Supporting Information

Total Synthesis of (+)-Cyanthiwigin AC

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General Experimental Details:

Air- and/or moisture-sensitive reactions were carried out under an atmosphere of dry nitrogen using flame-dried glassware and standard syringe/septa techniques. DME was distilled over sodium and benzophenone prior to use. All other solvents were purchased anhydrous in Seal Sure bottles. Reagents were used as such from the commercial source unless otherwise stated. All melting points were determined in open Pyrex capillaries and are uncorrected. Infrared spectra were obtained on an FT-IR spectrometer. ^1H NMR spectra were acquired at 400 MHz with chloroform (7.27 ppm) as internal reference. Signals are reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), td (triplet of doublets), br s (broad singlet) and m (multiplet). ^{13}C spectra were acquired on spectrometers operating at 100 or 125 MHz with chloroform- D (77.0 ppm) and toluene- D_8 (19.8 ppm for CD_3 group) as internal reference. NOESY, COSY, HSQC and HMBC data were acquired at 500 or 600 MHz. Mass spectral data were obtained using FAB or ESI techniques. Optical rotations were recorded in dichloromethane at 589 nm wavelength using sodium lamp, $c = 1 \text{ g}/100 \text{ mL}$. HPLC was carried out using a Chiralpak-ADTM column. Flash chromatography was carried out using 230-400 mesh silica gel 60 Å or using a CombiFlash chromatography system.

(+)-(1''*S*, 7*a*''*S*)-1''-[[*tert*-Butyl(dimethyl)silyl]oxy]-7*a*''-methyl-2'',6'',7'',7*a*''-tetrahydrodispiro[1,3-dioxolane-2,1'-cyclohexane-4',4''-inden]-5''(1''*H*)-one (**7b**):

To a stirred suspension of sodium hydride (95%, 1.73 g, 68.6 mmol, 3.5 eq) in THF (85 mL) at rt, was added a solution of TBS-ether **8b**¹ (5.5 g, 19.61 mmol) in THF (20 mL) over a period of 30 min. The reaction mixture was stirred at reflux for 3 h, cooled to 50 °C. To this was added a solution of dimesylate **9c** (9.36 g, 29.4 mmol, 1.5 eq) in DME (75 mL). The reaction mixture was heated at 60 °C for 4 h. An additional amount of dimesylate **9c**² (3.12 g, 9.8 mmol, 0.5 eq) in DME (25 mL) was added. After 2 h, the reaction was cooled to rt and quenched with aq. 1M citric acid (pH 5-6) and diluted with EtOAc. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with a saturated NaHCO_3 solution, brine, dried (Na_2SO_4) and concentrated. Hexanes were added and the unreacted dimesylate **9c** was filtered off. The filtrate was concentrated and purified on silica gel column chromatography using ethyl acetate-hexanes (0:100 to 15:85) to afford title product **7b** (4.75 g, 60%) as yellow gum. R_f (0.15, 5% EtOAc-hexanes); $[\alpha]_D^{22} +81.8$ (c 1.0, CH_2Cl_2); IR (neat) $\gamma_{\text{max}} \text{ cm}^{-1}$ 2931, 1710, 1121; ^1H NMR (400 MHz, CDCl_3): δ 5.54 (s, 1 H); 3.94-3.89 (m, 5 H); 2.54-2.45 (m, 1 H); 2.32-2.21 (m,

3 H); 2.16-2.02 (m, 1 H); 2.04-1.81 (m, 3 H); 1.81-1.68 (m, 4 H); 1.67-1.58 (m, 2 H); 1.12 (s, 3 H); 0.90 (s, 9 H); 0.04 (s, 6 H); ^{13}C NMR (100 MHz, CDCl_3): δ 214.5, 150.6, 122.8, 108.4, 80.4, 64.3, 64.2, 52.4, 47.2, 37.6, 35.8, 32.3, 32.1, 31.5, 31.2, 28.6, 25.8, 18.4, 18.0, -4.4, -4.9. HRMS (FAB^+) m/z calcd for $\text{C}_{23}\text{H}_{39}\text{O}_4\text{Si}[\text{M} + \text{H}]^+$ 407.2612, found, 407.2605.

(+)-tert-Butyl(dimethyl){[(1''S,7a''S)-7a''-methyl-5''-methylene-1'',2'',5'',6'',7'',7a''-hexahydrodispiro[1,3-dioxolane-2,1'-cyclohexane-4',4''-inden]-1''-yl]oxy}silane (10):

