Conjugate Addition Initiated Nazarov Cyclization

Joshua L. Brooks, Patrick A. Caruana, Alison J. Frontier*

Department of Chemistry, University of Rochester, Rochester, New York 14627

frontier@chem.rochester.edu

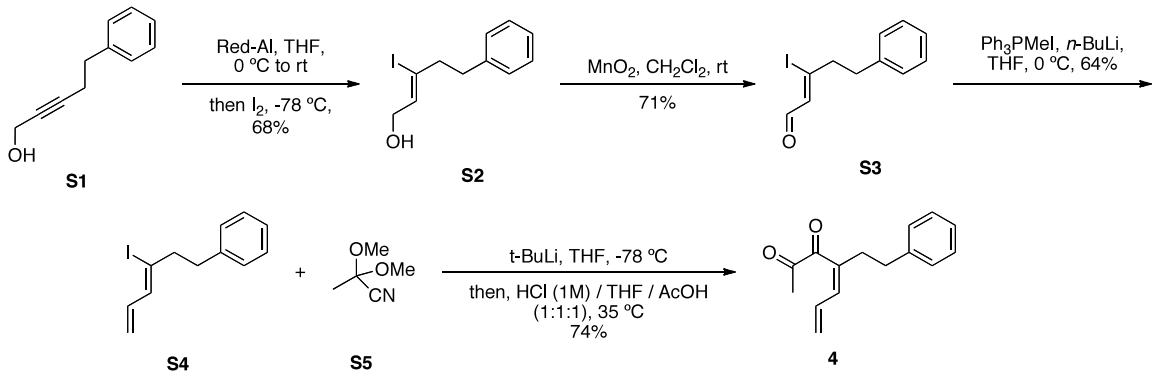
Table of Contents

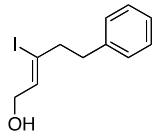
General Methods: All reactions were run in oven-dried glassware, and under argon. All reagents were used as sold by commercial supplier without further purification. Solvents were dried by dispensing from a Glass Contour solvent purification system. Column chromatography was preformed using EMD chemicals inc. silica gel 60 (230-400) mesh. Thin layer chromatography (TLC) performed using precoated silica gel 60 F254 glass-supported plates (EMD chemicals), and visualized by UV lamp, or by $KMnO_4$ stain. High-resolution mass spectra (HRMS) was measured by Mass Spectrometry Lab of the University of Illinois, Urbana. Infrared spectra (IR) was recorded on 8400S Shimadzu FTIR spectrometer. Infrared spectra (IR) were recorded on a 8400S Shimadzu FTIR spectrometer. Absorbance frequencies are given in cm^{-1} at the peak maximum.

Spectroscopic Data of Substrates: Structural assignment, including identification of relative stereochemistry, was determined by NMR spectroscopy on a Bruker AVANCE (500 MHz / 125 MHz respectively), or a Bruker AVANCE (400 MHz / 100 MHz respectively) (including nOe experiments), or by X-ray crystal structure. Chemical shifts are given in ppm, referenced to the residual proton resonance of the solvents (δ = 7.26 for chloroform or δ = 7.16 for benzene) or to the residual carbon resonance of the solvent (δ = 77.16 for chloroform). Coupling constants (*J*) are given in Hertz (Hz). The terms m, s, d, t, and q refer to multiplet, singlet, douplet, triplet, and quartet, respectively. Chloroform-D and benzene-D6 was purchased from Cambridge Isotope.

5-phenylpent-2-yn-1-ol[1] **S1**, 2,2-dimethoxypropanenitrile[2] **S5**, sulfone **S6**[3], and aldehyde **S7**[4] were prepared according to the literature. All spectra were in accordance with those reported in the literature.

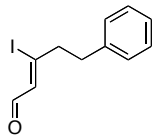
Synthesis of Diketone Substrate





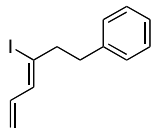
S2

(*Z*)-3-iodo-5-phenylpent-2-en-1-ol (S2): To a solution of **S1** (6.86 g, 42.9 mmol) in tetrahydrofuran (300 mL), at 0 ºC, was slowly added Red-Al (65% in toluene, 20.0 mL, 64.4 mmol) with stirring (vigorous reaction). The solution was allowed to warm to rt and stirred for 12 h. It was then cooled to -78 ºC and I_2 (32.4 g, 128 mmol) in tetrahydrofuran (200 mL) was added drop wise over a period of 30 min, and stirred at -78 ºC for 2 h. The reaction was then quenched with saturated Rochelle's salt (100 ml) and saturated $NaHCO_3$ (100 mL), extracted with diethyl ether (4 x 100 mL). The organic layers were combined washed with 10 % $NaHS_2O_3$ (2 x 100 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Flash chromatography on silica gel (hexane : ethyl acetate 9:1) yielded pure **S2** (8.73 g, 68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.4 Hz, 2H), 7.25 (dd, *J* = 12.8, 7.3 Hz, 3H), 5.81 (t, *J* = 5.8 Hz, 2H), 4.21 (d, *J* = 5.7 Hz, 2H), 2.95 – 2.89 (m, 2H), 2.89 – 2.83 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.3, 134.4, 128.7, 128.5, 126.3, 109.1, 67.3, 47.2, 35.7. IR (neat) (cm^{-1}) 3653-3086, 3024, 2924, 1643, 1600, 1496, 1454, 1060, 1018.



