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An Approach towards the Tetracyclic Skeleton of Palhinine Alkaloids

authored by

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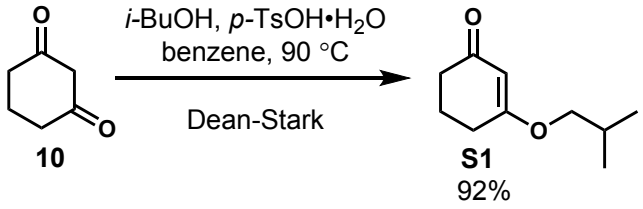
GENERAL EXPERIMENTAL INFROMATION.

All reactions were performed in flame-dried glassware under nitrogen atmosphere. Solvents were distilled prior to use. Reagents were used as purchased from Aladdin, Macklin, Innochem, or TCI unless otherwise noted. Chromatographic separations were performed using Silica Gel, AR, 200-300 mesh. ^{1}H and ^{13}C NMR spectra were obtained on Varian VI-400, VI-500 and VI-600 spectrometers using $CDCl_3$ as the solvent. Infrared spectra were obtained on Thermo Scientific Nicolet iS 50. TLC analysis was visualized using UV, *p*-anisoladehyde and phosphomolybdic acid stains. High-resolution mass spectra were obtained using AB SCIEX X500R QTOF. All spectral data obtained for new compounds are reported here.

EXPERIMENTAL PROCEDURES AND COMPOUND CHARACTERIZATION

Synthesis of S1.[1]

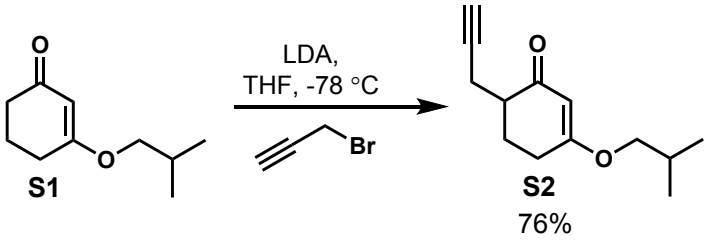


To a solution of cyclohexane-1,3-dione **10** (22.4 g, 200 mmol, 1.0 equiv) in benzene (123 mL) was added 2-methylpropan-1-ol (55 mL, 600 mmol, 3.0 equiv) and $TsOH{\cdot}H_2O$ (190 mg, 1.0 mmol, 0.005 equiv) at rt. The reaction mixture was heated with a Dean−Stark trap at 90 °C for 12 h. The solution was then concentrated under reduced pressure. The residue was purified using flash column chromatography (eluent: petroleum ether (PE)/EtOAc, ratio = 5:1) to give a yellow oil (30.9 g, 184 mmol, 92%) as the product **S1**.

S1: R_f = 0.27 (eluent: PE/EtOAc, ratio = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19 (s, 1H), 3.46 (d, J = 6.5 Hz, 2H), 2.28 (t, J = 6.3 Hz, 2H), 2.19 (t, J = 6.7 Hz, 2H), 1.95 –

1.80 (m, 3H), 0.90 – 0.79 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.5, 177.9, 102.6, 74.5, 36.7, 28.9, 27.6, 21.1, 19.0; IR (KBr) cm^{-1} 3455m, 2962s, 1650m, 1610s, 1373m,1218s, 1002m; HRMS: $C_{10}H_{17}O_2$ for $[M+H]^+$, calculated 169.1223, found 169.1222.

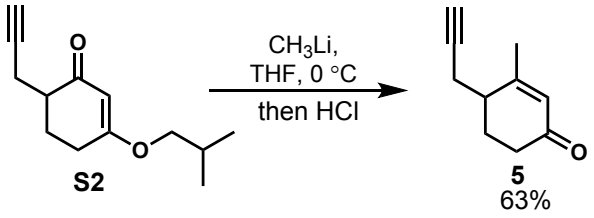
Synthesis of S2.[2]



To a solution of *i*-Pr_2NH (3.7 mL, 26.5 mmol, 1.1 equiv) in THF (100 mL) was added *n*-BuLi (15 mL, 1.6 M in hexanes, 24.0 mmol, 1.0 equiv) slowly at –78 °C. The reaction mixture was stirred at –78 °C for 45 min. Then compound **S1** (4.03 g, 24.0 mmol, 1.0 equiv) in THF (20 mL) was added slowly to the mixture at –78 °C. The mixture was left stirring at –78 °C for 45 min. Then to the solution was added 1-bromo-2-propyne (4.28 g, 36 mmol, 1.5 equiv) at –78 °C. The reaction was stirred at –78 °C for 2 h and then allowed to warm to rt. After 6 h, the reaction was quenched with sat aq NH_4Cl and extracted three times with ethyl acetate. The combined organic layers were washed with equal volume of sat aq NaCl and dried over anhyd $MgSO_4$. After filtration and concentration, the crude product was purified using flash column chromatography (eluent: PE/EtOAc, ratio = 20:1) to give a yellow oil (3.76 g, 18.2 mmol, 76%) as the product **S2**.

S2: R_f = 0.52 (eluent: PE/EtOAc, ratio = 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.18 (d, *J* = 1.3 Hz, 1H), 3.51 – 3.38 (m, 2H), 2.62 (dt, *J* = 16.1, 3.0 Hz, 1H), 2.43 – 2.27 (m, 2H), 2.26 – 2.08 (m, 3H), 1.96 – 1.80 (m, 2H), 1.76 – 1.61 (m, 1H), 0.83 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.2, 177.4, 102.0, 82.3, 74.7, 69.7, 44.1, 28.5, 27.6, 26.1, 19.03, 18.97, 18.95; IR (KBr) cm^{-1} 3286m, 2953s, 2869w, 1666m, 1604s, 1373s, 1203s, 547s; HRMS: $C_{13}H_{19}O_2$ for $[M+H]^+$, calculated 207.1380, found 207.1377.

