An Efficient Synthesis of the Fully Elaborated Isoindolinone Unit of Muironolide A

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Supplementary Information

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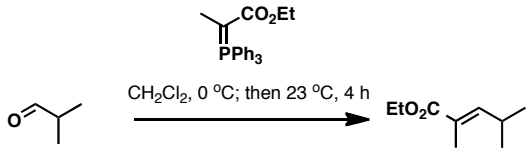
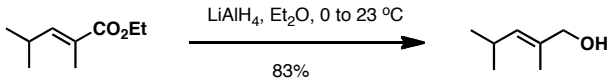
Synthesis

General Information. All reactions were carried out under an inert atmosphere of dry argon in oven or flame-dried glassware, unless the reaction procedure states otherwise. Tetrahydrofuran (THF) and ether (diethyl ether) were distilled from sodium-benzophenone in a continuous still under an atmosphere of argon. Dichloromethane, di-*iso*-propylamine and triethylamine were distilled from calcium hydride in a continuous still under and atmosphere of argon. Reaction temperatures were controlled by IKA ETS-D4 fuzzy thermo couples. Room temperature reactions were carried out between 22-24 °C. Analytical thin-layer chromatography (TLC) was performed using pre-coated TLC plates with Silica Gel 60 F_{254} (EMD no. 5715-7) and visualized using combinations of UV, anisaldehyde, ceric ammonium molybdate (CAM), potassium permanganate, and iodine staining. Flash column chromatography was preformed using 40-63 μm silica gel (Merck, Geduran, no. 11567-1) as the stationary phase. Proton magnetic resonance spectra were recorded at 400, 500, and 600 MHz on Varian Unity Inova. Carbon magnetic resonance spectra were recorded at 400 MHz, 500 MHz, and 600 MHz on Varian Unity Inova, and Varian Unity Inova spectrometers. All Chemical shifts were reported in δ units relative to tetramethylsilane. High Resolution mass spectral data were obtained by the Mass Spectrometry laboratory at the University of California, Santa Barbara.



5

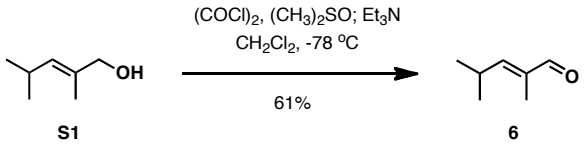
(*E*)-Ethyl 2,4-dimethylpent-2-enoate 5. Ethyl 2-(triphenylphosphoranylidene)propanoate (7.97 g, 22.0 mmol) in dry dichloromethane (25.0 mL) was cooled to 0 °C. Freshly distilled isobutyraldehyde (1.8 mL, 20.0 mmol) was added dropwise via syringe within 5 min. This mixture was warmed to 23 °C and stirred for an additional 4 h. The crude yellow mixture was concentrated and purified by column chromatography (silica, 10% diethyl ether – pentanes, then 30% diethyl ether – pentanes) to give the desired ester **5** (2.73 g, 17.5 mmol, 79% yield) as a clear liquid. ^{1}H NMR (500 MHz, $CDCl_3$); δ(ppm): 6.54 (dd, J = 9.7, 1.4 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 2.61 (dhept, J = 9.7, 6.7 Hz, 1H), 1.81 (d, J = 1.4 Hz, 3H), 1.29 – 1.26 (m, 3H), 1.00 (d, J = 6.7 Hz, 6H); ^{13}C NMR (500 MHz, $CDCl_3$); δ(ppm): 168.48, 148.68, 125.57, 60.34, 27.86, 21.91, 14.25, 12.21; HRMS-EI (*m/z*): [M+] calcd for $C_9H_{16}O_2$, 156.1150; found, 156.1156.



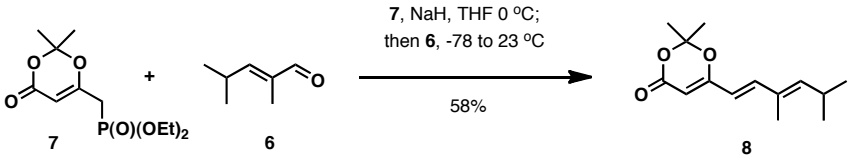
5 **S1**

(*E*)-2,4-Dimethylpent-2-en-1-ol. (*E*)-Ethyl 2,4-dimethylpent-2-enoate **5** (1.40 g, 8.96 mmol) in dry diethyl ether (10.0 mL) was added dropwise with a syringe over 5 min to a mixing solution of $LiAlH_4$ (0.850 g, 22.40 mmol) in diethyl ether (35.0 mL) at 0 °C. After stirring at 23 °C for 45 min, the solution was cooled to 0 °C. To the cooled mixture, H_2O (0.9 mL), 3 M NaOH (0.9 mL) and another portion of H_2O (2.6 mL) were added sequentially at 5 min intervals while stirring vigorously. The resultant mixture was warmed to 23 °C and stirred for 3 h. The salts were filtered and washed with ether (3 x 10 mL), and the combined filtrate was dried with magnesium sulfate and evaporated. The crude clear mixture was purified by column chromatography (silica, 20% diethyl ether – pentanes, then 40% diethyl ether – pentanes) to give the desired alcohol **S1** (0.844 g, 7.39 mmol, 82% yield) as a clear liquid. ^{1}H NMR (500 MHz, $CDCl_3$); δ(ppm): 5.22 (ddd, J = 9.2, 2.6, 1.3 Hz,

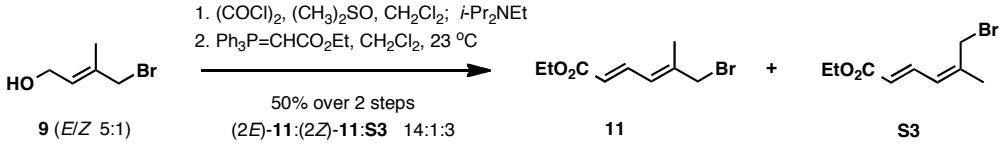
1H), 3.97 (d, J = 4.3 Hz, 2H), 2.58 – 2.48 (m, 1H), 1.66 (d, J = 1.3 Hz, 3H), 1.40 (t, J = 5.3 Hz, 1H), 0.95 (d, J = 6.7 Hz, 6H); ^{13}C NMR (500 MHz, $CDCl_3$) ; δ(ppm): 133.93, 132.34, 76.75, 69.00, 26.80, 22.87, 13.57.



