Supporting Information

An Investigation of the Mitsunobu Reaction of BINOL and Cinchona Alkaloids: Inversion or Retention of Configuration?

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1. General information

Flash column chromatography was performed over silica (200-300 mesh). ^1H -NMR and ^{13}C -NMR spectra were recorded at 400 and 100 MHz, respectively on Advance (Brucker) 400 MHz Nuclear Magnetic Resonance Spectrometer, and were referenced to the internal solvent signals. Thin layer chromatography was performed using silica gel; F₂₅₄ TLC plates and visualized with ultraviolet light. The cinchona alkaloids were commercial available and used directly. All the product was confirmed by ESI-MS, and usual spectral methods (^1H -NMR, ^{13}C -NMR). The ESI-MS analysis of the samples was operated on an LCQ advantage mass spectrometer (ThermoFisher Company, USA), equipped with an ESI ion source in the positive ionization mode, with data acquisition using the Xcalibur software (Version 1.4). The ESI-HR-MS analysis of the samples was operated on a micrOTOF-Q II (Brucker).

2. A typical procedure for Mitsunobu reaction of BINOL to cinchona alkaloids

To a mixture of triphenylphosphine (1.2 mmol) and (*R*)-BINOL (1.0 mmol) in dry THF (10 mL), quinine (1.2 mmol) was added to above mixture. And then DIAD (1.2 mmol) was added dropwise at 0 °C. After the addition of DIAD, the homogeneous mixture was stirred at 0 °C for 30 min. Then, the resulting solution was stirred at room temperature for 18 h. At last, the mixtures were going on stirring at 50 °C for 5 hours, until the reaction was completed (monitored by TLC). The solvent was removed in

vacuo and the crude mixture was directly purified by column chromatography (silica gel, dichloromethane methanol mixtures) to obtain pure products. and confirmed by NMR, ESI-MS (HRMS).

The analytical and spectral characterization data of reaction products

1-((R)-2-((quinolin-4-yl)((2S)-8-vinylquinuclidin-2-yl)methoxy)naphthalen-1-yl)naphthalen-2-ol (Y1).

57% yield, 79:21 *epi-r*. It is diastereoisomeric mixture of *epi*-ether and native ether with retention of configuration. ^1H NMR (400 Hz, CDCl_3): 8.85(d, $J = 4.4$ Hz, 1 H), 8.11 (d, $J = 8.4$ Hz, 1 H),

8.04 (d, $J = 8.4$ Hz, 1 H), 7.71 (m, 2 H), 7.55 (t, $J = 6.8$ Hz, 1 H), 7.31 (d, $J = 4.8$ Hz, 1 H), 7.25 (d, $J = 9.2$ Hz, 1 H), 7.13 (m, 1 H), 5.82 (m, 1 H), 5.07 (d, $J = 1.2$ Hz, 1 H), 5.03 (q, $J = 10.0$ Hz, 1 H), 3.15 (t, $J = 8.0$ Hz, 2 H), 2.92 (q, $J = 10.4$ Hz, 1 H), 2.66 (d, $J = 18.0$ Hz, 1 H), 2.42 (q, $J = 7.2$ Hz, 1 H), 2.36 (s, 1 H), 1.94 (s, 1 H), 1.64 (m, 2 H); ^{13}C NMR (100 Hz, CDCl_3): 154.7, 149.8, 148.3, 141.8, 140.7, 140.4, 129.9, 129.7, 129.5, 129.3, 129.1, 129.0, 127.7, 126.8, 126.5, 126.3, 126.0, 125.7, 124.1, 123.7, 123.2, 120.2, 116.1, 115.0, 114.9, 113.9, 54.7, 49.4, 39.6, 29.7, 28.8, 27.1. HRMS (ESI $^+$): calcd. For $\text{C}_{39}\text{H}_{34}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$, 563.2693; found 563.2701.

1-((R)-2-((6-methoxyquinolin-4-yl)((2S)-8-vinylquinuclidin-2-yl)methoxy)naphthalen-1-yl)naphthalen-2-ol (Y2).

