phenylmaleimide.[1d] Herein, we report a full account of these investigations within the context of the attempted synthesis of the hexahydro-1*H*-isoindolinone core of muironolide A. We show several 'dead-end' pathways and intriguing by-products, optimized synthesis and manipulation of several dienes, and we firmly demarcate the scope and limitation of these electronically deactivated and sterically hindered dienes (vide infra). Although capable of [4+2] cycloaddition, unfortunately these dienes are incapable of Diels–Alder cycloadditions that are synthetically useful toward the hexahydro-1*H*-isoindolinone core of muironolide A.

Initially, we proposed that cyclohexene-lactam **1** could serve as a productive form of the hexahydro-1*H*-isoindolinone core. Thus, cyclohexene-lactam **2**, upon opening of the lactam followed by capture of the ester with the resulting CBz-protected amine, could then be converted to the hexahydro-1*H*-isoindolinone **1**. Intramolecular Diels–Alder of diene **3** was expected to provide efficient access to cyclohexene-lactam **2**. Manipulation of aminal **4** via Wittig olefination[9] was anticipated as a route to provide the CBz-protected amine (not shown) that could then be acylated[10] to give the Diels–Alder precursor **3**. Thus, lactam-ester **5** was proposed as the first synthetic building block necessary in order to investigate the desired half-reduction toward the aminal **4** (Scheme 1).

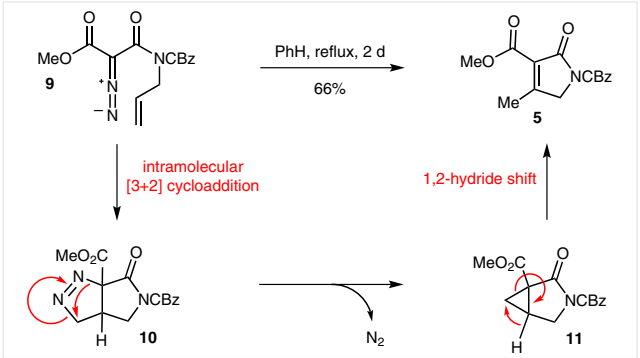


Scheme 1 Intramolecular retrosynthetic analysis of muironolide A

Allylamine **6** was protected as the CBz derivative[11] and treated with methyl malonyl chloride (**7**) to afford amide **8** (Scheme 2). Treatment with 4-acetamidobenzenesulfonyl azide (*p*-ABSA, **17**)[12] and Et_3N gave the α-diazo amide (not shown),[13] which was subjected to refluxing benzene to deliver the desired α,β-unsaturated lactam **5** (vide supra) in 37% yield over four steps. Transformation of the diazo functionality into the α,β-unsaturated lactam **5** likely proceeds via [3+2] cycloaddition to the bicyclic lactam **10** and then through a cyclopropane intermediate **11** followed by a 1,2-hydride shift (Scheme 3).[14]

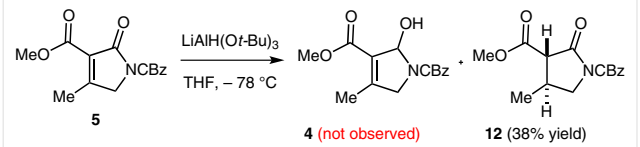


Scheme 2 Synthesis of lactam **5** from allylamine **6**



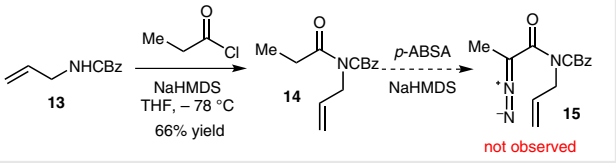
Scheme 3 Mechanistic rationale for the synthesis of lactam **5**

Several attempts to synthesize the aminal **4** by half-reduction[15] of α,β-unsaturated lactam-ester **5** were unsuccessful (Scheme 4).[1d] However, a saturated amide ester **12** was isolated, presumably resulting from conjugate addition by the hydride source. $LiAlH(t\text{-}BuO)_3$ proved to be the most efficient reducing agent, albeit unoptimized, and provided the ester **12** in 38% yield as a mixture of diastereomers (dr 6:1).[16]



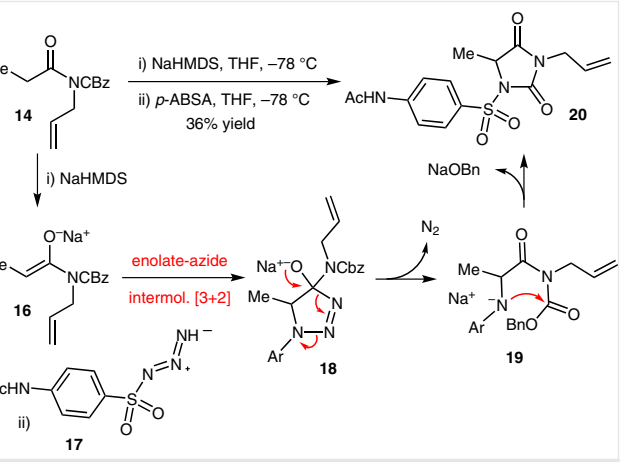
Scheme 4 Attempted half-reduction with $LiAlH(Ot\text{-}Bu)_3$ to aminal **4**

We next pursued a substrate without the ester (Scheme 5) in order to reduce the electrophilicity of the alkene and potentially to provide an avenue toward a simpler variant of aminal **4** (vide supra) that could perhaps undergo a late-stage allylic oxidation. Acylation of the CBz-protected allylamine **13**[11] delivered the necessary amide **14**, but treatment with *p*-ABSA and NaHMDS afforded hydantoin **20**[17] (vide infra) rather than the desired α-diazo amide **15**. This unexpected result may arise from an enolate-azide [3+2] cycloaddition[18] and subsequent attack upon the CBz protecting group (Scheme 6). Unfortunately, attempts to generalize this hydantoin formation or a more general α-amination proved unsuccessful since neither α-amino amides **22** or **24** were observed under similar conditions (Scheme 7). Oxazolidinone **24** would presumably be less likely to undergo capture akin to the CBz-protecting group.

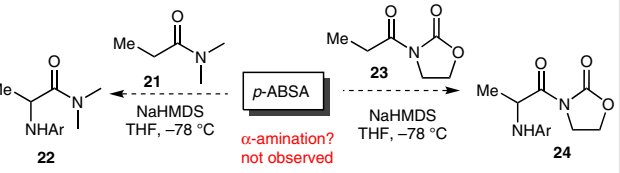


Scheme 5 Attempted synthesis of α-diazo amide **15**

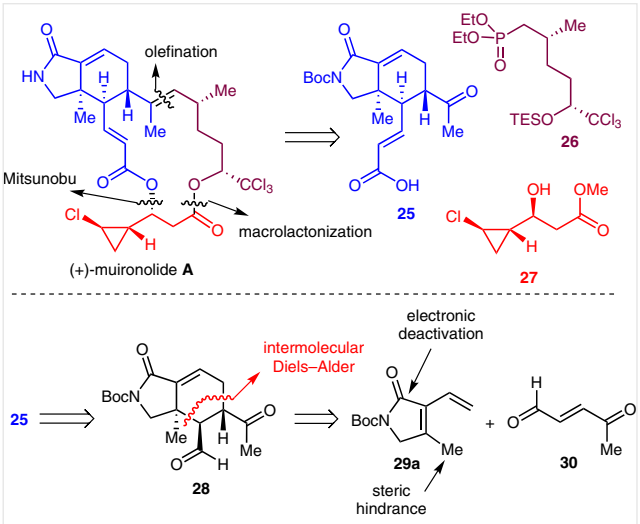
Since the intramolecular approach was leading further away from muironolide A, potential intermolecular routes were investigated (Scheme 8). Three disconnections of muironolide A were envisioned: olefination,[19] Mitsunobu,[20] and macrolactonization,[21] and synthetic intermediates from these disconnections were proposed: hexahydro-1*H*-isoindolinone **25**, phosphonate **26**, and chlorocyclopropyl carbinol **27**. Further retrosynthetic disconnection of hexahydro-1*H*-isoindolinone **25** afforded hexahydro-1*H*-isoindolinone **28**, which could be accessible via an intermolecular Diels–Alder cycloaddition. Although electronically deactivated and sterically hindered,[22] diene **29a** could potentially undergo Diels–Alder cycloaddition with a highly reactive dienophile such as the fumarate derivative **30**.[23] Although this route harbored risk, if successful would give direct access to the crucial hexahydro-1*H*-isoindolinone core.