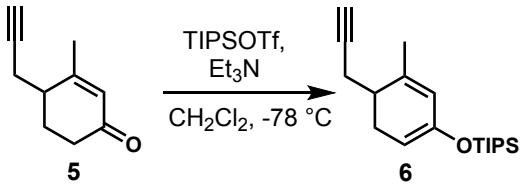
Synthesis of 5.[3]



To a solution of compound **S2** (4.13 g, 20 mmol, 1.0 equiv) in THF (100 mL) was added CH_3Li (37.5 mL, 1.6 M in ethyl ether, 60 mmol, 3.0 equiv) slowly at 0 °C. After stirred at rt for 1 h the mixture was treated with 1 M HCl (60 mL) at 0 °C. The reaction was stirred at rt for 30 min and then extracted with ethyl acetate (three times). The combined organic layers were washed with equal volume of sat aq $NaHCO_3$ and sat aq NaCl, then dried over anhyd $MgSO_4$. After filtration and concentration, the crude product was purified using flash column chromatography (eluent: PE/EtOAc, ratio = 20:1) to give a yellow oil (1.87 g, 12.6 mmol, 63%) as the product **5**.

5: R_f = 0.30 (eluent: PE/EtOAc, ratio = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (s, 1H), 2.49 – 2.38 (m, 4H), 2.31 – 2.23 (m, 1H), 2.10 – 2.05 (m, 2H), 2.02 – 1.97 (m, 1H), 1.95 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.9, 162.7, 127.9, 81.4, 70.7, 38.5, 34.6, 27.2, 22.6, 21.4; IR (KBr) cm^{-1} 3887m, 3810s, 2190m, 1666s, 1434w, 547m; HRMS: $C_{10}H_{13}O$ for $[M+H]^+$, calculated 149.0961, found 149.0962.

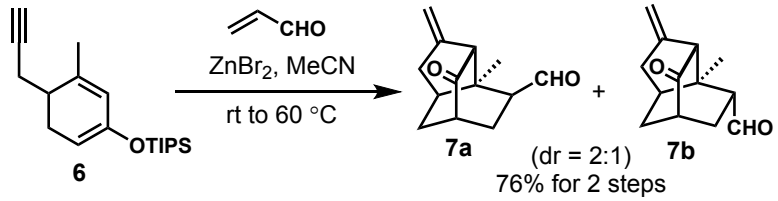
Synthesis of 6



To a solution of compound **5** (37.0 mg, 0.25 mmol, 1.0 equiv) in CH_2Cl_2 (2.5 mL) was added Et_3N (88.6 mg, 0.875 mmol, 3.5 equiv) and TIPSOTf (115 mg, 0.375 mmol, 1.5 equiv) at –78 °C. The reaction mixture was stirred at –78 °C for 1 h and then quenched with sat aq $NaHCO_3$. The mixture was extracted three times with ethyl acetate. The combined organic layers were washed with equal volume of sat aq NaCl and dried over anhyd $MgSO_4$. After filtration and concentration, the crude dienol

silane was flushed through a short column (Et_3N-neutralized silica gel, eluent: PE) and used directly in the next step.

Synthesis of 7



To a solution of $ZnBr_2$ (11.3 mg, 0.05 mmol, 0.2 equiv) in anhydrous acetonitrile (1.0 mL) was added freshly distilled acrolein (140 mg, 2.5 mmol, 10 equiv) at 0 °C. After 15 min, to the above mixture was added a solution of compound **6** (0.25 mmol, 1.0 equiv) in anhydrous acetonitrile (1.0 mL) at 0 °C. The reaction was stirred at rt for 6 h and then heated to 60 °C for 12 h. The reaction mixture was then diluted with ethyl acetate and washed with equal volume of sat aq NaCl. The organic layer was dried over anhyd $MgSO_4$. After filtration and concentration, the crude product was purified using flash column chromatography (eluent: PE/EtOAc, ratio = 15:1) to give a colorless oil (38.8 mg, 0.19 mmol, dr = 2:1, 76% total yield for two steps) as the product **7**. The ratio of **7a** and **7b** was determined by ^{1}H NMR.

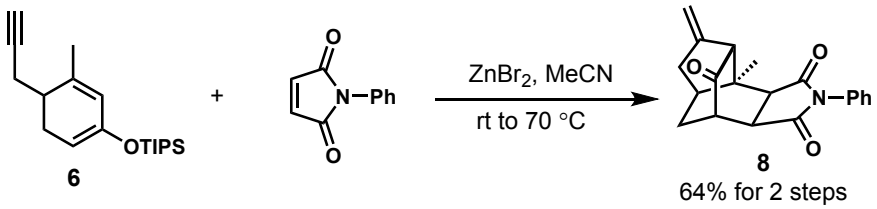
7 (diastereomeric mixture)**:** R_{f7a} = 0.34 (eluent: PE/EtOAc, ratio = 5:1), R_{f7b} = 0.31 (eluent: PE/EtOAc, ratio = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (d, *J* = 2.6 Hz, 2H), 9.60 (d, *J* = 3.8 Hz, 1H), 5.23 (d, *J* = 9.0 Hz, 3H), 4.96 (d, *J* = 11.1 Hz, 3H), 2.89 (s, 1H), 2.76 – 2.58 (m, 8H), 2.28 – 2.09 (m, 8H), 2.04 – 1.87 (m, 8H), 1.84 – 1.77 (m, 2H), 1.42 – 1.32 (m, 3H), 1.07 (s, 6H), 0.96 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.3, 211.8, 202.7, 202.3, 145.3, 144.2, 112.5, 112.4, 66.1, 63.1, 49.4, 48.7, 46.0, 45.6, 41.1, 40.8, 40.1, 39.3, 38.0, 36.6, 32.0, 31.6, 26.8,26.7, 21.4, 20.8; IR (KBr) cm^{-1} 3424s, 2925s, 2869w, 2530m, 1725s, 1450m, 1218m, 894w, 524m; HRMS: $C_{13}H_{17}O_2$ for $[M+H]^+$, calculated 205.1223, found 205.1220.

Further purification using column chromatography could give pure **7a**.