49% yield, 75:25 *epi-r*. It is diastereoisomeric mixture of *epi*-ether and native ether with retention of configuration. ^1H NMR (400 Hz, CDCl_3): 8.69 (d, $J = 4.8$ Hz, 1 H), 7.98 (d, $J = 8.8$

Hz, 1 H), 7.93-7.80 (m, 5 H), 7.69-7.64 (m, 1 H), 7.54-7.44 (m, 3 H), 7.34-7.29 (m, 3 H), 7.23-7.11 (m, 4 H), 6.67-6.85 (m, 1 H), 6.42 (s, 1 H), 5.97-5.84 (m, 1 H), 5.09 (d, $J = 6.8$ Hz, 1 H), 5.05 ($\text{C}_{11}\text{-H}$, s, 1 H), 4.96 (d, $J = 17.6$ Hz, 1 H), 3.95 (s, 3 H), 3.77 (s, 1 H), 3.28 (q, $J = 9.6$ Hz), 3.06-2.06 (m, 3 H), 2.82-2.71 (m, 4 H), 2.44-2.39 (m, 5 H), 2.04-2.00 (m, 1 H), 1.69-1.59 (m, 5 H); ^{13}C NMR (100 Hz, CDCl_3): 154.5, 149.5, 141.6, 140.2, 140.1, 133.7, 133.0, 130.0, 129.9, 129.0, 128.6, 128.4, 127.8, 127.5, 126.8, 126.6, 126.4, 126.3, 126.2, 126.1, 124.8, 124.7, 124.4, 124.0, 123.9, 123.5, 123.1, 120.0, 117.4, 115.9, 114.7, 54.5, 49.2, 39.4, 29.5, 28.6, 26.9. HRMS (ESI+) calcd. for $\text{C}_{40}\text{H}_{37}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$, 593.2804; found 593.2806.

1-((S)-2-((quinolin-4-yl)((2S)-8-vinylquinuclidin-2-yl)methoxy)naphthalen-1-yl)naphthalen-2-ol (Y3).

30% yield, 76:24 *epi-r*. It is diastereoisomeric mixture of *epi*-ether and native ether with retention of configuration. ^1H NMR (500 Hz, CDCl_3): 8.55(m, 1 H), 8.02 (t, $J = 6.8$ Hz, 1 H), 7.84 (dd,

$J = 6.4$ Hz, $J = 6.8$ Hz, 4 H), 7.65 (m, 2 H), 7.48 (m, 1 H), 7.31(m, 2 H), 7.21 (m, 3 H), 7.11 (m, 1 H), 7.05 (m, 2 H), 6.84 (m, 1 H), 5.85 (m, 1 H), 5.24 (m, $J = 1.2$ Hz, 1 H), 5.16 (t, $J = 1.2$ Hz, 1 H), 5.05 (m, 1 H), 4.59 (d, $J = 7.6$ Hz, 1 H), 3.22-3.13 (br, 1 H), 2.91 (m, 3 H), 2.67-2.56 (br, 1 H), 2.41 (m, 1H), 2.08 (br, 1H), 1.80 (m, 2H), 1.80 (m, 2H); ^{13}C NMR (150 Hz, CDCl_3): 153.6, 151.6, 149.7, 149.5, 148.5, 148.1, 142.0, 140.6, 140.4, 134.1, 133.8, 130.3, 129.3, 128.8, 128.7, 128.0, 128.0, 127.4, 127.0, 126.4, 126.1, 125.2, 124.9, 124.3, 124.2, 123.7, 122.9, 120.3, 117.7, 116.7, 116.4, 116.2, 115.0, 114.9, 114.8, 65.1, 48.7, 47.5, 40.8, 36.8, 30.6, 29.8. HRMS (ESI+): calcd. For $\text{C}_{39}\text{H}_{34}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$, 563.2693; found 563.2699.