S3

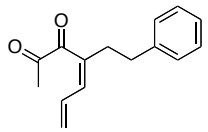
(*Z*)-3-iodo-5-phenylpent-2-enal (S3): To a solution of **S2** (8.37 g, 29.16 mmol) in dichloromethane (250 mL) was added MnO_2 (51 g, 538 mmol) and the solution was stirred for 12h at rt. The reaction mixture was then filtered through a pad of Celite, and concentrated to give aldehyde **S3** (5.90 g, 71%) as a single product. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.52 (d, *J* = 6.3 Hz, 1H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.25 – 7.15 (m, 3H), 6.12 (d, *J* = 6.3 Hz, 1H), 3.12 – 3.04 (t, *J* = 8.2, 2H), 2.99 – 2.90 (t, *J* = 8.2, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.7, 139.1, 132.7, 129.7, 128.7, 128.5, 126.7, 49.2, 35.2. IR (neat) (cm^{-1}) 3086, 3063, 3024, 2924, 1627, 1600, 1492, 1450, 1411, 1269, 1184. HRMS (EI): m/z, calcd for [$C_{11}H_{11}OI$]: 285.9855; found: 285.9843.



S4

(*Z*)-4-phenethylhepta-4,6-diene-2,3-dione (S4): To a solution of methyltriphenylphosphonium iodide (1.61 g, 4.39 mmol) in tetrahydrofuran (20 mL) at 0 ºC was added *n*-BuLi (2.5 M in hexanes, 1.76 mL) and the solution stirred for 0.5 h. Aldehyde **S3** (1.0 g, 3.51 mmol) was then added, in tetrahydrofuran (5 mL), to the reaction, and the solution allowed to warm to rt. After 1h, the reaction mixture was then quenched with saturated NH_4Cl (25 mL), the organic layer separated and aqueous layer was extracted with diethyl ether (3 x 25 mL). The organic fractions were combined, washed with brine (25 mL), dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Flash chromatography on silica gel (hexane : ethyl acetate 19:1) yielded diene **S4** (800 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.6 Hz, 2H), 7.22 (dd, *J* = 14.7, 8.4 Hz, 3H), 6.43 (dt, *J* = 16.9, 9.9 Hz, 1H), 6.09 (d, *J* = 9.6 Hz, 1H), 5.35 (d, *J* = 16.8 Hz, 1H), 5.26 (d, *J* = 10.3 Hz, 1H), 2.92 – 2.80 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.5, 139.0, 134.6, 128.6, 128.4, 126.2, 120.1, 109.5, 47.7, 36.0. IR

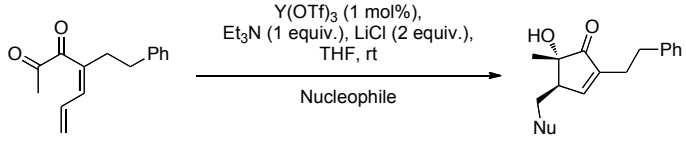
(neat) (cm^{-1}) 3024, 2924, 2854, 1631, 1600, 1492, 1454, 1411, 1269, 1184, 1060, 987, 910. HRMS (EI): m/z, calcd for [$C_{12}H_{13}I$]: 284.0062; found: 284.0069.



4

(*Z*)-4-phenethylhepta-4,6-diene-2,3-dione (4): To a solution of *t*-BuLi (1.15 M in pentane, 5.21 mL), in tetrahydrofuran (20 mL), at -78 ºC, was added the iodiodiene **S4** (800 mg, 2.81 mmol) drop wise as a solution in tetrahydrofuran (10 mL). The reaction mixture was then stirred at -78 ºC for 1 h and cyanoketal **S5** was then added as a solution in tetrahydrofuran (5 mL). The reaction mixture was stirred for an additional 6 h at -78 ºC. The solution was then quenched, at -78 ºC, with careful addition of a 1:1 ratio of glacial acetic acid and 1M HCl (70 mL). The reaction mixture was warmed to 35 ºC and stirred vigorously until complete conversion to the diketone was observed by TLC (ca. 5 h). The solution was then extracted with diethyl ether (4 x 20 mL), and the combined organic layers were washed with water amt (3 x 25 mL), saturated $NaHCO_3$ (25 mL), and brine (25 mL), and dried over Na_2SO_4. The reaction mixture was filtered, and the solvent was removed under reduced pressure. Flash chromatography on silica gel (hexane : ethyl acetate 39:1) gave diketone **4** (1.11 g, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 2H), 7.23 – 7.13 (m, 3H), 7.01 (d, *J* = 11.1 Hz, 1H), 6.61 (ddd, *J* = 16.7, 11.1, 10.0 Hz, 1H), 5.66 (d, *J* = 16.7 Hz, 1H), 5.57 (d, *J* = 10.0 Hz, 1H), 2.79 – 2.63 (m, 4H), 2.37 (s, 3H). ^{13}C NMR (126 125 MHz, $CDCl_3$) δ 201.9, 195.1, 146.5, 141.1, 135.5, 131.8, 128.7, 128.5, 128.3, 126.2, 35.3, 27.4, 27.0. IR (neat) (cm^{-1}) 3306, 3063, 3028, 2928, 2866, 1712, 1666, 1604, 1496, 1454, 1419, 1354, 1107, 1072, 1006. HRMS (EI): m/z, calcd for [$C_{15}H_{16}O_2Na$]: 251.1048; found: 251.1048.