7a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (d, *J* = 2.6 Hz, 1H), 5.28 (s, 1H), 5.00 (s, 1H), 2.76 (s, 1H), 2.69 – 2.59 (m, 2H), 2.32 – 2.28 (m, 1H), 2.25 – 2.19 (m, 1H), 2.16 –

2.11 (m, 1H), 2.02 – 1.91 (m, 2H), 1.86 – 1.79 (m, 1H), 1.38 – 1.32 (m, 1H), 1.07 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.8, 202.8, 144.0, 113.0 , 66.3, 49.7, 46.2, 41.2, 39.4, 36.73, 31.7, 27.0, 21.6; IR (KBr) cm^{-1} 3424s, 2925s, 2869w, 1725s, 1450m, 1218m, 1187w, 971w, 894w, 524m; HRMS: $C_{13}H_{17}O_2$ for $[M+H]^+$, calculated 205.1223, found 205.1220.

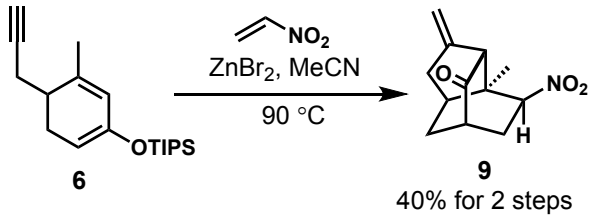
Synthesis of 8



To a solution of $ZnBr_2$ (11.3 mg, 0.05 mmol, 0.2 equiv) in anhydrous acetonitrile (1.0 mL) was added N-phenylmaleimide (432 mg, 2.5 mmol, 10 equiv) at 0 °C. After 15 min, to the above mixture was added a solution of compound **6** (0.25 mmol, 1.0 equiv) in anhydrous acetonitrile (1.0 mL) at 0 °C. The reaction mixture was stirred at rt for 6 h and then heated at 70 °C for 12 h. The reaction mixture was then diluted with ethyl acetate and washed with equal volume of sat aq NaCl. The organic layer was dried over anhyd $MgSO_4$. After filtration and concentration, the crude product was purified using flash column chromatography (eluent: PE/EtOAc, ratio = 5:1) to give a white solid (51.4 mg, 0.16 mmol, 64% in two steps from compound **5**) as the product **8**.

8: R_f = 0.32 (eluent: PE/EtOAc, ratio = 2:1); mp 242 – 244 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (t, J = 7.3 Hz, 2H), 7.39 (t, J = 7.3 Hz, 1H), 7.17 (d, J = 8.0 Hz, 2H), 5.34 (s, 1H), 5.09 (s, 1H), 3.23 (dd, J = 9.5, 3.5 Hz, 1H), 3.07 (d, J = 9.5 Hz, 1H), 2.89 – 2.80 (m, 3H), 2.27 – 2.21 (m, 1H), 2.19 – 2.10 (m, 1H), 2.06 (d, J = 16.8 Hz, 1H), 1.59 (dd, J = 13.8, 4.1 Hz, 1H), 1.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.0, 175.9, 175.3, 143.8, 131.5, 129.2, 128.9 , 126.6, 113.9, 63.8, 46.3, 45.8, 43.4, 43.2, 39.4 , 31.5 , 20.4; IR (KBr) cm^{-1} 3471m, 2314m, 1712s, 1496w, 1388s, 1203s, 694m; HRMS: $C_{20}H_{20}NO_3$ for $[M+H]^+$, calculated 322.1438, found 322.1436;

Synthesis of 9



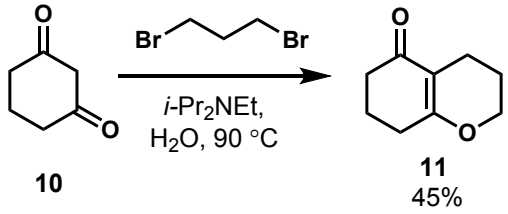
6 **9**

40% for 2 steps

To a solution of $ZnBr_2$ (11.3 mg, 0.05 mmol, 0.2 equiv) in anhydrous acetonitrile (1.0 mL) was added nitroethene (182 mg, 2.5 mmol, 10 equiv) at rt. After 15 min, to the above mixture was added a solution of compound **6** (0.25 mmol, 1.0 equiv) in anhydrous acetonitrile (1.0 mL) at rt. The reaction mixture was heated at 90 °C for 12 h (using a sealed tube). The reaction mixture was then diluted with ethyl acetate and washed with equal volume of sat aq NaCl. The organic layer was dried over anhyd $MgSO_4$. After filtration and concentration, the crude product was purified using flash column chromatography (eluent: PE/EtOAc, ratio = 15:1) to give a yellow solid (21.9 mg, 0.10 mmol, 40% in two steps from compound **5**) as the product **9**.

9: R_f = 0.31 (eluent: PE/EtOAc, ratio = 5:1); mp 89 – 92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (s, 1H), 5.02 (s, 1H), 4.88 (dd, J = 10.1, 5.2 Hz, 1H), 3.10 (s, 1H), 2.77 – 2.68 (m, 1H), 2.41 (m, 2H), 2.32 – 2.25 (m, 1H), 2.17 – 2.11 (m, 1H), 2.04 – 1.94 (m, 2H), 1.48 – 1.40 (m, 1H), 0.95 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.9, 144.0, 113.4, 86.1, 62.2, 47.6, 40.5, 38.6 , 38.5, 33.1, 31.5, 19.1; IR (KBr) cm^{-1} 3409m, 2962s, 1712s, 1550s, 1373s, 894s, 678s, 524s; HRMS: $C_{12}H_{16}NO_3$ for $[M+H]^+$, calculated 222.1125 , found 222.1121;

Synthesis of 11.[4]



