Synthesis of the Ring System of Phomactin D Using a Suzuki Macrocyclization

Nicholas C. Kallan and Randall L. Halcomb*

Department of Chemistry and Biochemistry
University of Colorado, Boulder, Colorado 80309-0215

Supporting Information: Spectral data for compounds **8**-**15**, **18**, **20**, the alcohol precursor to **21**, and **23** are given below.

(±)-2,3-Dimethyl-6-(4-methylphenyl)thiomethylenecyclohexanone (8). IR (thin film) 3006, 2963, 1654 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.60-7.58 (m, 1H), 7.32 (d, 2H, *J* = 8.1 Hz), 7.14 (d, 2H, *J* = 8.1 Hz), 2.63 (dddd, 1H, *J* = 17.0, 5.5, 3.7, 1.6 Hz), 2.37 (dddd, 1H, *J* = 17.0, 11.6, 6.0, 2.8 Hz), 2.33 (s, 3H), 1.95-1.86 (m, 2H), 1.68-1.59 (m, 1H), 1.46 (dddd, 1H, *J* = 13.3, 13.3, 11.3, 5.4 Hz), 1.16 (d, 3H, *J* = 6.9 Hz), 1.05 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.4, 140.8, 138.4, 131.1, 130.2, 129.5, 128.7, 50.4, 36.4, 30.5, 26.9, 21.3, 21.0, 14.5; HRMS (EI) calcd for $C_{16}H_{20}OS$ (M^+) 260.1235, found 260.1232.

(2*S,3*R**)-2,3-Dimethyl-2-(2-propenyl)-6-(4-methylphenyl)thiomethylenecyclohexanone (9).** IR (thin film) 3066, 2968, 1665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.59 (dd, 1H, *J* = 2.2, 2.2 Hz), 7.32 (d, 2H, *J* = 8.1 Hz), 7.14 (d, 2H, *J* = 8.1 Hz), 5.61 (dddd, 1H, *J* = 19.0, 10.3, 8.5, 6.2 Hz), 5.04-4.97 (m, 2H), 2.67 (dddd, 1H, *J* = 13.9, 6.2, 1.5, 1.5 Hz), 2.56 (dddd, 1H, *J* = 16.9, 6.3, 4.7, 1.7 Hz), 2.41 (dddd, 1H, *J* = 16.9, 9.7, 6.9, 2.8 Hz), 2.33 (s, 3H), 2.07 (dd, 1H, *J* = 13.9, 8.5 Hz), 2.04-1.98 (m, 1H), 1.79 (dddd, 1H, *J* = 13.7, 6.6, 4.6, 3.1 Hz), 1.62 (dddd, 1H, *J* = 13.7, 13.7, 9.9, 6.2 Hz), 0.99 (s, 3H), 0.93 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.7, 141.6, 138.4, 134.9, 131.2, 130.8, 130.5, 130.3, 117.6, 50.3, 41.6, 34.5, 26.4, 26.1, 21.3, 19.7, 15.8; HRMS (EI) calcd for $C_{19}H_{24}OS$ (M^+) 300.1549, found 300.1552.

(3*S,4*R**)-3,4-Dimethyl-3-(2-propenyl)-1-cyclohexenecarbaldehyde (10).** IR (thin film) 3060, 2702, 1687 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.40 (s, 1H), 6.48-6.46 (m, 1H), 5.68 (dddd, 1H, *J* = 18.0, 10.4, 7.4, 7.4 Hz), 5.07-5.01 (m, 2H), 2.31 (ddd, 1H, *J* = 17.6, 5.5, 2.1 Hz), 2.22-2.21 (m, 1H), 2.21-2.19 (m, 1H), 1.99 (dddd, 1H, *J* = 17.6, 11.4,

6.3, 2.2 Hz), 1.68-1.58 (m, 2H), 1.36 (dddd, 1H, *J* = 13.9, 11.4, 11.4, 5.5 Hz), 0.92 (s, 3H), 0.89 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.8, 159.6, 140.3, 134.4, 118.2, 44.6, 39.7, 34.9, 26.4, 21.5, 21.0, 15.6; HRMS (EI) calcd for $C_{12}H_{18}O$ (M^+) 178.1358, found 178.1360.

