Supporting Information

Synthesis of the C45-C53 tetrahydropyran domain of Norhalichondrins and C14-C22 tetrahydrofuran domain of Halichondrin Family

Gowravaram Sabitha, Gajangi Chandrashekhar, Jhillu Singh Yadav, Kavitha Rachineni and Bharatam Jagadeesh

\textsuperscript{a}Division of Natural Products Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 607, India.

\textsuperscript{b}Nuclear Magnetic Resonance Division, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 607, India.

Corresponding Author: E-mail: gowravaramsr@yahoo.com (G. Sabitha); Fax: +91-40-27160512

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1. General information

Unless otherwise mentioned, all reactions were carried out using standard syringe, septa and cannula techniques. All glassware was flame/oven-dried and cooled under an inert atmosphere of nitrogen unless otherwise stated. Column chromatography was performed using silica gel (60-120 mesh) and the column was usually eluted with ethyl acetate-Hexanes. The diastereomeric excess of the products were measured by chiral-phase HPLC using Chiralpak AS column. Analytical thin layer chromatography (TLC) was performed on precoated silica gel-60 F254 (0.5 mm) glass plates. Visualization of the spots on TLC plates was achieved either by exposure to iodine vapor or UV light or by dipping the plates to sulphuric acid-β-naphthol or to ethanolic anisaldehyde-sulphuric acid-acetic acid and heating the plates at 120 °C. 1H NMR spectra were recorded at 300, 500, 600 MHz & 13C NMR spectra were recorded at 75, 125 MHz in CDCl3 using Tetramethylsilane as the reference standard. s, brs, d, dd, ddd, dt, t, q, qt, and m refer to singlet, broad singlet, doublet, doublet of doublet, doublet of doublet of doublet, doublet of triplet, triplet, quartet, quintet and multiplet respectively unless otherwise mentioned. Infrared spectra were recorded on Perkin-Elmer Infrared–683 spectrophotometer with NaCl optics. Spectra were calibrated against the polystyrene absorption at 1610 cm\(^{-1}\). Samples were scanned neat. The optical rotations were measured on JASCO DIP-360 Digital Polarimeter. Mass spectra were recorded on Micro Mass VG-7070H mass spectrometer for ESI and EI are given in mass units (m/z). High-resolution mass spectra (HRMS) [ESI+] were obtained using either a TOF or a double focusing spectrometer.

2. Physical and spectroscopic data of the products

\((S,E)\)-ethyl 7-(benzyloxy)-4-(methoxymethoxy)hept-2-enoate (7):

\[
\begin{align*}
\text{BnO} & \quad \text{OMOM} \\
\text{CO}_2\text{Et} & \\
\end{align*}
\]

\([\alpha]_D^{25} = -40.4 \quad (c = 1.0, \text{CHCl}_3)\); IR (Neat): 2943, 1720, 1656, 1270, 1099, 1034 cm\(^{-1}\); \(^1\)H NMR (CDCl3, 500 MHz): δ 7.32-7.22 (m, 5H), 6.76 (dd, \(J = 5.9, 15.8 \text{ Hz, 1H}\)), 5.93 (d, \(J = 15.8 \text{ Hz, 1H}\)), 4.59 (d, \(J = 6.9 \text{ Hz, 1H}\)), 4.53 (d, \(J = 6.9 \text{ Hz, 1H}\)), 4.46 (s, 2H), 4.21-4.19 (m, 1H), 4.18 (q, \(J = 6.9 \text{ Hz, 2H}\)), 3.48-3.43 (m, 2H), 3.33 (s, 3H), 1.75-1.63 (m, 4H), 1.30 (t, \(J = 6.9 \text{ Hz, 3H}\)); \(^13\)C NMR (CDCl3, 75 MHz): δ 166.1, 147.5, 138.3, 128.2, 127.5, 127.4, 121.9, 94.5, 74.8, 72.8, 69.8, 60.3, 55.5, 31.4, 25.3, 14.1; ESI-MS: \(m/z = 345 [\text{M+Na}]^+\); HRMS calcd for \(\text{C}_{18}\text{H}_{26}\text{O}_5\text{Na}\): 345.16725; found: 345.16693.