10 **11**

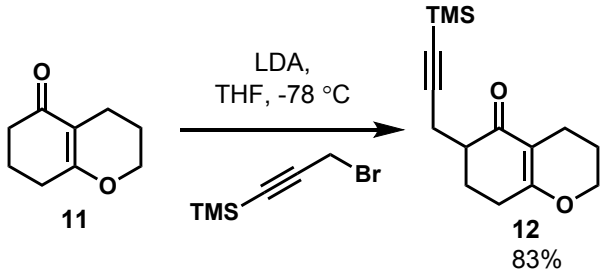
45%

To a solution of cyclohexane-1,3-dione **10** (67.3 g, 600 mmol, 1.0 equiv) in a mixed solvent of *N,N*-diisopropylethylamine (90 mL) and water (90 mL) was added 1,3-dibromopropane (30.6 mL, 300 mmol, 0.5 equiv) slowly at rt. The reaction mixture was heated at 90 °C for 3.5 h and then treated with 2 M HCl (150 mL) slowly at rt. After 15 min, the reaction was extracted four times with ethyl acetate. The combined

organic layers were washed with equal volume of sat aq $NaHCO_3$ and sat aq NaCl, then dried over anhyd $MgSO_4$. After filtration and concentration, the crude product was purified using flash column chromatography (eluent: PE/EtOAc, ratio = 2:1) to give a colorless oil (20.5 g, 135 mmol, 45%) as the product **11**.

11: R_f = 0.20 (eluent: PE/EtOAc, ratio = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03 (t, J = 5.1 Hz, 2H), 2.29 (m, 4H), 2.16 (t, J = 6.3 Hz, 2H), 1.92 – 1.84 (m, 2H), 1.83 – 1.76 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.1, 171.5, 111.6, 67.3, 36.6, 28.6, 21.4, 20.8, 17.5; IR (KBr) cm^{-1} 3517w, 2946m, 2360m, 1650s, 1619s, 1403s, 863m; HRMS: $C_9H_{13}O_2$ for $[M+H]^+$, calculated 153.0910, found 153.0907.

Synthesis of 12

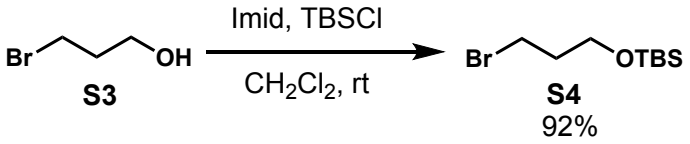


To a solution of *i*-Pr_2NH (7.4 mL, 53 mmol, 1.1 equiv) in THF (200 mL) was added *n*-BuLi (31.9 mL, 1.6 M in hexanes, 51 mmol, 1.06 equiv) slowly at –78 °C. The reaction mixture was stirred at –78 °C for 45 min. Then compound **11** (7.30 g, 48 mmol, 1.0 equiv) in THF (20 mL) was added slowly to the mixture at –78 °C. The mixture was left stirring at –78 °C for 1.5 h. Then to the reaction was added a solution of 3-trimethylsilyl-1-bromo-2-propyne (13.76 g, 72 mmol, 1.5 equiv) in THF (20 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 3 h and then allowed to warm to rt. After 6 h, the reaction was quenched with sat aq NH_4Cl and extracted three times with ethyl acetate. The combined organic layers were washed with equal volume of sat aq NaCl and dried over anhyd $MgSO_4$. After filtration and concentration, the crude product was purified using flash column chromatography (eluent: PE/EtOAc, ratio = 10:1) to give a white solid (10.50 g, 40 mmol, 83%) as the product **12**.

12: R_f = 0.36 (eluent: PE/EtOAc, ratio = 8:1); mp 71 – 75 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 – 4.07 (m, 1H), 4.05 – 3.92 (m, 1H), 2.88 (dd, J = 17.0, 3.6 Hz, 1H),

2.51 – 2.07 (m, 7H), 1.89 – 1.63 (m, 3H), 0.11 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.2 , 170.9, 110.8, 105.4, 85.8, 67.2, 43.9, 27.8, 25.6, 21.3, 20.8, 17.5, 0.00; IR (KBr) cm^{-1} 2962m, 2175s, 1866m, 1619s, 833s; HRMS: $C_{15}H_{23}O_2Si$ for $[M+H]^+$, calculated 263.1462, found 263.1455;

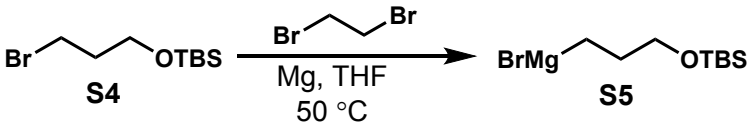
Synthesis of S4.[5]



To a solution of 3-bromopropan-1-ol **S3** (10.0 g, 72 mmol, 1.0equiv) in CH_2Cl_2 (180 mL) was added imidazole (7.82 g, 115 mmol, 1.6 equiv) at rt. After 15 min, TBSCl (12.9 g, 86 mmol, 1.2 equiv) was added to the mixture at 0 °C. The reaction mixture was stirred at rt for 18 h and then quenched with sat aq $NaHCO_3$. The mixture was extracted three times with ethyl acetate. The combined organic layers were washed with equal volume of sat aq NaCl and dried over anhyd $MgSO_4$. After filtration and concentration, the crude product was purified using flash column chromatography (eluent: PE) to give a colorless oil (16.7 g, 66 mmol, 92%) as the product **S4**.

S4: R_f = 0.48 (eluent: PE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (t, J = 5.7 Hz, 2H), 3.50 (t, J = 6.5 Hz, 2H), 2.07 – 1.97 (m, 2H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 60.4, 35.6, 30.5, 25.9, 18.3, -5.4; IR (KBr) cm^{-1} 3394s, 2931s, 2854m, 1249s, 1101s, 833s, 771s; HRMS could not be obtained.