(3*S,4*R**)-1-(*tert*-Butyldiphenylsilyl)oxymethyl-3,4-dimethyl-3-(2-propenyl)-1-cyclohexene (11).** IR (thin film) 3066, 2952, 1632 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (dd, 4H, *J* = 5.8, 1.4 Hz), 7.48-7.38 (m, 6H), 5.72 (dddd, 1H, *J* = 16.2, 11.4, 7.6, 7.6 Hz), 5.47 (broad s, 1H), 5.04 (broad s, 1H), 5.03-4.99 (m, 1H), 4.08 (broad s, 2H), 2.12 (d, 2H, *J* = 7.3 Hz), 1.97-1.92 (m, 2H), 1.63-1.53 (m, 2H), 1.50-1.39 (m, 1H), 1.09 (s, 9H), 0.89 (d, 3H, *J* = 6.9 Hz), 0.84 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.2, 135.8 (2 C), 135.7, 130.8, 129.7, 127.8, 116.7, 67.9, 45.6, 37.7, 35.0, 27.5, 27.1, 25.7, 22.0, 19.5, 15.8; HRMS (CI^+) calcd for $C_{28}H_{38}OSi$ $(M-H)^+$ 417.2614, found 417.2611.

(3*S,4*R**)-1-(*tert*-Butyldiphenylsilyl)oxymethyl-3,4-dimethyl-3-(3-oxopropyl)-1-cyclohexene (12).** IR (thin film) 3071, 2702, 1719 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73 (t, 1H, *J* = 1.8 Hz), 7.68-7.65 (m, 4H), 7.43-7.34 (m, 6H), 5.27 (broad s, 1H), 4.04 (broad s, 2H), 2.39-2.22 (m, 2H), 1.94-1.89 (m, 2H), 1.69 (ddd, 1H, *J* = 14.1, 10.5, 6.0 Hz), 1.60-1.50 (m, 2H), 1.50-1.36 (m, 2H), 1.05 (s, 9H), 0.85 (d, 3H, *J* = 6.6 Hz), 0.83 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.1, 137.1, 135.8, 134.1 (2 C), 130.0, 129.8, 127.8, 67.8, 39.8, 37.2, 34.4, 32.2, 27.4, 27.1, 25.8, 22.5, 19.5, 15.8; HRMS (ESI^+) calcd for $C_{28}H_{38}O_2Si$ $(M+Na)^+$ 457.2539, found 457.2518.

(3*S4*R**)-1-(*tert*-Butyldiphenylsilyl)oxymethyl-3-(3-butynyl)-3,4-dimethyl-1-cyclohexene (13).** IR (thin film) 3300, 3066, 2116 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.68-7.64 (m, 4H), 7.43-7.34 (m, 6H), 5.28 (broad s, 1H), 4.02 (broad s, 2H), 2.13-1.96 (m, 2H), 1.92-1.88 (m, 3H), 1.69 (ddd, 1H, *J* = 13.7, 11.0, 6.0 Hz), 1.55-1.45 (m, 3H), 1.44-1.33 (m, 1H), 1.04 (s, 9H), 0.84 (d, 3H, *J* = 6.6 Hz), 0.78 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.8, 135.8, 134.2, 134.1, 130.2, 129.8, 127.8, 85.8, 68.0, 67.9, 39.7, 37.6, 34.0, 27.4, 27.1, 25.8, 22.3, 19.5, 15.9, 13.9; HRMS (EI) calcd for $C_{29}H_{38}OSi$ (M^+) 430.2692, found 430.2692.

(3*S,4*R**)-1-Hydroxymethyl-2,3-dimethyl-3-(4-iodo-3-methyl-3-(*E*)-butenyl)-1-cyclohexene (14).** IR (thin film) 3321 (broad), 3060, 2957 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (q, 1H, *J* = 1.1 Hz), 5.31-5.29 (m, 1H), 4.02-3.92 (m, 2H), 2.14 (ddd, 1H,

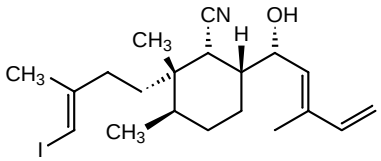
J = 13.3, 13.3, 5.5 Hz), 2.03 (dddd, 1H, *J* = 12.5, 12.5, 5.1, 1.1 Hz), 1.99-1.94 (m, 2H), 1.81 (d, 3H, *J* = 1.0 Hz), 1.60-1.49 (m, 3H), 1.46-1.38 (m, 1H), 1.34 (ddd, 1H, *J* = 13.5, 12.3, 4.6 Hz), 1.26 (broad s, 1H), 0.84 (d, 3H, *J* = 6.9 Hz), 0.79 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.9, 136.9, 132.1, 74.5, 67.6, 38.7, 37.6, 34.7, 34.0, 27.4, 25.9, 24.4, 22.6, 15.8; HRMS (ESI^+) calcd for $C_{14}H_{23}IO$ $(M+Na)^+$ 357.0691, found 357.0685.