(*E*)-2,4-Dimethylpent-2-enal 6. Dimethylsulfoxide (1.1 mL, 16.1 mmol) was added dropwise to a solution of $(COCl)_2$ (0.7 mL, 8.04 mmol) in dry dichloromethane (10.0 mL) at -78 °C. After stirring for 15 min, (*E*)-2,4-dimethylpent-2-en-1-ol **S1** (0.612 g, 5.36 mmol) in dry dichloromethane (7.0 mL) was added via syringe at -78 °C and stirred for 25 min. Triethylamine (3.4 mL, 24.1 mmol) was added over 5 min at -78 °C, and then the reaction mixture was warmed to 0 °C and stirred for an additional 25 min. The solution was diluted with diethyl ether (10 mL) and H_2O (10 mL) and stirred for 5 min. A 1:1 mixture of brine (10 mL) and 1 M HCl (10 mL) was added and the aquesous phase was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with a mixture of brine (10 mL) and saturated aqueous sodium bicarbonate (10 mL), dried with sodium sulfate, and the crude clear mixture was purified by column chromatography (silica, 20% diethyl ether – pentanes, then 40% diethyl ether – pentanes) to give the desired aldehyde **6** (0.367 g, 3.28 mmol, 61% yield) as a clear liquid. ^{1}H NMR (500 MHz, $CDCl_3$); δ(ppm): 9.34 (s, 1H), 6.26 (dd, J = 9.6, 1.3 Hz, 1H), 2.81 (dhept, J = 9.7, 6.7 Hz, 1H), 1.72 (d, J = 1.3 Hz, 3H), 1.06 (d, J = 6.7 Hz, 6H); ^{13}C NMR (500 MHz, $CDCl_3$) ; δ(ppm): 195.60, 161.15, 137.05, 28.16, 21.71, 9.05.



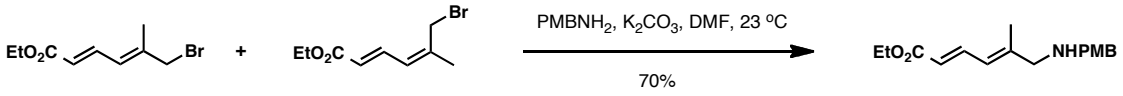
6-((1*E*,3*E*)-3,5-Dimethylhexa-1,3-dien-1-yl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one 8. Diethyl ((2,2-dimethyl-4-oxo-4*H*-1,3-dioxin-6-yl)methyl)phosphinate **7** (3.07 g, 11.0 mmol) was dissolved in dry THF (23.0 mL) and added dropwise to a suspension of NaH (60% in mineral oil, 0.463 g, 11.0 mmol) in dry THF (23.0 mL) at 0 °C. The resulting solution was warmed to 23 °C and stirred for an additional 30 min. A solution of (*E*)-2,4-Dimethylpent-2-enal **6** (1.30 g, 11.6 mmol) in dry THF (23.0 mL) was added via cannula at -78 °C over 15 min. The reaction mixture was warmed to 23 °C and stirred for 12 h and then quenched with H_2O (5 mL), diluted with ethyl acetate (20 mL), and washed with brine (20 mL). The organic layer was dried with sodium sulfate and evaporated. The crude product was purified by column chromatography (silica, 10% ethyl acetate – hexanes) to give a white crystalline solid **8** (1.58 g, 6.68 mmol, 58%). ^{1}H NMR (500 MHz, $CDCl_3$); δ(ppm): 6.92 (d, J = 15.6 Hz, 1H), 5.87 (d, J = 15.6 Hz, 1H), 5.68 (d, J = 9.4 Hz, 1H), 5.28 (s, 1H), 2.67 (ddt, J = 13.3, 9.4, 6.6 Hz, 1H), 1.78 (d, J = 1.1 Hz, 3H), 1.69 (s, 6H), 0.99 (d, J = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, CDCl3); δ(ppm): 164.11, 162.08, 148.89, 143.31, 130.80, 117.16, 106.10, 93.61, 27.96, 25.03, 22.45, 12.04; HRMS-ESI (*m/z*): [M+Na] calcd for $C_{14}H_{20}O_3Na$, 259.1310; found, 259.1298.



9 (*E*/*Z* 5:1) (2*E*)-**11**:(2*Z*)-**11**:**S3** 14:1:3 **11** **S3**

(2E,4E)-Ethyl 6-bromo-5-methylhexa-2,4-dienoate 11. The (*E*)-4-bromo-3-methylbut-2-en-1-ol **9** (*E*:*Z* mixture 5:1) was synthesized from isoprene according to a known procedure.[1] Dimethylsulfoxide (0.65 mL, 9.10 mmol) was added to a solution of oxalyl chloride (0.38 mL, 4.50 mmol) in dry dichloromethane (12.0 mL) at -78 °C. After 15 min, a solution of the 4-bromo-3-methylbut-2-en-1-ol **9** (0.500 g, 3.03 mmol, *E*:*Z* 5:1) in dichloromethane (12.0 mL total with 2 rinses) was added. The mixture was stirred for 45 min. Diisopropylethylamine (3.2 mL, 18.2 mmol) was added dropwise and after 30 min the mixture was warmed to 0 °C and stirred for 30 min. 20 mL of 1 M aqueous HCl were added. The aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with water, a saturated aqueous solution of sodium bicarbonate, dried with sodium sulfate, concentrated at 10 °C under the pressure of ~350 mbar until the volume of solution was approximately 20 mL (caution: the aldehyde is volatile), and this residue, containing a 5:1 mixture of the *E* and *Z* isomers of the expacted aldehyde, was used directly in the next step.