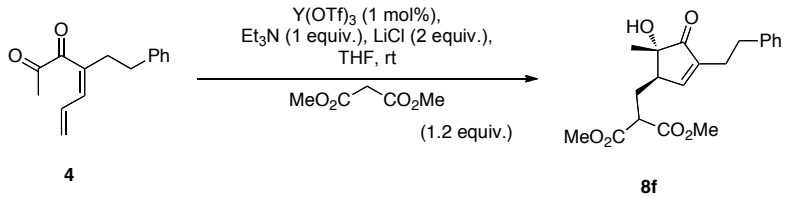
Typical Cyclization Procedure with nitrogen containing nucleophile.



4 8

To a solution of $Y(OTf)_3$ (1.2 mg, 0.0022 mmol), and LiCl (19 mg, 0.44 mmol) in tetrahydrofuran (1 mL) was added Et_3N (25. µl, 0.22 mmol) and Pyrrolidine (22 µL, 0.27 mmol) the resulting cloudy solution was then stirred for 5 min at rt. Diene **4** (50 mg, 0.22 mmol) was dissolved in tetrahydrofuran (1 mL) and added the resulting solution was then stirred for 15 min. The reaction was then quenched with 1 M (delete the space) HCl (1 mL) and extracted with diethyl ether (2 x 1 mL). The aqueous layer was then basified with 1M NaOH (to pH ≥ 10), and extracted with diethyl ether (3 x 1 mL). The organic layers were combined, washed with brine (1 mL), dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. This typically gave pure product without further need of purification; however if needed purification could be accomplished by recrystalization from ethanol and hexane.

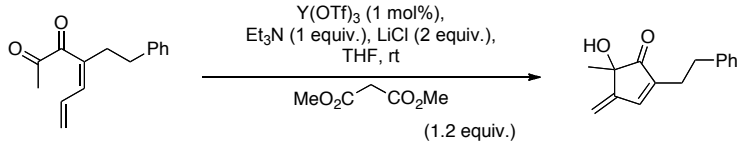
Typical Cyclization Procedure with malonate nucleophile.



4 **8f**

To a solution of $Y(OTf)_3$ (1.2 mg, 0.0022 mmol), and LiCl (19 mg, 0.44 mmol) in tetrahydrofuran (1 mL) was added Et_3N (25 µl, 0.22 mmol) and dimethyl malonate (31 µL, 0.27 mmol), the resulting cloudy solution was then stirred for 5 min at rt. Diene **4** (50 mg, 0.22 mmol) in tetrahydrofuran (1 mL) was then added and the solution stirred for 30 min. The reaction mixture was then quenched with 1 M HCl (1 mL) and extracted with diethyl ether (3 x 1 mL). The organic layers were combined, washed with brine (1 mL), dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. Flash chromatography on silica gel (hexane : ethyl acetate, 2 : 1) to give **8f**.

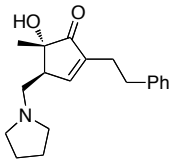
Typical Cyclization Procedure with catalytic malonate nucleophile.



4 **10**

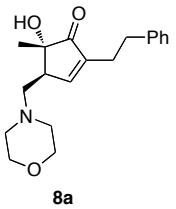
To a solution of $Y(OTf)_3$ (1.2 mg, 0.0022 mmol), and LiCl (19 mg, 0.44 mmol) in tetrahydrofuran (1 mL) was added 1,4-diazabicyclo[2.2.2]octane (DABCO) (0.25 mg, 0.0022 mmol) and dimethyl malonate (0.25 μL, 0.0022 mmol, 1 mol %), the resulting cloudy solution was then stirred for 5 min at rt. Diene **4** (50 mg, 0.22 mmol) in tetrahydrofuran (1 mL) was then added and the solution stirred for 1 h. The reaction was then quenched with 1 M HCl (1 mL) and extracted with diethyl ether (3 x 1 mL), the organic layers combined, washed with brine (1 mL), dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. Flash chromatography on silica gel (hexane : ethyl acetate 4 : 1) to give **10** (41 mg, 82%).

Characterization of α-hydroxyketones.



6

White crystalline solid, purified by acid-base extraction to give **6** (65 mg, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 1H), 7.24 – 7.21 (m, 1H), 7.17 (dd, J = 16.8, 7.3 Hz, 1H), 2.93 (s, 1H), 2.85 – 2.78 (m, 1H), 2.63 – 2.44 (m, 2H), 1.79 (t, J = 6.4 Hz, 1H), 1.20 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.7, 158.1, 141.2, 141.2, 128.5, 128.4, 126.1, 78.4, 55.4, 54.4, 49.2, 33.6, 26.9, 23.6, 21.4. IR (neat) (cm^{-1}) 3592-3105, 2962, 2928, 2793, 1708, 1454, 1361, 1141, 1053. HRMS (EI): m/z, calcd for [$C_{19}H_{26}NO_2$]: 300.1964; found: 300.1964.