(3*S,4*R**)-3,4-Dimethyl-3-(4-iodo-3-methyl-3-(*E*)-butenyl)-1-cyclohexene-carbaldehyde (15).** IR (thin film) 3049, 2711, 1678 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.41 (s, 1H), 6.40 (d, 1H, *J* = 1.4 Hz), 5.90-5.88 (m, 1H), 2.32 (ddd, 1H, *J* = 18.0, 5.3, 1.9 Hz), 2.19 (ddd, 1H, *J* = 13.2, 13.2, 4.8 Hz), 2.04-1.95 (m, 2H), 1.82-1.81 (m, 3H), 1.72-1.59 (m, 3H), 1.50 (ddd, 1H, *J* = 13.1, 13.1, 4.5 Hz), 1.37 (dddd, 1H, *J* = 13.2, 13.2, 11.2, 5.5 Hz), 0.92 (s, 3H), 0.89 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.6, 159.4, 148.0, 140.7, 75.2, 39.6, 38.0, 34.7, 34.0, 26.4, 24.4, 21.8, 21.6, 15.6; HRMS (ESI^+) calcd for $C_{14}H_{21}IO$ $(M+H)^+$ 333.0715, found 333.0715.

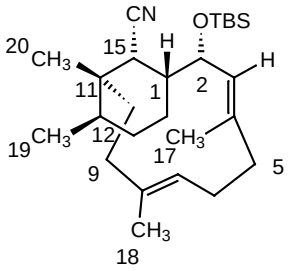
(2*R)-Cyano-(3*S**,4*R**)-dimethyl-3-(4-iodo-3-methyl-3-(*E*)-butenyl)-*N*-methoxy-*N*-methyl-(1*R**)-cyclohexanecarboxamide (18).** IR (thin film) 2497, 2230, 1660 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93-5.91 (m, 1H), 3.66 (s, 3H), 3.16 (s, 3H), 2.89 (dd, 1H, *J* = 3.3, 1.3 Hz), 2.85 (ddd, 1H, *J* = 12.7, 3.4, 3.4 Hz), 2.23 (ddd, 1H, *J* = 12.4, 12.4, 5.6 Hz), 2.11 (ddd, 1H, *J* = 12.1, 12.1, 5.0 Hz), 1.92-1.82 (m, 1H), 1.83 (d, 3H, *J* = 1.0 Hz), 1.80-1.73 (m, 1H), 1.72-1.56 (m, 4H), 1.29 (ddd, 1H, *J* = 26.2, 13.6, 4.3 Hz), 0.90 (s, 3H), 0.81 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 147.6, 118.5, 75.5, 61.6, 39.2, 38.6, 38.5, 37.4, 37.0, 33.0, 32.5, 29.8, 24.7, 24.1, 16.4, 15.6; HRMS (ESI^+) calcd for $C_{17}H_{27}IN_2O_2$ $(M+H)^+$ 419.1196, found 419.1197.

(2*R)-Cyano-(3*S**,4*R**)-dimethyl-3-(4-iodo-3-methyl-3-(*E*)-butenyl)-(1*R**)-(1-oxo-3-methyl-(2*E*,4)-pentadienyl)cyclohexane (20).** IR (thin film) 2936, 2240, 1584 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.37 (dd, 1H, *J* = 17.3, 10.7 Hz), 6.16 (s, 1H), 5.96-5.94 (m, 1H), 5.70 (d, 1H, *J* = 17.5 Hz), 5.48 (d, 1H, *J* = 10.5 Hz), 2.92 (dd, 1H, *J* = 3.2, 1.4 Hz), 2.59 (ddd, 1H, *J* = 13.1, 3.4, 3.4 Hz), 2.30 (ddd, 1H, *J* = 12.7, 12.7, 5.8 Hz), 2.24 (d, 3H, *J* = 1.0 Hz), 2.13 (ddd, 1H, *J* = 12.5, 12.5, 4.8 Hz), 2.07-2.01 (m, 1H), 1.86 (d, 3H, *J* = 0.8 Hz), 1.78-1.61 (m, 5H), 1.34 (ddd, 1H, *J* = 27.6, 13.3, 3.8 Hz), 0.88 (s, 3H), 0.84 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.0, 153.2, 147.8, 140.5, 124.2, 121.7,

118.9, 75.6, 48.1, 38.7, 38.6, 38.5, 37.2, 33.1, 30.2, 25.2, 24.2, 16.6, 15.6, 14.1; HRMS (FAB) calcd for $C_{20}H_{28}INO$ $(M+H)^+$ 426.1294, found 426.1287.