Scheme 6 Proposed mechanism of the formation of hydantoin **20**



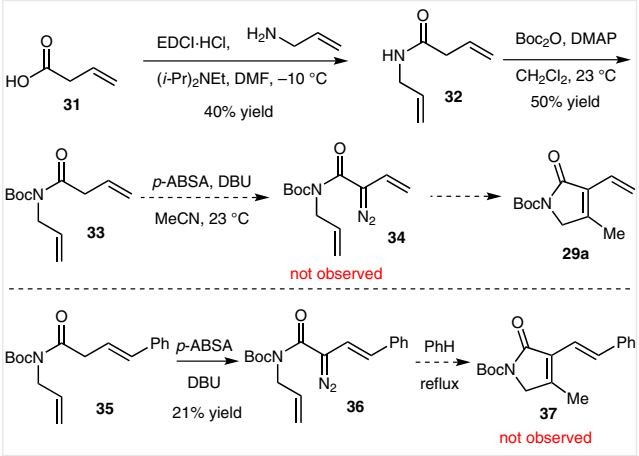
Scheme 7 Attempted α-amination utilizing *p*-ABSA and NaHMDS



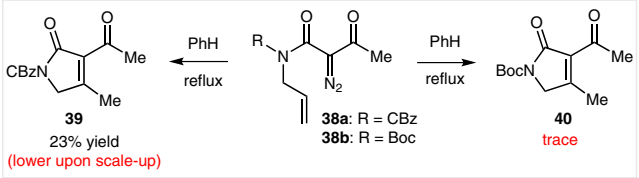
Scheme 8 Intermolecular retrosynthetic analysis of muironolide A

Our first attempt within this strategy relied on a direct synthesis of β,γ-unsaturated amides **33** and **35** (Scheme 9). Coupling of but-3-enoic acid **31** and allylamine with EDCI·HCl gave β,γ-unsaturated amide **32**.[24] While Boc-protection was realized, conversion to the α-diazo-β,γ-unsaturated amide **34** was unsuccessful. A small quantity of isomerized by-product (i.e., α,β-unsaturated amide corresponding to **33**, not shown) was observed. Also, a styrene variant **35** afforded the α-diazo-β,γ-unsaturated amide **36**, albeit in poor yield. Unfortunately, diazoalkene [3+2] cyclization to diene **37** was also unsuccessful.

We then attempted to utilize α-diazo-β-keto amides **38a**,**b** in order to access the requisite dienes (Scheme 10).[13,14] The syntheses of these β-keto-α-diazo amides **38a**,**b** were straightforward, but cyclization proved to be inefficient. Although the CBz-protected variant **38a** showed some potential, the yield dropped drastically upon increasing the scale. The Boc-protected version **38b** gave only trace lactam-ketone **40**. At this point, we abandoned this diazo-mediated approach in favor of an aldol-based strategy.

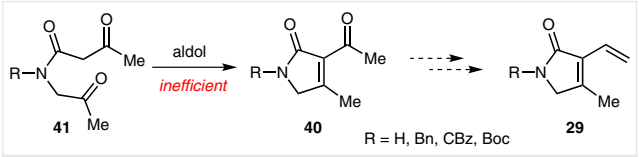


Scheme 9 Attempted direct synthesis of diene **29**

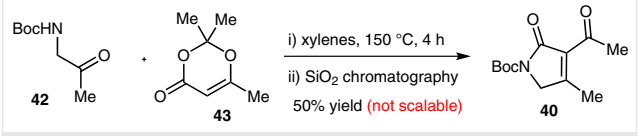


Scheme 10 Attempted diazo-mediated approach to enones **39**,**40**

While an aldol condensation presented an obvious approach (Scheme 11) toward α,β-unsaturated lactam **40**, it had also demonstrated significant shortcomings with several substrates (i.e., R = Cbz, Boc, Bn, H). However, we committed to the aldol strategy and chose the Boc variant for further investigation. Thus, Boc-protected aminoacetone **42**[25] was acylated with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **43**[26] and, upon exposure to silica gel,[27] gave the desired aldol adduct **40** (Scheme 12). Although minor quantity of diene **29a** could be accessed (vide infra), this route was not dependable or amenable to large scale.

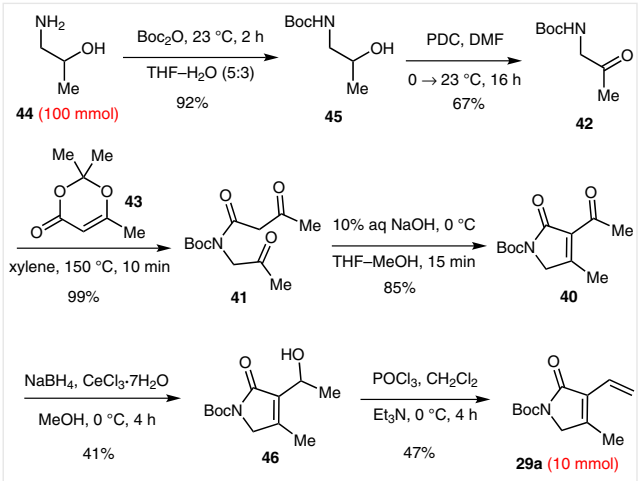


Scheme 11 Overview of the aldol cyclization strategy



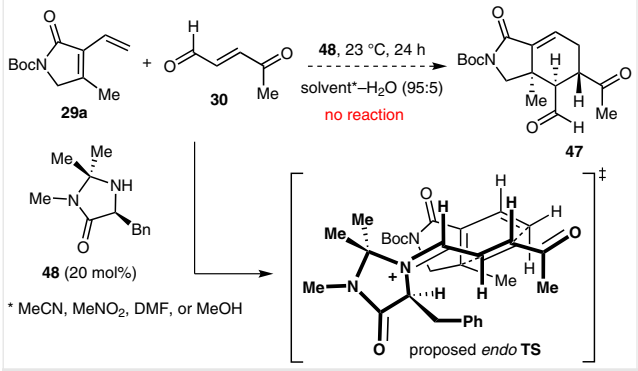
Scheme 12 Initial synthesis of unsaturated Boc-lactam **40**

Therefore, a scalable synthesis of the unsaturated lactam-diene **29a** was developed in order to investigate this intermolecular Diels–Alder strategy (Scheme 13). Boc-protection[28] of the amino alcohol **44** followed by oxidation gave α-amino ketone **42**.[25] Acylation with dioxinone **43**[26] and optimized aldol cyclization delivered enone **40**. $CeCl_3$-mediated Luche reduction[29] followed by $POCl_3$-mediated elimination afforded diene **29a**. This route proved to be dependable in order to deliver multi-gram quantity of requisite diene **29a**.

