Synthetic Efforts toward the Isoindolinone Core of Muironolide A

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GENERAL METHODS

All reactions were carried out under N₂ in oven-dried glassware. All commercially available reagents were used as received. Thin layer chromatography was performed with glass or aluminum plates (silica gel F₂₅₄, Art 5715, 0.25 mm), visualized by fluorescence quenching under UV light, and stained with potassium permanganate. Flash column chromatography was performed with silica gel 60 (200-400 mesh) as described by Still.¹ Mass spectral data was acquired using Electrospray Ionization (ESI) or Electron Ionization (EI) and a high resolution Time of Flight (TOF) mass spectrometer. Infrared spectra were acquired on a FTIR spectrometer and were reported as wavenumbers (cm⁻¹). ¹H spectra were acquired at 400 or 500 MHz and ¹³C spectra were acquired at 100 MHz or 125 MHz where noted. ¹H and ¹³C NMR chemical shifts are reported in ppm (δ) relative to the residual solvent peaks. ¹H NMR coupling constants (J) are reported in Hertz (Hz), and multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), dd (doublet of doublets), ddd (doublet of doublet of doublets), ddt (doublet of doublet of triplets), m (multiplet). Based on intensity in the ¹³C spectra, both magnetic and chemical shift equivalent peaks are noted in parentheses.

**PREPARATION AND CHARACTERIZATION OF NEW COMPOUNDS**

**α,β-Unsaturated Lactam Ester 12.** To a solution of CBz allylamine 13 (6.00 g, 32 mmol) in benzene (95 mL) was added methyl malonyl chloride (6.9 mL, 64 mmol) at 23 °C. This solution was heated to reflux at 80 °C, stirred for 2 h, and then quenched with sat. aq. NaHCO₃ (200 mL) and stirred for 10 min. The solution was diluted with Et₂O (400 mL), the combined organic extracts were separated and washed with additional sat. aq. NaHCO₃ (200 mL), water (200 mL), and brine (200 mL), and then dried over Na₂SO₄, decanted, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc 80:20) delivered CBz allylamide (7.70 g, 83%) as a clear oil. To a solution of CBz allylamide (1.00 g, 3.4 mmol) and p-ABSA (1.28 g, 5.1 mmol) in acetonitrile (41 mL) was added triethylamine (1.9 mL, 13.7 mmol) at 0 °C. The solution stirred while warming to 23 °C for 66 h and ~90% of the acetonitrile was removed under reduced pressure. The reaction was then triturated with hexanes:Et₂O (1:1), filtered through silica gel, and concentrated under reduced pressure to afford diazo ester 14 (753 mg, 69%) as a yellow oil. A solution of diazo ester 14 (820 mg, 2.7 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 α,β-unsaturated lactam ester 12 (569 mg, 66%) as a yellow solid: mp 107 °C; Rf = 0.38 (hexanes:EtOAc 30:70); IR (neat) 1751, 1699, 1187, 718, 697 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.40 (s, 3H), 3.88 (s, 3H), 4.33 (s, 2H), 5.33 (s, 2H), 7.34-7.47 (m, 5H); ¹³C NMR (125 MHz, CDCl₃) δ 15.6, 52.0, 159.6, 167.7, 168.3, 172.1, 176.4, 192.5, 201.2.