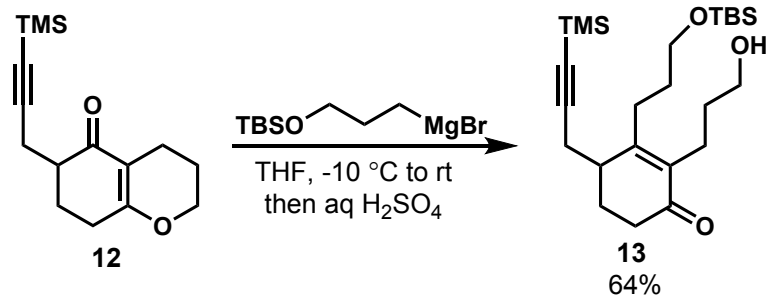
Synthesis of S5



To a mixture of magnesium turnings (4.32 g, 180 mmol, 3 equiv) in THF (46 mL) was added 1,2-dibromoethane (1.13 g, 6 mmol, 0.1 equiv) slowly at rt. The reaction mixture was stirred at rt for 20 min. Then compound **S4** (0.25 mmol, 1.0 equiv) in THF (46 mL) was added slowly to the mixture at 50 °C. After stirring at 50 °C for 15

min, THF was added slowly to the solution until the precipitate was completely dissolved at rt. The solution of **S5** was used directly in the next step.

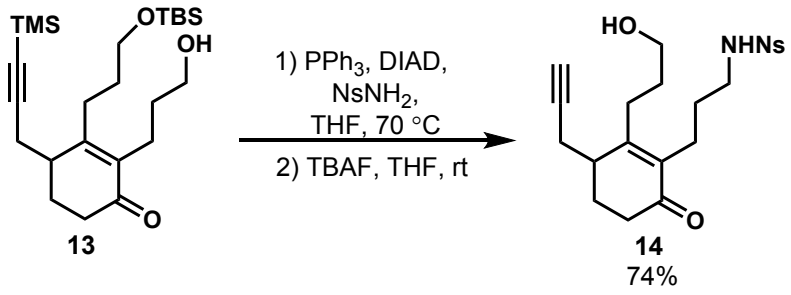
Synthesis of 13



To a solution of **12** (4.49 g, 17.1 mmol, 1.0 equiv) in THF (17 mL) was added Grignard reagent **S5** (120 mL, 60 mmol, 3.5 equiv) slowly at –10 °C. The reaction mixture was stirred at rt for 4 h and then treated with 1.5% H_2SO_4 (26 mL) slowly at 0 °C. After the reaction was stirred at rt for another 10 min, the mixture was extracted three times with ethyl acetate. The combined organic layers were washed with equal volume of sat aq $NaHCO_3$ and sat aq NaCl, then dried over anhyd $MgSO_4$. After filtration and concentration, the crude product was purified using flash column chromatography (eluent: PE/EtOAc, ratio = 4:1) to give a yellow oil (4.78g, 10.9 mmol, 64%) as the product **13**.

13: R_f = 0.19 (eluent: PE/EtOAc, ratio = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.56 (t, J = 5.8 Hz, 2H), 3.48 – 3.25 (m, 2H), 3.12 (s, 1H), 2.60 – 2.19 (m, 8H), 2.19 – 1.90 (m, 3H), 1.71 – 1.33 (m, 4H), 0.81 (s, 9H), 0.03 (s, 9H), -0.03 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.7, 161.7, 135.8, 104.5, 87.0, 62.4, 61.1, 37.5, 33.8, 32.4, 31.6, 29.0, 26.6, 25.9, 23.2, 20.8, 18.2, 0.0, -5.3; IR (KBr) cm^{-1} 3363m, 2951s, 2175s, 1650s, 1249s, 1187m, 1095s, 845s, 771s; HRMS: $C_{24}H_{45}O_3Si_2$ for $[M+H]^+$, calculated 437.2902, found 437.2894.

Synthesis of 14

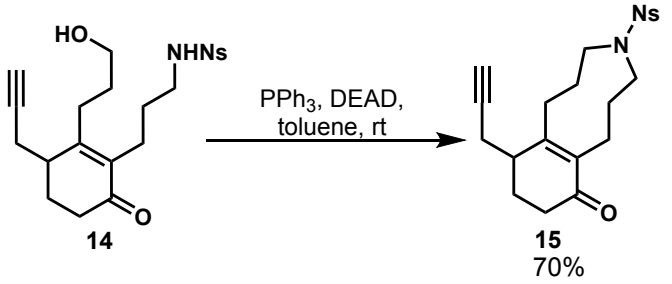


To a solution of **13** (1.44 g, 3.3 mmol, 1.0 equiv) in THF (35 mL) was added 2-nitrobenzenesulfonamide (2.00 g, 9.9 mmol, 3.0 equiv) and PPh_3 (1.21 g, 4.6 mmol, 1.4 equiv) at rt. After 10 min, DIAD (0.87 g, 4.3 mmol, 1.3 equiv) was added to the above mixture at rt. The reaction mixture was heated at 70 °C for 12 h before being concentrated under reduced pressure. The crude sulfonamide was flushed through a short column (silica gel, eluent: PE/EtOAc, ratio = 5:1) and then used directly in the next step.

To a solution of the crude sulfonamide in THF (35 mL) was added TBAF (1.0 M in THF; 13 mL, 13 mmol, 3.9 equiv) slowly at rt. The reaction mixture was stirred for 12 h at rt before being quenched with sat aq NH_4Cl. Then the mixture was extracted three times with ethyl acetate. The combined organic layers were washed with equal volume of sat aq NaCl and dried over anhyd $MgSO_4$. After filtration and concentration, the crude product was purified using flash column chromatography (eluent: PE/EtOAc, ratio = 1:1) to give a yellow oil (1.06 g, 2.4 mmol, 74%) as the product **14**.

14: R_f = 0.14 (eluent: PE/EtOAc, ratio = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.00 (m, 1H), 7.82 – 7.74 (m, 1H), 7.74 – 7.65 (m, 2H), 6.05 – 5.89 (m, 1H), 3.64 (t, *J* = 5.9 Hz, 2H), 3.17 – 2.85 (m, 2H), 2.82 – 1.83 (m, 13H), 1.79 – 1.69 (m, 1H), 1.69 – 1.40 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.0, 161.2, 148.0, 135.4, 133.7, 133.6, 132.8, 130.9, 125.2, 82.0, 70.7, 62.0, 43.4, 37.3, 33.6, 31.3, 29.3, 29.0, 26.3, 22.1, 21.7; IR (KBr) cm^{-1} 3293m, 2931s, 2329m, 1655s, 1543s, 1342s, 1172s, 848m, 740s; HRMS: $C_{21}H_{27}N_2O_6S$ for $[M+H]^+$, calculated 435.1584, found 435.1580.