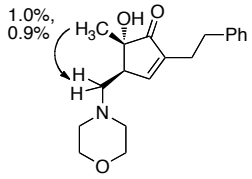


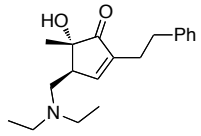
8a

White solid purified by acid-base extraction (60 mg, 87%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.12 (t, J = 7.3 Hz, 3H), 7.02 (dd, J = 18.2, 7.3 Hz, 2H), 6.71 (s, 1H), 3.68 – 3.38 (m,

4H), 2.82 (t, J = 7.3 Hz, 1H), 2.68 (t, J = 7.6 Hz, 2H), 2.46 (m, 2H), 2.27 – 2.04 (m, 5H), 1.87 (dd, J = 11.8, 9.5 Hz, 1H), 1.12 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.6, 157.9, 141.4, 141.1, 128.5, 128.4, 126.2, 78.3, 77.4, 77.1, 76.9, 67.1, 58.0, 53.9, 46.9, 33.6, 26.8, 21.3. IR (neat) (cm^{-1}) 3522-3159, 2850, 2808, 1708, 1454, 1114, 1003. HRMS (EI): m/z, calcd for [$C_{19}H_{26}NO_3$]: 316.1913; found: 316.1915.

nOe determined for **8a**.

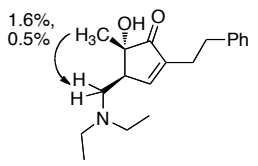


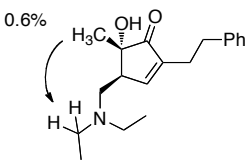


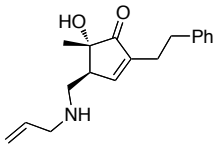
8b

Yellow oil purified by acid-base extraction (55 mg, 83%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.25 (t, J = 7.3 Hz, 2H), 7.15 (dd, J = 22.4, 7.2 Hz, 3H), 7.07 (s, 1H), 3.05 – 2.97 (m, 1H), 2.82 (t, J = 7.5 Hz, 3H), 2.68 – 2.60 (m, 2H), 2.60 – 2.49 (m, 5H), 2.41 (td, J = 13.7, 6.9 Hz, 3H), 2.22 – 2.14 (m, 1H), 1.26 (s, 3H), 1.05 (t, J = 7, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.0, 158.9, 141.1, 140.9, 128.5, 128.4, 126.1, 78.4, 52.3, 48.4, 47.2, 33.6, 26.8, 21.5, 11.8. IR (neat) (cm^{-1}) 3587-3244, 2970, 2808, 1708, 1454, 1381, 1168, 1072. HRMS (EI): m/z, calcd for [$C_{19}H_{27}NO_2$]: 301.2042; found: 301.2023.

nOe determined for **8b**.

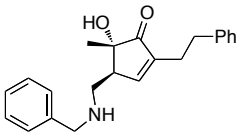






8c

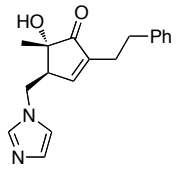
Colorless crystalline solid purified by recrystalization from EtOH – hexane (49 mg, 78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (t, *J* = 7.4 Hz, 2H), 7.04 (t, *J* = 7.4 Hz, 1H), 7.00 (d, *J* = 7.1 Hz, 2H), 6.70 (s, 1H), 5.76 (ddt, *J* = 16.1, 10.3, 5.9 Hz, 1H), 5.09 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.00 (dd, *J* = 10.3, 1.4 Hz, 1H), 3.02 – 2.91 (m, 2H), 2.66 (t, *J* = 7.7 Hz, 3H), 2.51 (dd, *J* = 11.3, 7.0 Hz, 1H), 2.49 – 2.34 (m, 2H), 2.17 (dd, *J* = 11.3, 8.4 Hz, 1H), 1.10 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.5, 157.3, 141.5, 141.1, 136.7, 128.5, 128.5, 126.2, 116.3, 78.4, 52.7, 50.8, 48.1, 33.6, 26.8, 21.4. IR (neat) (cm^{-1}) HRMS (EI): m/z, calcd for 3627-3111, 3063, 3028, 2974, 2924, 2854, 1705, 1627, 1601, 1546, 1496, 1454, 1365, 1261, 1234, 1145, 1118, 1053, 995, 918, 748, 698. HRMS (EI): m/z, calcd for [$C_{18}H_{24}NO_2$]: 286.1807; found: 286.1806.



8d

Yellow oil purified by flash chromatography (hexane : ethyl acetate 1:2; 50 mg, 68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (q, *J* = 7.4 Hz, 3H), 7.37 – 7.32 (m, 1H), 7.32 – 7.27 (m, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.18 (d, *J* = 7.3 Hz, 2H), 7.14 (s, 1H), 4.00 – 3.89 (m, 2H), 3.06 – 2.99 (m, 2H), 2.91 (dd, *J* = 11.8, 7.8 Hz, 1H), 2.84 (t, *J* = 7.7 Hz, 2H), 2.73 (dd, *J* = 11.8, 7.2 Hz, 1H), 2.56 (t, *J* = 7.5 Hz, 2H), 1.22 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.0, 156.5, 141.9, 141.1, 128.8, 128.8, 128.6, 128.5, 127.8, 126.3, 78.4, 53.7, 50.3, 47.6, 33.6, 26.8, 21.4. IR (neat) (cm^{-1}) 3484-3158, 3059, 3028, 2974, 2924, 2854, 1708, 1627, 1496, 1454, 1365, 1265, 1134, 748, 689. HRMS (EI): m/z, calcd for HRMS (EI): m/z, calcd for [$C_{22}H_{26}NO_2$]: 336.1964; found: 336.1962.