Ethyl 2-(triphenylphosphoranylidene)acetate (1.10 g, 3.30 mmol) was added to the solution of aldehyde in dichloromethane (20.0 mL) at 23 °C. The resultant mixture was stirred at 23 °C for 18 h and then the mixture was concentrated and purified by column chromatography (silica, 5% ethyl acetate – hexanes) to give an inseparable mixture of (*E*)-**11**, (*Z*)-**11**, and **S3** in a 14:1:3 ratio as a yellow oil (0.347 g, 50%). ^{1}H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.48 (ddd, J = 15.2, 12.8, 11.6 Hz, 1H), 6.30 – 6.20 (m, 1H), 5.91 (dd, J = 15.2, 2.5 Hz, 1H), 4.24 – 4.17 (q, J = 7.1, 2H), 4.07 (s, 1H), 4.01 (s, 1H), 1.99 (dd, J = 14.1, 1.2 Hz, 3H), 1.28 (t, J = 7.1, 3H); ^{13}C NMR (125 MHz, CDCl3); δ(ppm): 166.87, 166.84, 139.39, 139.24, 127.29, 126.75, 122.84, 122.79, 60.43, 60.41, 50.79, 39.43, 14.27; HRMS-EI (*m*/*z*): [M+] calcd for $C_9H_{13}BrO_2$, 232.0099; found, 232.0108.

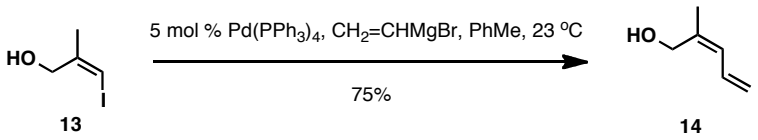


11 **S3** **12**

(2*E*)-**11**:(2*Z*)-**11**:**S3** 14:1:3

(2E,4E)-Ethyl 6-((4-methoxybenzyl)amino)-5-methylhexa-2,4-dienoate 12. K_2CO_3 (1.74 g, 12.6 mmol) was added to a mixture of 4-methoxybenzylamine (0.9 mL, 6.60 mmol) and (2E,4E)-ethyl 6-bromo-5-methylhexa-2,4-dienoate (1.48 g, 6.30 mmol) in dimethylformamide (20.0 mL) at 0 °C. The mixture was warmed to 23 °C and stirred for 2 h. The reaction mixture was diluted with H_2O and extracted with ethyl acetate (3 x 50 mL). The organic layer was washed with H_2O (3 x 20 mL) and brine, dried with sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (silica, 20% to 30% ethyl acetate – hexanes) to afford **12** (0.960 g, 70%) as a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$); δ(ppm): 7.60 (dd, J = 15.2, 11.6 Hz, 1H), 7.23 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 6.19 (d, J = 11.6 Hz, 1H), 5.84 (d, J = 15.2 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 3.68 (s, 2H), 3.27 (s, 2H), 1.91 (s, 3H), 1.47 (s, 1H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, CDCl3); δ(ppm): 167.67, 158.85, 147.47, 140.52, 132.42, 129.45, 123.28, 120.28, 113.97, 60.36, 56.49, 55.43, 52.73, 16.31, 14.51; HRMS-ESI (*m*/*z*): [M+Na] calcd for $C_{17}H_{23}NO_3Na$, 312.1576; found, 312.1564.

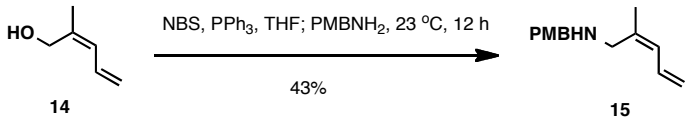
[1] Van, T. N.; De Kimpe, N. *Tetrahedron* **2000**, *56*, 7969-7973.



13 14

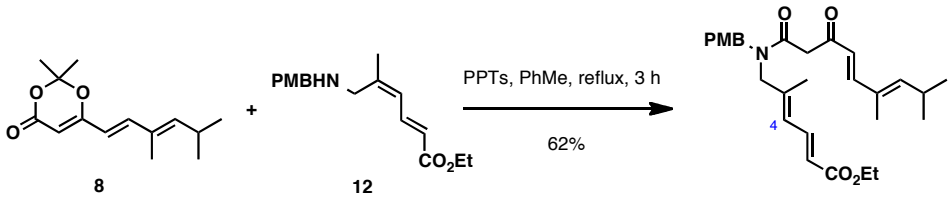
(Z)-2-Methylpenta-2,4-dien-1-ol 14. (Z)-3-Iodo-2-methylprop-2-en-1-ol **14** was synthesized from propargyl alcohol according to a known procedure.[2]

Tetrakis(triphenylphosphine)palladium (0.292 g, 0.250 mmol) was added to a solution of vinyl iodide **13** (2.00 g, 10.0 mmol) in dry, degassed toluene (135.0 mL) at 0 °C. After stirring for 20 min, vinyl magnesium bromide (1.25 M in THF, 24.0 mL, 30.0 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 30 min. The reaction was quenched by adding 20 ml of saturated aqueous ammonium chloride. The aqueous layer was extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with brine, dried with sodium sulfate, concentrated under reduced presuure at 10 °C, and the residue was purified by column chromatography on silica gel (silica, 30% diethyl ether – hexanes) to afford **14** (0.770 g, 75%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$); δ(ppm): 6.63 (dt, J = 16.7, 10.6 Hz, 1H), 5.96 (d, J = 11.1 Hz, 1H), 5.17 (d, J = 16.7 Hz, 1H), 5.07 (d, J = 10.2 Hz, 1H), 4.27 (d, J = 5.9 Hz, 2H), 1.89 (s, 3H), 1.24 (s, 1H); ^{13}C NMR (125 MHz, CDCl3); δ(ppm): 137.57, 131.96, 128.37, 116.57, 61.26, 21.34; HRMS-EI (*m/z*): [M+] calcd for $C_6H_{10}O$, 98.0732; found, 98.0730.