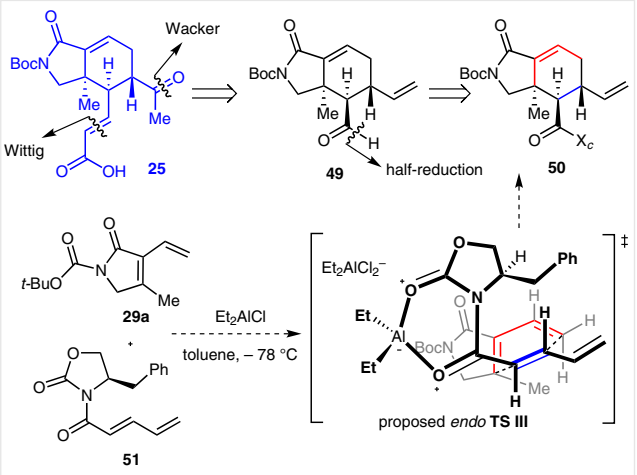


Scheme 13 Scalable synthesis of Boc-lactam diene **29a**

Upon accessing the necessary diene **29a**, several Diels–Alder strategies were envisioned (Schemes 14–17). Our initial strategy centered on imidazolidinone catalysts[30] (i.e., **48**) with fumarate derivative **30**, which was readily accessible from 2-methylfuran (Scheme 14).[23] However, a variety of conditions at ambient temperature afforded no reaction and heating the reaction only promoted decomposition or led to complex mixtures. Alternatively, an oxazolidinone chiral auxiliary-based approach was considered (Scheme 15).[31] However, we postulated that the Boc protecting group of the lactam could function as a competing imide and detract from the ability of the oxazolidinone imide to



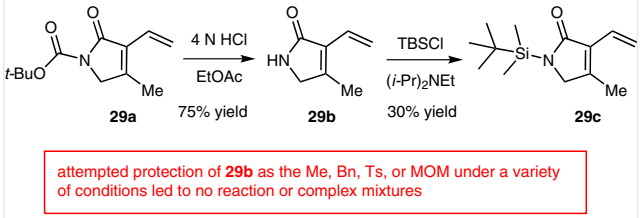
Scheme 14 Attempted imidazolidinone-catalyzed Diels–Alder reaction



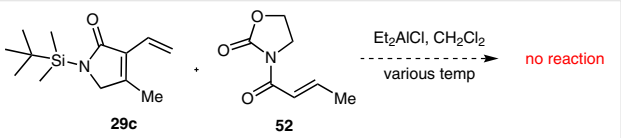
Scheme 15 Proposed oxazolidinone–Et_2AlCl Diels–Alder reaction

chelate to the Et_2AlCl effectively. This would thereby inhibit any productive lowering of the dienophile LUMO and presumably lead to no reaction. Indeed, when this reaction was attempted with an achiral oxazolidinone (vide infra), no cycloadduct and only Boc-deprotection was observed.

At this point, the Boc-protecting group had served the purpose of aiding in the synthesis of a diene that could conceivably be transformed to something more useful (Scheme 16). It was our hope to remove the Boc and replace it with a variety of protecting groups. Unfortunately, this proved to be exceptionally challenging. Upon successful deprotection with 4 N HCl in 1,4-dioxane, attempted re-protection of the lactam **29b** as the Me, Bn, Ts, or MOM under a variety of conditions led to no reaction or only to complex mixtures. Crude ^{1}H NMR analyses of these reactions suggest that the proton α to the nitrogen is relatively acidic due to the impending aromaticity. Attempts to synthesize dienes with other protecting groups (i.e., CBz, Bn, PMB, etc.) from simple starting materials utilizing diazo-mediated routes or aldol-based approaches were very problematic. Fortunately, a less common protecting group (i.e., TBS) was utilized for the lactam, albeit in relatively poor yield. However, the TBS-protected lactam **29c** could be isolated as a pure compound and it was subjected to the desired Diels–Alder cycloaddition conditions with oxazolidinone **52** and Et_2AlCl (Scheme 17). Again no reaction was observed, even at elevated temperatures, further indicating the deactivated nature of these hindered dienes regardless of protecting group (vide supra). It should be noted that diene **29b** was subjected to identical conditions with similar outcomes.

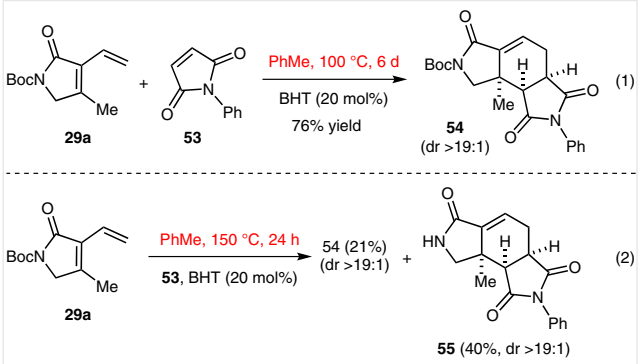


Scheme 16 Boc-deprotection and TBS-protection



Scheme 17 Attempted oxazolidinone–Et_2AlCl Diels–Alder reaction

Several reactive dipolarophiles were investigated in order to ascertain whether these dienes **29a**–**c** were capable of undergoing [4+2] cycloaddition (Schemes 18–21). Upon heating Boc-lactam diene **29a** with *N*-phenylmaleimide (**53**) in toluene, a single diastereomer of the protected hexahydro-1*H*-isoindolinone **54** was observed (Scheme 18, eq 1). Although heating to 150 °C resulted in Boc-deprotection (Scheme 18, eq 2), this proved to be fortuitous since X-ray crystallographic analysis[1d] was ascertained on this hexahydro-1*H*-isoindolinone **55** thus confirming the expected stereochemical outcome (Figure 3). Microwave (μW) irradiation[32] was attempted with mixed results (Table 1). Although rate enhancement was significant, Boc-deprotection was still observed. Alternative dienophiles such as dimethyl fumarate (**56**) and dimethyl acetylenedicarboxylate (**57**) gave no reaction (Scheme 19, eq 1 and 2). Lactam-dienes **29b**,**c** afforded unsatisfactory results with *N*-phenylmaleimide (Scheme 20); **29b** gave poor yield of the cycloadduct **55** (Scheme 20, eq 1) and **29c** gave no reaction (Scheme 20, eq 2).