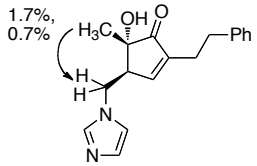
nOe determined for **8d**.

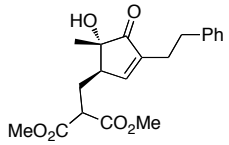


8e

White solid, purified by acid-base extraction (53 mg, 82%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.25 (s, 1H), 7.21 (s, 1H), 7.12 (t, *J* = 7.4 Hz, 2H), 7.04 (t, *J* = 7.4 Hz, 1H), 6.94 (d, *J* = 7.1 Hz, 2H), 6.37 (s, 1H), 6.11 (s, 1H), 3.46 (dd, *J* = 11.8, 4.2 Hz, 1H), 2.91 – 2.78 (m, 2H), 2.58 (m, 2H), 2.42 (m, 1H), 2.26 (m, 1H), 0.94 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.3, 154.1, 143.0, 140.7, 137.5, 130.1, 128.6, 128.6, 126.4, 119.1, 80.1, 51.1, 46.2, 33.4, 26.7, 21.4. IR (neat) (cm^{-1}) 3511-3209, 3113, 3063, 3028, 2974, 2924, 2854, 1712, 1508, 1454, 1369, 1230. HRMS (EI): m/z, calcd for [$C_{18}H_{20}N_2O_2$]: 296.1525; found: 296.1530.

nOe determined for **8e**.

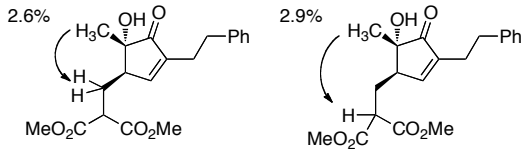


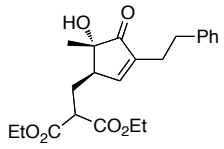


8f

Colorless oil purified by flash chromatography (hexane : ethyl acetate 2:1; 70.0 mg, 88%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.12 (t, *J* = 7.7 Hz, 2H), 7.04 (t, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 7.4 Hz, 2H), 6.38 (d, *J* = 2.0 Hz, 1H), 3.68 (dd, *J* = 8.7, 6.1 Hz, 1H), 3.34 (s, 3H), 3.30 (s, 3H), 3.02 (d, *J* = 19.4 Hz, 1H), 2.84 – 2.73 (m, 1H), 2.59 (dd, *J* = 11.5, 4.9 Hz, 2H), 2.45 – 2.24 (m, 2H), 2.16 – 1.99 (m, 2H), 1.05 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.2, 169.5, 169.4, 156.8, 141.7, 140.8, 128.5, 128.4, 126.2, 79.1, 52.9, 49.8, 47.9, 33.5, 28.0, 26.7, 21.8. IR (neat) (cm^{-1}) 3586-3252, 2955, 1732, 1712, 1435, 1346, 1234, 1199, 1153 HRMS (EI): m/z, calcd for [$C_{20}H_{24}O_6$]: 360.1573; found: 360.1578.

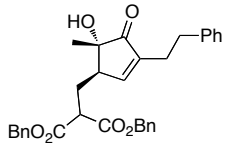
nOe determined for **8f**.





8g

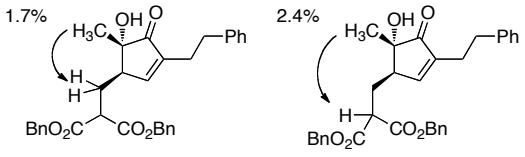
Colorless oil purified by flash chromatography (hexane : ethyl acetate 2:1; 70.0 mg, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.7 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.18 (d, *J* = 7.7 Hz, 2H), 7.00 (s, 1H), 4.32 – 4.21 (m, 4H), 3.60 (dd, *J* = 6.3, 2.4 1H), 2.86 – 2.80 (m, 3H), 2.79 – 2.74 (m, 1H), 2.62 – 2.51 (m, 2H), 2.23 – 2.17 (m, 1H), 2.07 – 2.01 (m, 1H), 1.32 (td, *J* = 7.3, 3.1 6H), 1.24 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.3, 169.2, 169.1, 157.0, 141.7, 141.0, 128.7, 128.3, 126.2, 79.1, 61.8, 61.6, 50.1, 47.9, 33.5, 27.9, 27.7, 26.8, 21.8, 14.2. IR (neat) (cm^{-1}) 3584-3179, 3063, 3028, 2982, 2935, 2870, 2495,2445, 2160, 2033, 1975, 1712, 1454, 1369, 1342, 1300, 1257, 1230, 1153, 1122, 1026. HRMS (EI): m/z, calcd for [$C_{22}H_{29}O_6$]: 389.1964; found: 389.1971