14 15

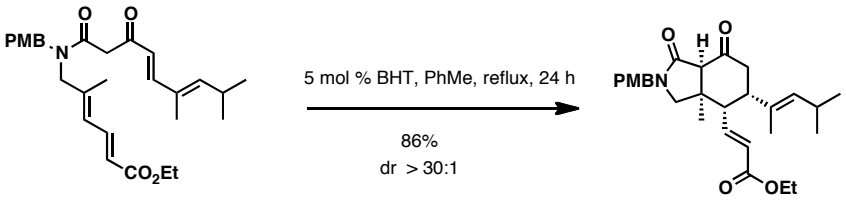
(Z)-N-(4-Methoxybenzyl)-2-methylpenta-2,4-dien-1-amine 15. N-Bromosuccimide (1.82 g, 10.2 mmol) was added to a stirred solution of triphenylphosphine (2.67 g, 10.2 mmol) and **14** (0.770 g, 7.80 mmol) in anhydrous THF (20.0 mL) at –10 °C over 2–3 min in small portions under argon. After 20 min, TLC showed a complete consumption of alcohol **14.** 4-Methoxybenzylamine (2.0 mL, 15.6 mmol) was injected via a syringe in one portion. The temperature was raised to 23 °C and the mixture was stirred at 23 °C for 12 h. Hexane (10 mL) was added to the reaction mixture and stirred for 0.5 h. to precipitate triphenylphosphine oxide and succinimide. The solid was filtered and washed with 1 N HCl. Then the aqueous layer was neutralized by sodium bicarbonate solution and extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried with anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel (silica, 60% ethyl acetate – hexanes) to afford **15** (0.730 g, 43%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.24 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.61 – 6.50 (m, 1H), 6.04 – 5.95 (m, 1H), 5.13 (ddd, J = 16.7, 1.3, 0.6 Hz, 1H), 5.00 (dd, J = 10.2, 1.8 Hz, 1H), 3.80 (s, 3H), 3.67 (s, 2H), 3.35 (s, 2H), 1.87 (s, 3H), 1.54 (bs, 1H); ^{13}C NMR (125 MHz, CDCl3); δ(ppm): 158.61, 137.28, 132.50, 132.42, 129.32, 128.75, 115.86, 113.74, 55.25, 52.43, 49.12, 22.56; HRMS-ESI (*m/z*): [M+H] calcd for $C_{14}H_{20}NO$, 218.1545; found, 218.1533.



8 12 (4*E*)-**4a**

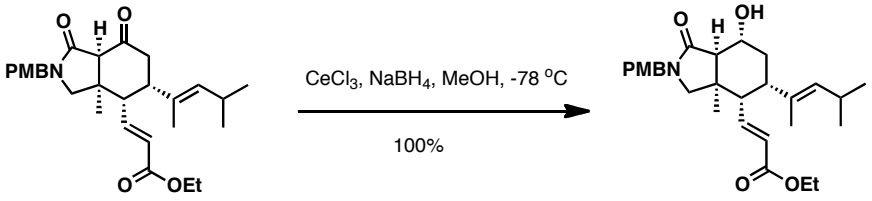
[2] (a) Duboudin, J. G.; Jousseaume, B., Saux, A. *J. Organomet. Chem.* **1979**, *168*, 1-11. (b) Liu, F.; Negishi, E. *J. Org. Chem.* **1997**, *62*, 8591–8594.

(2E,4E)-Ethyl 6-((4E,6E)-N-(4-methoxybenzyl)-6,8-dimethyl-3-oxonona-4,6-dienamido)-5-methylhexa-2,4-dienoate (4*E*)-4a. Pyridinium tosylate (4.3 mg, 0.0172 mmol) was added to a solution of 6-((1E,3E)-3,5-dimethylhexa-1,3-dienyl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one **8** (40.0 mg, 0.172 mmol) and (2*E*,4*E*)-ethyl 6-(4-methoxybenzylamino)-5-methylhexa-2,4-dienoate (50.0 mg, 0.172 mmol) **12** in dry toluene (3.5 mL). The resulting solution was heated to reflux for 2 h. Toluene was evaporated and the crude product was purified by column chromatography (silica, 40% ethyl acetate – hexanes) to give **(4*E*)-4a** as a white crystalline solid (50.0 mg, 0.106 mmol, 62%). ^{1}H NMR (600 MHz, $CDCl_3$); δ(ppm): 7.56 (ddd, J = 2.4, 11.4, 16.8 Hz, 2H), 7.19 (dd, J = 8.4, 12.5 Hz, 1H), 7.12 – 7.04 (m, 1H), 6.87 (ddd, J = 3.3, 8.5, 20.3 Hz, 2H), 6.18 (d, J = 16.2 Hz, 1H), 6.04 (d, J = 11.6 Hz, 1H), 5.97 (t, J = 13.4, 13.4 Hz, 1H), 5.89 – 5.75 (m, 1H), 5.62 (d, J = 9.3, 1H), 5.30 (s, 1H), 5.04 (s, 1H), 4.53 (d, J = 5.1 Hz, 2H), 4.45 - 4.37 (m, 2H), 4.21 (qd, J = 5.2, 7.1, 7.1, 7.1 Hz, 3H), 4.07 (d, J = 13.3 Hz, 2H), 3.84 – 3.77 (m, 5H), 3.69 (s, 2H), 2.74 – 2.61 (m, 1H), 1.85 (d, J = 6.3 Hz, 3H), 4.45 – 4.37 (m, 3H), 1.33 – 1.23 (m, 3H), 1.04 – 0.97 (m, 6H). HRMS-ESI (*m/z*): [M+Na] calcd for $C_{28}H_{37}NO_5Na$, 490.2569; found, 490.2552.