Scheme 18 Successful Diels–Alder cycloadditions with **29a**

Treatment of lactam-diene **29a** with 4-phenyl-1,2,4-triazoline-3,5-dione (**58**) in CH_2Cl_2 provided excellent yield of the desired cycloadduct **59a** (Scheme 21). This highly reactive dipolarophile **58** was treated with lactam-dienes **29b** and **29c** under similar conditions and delivered the expected cycloadducts **59b** and **59c** in good yields. X-ray crystallographic analysis was also obtained on cycloadduct **59b** (Fig-

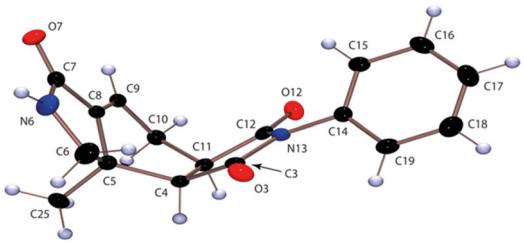
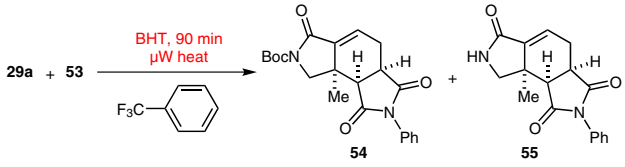
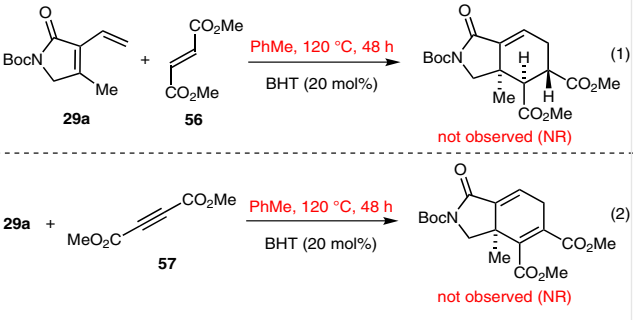


Figure 3 ORTEP of Diels–Alder cycloadduct **55**

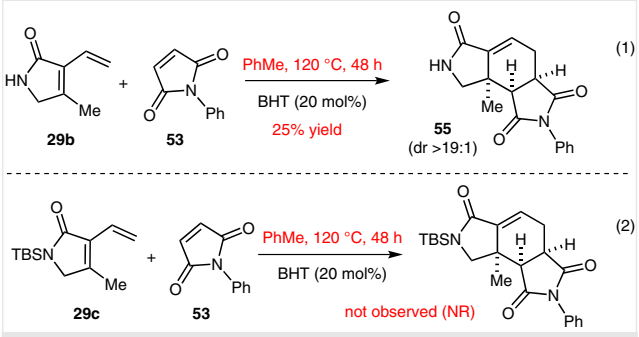
Table 1 Microwave-Promoted Diels–Alder Cycloadditions with **29a**



Entry	Temp (°C)	Conv. (%)	Result
1	140	37	**54** only
2	160	67	**54** and **55**
3	180	100	**55** only

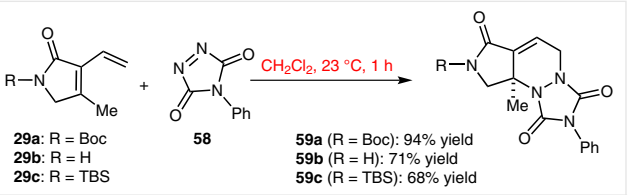


Scheme 19 Unsuccessful Diels–Alder cycloadditions with **29a**



Scheme 20 Attempted Diels–Alder cycloadditions with **29b,c**

ure 4). Interestingly, cycloadduct **59b** adopts a significantly different conformation as compared to hexahydro-1*H*-isoindolinone **55** (cf. Figure 3), presumably due to inversion at the nitrogen atoms of triazolinedione **59b**.



Scheme 21 Effective [4+2] cycloadditions with dipolarophile **58**

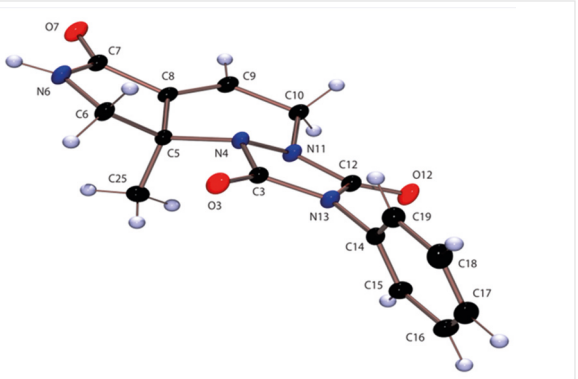


Figure 4 ORTEP of triazolinedione cycloadduct **59b**

In conclusion, our first-generation intramolecular Diels–Alder strategy was unsuccessful (cf. Scheme 1) and a second-generation intermolecular Diels–Alder strategy was employed (cf. Scheme 8). Upon optimization of a scalable synthesis of the Boc-lactam diene **29a** (cf. Scheme 13), a thorough investigation of this intermolecular Diels–Alder cycloaddition strategy was undertaken. Although Diels–Alder cycloadditions that could lead to muironolide A were unsuccessful with dienes **29a–c** (cf. Schemes 14, 15, 17), proof of principle regarding potential [4+2] cycloadditions was achieved when subjected to highly reactive species such as the dienophile *N*-phenylmaleimide (**53**) (cf. Scheme 18) and the dipolarophile 4-phenyl-1,2,4-triazoline-3,5-dione (**58**) (cf. Scheme 21). Taken together, these results serve to establish the scope and limitation of these electronically deactivated and sterically hindered dienes **29a–c**. Whereas our initial report of the Diels–Alder cycloaddition with *N*-phenylmaleimide demonstrated this important proof of principle, the results henceforth obtained and reported in this full account firmly demarcate the limits of these electronically deactivated and sterically hindered dienes. One noteworthy feature of these [4+2] cycloadditions is the efficient installation of the α,β-unsaturated amide that is embedded within the hexahydro-1*H*-isoindolinone. Although unfortunate that direct installation of the α,β-unsaturated amide was not amenable toward Diels–Alder cycloadditions that could lead to muironolide A, these developments will

allow further innovations toward this important synthetic target. Further investigation of alternative Diels–Alder strategies toward muironolide A will be reported in due course.

All reactions were carried out under argon atmosphere in oven-dried glassware. All commercially available anhydrous solvents and reagents were used as received. TLC was performed with glass plates (silica gel F_{254}, Art 5715, 0.25 mm), visualized by fluorescence quenching under UV light, and stained with $KMnO_4$ solution. Flash column chromatography was performed with silica gel 60 (200–400 mesh). Mass spectral data was acquired using positive mode Electrospray Ionization (ESI+) and a high-resolution Time of Flight (TOF) mass spectrometer. IR spectra were acquired on a FTIR spectrometer and reported as wavenumbers (cm^{-1}). ^1H NMR spectra were recorded at 400 or 500 MHz and ^{13}C NMR spectra at 100 MHz or 125 MHz.

N-(Benzyloxycarbonyl)allylamine (13)

To a solution of allylamine (**6**; 3.7 mL, 50.0 mmol) in H_2O (75 mL) was added K_2CO_3 (17.30 g, 125 mmol) and EtOAc (75 mL). The reaction was then cooled to 0 °C and benzyl chloroformate (7.1 mL, 50.0 mmol) was added over a period of 15 min. The mixture was allowed to warm to 23 °C and stirred for 2 h. The organic layer was separated and washed with aq 10% HCl (2 × 50 mL), brine (50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford CBz-allylamine **13** as a clear oil; yield: 9.37 g (98%).

CBz-Allylamide 8

To a solution of CBz-allylamine **13** (6.00 g, 32.0 mmol) in benzene (95 mL) was added methyl malonyl chloride (**7**; 6.9 mL, 64.0 mmol) at 23 °C. This solution was refluxed at 80 °C, stirred for 2 h, and then quenched with sat. aq $NaHCO_3$ (200 mL) and stirred for 10 min. The solution was diluted with Et_2O (400 mL), the combined organic extracts were separated, and washed with additional sat. aq $NaHCO_3$ (200 mL), H_2O (200 mL) and brine (200 mL), and then dried (Na_2SO_4), decanted, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes–EtOAc, 80:20) delivered CBz-allylamide **8** as a colorless oil; yield: 7.70 g (83%).