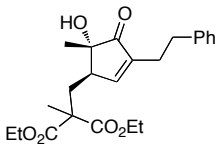


8h

Colorless oil purified by flash chromatography (hexane : ethyl acetate 2:1; 70 mg, 62%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.39 – 7.07 (m, 12H), 6.44 (s, 1H), 5.15 (q, *J* = 12.5 Hz, 2H), 5.09 (s, 2H), 3.89 (dd, *J* = 8.2, 6.4 Hz, 1H), 2.93 (t, *J* = 6.7 Hz, 1H), 2.76 (s, 1H), 2.70 (t, *J* = 7.7 Hz, 2H), 2.55 – 2.36 (m, 2H), 2.36 – 2.25 (m, 1H), 2.25 – 2.12 (m, 1H), 1.12 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.1, 168.8, 168.7, 156.7, 141.7, 140.9, 135.3, 135.2, 128.7, 128.7, 128.6, 128.5, 128.5, 128.3, 126.3, 79.1, 67.5, 50.1, 47.9, 33.5, 27.9, 26.7, 21.9. IR (neat) (cm^{-1}) 3649-3225, 3032, 1712, 1734, 1496, 1454, 1261, 1222, 1149 HRMS (EI): m/z, calcd for [$C_{32}H_{32}O_6$]: 512.2199; found: 512.2188.

nOe determined for **8g**.

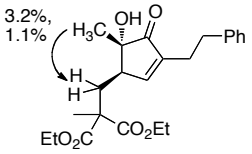


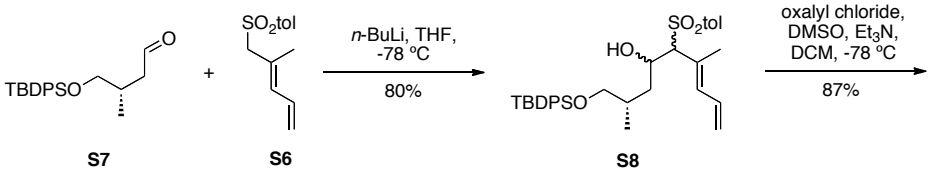


8i

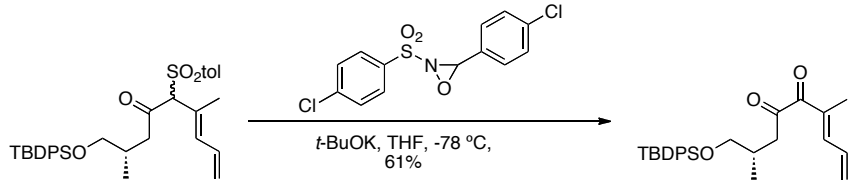
Colorless oil purified by flash chromatography (hexane : ethyl acetate 2:1; 69 mg, 78%). ^{1}H NMR (500 MHz, C_6D_6) δ 7.11 (t, *J* = 7.4 Hz, 2H), 7.03 (s, 1H), 6.98 (d, *J* = 7.3 Hz, 2H), 6.71 (s, 1H), 4.05 – 3.90 (m, 4H), 2.83 (d, *J* = 1.8 Hz, 1H), 2.63 (t, *J* = 7.2 Hz, 3H), 2.46 – 2.30 (m, 4H), 2.02 (dd, *J* = 14.5, 8.3 Hz, 1H), 1.56 (s, 4H), 1.05 (s, 4H), 0.93 (dd, *J* = 15.6, 7.3 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.1, 172.3, 158.5, 141.0, 141.0, 128.5, 128.5, 126.2, 79.5, 61.8, 61.6, 53.5, 46.5, 33.9, 33.6, 26.8, 22.8, 20.6, 14.1. IR (neat) (cm^{-1}) 3541-3279, 2982, 2935, 1712, 1454, 1365, 1242, 1195, 1134, 1103, 1022. HRMS (EI): m/z, calcd for [$C_{23}H_{30}O_6$]: 402.2042; found: 402.2051.

nOe determined for **8h**.





S7 **S6** **S8**



S9 **10S**

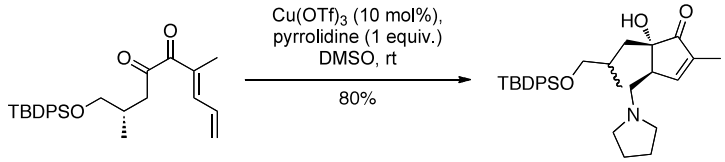
Synthesis of diketone S10:

To a solution of sulfone **S6** (2.75 g, 12.0 mmol) in THF (15 mL) at -78°C was added *n*-butyl lithium (1.6M in hexanes, 7.6 mL, 12.2 mmol) dropwise. The resulting deep red solution was stirred for 50 minutes at -78°C and then a solution of aldehyde **S7** (4.3 g, 12.6 mmol) in THF (15 mL) was added via dropwise addition. The reaction mixture was warmed to -40°C over 2.5 hours (some starting material remains), quenched with saturated NH_4Cl (15 mL), and then extracted with ether (3 x 10 mL). The combined organic phases were dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. Silica gel chromatography (slow drip gradient: 100% CH_2Cl_2 to 9/1 Et_2O / CH_2Cl_2 to 1/1 Et_2O / CH_2Cl_2) afforded sulfone **S8** (5.44 g, 80%) as a mixture of 4 diastereomers. This intermediate was used as obtained in the next step.