(4*E*)-**4a** **16**

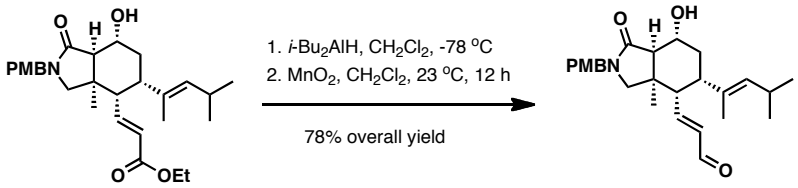
(*E*)-Ethyl 3-((3a*R*,4*S*,5*S*,7a*R*)-2-(4-methoxybenzyl)-3a-methyl-5-((*E*)-4-methylpent-2-en-2-yl)-1,7-dioxooctahydro-1*H*-isoindol-4-yl)acrylate 16. (2*E*,4*E*)-Ethyl 6-((4*E*,6*E*)-*N*-(4-methoxybenzyl)-6,8-dimethyl-3-oxonona-4,6-dienamido)-5-methylhexa-2,4-dienoate (4*E*-**4a**) (8.2 mg, 17.5 μmol) and BHT (0.4 mg, 1.70 μmol) were dissolved in dry toluene (0.6 mL) and heated at reflux for 18 h. Toluene was evaporated and the crude product was purified by column chromatography (silica, 50% ethyl acetate – hexanes) to give **16** as a yellowish oil (7.0 mg, 15.0 μmol, 86%). ^{1}H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.15 (t, J = 7.9 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 6.64 (dd, J = 15.3, 11.0 Hz, 1H), 5.62 (d, J = 15.3 Hz, 1H), 4.70 (t, J = 12.6 Hz, 1H), 4.53 (d, J = 14.4 Hz, 1H), 4.28 (d, J = 14.4 Hz, 1H), 4.19 – 4.11 (m, 2H), 3.77 (s, 3H), 3.22 (d, J = 10.2 Hz, 1H), 3.03 (s, 1H), 2.86 (d, J = 10.2 Hz, 1H), 2.55 – 2.48 (m, 2H), 2.46 – 2.30 (m, 3H), 1.46 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.04 (s, 3H), 0.86 (d, J = 6.6 Hz, 3H), 0.78 (d, J = 6.6 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) ; δ(ppm): 204.94, 168.38, 165.44, 159.46, 143.21, 135.09, 130.30, 129.88, 127.90, 125.55, 114.36, 62.73, 60.66, 57.39, 55.44, 48.38, 46.36, 43.34, 41.19, 39.35, 27.91, 27.28, 22.94, 22.92, 16.65, 14.42; HRMS-ESI (*m/z*): [M+Na] calcd for $C_{28}H_{37}NO_5Na$, 490.2569; found, 490.2565.



16 **17**

(*E*)-Ethyl 3-((3a*R*,4*S*,5*S*,7*R*,7a*R*)-7-hydroxy-2-(4-methoxybenzyl)-3a-methyl-5-((*E*)-4-methylpent-2-en-2-yl)-1-oxooctahydro-1*H*-isoindol-4-yl)acrylate 17. Sodium borohydride (8.0 mg, 20.0 μmol) was added to a solution of (*E*)-ethyl 3-((3a*R*,4*S*,5*S*,7a*R*)-2-(4-methoxybenzyl)-3a-methyl-5-((*E*)-4-methylpent-2-en-2-yl)-1,7-dioxooctahydro-1*H*-isoindol-4-yl)acrylate **16** (10.0 mg, 21.0 μmol) and $CeCl_3 \cdot 7H_2O$ (74.0 mg, 20.0 μmol) in dry MeOH (1.5

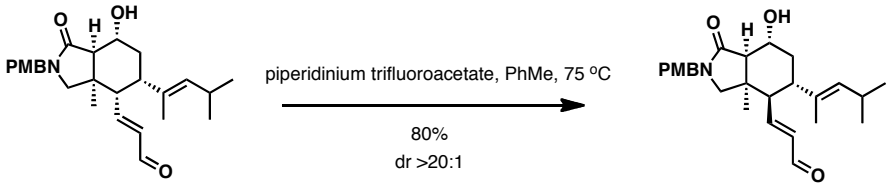
mL) at -78 °C for 20 min. Ammonium chloride (3 mL) and H_2O (10 mL) were added and the mixture was extracted with ethyl acetate (3 x 15 mL). The organic layers were combined, dried with sodium sulfate, and concentrated. Purification with column chromatography (silica, 60% ethyl acetate – hexanes) gave a yellowish oil **17** (10.0 mg, 21.0 μmol, 100%). ^{1}H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.15 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 6.67 (dd, J = 15.4, 11.3 Hz, 1H), 5.58 (d, J = 15.4 Hz, 1H), 4.83 (d, J = 9.1 Hz, 1H), 4.44 (d, J = 14.4 Hz, 1H), 4.35 (d, J = 14.4 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 3.59 (td, J = 11.5, 4.6 Hz, 1H), 3.23 (d, J = 9.7 Hz, 1H), 3.04 (s, 1H), 2.68 (d, J = 9.6 Hz, 1H), 2.45 – 2.36 (m, 1H), 2.22 (dd, J = 11.2, 3.8 Hz, 1H), 2.15 (d, J = 12.5 Hz, 1H), 2.08 – 2.00 (m, 1H), 1.85 – 1.73 (m, 1H), 1.62 – 1.53 (m, 1H), 1.49 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H), 0.90 (s, 3H), 0.87 (d, J = 6.6 Hz, 3H), 0.75 (d, J = 6.6 Hz, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) ; δ(ppm): 176.07, 165.77, 159.41, 145.38, 134.36, 131.87, 129.79, 128.25, 123.64, 114.38, 71.68, 60.46, 56.33, 55.85, 55.45, 46.27, 46.03, 42.87, 39.69, 30.72, 27.97, 27.18, 23.07, 22.92, 16.52, 14.46; HRMS-ESI (*m/z*): [M+Na] calcd for $C_{28}H_{39}NO_5Na$, 492.2726; found, 492.2720.



17 **18**

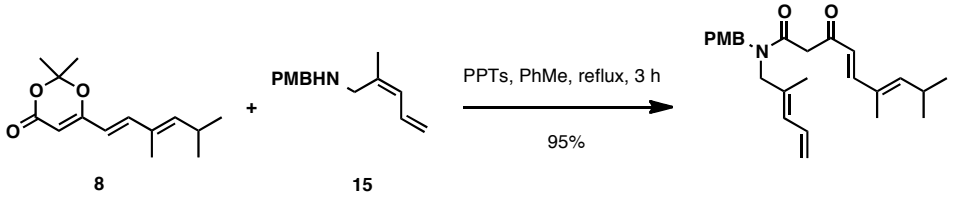
(*E*)-3-((3a*R*,4*S*,5*S*,7*R*,7a*R*)-7-Hydroxy-2-(4-methoxybenzyl)-3a-methyl-5-((*E*)-4-methylpent-2-en-2-yl)-1-oxooctahydro-1*H*-isoindol-4-yl)acrylaldehyde 18. Diisobutylaluminum hydride (1 M in toluene, 0.2 mL, 0.200 mmol) was added dropwise to a solution of ester **17** (10.0 mg, 21.0 μmol) in dry dichloromethane (1.0 mL) at -78 °C. After 20 min, a saturated solution of Rochelle's salt (5 mL) was added and then the mixture was diluted with ethyl acetate (20 mL). The mixture was stirred vigorously for 2 h at room temperature. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The organic layers were dried with sodium sulfate, concentrated, and the residue was purified by column chromatography on silica gel (silica, 70% to 90% ethyl acetate – hexanes) to afford the expected allylic alcohol (8.0 mg, 80%).