1-((S)-2-((6-methoxyquinolin-4-yl)((2S)-8-vinylquinuclidin-2-yl)methoxy)naphthalen-1-yl)naphthalen-2-ol (Y4). 46% yield, 74:26 *epi-r*. It is diastereoisomeric mixture of *epi*-ether and native ether with retention of configuration. ¹H NMR (400 Hz, CDCl₃): 8.83(d, *J* = 4.4 Hz, 1 H), 8.10 (d, *J* = 8.4 Hz, 1 H), 7.90 (d, *J* = 8.4 Hz, 1 H), 7.83 (d, *J* = 8.4 Hz, 1 H), 7.72-7.68 (m, 1 H), 7.56-7.49 (m, 1 H), 7.37-7.33 (m, 1 H), 7.30 (d, *J* = 4.4 Hz, 1 H), 7.24-7.13 (m, 1 H), 7.07-7.04 (m, 1 H), 6.97 (s, 1 H), 5.82 (m, 1 H), 5.07 (s, 1 H), 5.03 (m, 1 H), 3.46-3.36 (m, 1 H), 3.14 (t, *J* = 8.0 Hz, 1 H), 2.90 (q, *J* = 10.4 Hz, 1 H), 2.69-2.58 (m, 2 H), 2.45-2.26 (m, 2 H), 1.95 (m, 1 H), 1.67-1.57 (m, 1 H), 1.44-1.19 (m, 2 H); ¹³C NMR (100 Hz, CDCl₃): 158.2, 157.6, 154.4, 152.4, 147.2, 146.9, 144.1, 143.1, 141.5, 140.3, 134.4, 134.2, 131.6, 131.0, 129.9, 129.5, 129.0, 128.9, 127.9, 127.7, 126.8, 126.1, 126.0, 124.9, 123.8, 122.9, 122.1, 121.8, 120.3, 117.8, 116.1, 115.6, 114.9, 114.2, 101.8, 59.1, 57.1, 55.6, 55.4, 54.7, 49.3, 43.2, 39.5, 39.4, 30.8, 29.5, 28.7, 27.3, 27.0, 25.8; HRMS (ESI⁺): calcd. For C₃₉H₃₄N₂O₂ [M+H]⁺, 593.2804; found 593.2802.

1-((R)-2-((quinolin-4-yl)((2R)-8-vinylquinuclidin-2-yl)methoxy)naphthalen-1-yl)naphthalen-2-ol (Y5). 51% yield, 73:27 *epi-r*. It is diastereoisomeric mixture of *epi*-ether and native ether with retention of configuration. ¹H NMR (400 Hz, CDCl₃): 8.83(d, *J* = 4.4 Hz, 1 H), 8.10 (d, *J* = 8.4 Hz, 1 H), 7.90 (d, *J* = 8.4 Hz, 1 H), 7.83 (d, *J* = 8.4 Hz, 1 H), 7.72-7.68 (m, 1 H), 7.56-7.49 (m, 1 H), 7.37-7.33 (m, 1 H), 7.30 (d, *J* = 4.4 Hz, 1 H), 7.24-7.13 (m, 1 H), 7.07-7.04 (m, 1 H), 6.97 (s, 1 H), 5.82 (m, 1 H), 5.07 (s, 1 H), 5.03 (m, 1 H), 3.46-3.36 (m, 1 H), 3.14 (t, *J* = 8.0 Hz, 1 H), 2.90 (q, *J* = 10.4 Hz, 1 H), 2.69-2.58 (m, 2 H), 2.45-2.26 (m, 2 H), 1.95 (m, 1 H), 1.67-1.57 (m, 1 H), 1.44-1.19 (m, 2 H); ¹³C NMR (100 Hz, CDCl₃): 154.7, 154.0, 151.7, 149.7, 149.3, 148.7, 148.3, 146.1, 141.8, 140.4, 133.9, 133.9, 130.1, 130.0, 129.8, 129.7, 129.2, 128.8, 128.6, 128.0, 127.7, 126.9, 126.8, 126.5, 126.3, 125.1, 124.9, 124.6, 124.1, 123.7, 123.3, 120.2, 120.1, 119.5, 117.7,

117.0, 116.1, 115.2, 114.9, 58.7, 54.7, 49.4, 40.3, 39.6, 39.6, 30.0, 29.7, 28.8, 28.0, 27.2, 27.1, 26.1. HRMS (ESI⁺): calcd. For C₃₉H₃₄N₂O₂ [M+H]⁺, 563.2693; found 563.2695.

1-((R)-2-(((6-methoxyquinolin-4-yl)((2R)-8-vinylquinuclidin-2-yl)methoxy)naphthalen-1-yl)naphthalen-2-ol (Y6).