To a solution of oxalyl chloride (2M in CH_2Cl_2, 0.94 mL, 1.9 mmol) in CH_2Cl_2 (6 mL) at -78°C was added DMSO (0.27 mL, 3.8 mmol) in a dropwise fashion. After stirring for 15 minutes, sulfone **S8** (0.9 g, 1.6 mmol) in CH_2Cl_2 (6 mL) was added dropwise, and the resulting slurry was stirred for 35 minutes. Triethylamine (0.65 mL, 4.7 mmol) was then added and the reaction was warmed to -63°C over 75 minutes, or until judged complete by TLC. The reaction was quenched with brine (10 mL), diluted with ether (10 mL), and warmed to room temperature. The aqueous phase was washed immediately with ether (3 x 10 mL), and the combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. Flash chromatography on silica gel (hexane : ethyl acetate 6:1) yielded α-sulfonylketone **S9** (0.79 g, 87% yield) as a foamy oil, which was used immediately for oxidative desulphonylation. Careful handling of the oil (kept as a neat oil under weak vacuum until THF was added for the next step) ensured its longevity. Also, a strong vacuum was avoided to prevent a significant loss of material (due to foamy nature).

To a solution of potassium *t*-butoxide (0.16g, 1.5 mmol) in THF (8 mL) at r.t. was added α-sulfonylketone **S9** (0.76 g, 1.3 mmol) in THF (8 mL) dropwise. After 2 hours of stirring in which the solution changed from clear orange/red solution to a red/brown slurry, the reaction was cooled to -78°C and 2-[(p-chlorophenyl)sulfonyl]-3(p-chlorophenyl) oxaziridine[5] (0.68 g, 2.1 mmol) in THF (3 mL) was added dropwise. The

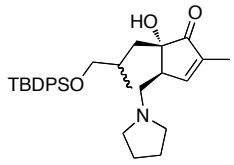
reaction was then warmed to -50°C over 90 minutes and then quenched with brine (10 mL) (crude mixture can be put in freezer overnight). Upon warming to r.t., the aqueous phase was extracted with ether (3 x 10 mL), and the combined organic extracts were dried with anhydrous $MgSO_4$ and concentrated reduced pressure. Flash chromatography on silica gel (hexane : ethyl acetate, 1% Et_3N 9:1) yielded diketone **S10** (0.36g, 61% yield) as a bright yellow oil, which was used immediately. ^1H NMR (400 MHz, C_6D_6): δ 7.83 (m, 4H), 7.31 (m, 6H), 7.16 (d, J = 11.2 Hz, 1H), 6.41 (m, 1H), 5.20 (m, 2H), 3.59 (dd, J = 10, 5.6 Hz, 1H), 3.50 (dd, J = 10, 5.6 Hz, 1H), 3.03 (dd, J = 17.2, 4.8 Hz, 1H), 2.60-2.46 (m, 2H), 1.83 (s, 3H), 1.23 (s, 9H), 0.96 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 203.3, 195.5, 144.8, 135.8, 133.8, 132.5, 132.2, 129.8, 127.9, 126.6, 68.0, 42.7, 31.4, 26.9, 19.3, 16.6, 10.6; HRMS (ES^+): Calculated for $C_{27}H_{34}O_3NaSi$ $(M+Na)^+$ 457.2169, Found: 457.2161.



7 9a / 9b

Cyclization of S10 to give 9

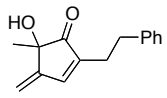
To a vial containing $Cu(OTf)_2$ (13 mg, 0.0355 mmol) was added a solution of diketone **S10** (0.154 g, 0.355 mmol) in DMSO (3.5 mL) (on occasion, diketone **S10** partially clumped together in DMSO; in this case, minimal amounts of CH_2Cl_2 was used as a co-solvent). Pyrrolidine (30 μL, 0.355 mmol) was then added, and the resulting solution was stirred at room temperature until judged complete by TLC (35 minutes). The reaction was diluted with ether (5 mL) and quenched with water (5 mL). The aqueous layer was extracted with ether (3 x 5 mL), and then the organic extracts were combined and washed with water (5 mL) and brine (5 mL). The organic layer was dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. Flash chromatography on silica gel (100% ethyl acetate, 1% NEt_3) yielded α-hydroxy cyclopentenones **7j-a** (higher R_f) and **7j-b** (lower R_f); (0.142 g combined, 80%) as yellow oils.