\((2R,3R)-3-((S)-4-(benzyloxy)-1-(methoxymethoxy)butyl)oxiran-2-yl)methanol (4):

\[
\begin{align*}
\text{BnO} & \quad \text{OMOM} \\
\text{OH} & \\
\end{align*}
\]
[α]D^25 = −15.6 (c = 1.0, CHCl₃); IR (Neat): 3446, 2933, 1637, 1098, 1033 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 7.34-7.22 (m, 5H), 4.81 (d, J = 6.7 Hz, 1H), 4.59 (d, J = 6.7 Hz, 1H), 4.47 (s, 2H), 3.88-3.81 (m, 1H), 3.65-3.56 (m, 1H), 3.49-3.42 (m, 2H), 3.37-3.30 (m, 1H), 3.35 (s, 3H), 2.98 (dd, J = 2.2, 7.5 Hz, 1H), 2.91 (q, J = 2.2, 1H), 1.77-1.57 (m, 4H); ¹³C NMR (CDCl₃, 75 MHz): δ 138.1, 128.3, 127.6, 127.5, 95.3, 76.8, 72.8, 69.8, 61.1, 57.9, 55.5, 55.4, 28.9, 25.5; ESI-MS: m/z = 319 [M+Na]^+; HRMS calcd for C₁₆H₂₄O₅Na: 319.15160; found: 319.15126.

(2S,3S,4S)-7-(benzyloxy)-4-(methoxymethoxy)-2-methylheptane-1,3-diol (9):

[α]D^25 = +31.6 (c = 1.0, CHCl₃); IR (Neat): 3422, 2934, 2879, 1453, 1096, 1033 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.32-7.22 (m, 5H), 4.66 (q, J = 6.9, 2H), 4.46 (s, 2H), 3.69 (dd, J = 2.9, 10.8 Hz, 1H), 3.64 (q, J = 5.9, 1H), 3.58 (dd, J = 5.9, 10.8 Hz, 1H), 3.45 (t, J = 5.9 Hz, 2H), 3.39 (s, 3H), 3.41-3.35 (m, 1H), 1.88-1.80 (m, 1H), 1.74-1.56 (m, 4H), 0.95 (d, J = 6.9 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 138.2, 128.3, 127.6, 127.5, 96.3, 79.4, 77.8, 72.9, 70.0, 66.8, 55.9, 36.4, 27.5, 25.4, 14.1; ESI-MS: m/z = 335 [M+Na]^+; HRMS calcd for C₁₇H₂₈O₅Na: 335.18290; found: 335.18201.

(4R,6S,E)-ethyl 4-hydroxy-6-(methoxymethoxy)-6-((4S,5S)-2,2,5-trimethyl-1,3-dioxan-4-yl)hex-2-enoate (12):

[α]D^25 = +21.3 (c = 1.0, CHCl₃); IR (Neat): 3441, 2934, 1718, 1374, 1269, 1036 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz): δ 6.95 (dd, J = 3.7, 15.1 Hz, 1H), 6.10 (dd, J = 2.2, 15.8 Hz, 1H), 4.71 (q, J = 6.7, 2H), 4.56-4.46 (m, 1H), 4.21 (q, J = 7.5 Hz, 2H), 3.99-3.92 (m, 1H), 3.74 (dd, J = 5.2, 11.3 Hz, 1H), 3.62 (dd, J = 2.2, 10.5 Hz, 1H), 3.57-3.51 (m, 1H), 3.42 (s, 3H), 2.19-2.02 (m, 2H), 1.81-1.69 (m, 1H), 1.45 (s, 3H), 1.43 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 166.6, 149.8, 120.0, 98.6, 96.1, 76.0, 74.6, 67.7, 65.8, 60.3, 56.0, 37.2, 29.5, 29.3, 18.8, 14.1, 12.3; ESI-MS: m/z = 369 [M+Na]^+; HRMS calcd for C₁₇H₃₀O₇Na: 369.18837; found: 369.18838.

(4R,6S,7S,8S,E)-ethyl 7,9-dihydroxy-4,6-bis(methoxymethoxy)-8-methylnon-2-enoate (13):
([α]D)25 = +87.3 (c = 1.0, CHCl3); IR (Neat): 3430, 2932, 1718, 1153, 1029 cm⁻¹; ¹H NMR (CDCl3, 300 MHz): δ 6.83 (dd, J = 6.7, 15.8 Hz, 1H), 6.01 (d, J = 15.8 Hz, 1H), 4.75-4.56 (m, 4H), 4.21 (q, J = 6.7 Hz, 2H), 3.88-3.80 (m, 1H), 3.79-3.62 (m, 2H), 3.56-3.49 (m, 1H), 3.42 (s, 3H), 3.38 (s, 3H), 2.08-1.84 (m, 3H), 1.30 (t, J = 7.5 Hz, 3H), 0.95 (d, J = 7.5 Hz, 3H), 13C NMR (CDCl3, 75 MHz): δ 166.0, 147.0, 122.2, 96.2, 94.7, 77.5, 75.8, 72.6, 67.0, 60.5, 56.0, 55.9, 36.6, 36.0, 14.1, 13.8; ESI-MS: m/z = 373 [M+Na]+; HRMS calcd for C16H30O8Na: 373.18329; found: 369.18333.