Activated MnO_2 (80.0 mg) was added to a solution of the allylic alcohol in dry dichloromethane (1.5 mL). The mixture was stirred at room temperature for 12 h, and then directly submitted to purification by column chromatography (70% ethyl acetate – hexane) to give pure aldehyde **18** (7.0 mg 88% yield) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$); δ(ppm): 9.45 (d, J = 7.8 Hz, 1H), 7.18 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 6.56 (dd, J = 15.4, 11.1 Hz, 1H), 5.92 (dd, J = 15.4, 7.8 Hz, 1H), 4.86 (d, J = 9.1 Hz, 1H), 4.47 – 4.43 (d, J = 14.4 Hz, 1H), 4.38 (d, J = 14.4 Hz, 1H), 3.81 (s, 3H), 3.67 – 3.59 (m, 1H), 3.27 (d, J = 9.7 Hz, 1H), 3.01 (s, 1H), 2.73 (d, J = 9.7 Hz, 1H), 2.44 – 2.33 (m, 2H), 2.23 (d, J = 8.0 Hz, 1H), 2.05 (d, J = 9.4 Hz, 1H), 1.91 – 1.85 (m, 1H), 1.49 (d, J = 0.9 Hz, 3H), 0.92 (s, 3H), 0.87 (d, J = 3.1 Hz, 3H), 0.75 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$); δ(ppm): 193.02, 175.58, 159.28, 154.32, 134.92, 134.40, 131.43, 129.62, 127.89, 114.24, 71.33, 56.19, 55.98, 55.57, 55.27, 46.33, 45.87, 42.51, 39.45, 29.70, 27.83, 26.98, 22.99, 22.84; HRMS-ESI (*m/z*): [M+Na] calcd for $C_{26}H_{35}NO_4Na$, 448.2464; found, 448.2462.



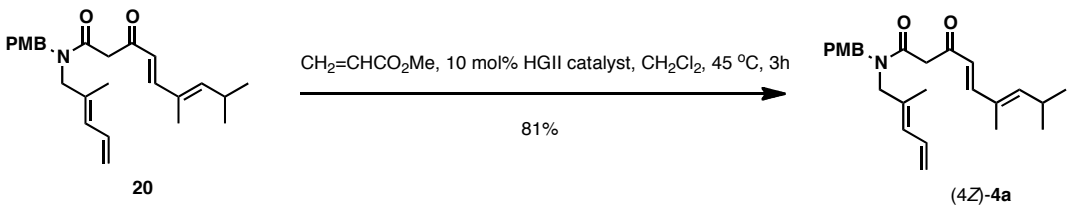
18 **19**

The aldehyde **18** (2.5 mg, 5.80 μmol) was dissolved in dry toluene (1.0 mL) and piperidium trifluoroacetate (1.5 mg, 7.50 μmol) was added. The mixture was heated to 75 °C for 2.5 h, and then finally cooled to 23 °C. The solution was directly applied on a silica column (silica, 60% ethyl acetate – hexanes) to afford product (2.0 mg, 47.0 μmol, 80%). ^{1}H NMR (500 MHz, $CDCl_3$); δ(ppm): 9.38 (d, J = 7.7 Hz, 1H), 7.15 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 6.23 (dd, J = 15.6, 10.3 Hz, 1H), 6.04 (dd, J = 15.5, 7.6 Hz, 1H), 4.97 (d, J = 9.1 Hz, 1H), 4.46 (d, J = 14.5 Hz, 1H), 4.35 (d, J = 14.4 Hz, 1H), 3.82 (s, 3H), 3.59 (dd, J = 13.9, 7.1 Hz, 1H), 3.28 (d, J = 9.5 Hz, 1H), 3.06 (s, 1H), 2.59 (d, J = 9.6 Hz, 1H), 2.39 (m, 1H), 2.28 (t, J = 10.9 Hz, 1H), 2.07 – 1.94 (m, 2H), 1.89 (d, J = 11.2 Hz, 1H), 1.44 (d, J = 1.1 Hz, 3H), 1.08 (s, 3H), 0.87 (d, J = 6.6 Hz, 3H), 0.77 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$); δ(ppm): 192.77, 175.36, 159.28, 155.66, 135.95, 135.57, 131.87, 129.47, 127.87, 114.28, 70.10, 57.98, 55.28, 52.27, 49.82, 46.28, 45.94, 39.86, 35.96, 28.32, 26.70, 22.98, 22.75, 12.19; HRMS-ESI (*m/z*): [M+Na] calcd for $C_{26}H_{35}NO_4Na$, 448.2464; found, 448.2447.



8 **15** **20**

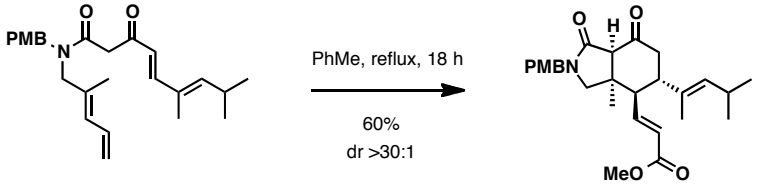
(4E,6E)-N-(4-Methoxybenzyl)-6,8-dimethyl-N-((Z)-2-methylpenta-2,4-dien-1-yl)-3-oxonona-4,6-dienamide 20. Pyridinium *p*-toluenesulfonate (35.0 mg, 0.138 mmol) was added to a solution of dioxinone **8** (0.326 g, 1.38 mmol) and amine **15** (0.300 g, 1.38 mmol) in toluene (25.0 mL), and the mixture was stirred and heated at reflux for 3 h. After cooling, the mixture was concentrated and the resultant red oil was purified by silica gel flash chromatography (silica, 20% ethyl acetate – hexanes) yielding the title compound **20** as a yellow oil (0.520 g, 95%). ^{1}H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.30 – 7.15 (m, 1H), 7.10 – 7.03 (m, 2H), 6.88 – 6.80 (m, 2H), 6.46 – 6.14 (m, 1H), 6.07 – 6.00 (m, 1H), 5.83 – 5.73 (m, 1H), 5.59 (d, J = 10.0, 1H), 5.28 (d, J = 15.2, 1H), 5.22 – 4.90 (m, 2H), 4.48 (d, J = 3.5, 2H), 4.32 (s, 2H), 4.20 (d, J = 2.2, 2H), 3.97 – 9.92 (d, J = 7.0, 2H), 3.80 – 3.75 (m, 5H), 2.74 – 2.60 (m, 1H), 1.79 – 1.75 (m, 3H), 1.73 (d, J = 8.2, 3H), 1.03 – 0.95 (m, 6H). HRMS-ESI (*m/z*): [M+Na] calcd for $C_{25}H_{33}NO_3Na$, 418.2358; found, 418.2343.