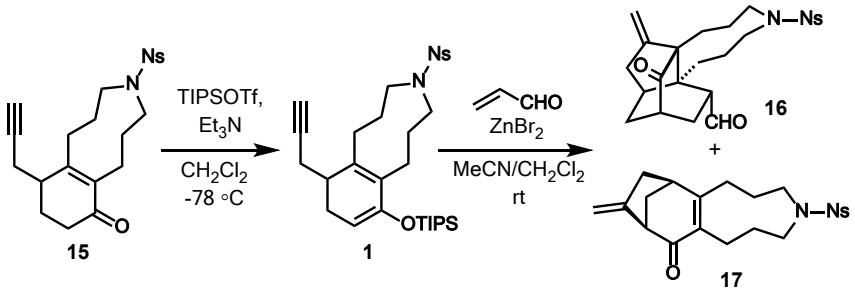
Synthesis of 15



To a solution of compound **14** (1.30 g, 3 mmol, 1.0 equiv) in toluene (200 mL) was added PPh_3 (2.44 g, 9.3 mmol, 3.1 equiv) at rt. After 10 min, a solution of DEAD (1.57 g, 9 mmol, 3.0 equiv) in toluene (4 mL) was added slowly to the above mixture at rt. The reaction was stirred at rt for 1 h before being concentrated under reduced pressure. The crude product was purified using flash column chromatography (eluent: PE/EtOAc, ratio = 1:1) to give the crude **15**. To a mixture of the crude **15** in EtOH (30 mL) was added $ZnCl_2$ (0.82 g, 6 mmol) at rt. The reaction mixture was stirred at rt for 18 h before being filtered and concentrated. The crude product was purified using flash column chromatography (eluent: PE/EtOAc, ratio = 2:1) to give a white solid (0.86 g, 2.1 mmol, 70%) as the product **15**.

15: R_f = 0.23 (eluent: PE/EtOAc, ratio = 2:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.68 (m, 2H), 7.57 (dd, *J* = 7.7, 1.3 Hz, 1H), 3.52 (dt, *J* = 15.0, 4.9 Hz, 1H), 3.38 (dt, *J* = 15.0, 5.1 Hz, 1H), 3.04 (td, *J* = 13.2, 4.2 Hz, 1H), 2.91 (ddd, *J* = 14.6, 9.8, 4.5 Hz, 1H), 2.82 (ddd, *J* = 14.6, 9.6, 4.6 Hz, 1H), 2.71 (dt, *J* = 13.7, 4.7 Hz, 1H), 2.64 – 2.52 (m, 3H), 2.51 – 2.45 (m, 1H), 2.43 – 2.31 (m, 3H), 2.27 – 2.16 (m, 2H), 2.11 – 1.99 (m, 3H), 1.92 – 1.81 (m, 1H), 1.82 – 1.73 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 197.9, 159.2, 148.8, 136.2, 133.8, 131.4, 130.7, 130.6, 124.0, 82.0, 70.6, 53.7, 53.3, 36.5, 33.7, 28.0, 27.4, 27.3, 26.1, 21.8, 21.5; IR (KBr) cm^{-1} 3452s, 1650s, 1357m, 848w, 740w, 571s; HRMS: $C_{21}H_{25}N_2O_5S$ for $[M+H]^+$, calculated 417.1479, found 417.1476; m.p. = 139-141 ℃.

Synthesis of 16 (optimized procedure)



To a solution of 1**5** (33.3 mg, 0.08 mmol, 1.0 equiv) in CH_2Cl_2 (0.8 mL) was added Et_3N (28.3 mg, 0.28 mmol, 3.5 equiv) and TIPSOTf (36.7 mg, 0.12 mmol, 1.5 equiv) at –78 °C. The reaction mixture was stirred at –78 °C for 1.5 h before being quenched with sat aq $NaHCO_3$. The mixture was extracted three times with ethyl acetate. The combined organic layers were washed with equal volume of sat aq NaCl and dried over anhyd $MgSO_4$. After filtration and concentration, the crude dienol silane **1** was flushed through a short column (Et_3N-neutralized silica gel, eluent: PE/EtOAc, ratio = 5:1) and then used directly in the next step.

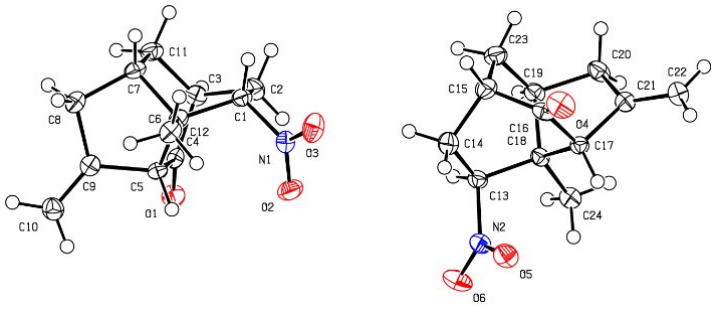
To a solution of $ZnBr_2$ (3.6 mg, 0.016 mmol, 0.2 equiv) in anhydrous acetonitrile (0.4 mL) was added freshly distilled acrolein (44.8 mg, 0.8 mmol, 10 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min. After that, the reaction mixture was treated with a solution of crude **1** (prepared from 0.08 mmol **15**, 1.0 equiv) in 0.4 mL mixed MeCN/CH_2Cl_2 (1.5:1) at 0 °C. The reaction mixture was stirred at rt for 18 h and then diluted with ethyl acetate. The organic layer was washed with equal volume of sat aq NaCl and dried over anhyd $MgSO_4$. After filtration and concentration, the crude product was purified using flash column chromatography (eluent: PE/EtOAc, ratio = 4:1) to give a white solid (24.8 mg, 0.053 mmol, 66% in two steps from compound **15**) as the product **16**, a white solid (5.1 mg, 0.012 mmol, 15% in two steps from compound **15**) as the product **17** and a white solid (4.1 mg, 0.010 mmol, 12%) as the compound **15**. The reaction could be scale up to a 1.2 g scale using the same procedure.