(2*R)-Cyano-(3*S**,4*R**)-dimethyl-3-(4-iodo-3-methyl-3-(*E*)-butenyl)-(1*R**)-((1*S**)-3-methyl-(2*E*,4)-pentadienyl)cyclohexane (alcohol precursor to 21).** IR (thin film) 3424, 3088, 2230 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.37 (dd, 1H, *J* = 17.5, 10.7 Hz), 5.92 (s, 1H), 5.31 (d, 1H, *J* = 9.5 Hz), 5.29 (d, 1H, *J* = 17.5 Hz), 5.13 (d, 1H, *J* = 10.7 Hz), 4.43 (dd, 1H, *J* = 9.1, 9.1 Hz), 2.44-2.41 (m, 1H), 2.17-2.05 (m, 3H), 1.91 (d, 3H, *J* = 1.0 Hz), 1.84 (s, 3H), 1.69 (dddd, 1H, *J* = 12.5, 9.0, 3.5, 3.5 Hz), 1.66-1.55 (m, 4H), 1.51 (broad s, 1H), 1.42 (ddd, 1H, *J* = 26.2, 13.3, 3.9 Hz), 1.30-1.20 (m, 1H), 0.84 (s, 3H), 0.81 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.8, 140.6, 139.3, 131.5, 119.4, 115.0, 75.6, 71.0, 40.9, 39.5, 38.7, 38.4, 37.7, 33.2, 30.0, 25.4, 24.1, 16.7, 15.8, 12.8; HRMS (EI) calcd for $C_{20}H_{30}INO$ (M^+) 427.1372, found 427.1391.



(phomactin D numbering used)

Macrocycle 23. ^1H NMR (500 MHz, $CDCl_3$; assignments based on ^1H-^1H COSY analysis) δ 5.04 (d, 1H, *J* = 11.7 Hz, *H*-7), 4.83 (d, 1H, *J* = 9.9 Hz, *H*-3), 4.42-4.39 (m, 1H, *H*-15), 4.14 (dd, 1H, *J* = 9.3, 9.3 Hz, *H*-2), 2.62-2.52 (m, 1H, *H*-6_a), 2.37-2.26 (m, 2H, *H*-5_a, *H*-9_a), 2.14 (ddd, 1H, *J* = 12.7, 12.7, 3.5 Hz, *H*-5_b), 2.09-1.99 (m, 2H, *H*-6_b, *H*-9_b), 1.97-1.91 (m, 1H, *H*-14_{eq}), 1.82 (s, 3H, C*H*$_3$-18), 1.78-1.71 (m, 1H, *H*-10_a), 1.75 (s, 3H, C*H*$_3$-17), 1.71-1.60 (m, 1H, *H*-12), 1.58-1.48 (m, 2H, *H*-10_b, *H*-13_{eq}), 1.43-1.30 (m, 2H, *H*-1, *H*-14_{ax}), 1.28-1.18 (m, 1H, *H*-13_{ax}), 0.85 (s, 12H, Si(C*H*$_3$)$_3$, C*H*$_3$-20), 0.72 (d, 3H, *J* = 6.7 Hz, C*H*$_3$-19), 0.03 (s, 3H, SiC*H*$_3$), 0.00 (s, 3H, SiC*H*$_3$); ^{13}C NMR (126 MHz,

$CDCl_3$) δ 139.3, 138.8, 129.8, 129.3, 122.5, 73.1, 41.5, 41.3, 40.8, 39.6, 36.6, 36.0, 33.3, 30.6, 26.3, 26.1, 25.2, 18.4, 17.2, 16.9, 16.8, 15.0, -4.0, -4.6; HRMS (FAB) calcd for $C_{26}H_{45}NOSi$ $(M+H)^+$ 416.3349, found 416.3336.