20 (4*Z*)-**4a**

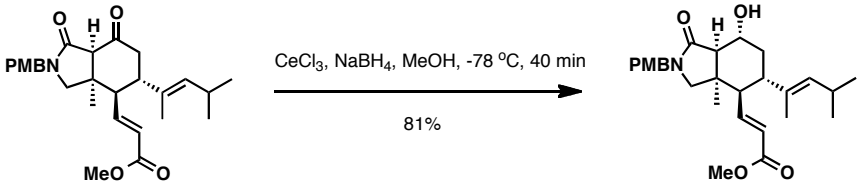
(2E,4Z)-Methyl 6-((4E,6E)-N-(4-methoxybenzyl)-6,8-dimethyl-3-oxonona-4,6-dienamido)-5-methylhexa-2,4-dienoate (4*Z*)-4a. Alkene **20** (0.520 g, 1.31 mmol) and methyl acrylate (35.0 μL, 3.94 mmol) were dissolved in dichloromethane (35.0 mL), and Hoveyda-Grubbs

second generation catalyst (20.0 mg, 33.0 μmol) was added in one portion. The reaction was stirred at 45 °C for 3 h and then concentrated. The residue was purified by column chromatography (silica, 20% to 30% ethyl acetate – hexanes) to give the desired product **(4*Z*)-4a** (0.480 g, 81%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.61 – 7.38 (m, 1H), 7.38 – 7.31 (m, 1H), 7.30 – 7.20 (m, 2H), 7.09 – 6.94 (m, 2H), 6.33 – 6.27 (m, 1H), 6.03 – 5.92 (m, 1H), 5.78 (d, J = 9.4 Hz, 1H), 5.53 (s, 1H), 5.52 – 5.42 (m, 1H), 4.66 (d, J = 10.2 Hz, 2H), 4.49 (d, J = 3.57 Hz, 2H), 4.45 (d, J = 4.8 Hz, 2H) 4.22 (d, J = 9.61 Hz, 2H), 4.00 (s, 2H), 3.96 (dt, J = 4.3, 4.3, 8.1 Hz, 3H), 3.90 (s, 2H), 3.88 – 3.83 (m, 3H), 2.93 – 2.77 (m, 1H), 2.05 (s, 3H), 2.01 – 1.98 (d, J = 6.9 Hz, 3H), 1.97 – 1.91 (M, 3H), 1.17 (dd, J = 6.5, 10.5 Hz, 6H). HRMS-ESI (*m/z*): [M+Na] calcd for $C_{27}H_{35}NO_5Na$, 476.2413; found, 476.2403.



(4*Z*)-**4a** **3a**

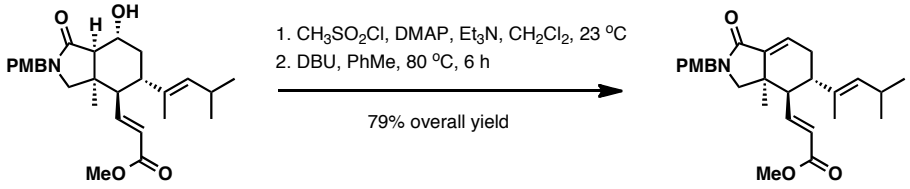
(E)-Ethyl 3-((3aR,4R,5S,7aR)-2-(4-methoxybenzyl)-3a-methyl-5-((E)-4-methylpent-2-en-2-yl)-1,7-dioxooctahydro-1H-isoindol-4-yl)acrylate 3a. A solution of (4*Z*)-**4a** (24.0 mg, 53.0 μmol) in toluene (1.8 mL) was heated at reflux for 18 h. After cooling, the mixture was concentrated and the resultant red oil was purified by silica gel flash chromatography (silica, 20% to 60% ethyl acetate – hexanes) yielding the title compound **3a** as a yellow oil (14.4 mg, 60%). ^{1}H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.15 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 6.36 (dd, J = 15.5, 9.8 Hz, 1H), 5.79 (d, J = 15.5 Hz, 1H), 4.95 (dd, J = 9.2, 1.0 Hz, 1H), 4.47 (d, J = 14.5 Hz, 1H), 4.34 (d, J = 14.7 Hz, 1H), 3.79 (s, 3H), 3.68 (s, 3H), 3.30 (d, J = 10.2 Hz, 1H), 2.97 (s, 1H), 2.62 (d, J = 10.2 Hz, 1H), 2.52 – 2.28 (m, 5H), 1.43 (d, J = 1.0 Hz, 3H), 1.15 (s, 3H), 0.85 (d, J = 6.6 Hz, 3H), 0.77 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$); δ(ppm): 204.46, 168.56, 165.76, 159.21, 145.37, 137.07, 130.17, 129.53, 127.77, 124.57, 114.20, 63.88, 55.23, 52.19, 51.57, 49.53, 47.71, 46.10, 44.66, 42.75, 28.10, 26.78, 22.59, 22.57, 11.66; HRMS-ESI (*m/z*): [M+Na] calcd for $C_{27}H_{35}NO_5Na$, 476.2413; found, 476.2405.