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Lactam-Ester 15. To a solution of α,β-unsaturated lactam ester 12 (115 mg, 0.39 mmol) in THF (6 mL) was added Li(tBuO)₃AlH (360 μL, 1.1 M in THF, 0.40 mmol) at -78 °C. The solution stirred for 15 min at -78 °C before warming to 0 °C slowly over a period of 2 hr. The reaction was stirred at 0 °C for 30 min, quenched with H₂O (10 mL), and warmed to 23 °C. The reaction was filtered over Celite with EtOAc and the filtrate was washed with H₂O (10 mL). The organic layer was dried over Na₂SO₄, decanted, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc 60:40) delivered lactam-ester 15 (45 mg, 38%) as a colorless oil: Rᵓ = 0.47 (hexanes:EtOAc 60:40); IR (neat) 1724, 1700, 1273 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.18 (d, J = 6.7 Hz, 3H), 2.79 (m, 1H), 3.20 (d, J = 9.2 Hz, 1H), 3.32 (dd, J = 8.0, 10.7 Hz, 1H), 3.79 (s, 3H), 4.04 (dd, J = 7.9, 10.7 Hz, 1H), 5.26 (d, J = 12.4 Hz, 1H), 5.30 (d, J = 12.4 Hz, 1H), 7.37 (m, 5H); ¹³C NMR (125 MHz, CDCl₃) δ 17.9, 30.7, 51.7, 53.0, 57.8, 68.5, 128.3(2), 128.6, 128.8(2), 135.2, 151.3, 168.4, 168.6; ESI-HRMS calcd for C₁₅H₁₈NO₅ [M + H]⁺ 292.1185, found 292.1190.
Diene 6. To a solution of Boc-amino acetone\(^3\) 17 (4.21 g, 24.3 mmol) in xylenes (24 mL) was added 2,2,6-trimethyl-4H-1,3-dioxin-4-one 18 (7.1 mL, 48.6 mmol). The reaction was heated to reflux (130 °C) for 4 h, was cooled to 23 °C and concentrated under reduced pressure to afford crude β-ketoamide. Purification by flash column chromatography (CH\(_2\)Cl\(_2\)::Et\(_2\)O 90:10) provided mixed fractions of β-ketoamide and α,β-unsaturated lactam 19. α,β- Unsaturated lactam 19 was isolated (1.37, 24%) as a yellow oil. The mixed fractions were re-subjected to flash column chromatography (CH\(_2\)Cl\(_2\)::Et\(_2\)O 90:10) which provided α,β-unsaturated lactam 19 (1.78 g, 31%) for a combined yield of 3.15 g (55%) of a yellow oil. To a solution of α,β-unsaturated lactam 19 (1.40 g, 6.0 mmol) in toluene (120 mL) was added DIBAL-H in hexanes (12 mL, 1.0 M solution, 12 mmol) at -78 °C. The reaction was stirred for 4 h, quenched with EtOAc (10 mL) and Rochelle's salt (20 mL) at -78 °C, and allowed to warm to 23 °C while stirring vigorously overnight. The solution was diluted with CH\(_2\)Cl\(_2\) (300 mL) and poured over Celite. The organic extracts were separated and washed with brine (60 mL), dried over Na\(_2\)SO\(_4\), decanted, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc 40:60) delivered allylic alcohol (408 mg, 28%) as an orange oil: \(R_f = 0.23\) (hexanes:EtOAc 40:60); IR (neat) 3480, 1761, 1712, 1154 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 1.45 (d, \(J = 6.7\) Hz, 3H), 1.54 (s, 9H), 2.03 (s, 3H), 3.47 (bs, 1H), 4.12 (s, 2H), 4.66 (q, \(J = 6.7\) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 13.2, 23.1, 28.2(3), 53.3, 63.7, 83.2, 134.3, 149.2, 149.5, 169.8; ESI-HRMS calcd for C\(_{12}\)H\(_{20}\)NO\(_4\) [M + H]\(^+\) 242.1392, found 242.1397. To a solution of allylic alcohol (654 mg, 2.7 mmol) in CH\(_2\)Cl\(_2\) (44 mL) was added triethylamine at 23 °C. The solution was cooled to 0 °C and a solution of phosphorus oxychloride (500 μL, 5.4 mmol) in CH\(_2\)Cl\(_2\) (10

mL) was added. The reaction was allowed to stir while warming slowly to 23 °C for 6 h then diluted with Et₂O (100 mL). The combined organic extracts were separated and washed with water (3 x 20 mL), brine (3 x 20 mL), and then dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (hexanes:EtOAc 80:20) delivered diene 6 (217 mg, 36%) as a white solid: mp 82 °C; Rᶠ = 0.20 (hexanes: EtOAc 80:20); IR (neat) 1726, 1712, 1318, 1151, 769 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.56 (s, 9H), 2.11 (s, 3H), 4.15 (s, 2H), 5.44 (dd, J = 11.6, 17.7 Hz, 1H), 6.29 (dd, J = 2.2, 17.7 Hz, 1H), 6.41 (dd, J = 2.2, 11.6 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 13.8(3), 28.3, 52.7, 82.9, 120.2, 125.0, 128.5, 150.0, 150.5, 168.2; ESI-HRMS calcd for C₁₂H₁₇NO₃Na [M + Na]⁺ 246.1115, found 246.1106.

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 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. Purification by flash column chromatography (hexanes:EtOAc 60:40) delivered isoindolinone 21 (75 mg, 76%) as a white solid: mp 80-82 °C; Rᶠ = 0.13 (hexanes:EtOAc 60:40); IR (neat) 1769, 1705, 1147, 727, 691 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 1.39 (s, 3H), 1.54 (s, 9H), 2.71 (ddd, J = 2.8, 9.0, 17.8 Hz, 1H), 3.10 (ddd, J = 1.3, 7.5, 17.8 Hz, 1H), 3.36 (d, J = 8.9 Hz, 1H), 3.49 (ddd, J = 1.3, 8.9, 9.0 Hz, 1H), 3.63 (d, J = 11.6 Hz, 1H), 4.73 (d, J = 11.6 Hz, 1H), 6.97 (dd, J = 2.8, 7.5 Hz, 1H), 7.18-7.20 (m, 2H), 7.38-7.48 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) 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; ESI-HRMS calcd for C₂₂H₂₅N₂O₅ [M + H]⁺ 397.1763, found 397.1769.
Deprotected Isoindolinone 22. \(N\)-Phenylmaleimide 20 (77 mg, 0.45 mmol), BHT (10 mg, 0.04 mmol), and diene 6 (50 mg, 0.22 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 isoindolinone 21 (19 mg, 21%) and deprotected isoindolinone 22 (27 mg, 40%) as a solid: mp 180-184 °C (decomp.); \(R_f = 0.13\) (EtOAc); IR (neat) 1699, 1678, 1387, 1195, 689 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.37 (s, 3H), 2.68 (ddd, \(J = 2.8, 8.7, 17.5\) Hz, 1H), 3.05 (ddd, \(J = 1.3, 7.4, 17.5\) Hz, 1H), 3.22 (d, \(J = 10.3\) Hz, 1H), 3.32 (d, \(J = 8.8\) Hz, 1H), 3.45 (ddd, \(J = 1.3, 8.7, 8.8\) Hz, 1H), 4.49 (d, \(J = 10.3\) Hz, 1H), 6.75 (dd, \(J = 2.8, 7.4\) Hz, 1H), 6.79 (bs, 1H), 7.17-7.4 (m, 5H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 24.3, 26.8, 39.3, 39.5, 48.1, 50.4, 126.6(2), 127.6, 129.0, 129.3(2), 131.6, 140.0, 168.1, 175.9, 177.8; ESI-HRMS calcd for C\(_{17}\)H\(_{17}\)N\(_2\)O\(_3\) [M + H]\(^+\) 297.1239, found 297.1237.