Diazo Amide 9

To a solution of CBz-allylamide **8** (1.00 g, 3.43 mmol) and *p*-ABSA (1.28 g, 5.15 mmol) in MeCN (41 mL) was added Et_3N (1.9 mL, 13.7 mmol) at 0 °C. The solution was stirred while warming to 23 °C for 66 h and then most (~80%) of the MeCN was removed under reduced pressure using a rotary evaporator. The reaction mixture was then triturated with hexanes–Et_2O (1:1), filtered through a silica gel plug, and concentrated again under reduced pressure to afford diazo amide **9** as a yellow oil; yield: 753 mg (69%).

Unsaturated CBz-Lactam Ester 5

A solution of diazo amide **9** (820 mg, 2.70 mmol) in benzene (27 mL) was heated to reflux (80 °C) for 42 h. The reaction was allowed to cool to 23 °C and then concentrated under reduced pressure. Purification by flash column chromatography (hexanes–EtOAc, 30:70) delivered CBz-lactam ester **5** as a yellow solid; yield: 569 mg (66%); mp 107 °C; R_f = 0.38 (hexanes–EtOAc, 30:70).

IR (neat): 1751, 1699, 1187, 718, 697 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.34 (m, 5 H), 5.33 (s, 2 H), 4.33 (s, 2 H), 3.88 (s, 3 H), 2.40 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.9, 164.0, 162.2, 150.7, 135.2, 128.6 (2), 128.4, 128.0 (2), 124.4, 68.1, 53.1, 52.0, 15.6.

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}NO_5$: 290.1028; found: 290.1037.

Saturated CBz-Lactam Ester 12

To a solution of CBz-lactam ester **5** (115 mg, 0.400 mmol) in THF (6.4 mL) was added LiAlH(*t*-BuO)$_3$ (360 µL, 0.400 mmol) at –78 °C. The solution stirred for 15 min at –78 °C before warming to 0 °C slowly over a period of 2 h. The reaction mixture was stirred at 0 °C for 30 min before quenching with H_2O (10 mL) and warming to 23 °C. The mixture was filtered over a Celite pad with EtOAc and the filtrate was washed with H_2O (10 mL). The organic layer was dried (Na_2SO_4), decanted, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes–EtOAc, 60:40) delivered saturated lactam ester **12** as a colorless oil; yield: 45 mg (38%); R_f = 0.47 (hexanes–EtOAc, 60:40).

IR (neat): 1724, 1700, 1273, 763, 697 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.44–7.31 (m, 5 H), 5.30 (d, *J* = 12.4 Hz, 1 H), 5.26 (d, *J* = 12.4 Hz, 1 H), 4.04 (dd, *J* = 10.7, 7.9 Hz, 1 H), 3.79 (s, 3 H), 3.32 (dd, *J* = 10.7, 8.0 Hz, 1 H), 3.20 (d, *J* = 9.2 Hz, 1 H), 2.79 (m, 1 H), 1.18 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.6, 168.4, 151.3, 135.2, 128.8 (2), 128.6, 128.3 (2), 68.5, 57.8, 53.0, 51.7, 30.7, 17.9.

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{17}NO_5$: 292.1185; found: 292.1190.

Propionyl Amide 14

To a solution of CBz allylamine **13** (3.50 g, 18.3 mmol) in THF (91 mL) was added NaHMDS at –78 °C. After stirring for 1 h, propionyl chloride (2.0 mL, 22.0 mmol) was added and the mixture was allowed to stir for 2 h at –78 °C. The mixture was then quenched with sat. aq NH_4Cl (90 mL) and allowed to warm to 23 °C while stirring vigorously for 10 min. The solution was diluted with EtOAc (300 mL), the combined organic extracts were separated, and washed with sat. aq $NaHCO_3$ (100 mL), brine (100 mL), dried (Na_2SO_4), decanted, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes–EtOAc, 95:5) delivered propionyl amide **14** as a colorless oil; yield: 3.00 g (66%); R_f = 0.60 (hexanes–EtOAc, 80:20).

IR (neat): 1732, 1701, 1197, 736, 696 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.35 (m, 5 H), 5.85–5.75 (m, 1 H), 5.22 (s, 2 H), 5.13–5.08 (m, 2 H), 4.36 (dt, *J* = 5.7, 1.4 Hz, 2 H), 2.92 (q, *J* = 7.3 Hz, 2 H), 1.14 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.5, 154.4, 135.3, 133.3, 128.8 (2), 128.7, 128.4 (2), 117.0, 68.6, 46.4, 31.8, 9.4.

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{17}NO_3$: 248.1287; found: 248.1282.

Hydantoin 20

To a solution of propionyl amide **14** (495 mg, 2.0 mmol) in THF (20 mL) cooled to –78 °C was added NaHMDS (2.0 mL of a 2 M solution, 4.0 mmol) dropwise. After 1 h, *p*-ABSA (481 mg, 2.0 mmol) was added and allowed to stir for 5 h at –78 °C. The reaction was quenched with sat. aq NH_4Cl (30 mL) and allowed to warm slowly to 23 °C. The mixture was diluted with EtOAc (100 mL), the organic layer was separated, and washed with additional sat. aq NH_4Cl (30 mL), H_2O (30 mL) and brine (30 mL), dried (Na_2SO_4), decanted, and concentrated under reduced pressure. The crude solid was then triturated with hexanes–EtOAc (90:10) to afford a solid. Purification by flash column chroma-

tography (CH_2Cl_2–MeOH, 90:10) delivered hydantoin **20** as an off-white solid; yield: 250 mg (36%); mp 106 °C (dec.); R_f = 0.32 (CH_2Cl_2–MeOH, 90:10).

IR (neat): 3345, 1747, 1266, 1163, 838 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.9 Hz, 2 H), 7.73 (d, *J* = 8.9 Hz, 2 H), 7.43 (br s, 1 H), 5.85–5.75 (m, 1 H), 5.32–5.26 (m, 2 H), 4.62 (q, *J* = 6.8 Hz, 1 H), 4.21 (dt, *J* = 6.1, 1.3 Hz, 2 H), 2.23 (s, 3 H), 1.61 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5, 169.4, 151.1, 144.4, 131.2 (2), 129.6 (2), 128.2, 120.0, 119.6, 55.9, 41.9, 24.9, 14.6.

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{17}NO_5S$: 352.0967; found: 352.0964.

β-Keto-α-Diazo Amide 38a

To a solution of CBz-allylamine **13** (2.87 g, 15.0 mmol) in *p*-xylene (15 mL) was added dioxinone **43** (3.3 mL, 22.5 mmol) at 23 °C. This solution was heated to reflux at 150 °C, stirred for 1.5 h, cooled to 23 °C, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes–EtOAc, 70:30) delivered the corresponding β-keto amide (3.05 g, 74%) as a yellow oil. To a solution of this amide (2.00 g, 7.3 mmol) in MeCN (36 mL) at 0 °C was added *p*-ABSA (2.70 g, 10.9 mmol) and Et_3N (4.0 mL, 29.0 mmol). The reaction was allowed to warm to 23 °C while stirring for 20 h and concentrated under reduced pressure. The crude solid was triturated with hexanes–EtOAc (1:1), filtered over silica gel, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes–EtOAc, 80:20) delivered β-keto-α-diazo amide **38a** as a yellow oil (1.27 g, 58%).