3a **S2**

(E)-Ethyl 3-((3aR,4R,5S,7R,7aR)-7-hydroxy-2-(4-methoxybenzyl)-3a-methyl-5-((E)-4-methylpent-2-en-2-yl)-1-oxooctahydro-1H-isoindol-4-yl)acrylate. Sodium borohydride (15.0 mg, 0.400 mmol) was added to a stirred solution of cerium(III) chloride heptahydrate (61.0 mg, 0.160 mmol) and **3a** (37.0 mg, 81.0 μmol) in anhydrous methanol (4.0 mL) at –78 °C. After 40 min, saturated aqueous ammonium chloride (4 mL) was added. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine, dried with sodium sulfate, concentrated, and the residue was purified by column chromatography on silica gel (silica, 50% to 70% ethyl acetate – hexanes) to afford the desired alcohol **S2** (30.0 mg, 81%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.14 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 6.34 (dd, J = 15.5, 10.5 Hz, 1H), 5.72 (d, J = 15.5 Hz, 1H), 4.93 (dd, J = 9.1, 1.1 Hz, 1H), 4.42 (d, J = 14.5 Hz, 1H), 4.33 (d, J =

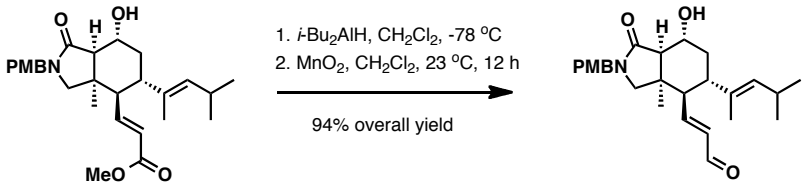
14.4 Hz, 1H), 3.81 (s, 3H), 3.67 (s, 3H), 3.56 (ddd, J = 11.5, 9.7, 4.2 Hz, 1H), 3.24 (d, J = 9.8 Hz, 1H), 3.12 (s, 1H), 2.59 (d, J = 9.8 Hz, 1H), 2.43 – 2.34 (m, 1H), 2.10 (t, J = 11.0 Hz, 1H), 1.97 (m, 2H), 1.85 (ddd, J = 12.4, 4.0, 2.6 Hz, 1H), 1.42 (d, J = 1.1 Hz, 3H), 1.05 (s, 3H), 0.86 (d, J = 6.6 Hz, 3H), 0.76 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$); δ(ppm): 175.52, 166.07, 159.21, 147.05, 135.66, 131.94, 129.50, 127.99, 123.84, 114.24, 70.14, 58.05, 55.25, 52.37, 51.46, 49.56, 46.13, 45.91, 39.73, 36.05, 28.23, 26.68, 22.77, 22.72, 12.30; HRMS-ESI (*m/z*): [M+Na] calcd for $C_{27}H_{37}NO_5Na$, 478.2569; found, 478.2548.



S2 **21**

(E)-Ethyl 3-((3aR,4R,5S)-2-(4-methoxybenzyl)-3a-methyl-5-((E)-4-methylpent-2-en-2-yl)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-isoindol-4-yl)acrylate 21. Methanesulfonyl chloride (25.0 μL, 0.330 mmol) was added to the solution of alcohol **S2** (30.0 mg, 66.0 μmol) and triethylamine (92.0 μL, 0.660 mmol) in dichloromethane (5.0 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min. The reaction mixture was poured into a saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate. The combined organic leyers were washed with 1 M HCl, brine, dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure, and the residue was used directly in the next step.

The residue was dissolved in toluene (4.0 mL) and treated with 1,8-diazabicyclo(5.4.0)-undec-7-ene (93.0 μL, 0.660 mmol) at 25 °C. The reaction mixture was stirred at 80 °C for 6 h and then poured into a mixture of 1 M HCl and ethyl acetate. The organic layer was separated and washed with saturated aqueous solution of sodium bicarbonate, brine, then dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (silica, 30% ethyl acetate – hexanes) to afford **21** (23.0 mg, 79%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$); δ(ppm): 7.14 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 6.74 (dd, J = 5.7, 4.7 Hz, 1H), 6.56 (dd, J = 15.5, 10.3 Hz, 1H), 5.77 (d, J = 15.5 Hz, 1H), 4.99 (d, J = 9.2 Hz, 1H), 4.63 (d, J = 14.6 Hz, 1H), 4.17 (d, J = 14.6 Hz, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 3.09 (d, J = 9.2 Hz, 1H), 2.55 (d, J = 9.2 Hz, 1H), 2.46 – 2.41 (m, 1H), 2.38 (d, J = 10.7 Hz, 1H), 2.20 – 2.13 (m, 2H), 1.96 (ddd, J = 10.7, 8.9, 5.7 Hz, 1H), 1.48 (d, J = 1.2 Hz, 3H), 1.14 (s, 3H), 0.88 (d, J = 6.6 Hz, 3H), 0.81 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$); δ(ppm): 167.18, 166.21, 159.05, 148.05, 140.17, 135.89, 132.03, 129.52, 129.35, 128.40, 122.55, 114.07, 55.24, 53.83, 51.48, 49.84, 49.51, 46.06, 41.53, 29.28, 28.35, 26.84, 22.86, 22.72, 12.79; HRMS-ESI (*m/z*): [M+Na] calcd for $C_{27}H_{35}NO_4Na$, 460.2464; found, 460.2442.



S2 **19**

(E)-3-((3aR,4R,5S,7R,7aR)-7-Hydroxy-2-(4-methoxybenzyl)-3a-methyl-5-((E)-4-methylpent-2-en-2-yl)-1-oxooctahydro-1H-isoindol-4-yl)acrylaldehyde 19.

Diisobutylaluminum hydride (1 M in toluene, 0.2 mL, 0.200 mmol) was added dropwise to a solution of ester **S2** (4.0 mg, 8.80 μmol) in dry dichloromethane (1.0 mL) at -78 °C. After 20 min, a saturated solution of Rochelle's salt (5 mL) was added and then the mixture was diluted with ethyl acetate (20 mL). The mixture was stirred vigorously for 2 h at room temperature. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 5 mL). The organic layers were dried with sodium sulfate, concentrated, and the residue was purified by column chromatography on silica gel (silica, 70% to 90% ethyl acetate – hexanes) to afford the expected allylic alcohol (4.0 mg, 99%).

Activated MnO_2 (40.0 mg) was added to a solution of the allylic alcohol in dry dichloromethane (1.0 mL). The mixture was stirred at room temperature for 12 h, and then directly submitted to purification by column chromatography (100% ethyl acetate) to give pure aldehyde **19** as an oil (4.0 mg 95% yield). The 1H and 13C NMR data were identical to the material prepared previously (page S8).

Figure S1. Kinetic profile for the IMDA reaction for (4*E*)-**4a**, (4*E*)-**4a** with Et_3N, and (4*Z*)-**4a** in toluene at reflux.