9a / 9b

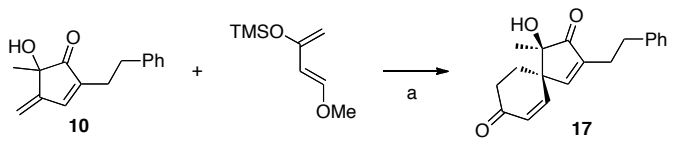
7j-a: ^{1}H NMR (500 MHz, C_6D_6): δ 8.03-7.92 (m, 4H), 7.37-7.29 (m, 6H), 7.00 (s, 1H), 4.94 (br s, 1H), 3.74 (dd, J = 10, 4.5 Hz, 1H), 3.55 (m, 1H), 3.14 (m, 1H), 2.68-2.64 (m, 2H), 2.54-2.49 (m, 5H), 2.12 (dd, J = 14.5, 7.5 Hz, 1H), 1.74-1.69 (m, 7H), 1.40 (dd, J = 14.5, 3.5 Hz, 1H), 1.33 (s, 9H), 0.70 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.4, 156.0, 138.3, 135.8, 135.7, 133.1, 132.7, 129.81, 129.77, 127.78, 127.73, 79.8, 70.5, 54.8, 54.4, 49.7, 40.3, 29.6, 26.8, 23.6, 19.3, 19.1, 10.6; IR (neat, cm^{-1}) 3358, 3070, 3047, 2956, 2929, 2856, 2790, 1708, 1471, 1427; HRMS (ES^+): Calculated for $C_{31}H_{44}O_3NSi$ (M^+) 506.3085, Found: 506.30890.

7j-b: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (m, 4H), 7.45-7.33 (m, 7H), 3.63 (br s, 1H), 3.43 (dd, J = 10, 5.2 Hz, 1H), 3.28 (m, 1H), 2.95 (m, 1H), 2.61-2.50 (m, 6H), 2.02 (m, 1H), 1.91-1.77 (m, 8H), 1.44 (d, J = 14.8, 6 Hz, 1H), 1.05 (s, 9H), 0.90 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 210.4, 157.4, 138.2, 135.7, 135.6, 133.25, 133.15, 129.7, 127.7, 80.5, 69.9, 55.3, 54.4, 50.6, 38.3, 31.0, 26.8, 23.5, 19.2, 18.5, 10.5; IR (neat, cm^{-1}) 3400, 3070, 3047, 2956, 2930, 2856, 2793, 1709, 1461, 1427, 1388; HRMS (ES^+): Calculated for $C_{31}H_{44}O_3NSi$ (M^+) 506.3085, Found: 506.3090.



10

White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.23 (dd, *J* = 18.0, 7.3 Hz, 3H), 5.45 (s, 1H), 5.32 (s, 1H), 3.03 (s, 1H), 2.90 (t, *J* = 7.7 Hz, 2H), 2.74 – 2.61 (m, 2H), 1.41 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.8, 152.6, 150.6, 142.8, 140.8, 128.5, 128.4, 126.2, 110.4, 77.4, 77.2, 76.9, 74.4, 33.5, 26.7, 24.3. IR (neat) (cm^{-1}) 3567-3168, 3059, 3028, 2974, 2924, 2858, 1705, 1643, 1593, 1496, 1454, 1361, 1284, 1145, 1118, 929, 748, 698. HRMS (EI): m/z, calcd for [$C_{15}H_{16}O_2$]: 228.1150; found: 228.1145.



Synthesis of 16: To a solution of diene **10** (10 mg, 0.044 mmol) in toluene (1 ml) was added Danishefsky's diene (38 mg, 0.22 mmol), and the solution was heated at 180 ºC, with stirring, in a sealed tube for 24 h. The reaction was then cooled to rt and trifluoroacetic acid (4 µl, 0.05 mmol) was added and the solution stirred for 30 minutes. The solvent was then evaporated under reduced pressure, and the product was purified by flash chromatography (hexane : ethyl acetate 2:1) to give **17** (10 mg, 80%), this product could also be purified by recrystalization from benzene. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 4H), 7.27 – 7.22 (m, 1H), 7.18 (d, *J* = 7.5 Hz, 2H), 7.00 (s, 1H), 6.38 (d, *J* = 10.2 Hz, 1H), 6.04 (d, *J* = 10.2 Hz, 1H), 2.90 (t, *J* = 7.5 Hz, 2H), 2.70 – 2.63 (m, 3H), 2.59 (dd, *J* = 11.3, 5.6 Hz, 2H), 2.38 – 2.28 (m, 1H), 2.01 (d, *J* = 13.8 Hz, 1H), 1.29 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.73, 197.72, 155.88, 152.32, 142.21, 140.48, 129.12, 128.62, 126.51, 81.84, 77.41, 77.16, 76.91, 51.15, 33.94, 33.42, 26.93, 26.85, 23.96. IR (neat) (cm^{-1}) 3576-3144, 2920, 2850, 2360, 2322, 2283, 1716, 1674, 1454, 1377, 1230, 1157, 1080. HRMS (EI): m/z, calcd for [$C_{19}H_{20}O_3$]: 296.1413; found: 296.1418.

---

[1] Mori, M.; Tonogaki, K.; Kinoshita, A. *Org. Synth.* **2005**, *81,* 1–13.

[2] Kirchmeyer, S.; Mertens, A.; Arvanaghi, M.; Olah, G. A. *Synthesis* **1983**, 498–500.

[3] Back, T.G.; Muralidharan, K.R. *J. Org. Chem.* **1989**, *54*, 121–125.

[4] Keyling-Bilger, F.; Schmitt, G.; Beck, A.; Luu, B. *Tetrahedron* **1996**, *52*, 14891–14904.

[5] Williams, D. R.; Robinson, L. A.; Amato, G. S.; Osterhout, M. H. *J. Org. Chem.* **1992**, *57*, 3740–3744.