CBz-Lactam Ketone 39

A solution of **38a** (820 mg, 2.7 mmol) in benzene (78 mL) was heated to reflux (80 °C) for 60 h. The mixture was cooled to 23 °C and concentrated under reduced pressure. Purification by flash column chromatography (hexanes–EtOAc, 70:30) delivered CBz-lactam ketone **39** as a yellow solid; yield: 172 mg (23%); mp 105–107 °C; R_f = 0.33 (hexanes–EtOAc, 60:40).

IR (neat): 1738, 1716, 1679, 1313, 744, 699 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.46–7.34 (m, 5 H), 5.34 (s, 2 H), 4.32 (s, 2 H), 2.56 (s, 3 H), 2.30 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.5, 166.8, 166.3, 1507, 135.2, 130.5, 128.7 (2), 128.6, 128.4 (2), 68.3, 53.4, 30.5, 15.9.

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}NO_4$: 274.1079; found: 274.1087.

β-Keto-α-diazo Amide (38b)

To a solution of allylamine (**6**; 3.0 mL, 39.8 mmol) in THF (20 mL) was added *i*-Pr_2NEt (13 mL, 80.0 mmol) and Boc_2O (9.0 mL, 39.9 mmol). After stirring 1 h, the reaction mixture was diluted with Et_2O (50 mL), the organic layer was separated, and washed with sat. aq NH_4Cl (3 × 20 mL), H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4), poured over a silica gel plug, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes–EtOAc, 90:10) delivered the corresponding Boc-allylamine (5.16 g, 81%) as a clear oil. To a solution of this Boc-allylamine (2.60 g, 16.4 mmol) in *p*-xylene (16 mL) was added dioxinone **43** (3.6 mL, 24.7 mmol). The reaction mixture was heated to reflux (150 °C) for 1.5 h, then allowed to cool to 23 °C, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes–EtOAc, 80:20) delivered the corresponding β-keto amide (2.35 g, 59%) as a yellow oil. To a solution of this β-keto amide (2.66 g, 11.0 mmol) in MeCN (55 mL) was added *p*-ABSA (4.01 g, 16.5 mmol) and Et_3N (6.2 mL, 44.1 mmol) at 0 °C. The reaction was allowed to warm to 23 °C and stirred for 16 h. The mixture was concentrated and triturated with hexanes–EtOAc (1:1), poured over silica gel, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes–EtOAc, 80:20) delivered **38b** as a yellow oil; yield: 2.45 g (83%); R_f = 0.60 (hexanes–EtOAc, 70:30).

IR (neat): 2128, 1726, 1657, 1141 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.86 (m, 1 H), 5.18 (m, 2 H), 4.20 (dt, *J* = 5.7, 1.4 Hz, 2 H), 2.43 (s, 3 H), 1.48 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.6, 163.8, 152.0, 133.3, 117.5, 84.0, 81.2, 48.4, 28.3, 27.9 (3).

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{17}N_3O_4Na$: 290.1117; found: 290.1115.

Unsaturated Boc-Lactam 40

From Boc-aminoacetone ***42***: To a solution of Boc-aminoacetone **42** (4.21 g, 24.3 mmol) in *p*-xylene (24 mL) was added dioxinone **43** (7.1 mL, 48.6 mmol). The reaction was heated to reflux (150 °C) for 4 h, cooled to 23 °C, and concentrated under reduced pressure to afford the crude β-keto amide. Purification by flash column chromatography (CH_2Cl_2–Et_2O, 90:10) provided mixed fractions of β-keto amide and unsaturated Boc-lactam **40**. Unsaturated Boc-lactam **40** was isolated (1.37 g, 24%) as a yellow oil. The mixed fractions were re-introduced to flash column chromatography (CH_2Cl_2–Et_2O, 90:10), which provided an additional amount of lactam **40** (1.78 g, 31%) as a yellow oil; combined total yield: 3.15 g (55%).

Boc-1-Aminopropan-2-ol 45

To a solution of 1-aminopropan-2-ol (**44**; 8.2 mL, 100 mmol) in THF–H_2O (38 mL:38 mL) was added Boc_2O (23 mL, 100 mmol) in THF (25 mL). The mixture was stirred at 23 °C for 2 h and concentrated. The organic layer was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with aq NH_4Cl (2 × 50 mL) and brine (100 mL), dried ($MgSO_4$), filtered, and concentrated to give **45** as a colorless oil; yield: 16.0 g (92.0 mmol, 92%).

Boc-Aminoacetone 42

To a solution of PDC (68.9 g, 183 mmol) in DMF (50 mL) was added **45** (16.0 g, 92.0 mmol) in DMF (42 mL) at 0 °C. The reaction was allowed to stir for 16 h while warming to 23 °C. The reaction mixture was poured over a plug of Celite with Et_2O, quenched with brine (200 mL), and diluted with Et_2O (700 mL). The combined Et_2O layers were washed with aq NH_4Cl (2 × 200 mL), H_2O (2 × 200 mL), and brine (2 × 200 mL), dried ($MgSO_4$), filtered, and concentrated to give Boc-aminoacetone **42** as a yellow oil; yield: 10.6 g (61.0 mmol, 61%).

β-Keto Amide 41

To a round-bottomed flask was added **42** (10.6 g, 61.0 mmol), dioxinone **43** (8.9 mL, 61.0 mmol), and xylenes (61 mL), and heated to 150 °C for 10 min. The reaction was allowed to cool and the mixture was concentrated under reduced pressure to give β-keto amide **41** as a brown solid; yield: 15.54 g (60.4 mmol, 99%). Due to the propensity to form the aldol adduct, this compound was not fully characterized.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.52 (s, 2 H), 4.05 (s, 2 H), 2.26 (s, 3 H), 2.17 (s, 3 H), 1.44 (s, 9 H).

Unsaturated Boc-Lactam 40

*From β-Keto Amide **41***: In a round-bottomed flask was added β-keto amide **41** (15.54 g, 60.4 mmol), THF (92 mL), and MeOH (31 mL), and cooled to 0 °C. Aq 10% NaOH (31 mL) was added to the mixture and it was allowed to stir for 15 min. The mixture was concentrated and then diluted with EtOAc (400 mL). The EtOAc layer was washed with aq NH_4Cl (2 × 100 mL), H_2O (2 × 100 mL) and brine (2 × 100 mL), dried ($MgSO_4$), filtered, and concentrated to give unsaturated Boc-lactam **40** as a brown solid, yield: 12.3 g (52.0 mmol, 85%). Immediate conversion to the subsequent allylic alcohol was generally employed due to mild instability of the aldol adduct.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.26 (s, 2 H), 2.56 (s, 3 H), 2.38 (s, 3 H), 1.57 (s, 9 H).

Allylic Alcohol 46

$CeCl_3·7H_2O$ (38.3 g, 103 mmol) was dissolved in MeOH (130 mL) and stirred for 5 min. Unsaturated Boc-lactam **40** (12.3 g, 52.0 mmol) was added, stirred for 5 min, and cooled to 0 °C. $NaBH_4$ (3.89 g, 103 mmol) was added slowly and the mixture was allowed to stir for 4 h at 0 °C. The reaction was quenched with aq 1 M HCl (200 mL) and extracted with EtOAc (3 × 300 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by flash column chromatography (hexanes–EtOAc, 40:60) delivered allylic alcohol **46** as a yellow oil; yield: 5.14 g (21.3 mmol, 42%); R_f = 0.23 (hexanes–EtOAc 40:60).

IR (neat): 3481, 1761, 1712, 1670 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.66 (q, *J* = 6.7 Hz, 1 H), 4.12 (s, 2 H), 3.47 (br s, 1 H), 2.03 (s, 3 H), 1.54 (s, 9 H), 1.45 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.8, 149.5, 149.2, 134.3, 83.2, 63.7, 53.3, 28.2 (3), 23.1, 13.2;

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{19}NO_4$: 242.1392; found: 242.1397.