43% yield, 65:35 *epi-r*. It is diastereoisomeric mixture of *epi*-ether and native ether with retention of configuration. ¹H NMR (400 Hz, CDCl₃): 8.65(d, *J* = 4.4 Hz, 1 H), 7.96 (t, *J* = 8.8 Hz, 1 H), 7.88 (q, *J* = 9.2 Hz, 2 H), 7.82-7.77 (m, 2 H), 7.34-7.28 (m, 2 H), 7.27-7.24 (m, 2 H), 7.21-7.19 (m, 2 H), 7.157-7.12 (m, 1 H), 6.90 (s, 1 H), 5.96-5.71 (m, 1 H), 5.08-4.99 (m, 3 H), 3.88 (s, 3 H), 3.49-3.36 (m, 1 H), 3.16-3.12 (t, *J* = 7.6 Hz, 1 H), 3.02-2.96 (m, 1 H), 2.92-2.87 (m, 1 H), 2.78-2.51 (m, 2 H), 2.42-2.38 (m, 2 H), 2.31-2.20 (m, 1 H), 1.94-1.38 (m, 1 H), 1.72-1.65 (m, 2 H), 1.44-1.39 (m, 2H); ¹³C NMR (100 Hz, CDCl₃): 157.5, 157.40, 157.2, 154.1, 147.4, 147.0, 146.6, 144.5, 144.1, 140.6, 140.3, 140.2, 134.0, 133.9, 131.1, 130.1, 129.7, 129.6, 129.5, 128.6, 127.9, 127.7, 127.5, 126.5, 126.4, 125.1, 124.9, 124.9, 124.4, 123.2, 123.1, 121.8, 121.4, 121.0, 120.8, 120.6, 120.6, 120.3, 117.9, 117.6, 116.1, 115.4, 114.9, 114.7, 114.3, 102.0, 101.9, 101.7, 70.0, 56.7, 55.4, 55.2, 54.6, 53.6, 49.3, 47.7, 42.9, 39.5, 39.4, 39.2, 30.4, 29.5, 29.4, 28.6, 27.2, 27.0, HRMS (ESI⁺): calcd. For C₃₉H₃₄N₂O₂ [M+H]⁺, 593.2804; found 593.2806.

1-((S)-2-((quinolin-4-yl)((2R)-8-vinylquinuclidin-2-yl)methoxy)naphthalen-1-yl)naphthalen-2-ol (Y7).

56% yield, 55:45 *epi-r*. It is diastereoisomeric mixture of *epi*-ether and native ether with retention of configuration. ¹H NMR (500 Hz, CDCl₃): 8.78(t, *J* = 3.6 Hz, 1 H), 8.56 (t, *J* = 3.6 Hz, 1 H), 7.84 (dd, *J* = 6.4 Hz, *J* = 6.8 Hz, 4 H), 7.65 (m, 2 H), 7.48 (m, 1 H), 7.31(m, 2 H), 7.21 (m, 3 H), 7.11 (m, 1 H), 7.05 (m, 2 H), 6.84 (m, 1 H), 5.85 (m, 1 H), 5.24 (m, *J* = 1.2 Hz, 1 H), 5.16 (t, *J* = 1.2 Hz, 1 H), 5.05 (m, 1 H), 4.59 (d, *J* = 7.6 Hz, 1 H),

3.22-3.13 (br, 1 H), 2.91 (m, 3 H), 2.67-2.56 (br, 1 H), 2.41 (m, 1), 2.08 (br, 1H), 1.80 (m, 2H), 1.80 (m, 2H); ^{13}C NMR (150 Hz, CDCl_3): 154.6, 153.7, 152.1, 149.6, 149.2, 148.5, 148.1, 145.9, 141.97, 140.4, 134.2, 133.7, 130.1, 129.9, 129.8, 129.7, 129.2, 128.5, 128.5, 127.9, 127.7, 127.6, 126.9, 126.8, 126.4, 126.2, 125.2, 124.5, 124.3, 124.1, 123.5, 123.0, 120.2, 120.1, 118.1, 117.2, 116.2, 115.3, 115.1, 115.0, 69.5, 56.6, 54.7, 49.4, 42.9, 39.6, 39.3, 29.7, 29.5, 28.8, 27.3, 27.1. HRMS (ESI+): calcd. For $\text{C}_{39}\text{H}_{34}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$, 563.2693; found 563.2679.

1-((S)-2-((6-methoxyquinolin-4-yl)((2R)-8-vinylquinuclidin-2-yl)methoxy)naphthalen-1-yl)naphthalen-2-ol (Y8).

47% yield, 62:38 *epi-r*. It is diastereoisomeric mixture of *epi*-ether and native ether with retention of configuration.