16: R_f = 0.24 (eluent: PE/EtOAc, ratio = 2:1), mp 168 – 171 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (d, J = 1.9 Hz, 1H), 7.93 – 7.87 (m, 1H), 7.72 – 7.62 (m, 2H), 7.62 –

7.55 (m, 1H), 5.25 (dd, J = 2.4, 1.4 Hz, 1H), 5.05 (d, J = 1.3 Hz, 1H), 3.43 – 3.29 (m, 2H), 3.27 – 3.06 (m, 3H), 2.77 – 2.59 (m, 2H), 2.45 – 2.32 (m, 1H), 2.28 – 2.20 (m, 2H), 2.03 – 1.80 (m, 9H), 1.76 – 1.67 (m, 1H), 1.36 (dt, J = 13.8, 3.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.5, 202.5, 148.4, 146.5, 133.6, 132.0, 131.6, 130.5, 124.1, 114.6, 68.2, 50.7, 50.0, 49.3, 44.2, 41.5, 39.7, 39.7, 31.0, 30.4, 26.5, 25.1, 23.3; IR (KBr) cm^{-1} 3101m, 2962s, 1726s, 1527s, 1157s, 848m, 740s, 571s; HRMS: $C_{24}H_{29}N_2O_6S$ for $[M+H]^+$, calculated 473.1741, found 473.1744;

17: R_f = 0.26 (eluent: PE/EtOAc, ratio = 2:1); mp 176 – 178 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, J = 7.6, 1.7 Hz, 1H), 7.75 – 7.64 (m, 2H), 7.57 (dd, J = 7.5, 1.6 Hz, 1H), 5.27 (s, 1H), 5.01 (s, 1H), 3.42 (d, J = 4.2 Hz, 1H), 3.40 – 3.31 (m, 1H), 3.26 – 3.16 (m, 1H), 3.08 – 2.83 (m, 4H), 2.66 – 2.50 (m, 3H), 2.46 – 2.37 (m, 1H), 2.27 – 2.14 (m, 2H), 2.10 – 1.96 (m, 3H), 1.89 – 1.78 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.9, 163.5, 148.9, 145.9, 133.8, 131.9, 131.3, 130.7, 130.4, 124.0, 111.2, 58.1, 54.3, 54.0, 40.9, 39.8, 36.2, 29.3, 27.6, 27.0, 21.1; IR (KBr) cm^{-1} 2926m, 1664s, 1538s, 1355m, 1165s, 892m, 742m, 577s; HRMS: $C_{21}H_{25}N_2O_5S$ for $[M+H]^+$, calculated 417.1479, found 417.1474;

CRYSTALLOGRAPHIC DATA OF 9 (CCDC 1974776)

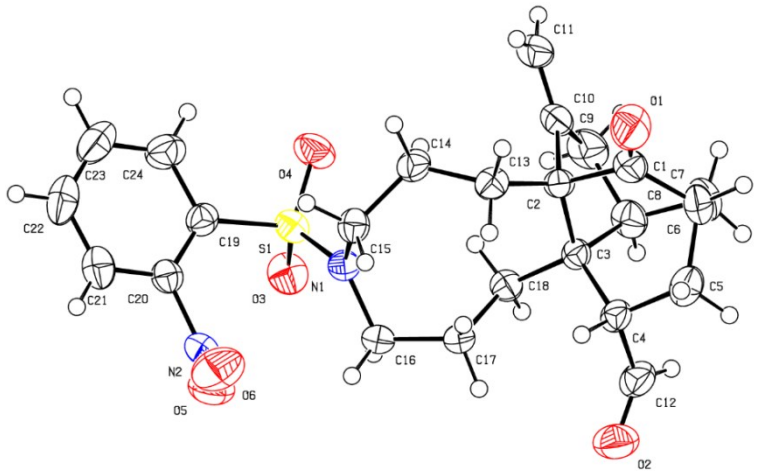


Supplementary Figure 1 X-ray structure of **9**.

Identification code	exp_6289
Empirical formula	$C_{12}H_{15}NO_3$
Formula weight	221.25
Temperature / K	110 (2) K
Crystal system	triclinic
Space group	P-1
Unit cell dimensions	a = 8.0155 (6) Å
	b = 11.8959 (9) Å
	c = 12.3411Å
α/°, β/°, γ/°	77.623 (6) °, 81.660 (6) °, 71.099 (7) °
Volume	1083.77 (13) $Å^3$
Z	4
Density (calculated)	1.356 mg mm^{-3}
μ / mm^{-1}	0.098
F(000)	472
Crystal size	0.33 × 0.25 × 0.24 mm^3

2Θ range for data collection	6.6 to 52°
Index ranges	$-9 \leq h \leq 9$, $-14 \leq k \leq 14$, $-15 \leq l \leq 15$
Reflections collected	14444
Independent reflections	4254[R (int) = 0.0331 (inf-0.9Å)]
Data/restraints/parameters	4254/0/291
Goodness-of-fit on F^2	1.031
Final R indexes [$I>2\sigma$ (I) i.e. $F_o>4\sigma$ (F_o)]	$R_1 = 0.0409$, $wR_2 = 0.0940$
Final R indexes [all data]	$R_1 = 0.0520$, $wR_2 = 0.1009$
Largest diff. peak/hole / e $Å^{-3}$	0.258/-0.233
Flack Parameters	N
Completeness	0.9982

CRYSTALLOGRAPHIC DATA OF 16 (CCDC 1905335)



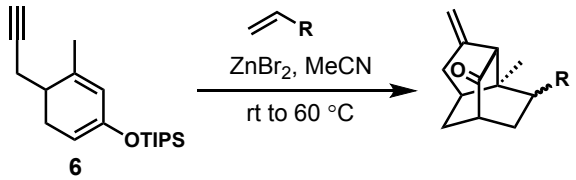
Supplementary Figure 2 X-ray structure of 16.