Boc-Lactam Diene 29a

To a round-bottomed flask was added allylic alcohol **46** (5.14 g, 21.3 mmol), Et_3N (36 mL, 256 mmol), and CH_2Cl_2 (375 mL). The solution was cooled to 0 °C and a solution of $POCl_3$ (8 mL, 85.0 mmol) in CH_2Cl_2 (50 mL) was added. The reaction mixture was allowed to stir for 4 h while slowly warming to 23 °C. The resulting solution was diluted with Et_2O (700 mL), washed with H_2O (3 × 300 mL) and brine (3 × 300 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by flash column chromatography (hexanes–EtOAc, 85:15) delivered lactam-diene **29a** as a white solid; yield: 2.23 g (10.0 mmol, 47%); mp 82 °C; R_f = 0.20 (hexanes–EtOAc, 80:20).

IR (neat): 1726, 1712, 1655, 1151 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.41 (dd, *J* = 11.6, 2.2 Hz, 1 H), 6.29 (dd, *J* = 17.7, 2.2 Hz, 1 H), 5.44 (dd, *J* = 17.7, 11.6 Hz, 1 H), 4.15 (s, 2 H), 2.11 (s, 3 H), 1.56 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.2, 150.5, 150.0, 128.5, 125.0, 120.2, 82.9, 52.7, 28.3 (3), 13.8.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{17}NO_3Na$: 246.1115; found: 246.1106.

Lactam Diene 29b

To a round-bottomed flask was added Boc-lactam diene **29a** (1.12 g, 5.0 mmol) and EtOAc (10 mL). The resulting solution was cooled to 0 °C followed by the addition of aq 4 N HCl in 1,4-dioxane (12.5 mL, 50.0 mmol). The ice bath was removed and the reaction was allowed to warm to r.t. over 1 h. The solution was diluted with CH_2Cl_2 (100 mL), washed with sat. aq Na_2CO_3 (2 × 50 mL), H_2O (2 × 50 mL) and brine (2 × 50 mL), and dried ($MgSO_4$). The resulting solution was poured over a pad of silica gel with EtOAc (300 mL) and concentrated to afford lactam diene **29b** as a red solid; yield: 459 mg (75%); mp 84–86 °C; R_f = 0.20 (hexanes–EtOAc, 10:90).

IR (neat): 1670, 1645 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (br s, 1 H), 6.45 (dd, *J* = 17.7, 11.5 Hz, 1 H), 6.20 (dd, *J* = 17.7, 2.1 Hz, 1 H), 5.42 (dd, *J* = 11.5, 2.1 Hz, 1 H), 3.85 (s, 2 H), 2.08 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.8, 151.1, 128.4, 125.8, 119.0, 49.9, 13.7.

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for C_7H_9NO: 124.0762; found: 124.0764.

TBS-Lactam Diene 29c

To a round-bottomed flask was added **29b** (123 mg, 1.0 mmol), *i*-Pr_2NEt (348 μL, 2.0 mmol), and CH_2Cl_2 (5 mL). The solution was cooled to 0 °C and TBSCl (181 mg, 1.2 mmol) was added. The reaction was allowed to stir at r.t. for 24 h. The resulting solution was diluted with EtOAc (20 mL), washed aq NH_4Cl (10 mL), H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated. Purification by flash column chromatography (hexanes–Et_2O, 95:5) delivered TBS-lactam diene **29c** as a white solid; yield: 71 mg (30%); R_f = 0.27 (hexanes–Et_2O, 90:10).

IR (neat): 1670, 1660 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.45 (dd, *J* = 17.7, 11.6 Hz, 1 H), 6.23 (dd, *J* = 17.7, 2.5 Hz, 1 H), 5.37 (dd, *J* = 11.6, 2.5 Hz, 1 H), 3.79 (s, 2 H), 2.06 (s, 3 H), 0.96 (s, 9 H), 0.31 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.9, 152.1, 129.3, 125.9, 118.7, 54.5, 26.7 (3), 19.4, 13.5, -5.2 (2).

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{23}NOSi$: 238.1622; found: 238.1621.

Boc-hexahydro-1*H*-isoindolinone 54

N-Phenylmaleimide (**53**; 89 mg, 0.500 mmol), butylated hydroxytoluene (BHT; 11 mg, 0.050 mmol), and Boc-lactam-diene **29a** (56 mg, 0.250 mmol) were dissolved in toluene (1 mL). The solution was sealed in a Teflon capped vial with Teflon tape, heated to 100 °C for 6 days, cooled to 23 °C, and concentrated under reduced pressure to afford 95% conversion (crude ^{1}H NMR analysis). Purification by flash column chromatography (hexanes–EtOAc, 60:40) delivered **54** as a white solid; yield: 74 mg (74%); mp 80–82 °C; R_f = 0.13 (hexanes–EtOAc, 60:40).

IR (neat): 1769, 1705, 1147, 727, 691 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.48–7.38 (m, 3 H), 7.20–7.18 (m, 2 H), 6.97 (dd, *J* = 7.5, 2.8 Hz, 1 H), 4.73 (d, *J* = 11.6 Hz, 1 H), 3.63 (d, *J* = 11.6 Hz, 1 H), 3.49 (ddd, *J* = 9.0, 8.9, 1.3 Hz, 1 H), 3.36 (d, *J* = 8.9 Hz, 1 H), 3.10 (ddd, *J* = 17.8, 7.5, 1.3 Hz, 1 H), 2.71 (ddd, *J* = 17.8, 9.0, 2.8 Hz, 1 H), 1.54 (s, 9 H), 1.39 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.5, 175.5, 163.7, 150.4, 139.9, 131.6, 131.4, 129.3 (2), 129.0, 126.5 (2), 83.3, 53.9, 47.8, 39.1, 35.8, 28.1 (3), 26.7, 24.5.

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{24}N_2O_5$: 397.1763; found: 397.1769.

Isoindolinone (54)/Deprotected Isoindolinone 55

N-Phenylmaleimide **53** (77 mg, 0.450 mmol), BHT (10 mg, 0.040 mmol), and Boc-lactam diene **29a** (50 mg, 0.220 mmol) were dissolved in toluene (1.2 mL). The solution was sealed in a Teflon capped vial with Teflon tape, heated to 150 °C for 24 h, cooled to 23 °C, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes–EtOAc, 50:50) delivered Boc-hexahydro-1*H*-isoindolinone **54** (19 mg, 21%) and deprotected hexahydro-1*H*-isoindolinone **55** (27 mg, 40%) as white solids; mp 180–184 °C (dec.); R_f = 0.13 (EtOAc).

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IR (neat): 1699, 1678, 1195, 758, 689 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.17 (m, 5 H), 6.79 (br s, 1 H), 6.75 (dd, *J* = 7.4, 2.8 Hz, 1 H), 4.49 (d, *J* = 10.3 Hz, 1 H), 3.45 (ddd, *J* = 8.8, 8.7, 1.3 Hz, 1 H), 3.32 (d, *J* = 8.8 Hz, 1 H), 3.22 (d, *J* = 10.3 Hz, 1 H), 3.05 (ddd, *J* = 17.5, 7.4, 1.3 Hz, 1 H), 2.68 (ddd, *J* = 17.5, 8.7, 2.8 Hz, 1 H), 1.37 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.8, 175.9, 168.1, 140.0, 131.6, 129.3 (2), 129.0, 127.6, 126.6 (2), 50.4, 48.1, 39.5, 39.3, 26.8, 24.3.