Crystallographic Experimental Details of Isoindolinone 22

X-ray quality crystals of racemic 22 were obtained by slow evaporation in hexanes. The crystals were suspended in mineral oil at ambient temperature and a suitable crystal was selected. A mineral oil coated colorless long plate thereby obtained of approximate dimensions 0.23 x 0.05 x 0.03 mm was mounted on a 50 \(\mu\)m MicroMesh MiTeGen Micromount and transferred to a Bruker AXS SMART APEX-II CCD X-ray diffractometer. The X-ray diffraction data were collected at -173 °C using Mo-K\(_{\alpha}\) (\(\lambda = 0.71073\) Å) radiation. Data collection and cell refinement were performed using SMART and SAINT+, respectively.\(^4\) The unit cell parameters were obtained from a least-squares refinement of 6315 centered

reflections. Compound 22 was found to crystallize in the monoclinic crystal system with the following unit cell parameters: $a = 14.6738(4)$ Å, $b = 6.9134(2)$ Å, $c = 14.7477(4)$ Å, $\beta = 103.952(2)^\circ$, $Z = 4$. The structure solved in the centrosymmetric space group $P2_1/n$ (no. 14). A total of 44029 reflections were collected, of which 3314 were unique, and 2512 were observed $F_o^2 > 2 \sigma(F_o^2)$. Limiting indices were as follows: $-19 \leq h \leq 19$, $-8 \leq k \leq 8$, $-19 \leq l \leq 19$. Data reduction were accomplished using SAINT. The data were corrected for absorption using the SADABS procedure.

Solution and data analysis were performed using the WinGX software package. The structure of 22 was solved by charge-flipping methods using the program SUPERFLIP and the refinement was completed using the program SHELX-2013. 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, $(\Delta/\sigma)_{max} = 0.001$, $(\Delta/\sigma)_{mean} = 0.0000$, with $R_1 = 0.0378$ and $wR_2 = 0.0938$ for 3314 data with $F_o^2 > 2\sigma(F_o^2)$ using 0 restraints and 204 parameters. A final difference Fourier synthesis showed features in the range of $\Delta \rho_{max} = 0.276 \text{e}/\text{Å}^3$ to $\Delta \rho_{min} = -0.188 \text{e}/\text{Å}^3$, which were deemed of no chemical significance. Molecular diagrams were generated using ORTEP-3. CCDC 940982 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

SPECTRA FOR NEW COMPOUNDS
$^1$H NMR (400 MHz) of $\alpha,\beta$-Unsaturated Lactam Ester 12 in CDCl$_3$
$^{13}$C NMR (125 MHz) of $\alpha,\beta$-Unsaturated Lactam Ester 12 in CDCl$_3$
$^1$H NMR (500 MHz) of Lactam Ester 15 in CDCl$_3$
$^{13}$C NMR (125 MHz) of Lactam Ester 15 in CDCl$_3$
$^1$H NMR (500 MHz) of Allylic Alcohol in CDCl$_3$
$^{13}$C NMR (125 MHz) of Allylic Alcohol in CDCl$_3$
\[ \text{\textsuperscript{1}H NMR (500 MHz) of Diene 6 in CDCl}_3 \]
$^{13}$C NMR (125 MHz) of Diene 6 in CDCl$_3$
$^1$H NMR (500 MHz) of Isoindolinone 21 in CDCl$_3$
$^{13}$C NMR (125 MHz) of Isoindolinone 21 in CDCl$_3$
$\text{HNMR (400 MHz)}$ of Deprotected Isoindolinone 22 in CDCl$_3$
$^{13}$C NMR (100 MHz) of Deprotected Isoindolinone 22 in CDCl$_3$