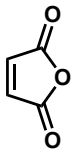
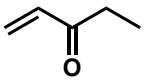
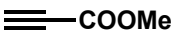
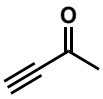
Identification code	190322c
Empirical formula	$C_{24}H_{28}N_2O_6S$
Formula weight	472.54
Temperature / K	298 (2) K
Crystal system	Monoclinic
Space group	P2 (1)/c
Unit cell dimensions	a = 8.7885 (9) Å
	b = 8.7617 (9) Å
	c = 28.539 (3)Å
α/°, β/°, γ/°	90 °, 94.8440 (10)°, 90°
Volume	2189.7 (4) $Å^3$
Z	4
Density (calculated)	1.433 mg mm^{-3}
μ / mm^{-1}	0.194

F(000)	1000
Crystal size	0.45 × 0.32 × 0.27 mm^3
2Θ range for data collection	2.43 to 25.02°
Index ranges	$-8 \leq h \leq 10$, $-9 \leq k \leq 10$, $-24 \leq l \leq 33$
Reflections collected	10584
Independent reflections	3868 [R (int) = 0.0370]
Data/restraints/parameters	3868 / 0 / 298
Goodness-of-fit on F^2	1.031
Final R indexes [$I>2\sigma$ (I) i.e. $F_o>4\sigma$ (F_o)]	$R_1 = 0.0489$, $wR_2 = 0.1071$
Final R indexes [all data]	$R_1 = 0.0781$, $wR_2 = 0.1186$
Largest diff. peak/hole / e $Å^{-3}$	0.238 / -0.304
Completeness	0.998

DETAILED STUDIES OF REATION SCOPE AND REACTION CONDITIONS

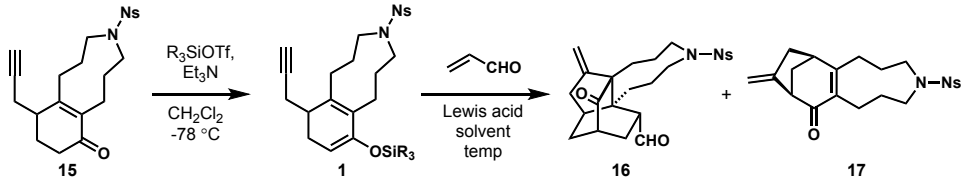
Supplementary Table 1. Model Study using other dienophiles



Entry[a]	Dienophile	Product
1		-
2		unstabled product
3		-
4		-
5		< 5%

[a]Reactions are carried out with 0.2 mmol **6,** 2 mmol dienophile, 0.04 mmol $ZnBr_2$ in 1.6mL MeCN.

Supplementary Table 2. Optimization of the key reaction



						yield (%)[c]		
entry [a]	-SiR_3	temp	solvent	acid	Equiv[b]	**16**	**17**	**15**
1	TIPS	rt to 60 °C	MeCN	$ZnBr_2$	0.2	28	33	24
2	TIPS	0 °C	MeCN	$ZnBr_2$	0.2	–	–	95
3	TIPS	rt	MeCN	$ZnBr_2$	0.2	44	21	28
4	TIPS	rt	CH_2Cl_2	$ZnBr_2$	0.2	30	32	36
5	TIPS	rt	THF	$ZnBr_2$	0.2	19	12	62
6	TIPS	rt	toluene	$ZnBr_2$	0.2	23	16	53
7	TIPS	rt	MeCN : CH_2Cl_2 = 5:1	$ZnBr_2$	0.2	56	22	20
8	TIPS	rt	MeCN : CH_2Cl_2 = 4:1	$ZnBr_2$	0.2	66	15	12
7	TIPS	rt	MeCN : CH_2Cl_2 = 3:1	$ZnBr_2$	0.2	52	24	20
9	TMS	rt	MeCN : CH_2Cl_2 = 4:1	$ZnBr_2$	0.2	6	16	74
10	TES	rt	MeCN : CH_2Cl_2 = 4:1	$ZnBr_2$	0.2	21	28	47
11	TBS	rt	MeCN : CH_2Cl_2 = 4:1	$ZnBr_2$	0.2	38	32	30
12	TIPS	rt	MeCN : CH_2Cl_2 = 4:1	$ZnCl_2$	0.2	42	23	28
13	TIPS	rt	MeCN : CH_2Cl_2 = 4:1	ZnI_2	0.2	47	19	26
14	TIPS	rt	MeCN : CH_2Cl_2 = 4:1	$InCl_3$	0.2	13	18	56
15	TIPS	rt	MeCN : CH_2Cl_2 = 4:1	$AlCl_3$	0.2	–	34	53
16	TIPS	rt	MeCN : CH_2Cl_2 = 4:1	$FeCl_3$	0.2	–	28	62
17	TIPS	rt	MeCN : CH_2Cl_2 = 4:1	$BF_3 \bullet OEt_2$	0.2	–	–	92
18	TIPS	rt	MeCN : CH_2Cl_2 = 4:1	Et_2AlCl	0.2	–	–	84
19	TIPS	rt	MeCN : CH_2Cl_2 = 4:1	$ZnBr_2$	0.1	24	17	52
20	TIPS	rt	MeCN : CH_2Cl_2 = 4:1	$ZnBr_2$	0.15	40	19	36
21	TIPS	rt	MeCN : CH_2Cl_2 = 4:1	$ZnBr_2$	0.25	42	26	28
22	TIPS	rt	MeCN : CH_2Cl_2 = 4:1	$ZnBr_2$	0.3	28	36	34
23[d]	TIPS	rt	MeCN : CH_2Cl_2 = 4:1	$ZnBr_2$	0.2	53	21	24

[a]All reactions were carried out using crude dienol silane **1** (prepared from 0.08 mmol **15**), 0.8 mmol acrolein and 0.016 mmol Lewis acid with the indicated solvent and reaction temperature. [b]Amout of the added Lewic acid. [c]Isolated yield for two steps. [d]1.2 g scale reaction.

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