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{16}N_2O_3$: 297.1239; found: 297.1237.

Boc-Triazolinedione 59a

In a vial, **29a** (112 mg, 0.500 mmol) and 4-phenyl-1,2,4-triazoline-3,5-dione (**58**; 105 mg, 0.600 mmol) were dissolved in anhydrous CH_2Cl_2 (2.5 mL). The reaction mixture was allowed to stir for 1 h at 23 °C. The resulting solution was concentrated and purification by flash column chromatography (hexanes–EtOAc, 60:40) delivered Boc-triazolinedione **59a** as a white solid; yield: 187 mg (94%); mp 175–177 °C; R_f = 0.25 (hexanes–EtOAc, 60:40).

IR (neat): 1756, 1701, 764, 697 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.51–7.47 (m, 4 H), 7.41–7.38 (m, 1 H), 6.84 (dd, *J* = 3.2, 3.0 Hz, 1 H), 4.66 (dd, *J* = 19.1, 3.2 Hz, 1 H), 4.24 (m, 1 H), 4.19 (m, 1 H), 3.98 (dd, *J* = 10.9, 0.7 Hz, 1 H), 1.57 (m, 3 H), 1.56 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.4, 152.9, 152.0, 149.9, 136.7, 130.9, 129.4 (2), 128.6, 125.9, 125.3 (2), 84.3, 57.7, 55.1, 43.7, 28.2 (3), 20.5.

ESI-HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{22}N_4O_5Na$: 421.1488; found: 421.1496.

Triazolinedione 59b

In a vial, **29b** (62 mg, 0.500 mmol) and 4-phenyl-1,2,4-triazoline-3,5-dione (**58**; 105 mg, 0.600 mmol) were dissolved in CH_2Cl_2 (2.5 mL). The reaction mixture was allowed to stir for 1 h at 23 °C. The resulting solution was concentrated and purification by flash column chromatography (hexanes–EtOAc, 5:95) delivered triazolinedione **59b** as a white solid; yield: 105 mg (71%); mp 214–216 °C; R_f = 0.30 (EtOAc).

IR (neat): 3208, 1699, 1693, 747, 690 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.53–7.38 (m, 5 H), 6.70 (dd, *J* = 3.1, 3.0 Hz, 1 H), 6.36 (br s, 1 H), 4.66 (dd, *J* = 18.7, 3.1 Hz, 1 H), 4.20 (dd, *J* = 18.7, 3.0 Hz, 1 H), 3.85 (d, *J* = 9.7 Hz, 1 H), 3.78 (d, *J* = 9.7 Hz, 1 H), 1.59 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.9, 153.0, 152.0, 136.5, 131.0, 129.4 (2), 128.6, 125.4 (2), 122.7, 60.7, 51.9, 43.5, 20.5.

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{14}N_4O_3$: 299.1144; found: 299.1128.

X-ray Crystal Data

Crystals of **59b** were obtained by slow evaporation and suspended in mineral oil at r.t. and a suitable crystal was selected. A mineral oil coated brown plate thereby obtained of approximate dimensions 0.205 mm × 0.148 mm × 0.117 mm was mounted on a 50 µm Micro-Mesh MiTeGen Micromount and transferred to a Bruker AXS SMART APEX CCD X-ray diffractometer. The X-ray diffraction data were collected at 100(2) K using MoK_α (λ = 0.71073 Å) radiation. A total of 3672 frames were collected. The total exposure time was 8.16 h. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm.[33] The integration of the data using a triclinic unit cell yielded a total of 28119 reflections to a maximum θ angle of 32.028° (0.67 Å resolution), of which 4661 were independent (average redundancy 6.033, completeness = 96.2%, R_{int} = 2.84%, R_{sig} = 2.11%) and 3900 (83.67%) were observed with $F_o^2 > 2\sigma(F_o^2)$. The final cell constants of *a* = 7.8560(2) Å, *b* = 8.1380(2) Å, *c* = 11.2941(3) Å, α = 74.704(2)°, β = 88.544(2)°, γ = 87.086(2)°, volume = 695.52(3) Å^3, are based upon the refinement of the XYZ-centroids of 9497 reflections above 20 σ(*I*) with 5.20° < 2θ < 63.48°. Limiting indicies were as follows: −11 ≤ *h* ≤ 11, −12 ≤ *k* ≤ 12, −16 ≤ *l* ≤ 16. Data were corrected for absorption effects using the multi-scan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.956 with minimum and maximum SADABS generated transmission coefficients of 0.7135 and 0.7463. Solution and data analysis were performed using the WinGX software package.[34] The structure was solved and refined in the space group *P*-1 (no. 2) with *Z* = 2.[35] The solution was achieved by charge-flipping methods using the program SUPERFLIP[36] and the refinement was completed using the program SHELXL-2014/7.[37] All non-H atoms were refined anisotropically. The H atom attached to N was freely refined isotropically after identification by difference Fourier. All other H atoms were initially identified by difference Fourier then included in the final refinement using the riding-model approximation [C–H = 0.95, 0.98, 0.99 and 1.00 Å for Ar–H, CH_3, CH_2, and CH; U_{iso}(H) = 1.2U_{eq}(C) except for methyl groups, where U_{iso}(H) = 1.5U_{eq}(C)]. Full-matrix least-squares refinement on F^2 led to convergence, $(\Delta/\sigma)_{max}$ = 0.001, $(\Delta/\sigma)_{mean}$ = 0.000, with R_1 = 0.0399 and wR_2 = 0.1108 for 4661 data with $F_o^2 > 2\sigma(F_o^2)$ using 0 restraints and 203 parameters. A final difference Fourier synthesis showed features in the range of $\Delta\rho_{max}$ = 0.422 e$^-$/Å^3 to $\Delta\rho_{min}$ = −0.218 e$^-$/Å^3. All residual electron density away was within accepted norms and was deemed of no chemical significance. Molecular diagrams were generated using ORTEP-3.[38,39]

TBS-Triazolinedione 59c

To a vial was added **29c** (34 mg, 0.140 mmol) and 4-phenyl-1,2,4-triazoline-3,5-dione **58** (30 mg, 0.150 mmol) and dissolved in CH_2Cl_2 (700 µL). The reaction mixture was allowed to stir for 1 h at 23 °C. The resulting solution was concentrated and purification by flash column chromatography (hexanes–EtOAc, 55:35) delivered TBS-triazolinedione **59c** as a white solid; yield: 40 mg (0.10 mmol, 68%); mp 131–136 °C (dec.); R_f = 0.38 (hexanes–EtOAc, 60:40).

IR (neat): 1712, 1694, 1682, 745, 692 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.50–7.40 (m, 5 H), 6.61 (dd, *J* = 3.1, 3.0 Hz, 1 H), 4.63 (dd, *J* = 18.5, 3.1 Hz, 1 H), 4.18 (dd, *J* = 18.5, 3.0 Hz, 1 H), 3.78 (d, *J* = 10.3 Hz, 1 H), 3.74 (d, *J* = 10.3 Hz, 1 H), 1.54 (s, 3 H), 0.99 (s, 9 H), 0.36 (s, 3 H), 0.33 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.9, 152.9, 152.0, 138.6, 131.1, 129.4 (2), 128.5, 125.4 (2), 121.3, 60.6, 56.2, 43.4, 26.7 (3), 20.5, 19.7, −5.1, −5.2.

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{28}N_4O_3Si$: 413.2009; found: 413.1987.

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Supporting Information

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