([α]D)25 = +8.0 (c = 0.4, CHCl3); IR (Neat): 3444, 2925, 2932, 1714, 1456, 1151, 1042 cm⁻¹; ¹H NMR (CDCl3, 600 MHz): δ 4.81 (d, J = 7.1 Hz, H Da), 4.70 (d, J = 6.9 Hz, H Fa), 4.66 (d, J = 6.9 Hz, HFb), 4.63 (d, J = 7.1 Hz, H Db), 4.40 (dd, J = 4.0, 10.1 Hz, H 6), 4.22 (m, HJa), 4.18 (m, HJb), 3.82 (td, J = 4.0, 1.9 Hz, H3), 3.75 (dd, J = 2.8, 11.3 Hz, HBa), 3.58 (q, J = 4.1 Hz, H5), 3.53 (dd, J = 1.9, 10.1 Hz, H 2), 3.49 (dd, J = 5.2, 11.2 Hz, H Bb), 3.42 (s, H E), 3.38 (s, H G), 2.73 (dd, J = 10.1, 14.3 Hz, HHa), 2.54 (dd, J = 4.0, 14.3 Hz, Hhb), 2.24 (m, H A), 2.22 (m, H 4a), 1.86 (td, J = 4.0, 15.2 Hz, H 4b), 1.28 (t, J = 7.0 Hz, H K), 0.93 (d, J = 7.0 Hz, H C); 13C NMR (CDCl3, 125 MHz): δ 171.2, 94.6, 94.4, 75.0, 73.2, 70.2, 68.3, 65.8, 61.1, 55.9, 55.5, 36.2, 34.8, 27.9, 14.0, 12.9; ESI-MS: m/z = 351 [M+H]+; HRMS calcd for C16H30O8Na: 373.18329; found: 373.18286.

(4R,6S,E)-ethyl 6-(tert-butyldimethylsilyloxy)-4-hydroxynona-2,8-dienoate (20):

([α]D)25 = +12.1 (c = 1.0, CHCl3); IR (Neat): 3476, 3076, 2933, 2858, 1716, 1259, 1081 cm⁻¹; ¹H NMR (CDCl3, 300 MHz): δ 6.90 (dd, J = 3.9, 15.0 Hz, 1H), 6.09 (dd, J = 2.0, 15.9 Hz, 1H), 5.82-5.71 (m, 1H), 5.12-5.03 (m, 2H), 4.49-4.43 (m, 1H), 4.19 (q, J = 7.9, 2H), 4.06-4.00 (m, 1H), 3.38 (brs, OH), 2.34-2.28 (m, 2H), 1.78 (dt, J = 13.9, 2.9 Hz, 1H), 1.67-1.60 (m, 1H), 1.28 (t, J = 6.9 Hz, 3H), 0.92 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H), 13C NMR (CDCl3, 75 MHz): δ 166.6, 150.3, 134.0, 119.8, 117.8, 70.4, 67.8, 60.3, 41.0, 40.6, 25.7, 17.9, 14.2, -4.4, -4.8; ESI-MS: m/z = 351 [M+Na]+.

methyl 2-((2S,3R,5S)-5-allyl-3-hydroxytetrahydrofuran-2-yl)acetate (21):
[α]D 25 = +11.0 (c = 1.0, CHCl 3); IR (Neat): 3442, 3076, 2926, 1734, 1438, 1270, 1080 cm -1; 1H NMR (CDCl 3, 500 MHz): δ 5.86-5.75 (m, 1H), 5.15-5.06 (m, 2H), 4.19-4.06 (m, 3H), 3.71 (s, 3H), 2.75 (dd, J = 6.0, 16.8Hz, 1H), 2.52 (dd, J = 7.9, 15.8Hz, 1H), 2.46-2.29 (m, 3H), 1.77-1.70 (m, 1H); 13C NMR (CDCl 3, 75 MHz): δ 172.5, 134.2, 117.4, 80.3, 76.9, 76.5, 51.9, 40.2, 39.3, 38.2; ESI-MS: m/z = 223 [M+Na] +. HRMS calcd for C 10 H 16 O 4 Na: 223.09408; found: 223.09404.

methyl 2-((2S,5S)-5-allyl-3-oxotetrahydrofuran-2-yl)acetate (14):
COSY NMR Spectrum of compound 1 in CDCl₃ solution at 600 MHz

HSQC NMR Spectrum of compound 1 in CDCl₃ solution at 600 MHz
Expanded NOESY NMR Spectrum of compound 1 in CDCl₃ solution at 600 MHz
COSY NMR Spectrum of compound 21 in CDCl3 solution at 600MHz

HSQC NMR Spectrum of compound 21 in CDCl3 solution at 600MHz
NOESY NMR Spectrum of compound 21 in CDCl₃ solution at 600MHz