^1H NMR (400 Hz, CDCl_3): 8.59 (d, $J = 4.8$ Hz, 0.9 H), 8.34 (d, $J = 4.0$ Hz, 1 H), 7.94-7.81 (m, 5 H), 7.75 (d, $J = 7.6$ Hz, 2 H), 7.67 (d, $J = 8.8$ Hz, 1 H), 7.45 (d, $J = 8.8$ Hz, 1 H), 7.33-7.18 (m, 9 H), 7.12-7.07 (m, 4 H), 6.93-6.86 (m, 2 H), 6.54 (d, $J = 4.4$ Hz, 1 H), 5.90-5.81 (m, 2 H), 5.10-5.01 (m, 3 H), 4.87 (s, 1 H), 3.91 (s, 1 H), 3.86 (s, 3 H), 3.42 (q, $J = 13.4$ Hz, 1 H), 3.13-2.95 (m, 4 H), 2.79-2.71 (m, 1 H), 2.43-2.39 (m, 3 H), 2.31-2.20 (m, 2 H), 1.90-1.77 (m, 3 H), 1.46-1.17 (m, 4 H); ^{13}C NMR (100 Hz, CDCl_3): 157.2, 157.1, 154.4, 153.4, 153.0, 152.7, 147.2, 146.3, 144.3, 144.0, 143.9, 140.5, 140.1, 139.7, 134.0, 133.8, 130.8, 130.0, 129.3, 129.3, 129.2, 128.3, 128.2, 128.2, 127.7, 127.6, 127.4, 126.4, 126.0, 125.1, 124.2, 124.1, 123.5, 122.7, 121.3, 121.1, 120.8, 120.7, 118.6, 117.5, 115.6, 115.2, 115.0, 114.6, 114.1, 101.7, 101.4, 69.8, 56.6, 55.3, 55.0, 53.5, 47.6, 42.8, 39.4, 30.3, 29.3, 29.2, 26.9; HRMS (ESI+): calcd. For $\text{C}_{39}\text{H}_{34}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$, 593.2804; found 593.2787.

3. $^1\text{H}/^{13}\text{C}$ -NMR Spectrum

Y1 (*R*)-BINOL+CD

Y2 (R)-BINOL+QN

Y3 (S)-BINOL+CD

Y4 (S)-BINOL+QN

Chemical structure of compound 10: C=C[C@H]1CN[C@H]1C[C@@H](c2cnc3ccccc23)c2cc(O)c3ccccc32

¹H NMR spectrum (CDCl₃):

Chemical Shift (ppm)	Integration
7.705, 7.688, 7.685, 7.641, 7.623, 7.566, 7.563, 7.545, 7.528, 7.511, 7.513, 7.373, 7.370, 7.368, 7.356, 7.353, 7.339, 7.336, 7.333, 7.306, 7.295, 7.260, 7.240, 7.231, 7.228, 7.223, 7.210, 7.190, 7.169, 7.157, 7.134, 7.079, 7.064, 7.057, 7.043, 6.973, 6.503, 6.492, 5.863, 5.845, 5.837, 5.820, 5.802, 5.794, 5.776, 5.076, 5.036, 5.033, 5.011, 4.306, 4.281, 3.903, 3.426, 3.401	-> 1.00, -> 0.41, -> 1.07, -> 0.47, -> 0.89, -> 1.49, -> 0.93, -> 1.68, -> 0.97, -> 0.43, -> 1.13, -> 2.07, -> 0.49, -> 0.13, -> 1.44, -> 2.09, -> 1.11, -> 1.99, -> 2.86, -> 2.13, -> 2.75, -> 3.23

Y6 (R)-BINOL+QD

Y7 (S)-BINOL+CN

Y8 (S)-BINOL+QD

ESI-MS Spectrum

Y1

T: + c ESI Full ms [100.00-2000.00]

Y2

T: + c ESI Full ms [50.00-1500.00]

Y3

T: - c ESI Full ms [65.00-1000.00]

Y4

T: + c ESI Full ms [65.00-1000.00]

Y5

T: - c ESI Full ms [65.00-1000.00]

Y6

T: + c ESI Full ms [100.00-800.00]

Y7

T: + c ESI Full ms [110.00-800.00]

Y8

T: + c ESI Full ms [65.00-1000.00]

HPLC chromatogram of Y1

HPLC analysis: chiralcel IA column, *i*-PrOH/hexane 20:80, flow rate 1.0 mL/min, $t_{\text{major}}=19.919$ min, $t_{\text{minor}}=16.726$ min.