A solution of titanium (IV) chloride (1M, 5 mL, 5 mmol, 4.0 eq) in CH_2Cl_2 was added to magnesium powder (300 mg, 12.3 mmol, 10.0 eq), and stirred for 10 min. To this was added dropwise a solution of spiro ketone **7b** (500 mg, 1.23 mmol) in THF-DCM (6.2 mL, 1:1.5, 0.2 M) at 0°C . The reaction was stirred for 30 min. and the cooling bath removed, followed by stirring for 15 min at rt. The reaction mixture was cooled to 0°C , quenched with a saturated solution of potassium carbonate and diluted with ether. After filtration through a pad of celite, the filtrate was extracted with ether (3 x 50 mL), dried (Na_2SO_4) and concentrated. The residue was purified on silica gel column chromatography using ethyl acetate-hexanes (0:100 to 15:85) as eluent to afford the title product **10** (235 mg, 47%). R_f (0.7, 20% EtOAc-hexanes); $[\alpha]_D^{22} +6.1$ (c 2.0, CH_2Cl_2); IR (neat) $\gamma_{\text{max}} \text{ cm}^{-1}$ 1638, 1121, 1110; ^1H NMR (400 MHz, CDCl_3): δ 5.39 (s, 1 H); 4.90 (s, 1 H); 4.82 (s, 1 H); 4.00-3.90 (m, 4 H); 3.82 (dd, $J = 9.2, 7.5$ Hz, 1 H); 2.53-2.42 (m, 1 H); 2.32-1.79 (m, 9 H); 1.58-1.49 (m, 2 H); 1.45-1.19 (m, 3 H); 1.11 (s, 3 H); 0.904 (s, 9 H); 0.04 (s, 6 H); ^{13}C NMR (100 MHz, CDCl_3): δ 154.8, 153.7, 118.1, 109.1, 108.5, 83.1, 64.2, 64.1, 47.6, 43.5, 40.6, 37.7, 34.4, 32.0, 31.2, 30.9, 30.1, 25.8, 18.2, 18.1, -4.5, -4.9. HRMS (FAB^+) m/z calcd for $\text{C}_{24}\text{H}_{41}\text{O}_3\text{Si}[\text{M} + \text{H}]^+$ 405.2820, found, 405.2816.

(+)-(7a''S)-7a''-Methyl-5''-methylene-5'',6'',7'',7a''-tetrahydrodispiro[1,3-dioxolane-2,1'-cyclohexane-4',4''-inden]-1''(2''H)-one (11):

Step 1: To a solution of spiro silylalkene **10** (960 mg, 2.37 mmol) in THF (9.3 mL, 0.25 M) at rt, was added TBAF solution (1M, 7.1 mL, 7.1 mmol, 3 eq) in THF. The reaction mixture was stirred at 45°C for 1.5 h, diluted with water and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified on CombiFlash silica gel chromatography, eluted with gradient ethyl acetate-hexanes (10:90 to 60:40) to afford the alcohol (469 mg, 68%) as light yellow oil. R_f (0.15, 30% EtOAc-hexanes); $[\alpha]_D^{22} +12.7$ (c 1.0, CH_2Cl_2); IR (neat) $\gamma_{\text{max}} \text{ cm}^{-1}$

3425, 1638, 1106, 1035; ^1H NMR (400 MHz, CDCl_3): δ 5.40 (s, 1 H); 4.87 (s, 1 H); 4.81 (s, 1 H); 3.93 (s, 4 H), 4.0-3.8 (m, 1 H); 2.48-2.37 (m, 2 H); 2.20-2.08 (m, 2 H); 2.07-1.73 (m, 8 H); 1.60-1.49 (m, 2 H); 1.47-1.32 (m, 1 H); 1.11 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 154.4, 153.5, 118.5, 109.1, 108.7, 82.8, 64.2, 64.2, 47.3, 43.6, 39.7, 37.4, 34.5, 32.0, 31.3, 31.1, 30.0, 17.7; HRMS (FAB^+) m/z calcd for $\text{C}_{18}\text{H}_{27}\text{O}_3[\text{M} + \text{H}]^+$ 291.1955, found, 291.1952. **Step 2:** To a stirred solution of the secondary alcohol, obtained in step 1, (469 mg, 1.62 mmol) in CH_2Cl_2 (15 mL, 0.11M) at rt, was sequentially added pyridine (210 μL , 2.6 mmol, 1.6 eq) and Dess-Martin (D-M) periodinane (1.09 g, 2.58 mmol, 1.6 eq). The reaction mixture was stirred at rt for 1.5 h and a saturated NaHCO_3 solution (10 mL) and a 10% aq. $\text{Na}_2\text{S}_2\text{O}_3$ solution (10 mL) were added and the mixture was stirred for 2 h at rt, then extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified on CombiFlash silica gel chromatography, eluted with gradient ethyl acetate-hexanes (5:95 to 30:70) to afford title product **11** (466 mg, quant.) as colorless oil. R_f (0.4, 20% EtOAc-hexanes); $[\alpha]_D^{22} +93.2$ (c 1.0, CH_2Cl_2); IR (neat) γ_{max} cm^{-1} 1744, 1109; ^1H NMR (400 MHz, CDCl_3): δ 5.76 (s, 1 H); 4.78 (s, 1 H); 4.73 (s, 1 H); 3.93-3.91 (m, 4 H); 3.01 (d, $J = 23.2$ Hz, 1 H); 2.78 (dd, $J = 23.3, 2.5$ Hz, 1 H); 2.57 (td, $J = 13.6, 4.2$ Hz, 1 H); 2.16-1.70 (m, 8 H); 1.62-1.47 (m, 2 H); 1.44-1.33 (m, 1 H); 1.31 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 221.5, 153.5, 152.7, 118.0, 108.9, 108.1, 64.23, 64.2, 52.0, 44.4, 41.1, 35.7, 33.1, 31.8, 31.6, 30.4, 29.5, 22.9. HRMS (FAB^+) m/z calcd for $\text{C}_{18}\text{H}_{25}\text{O}_3[\text{M} + \text{H}]^+$ 289.1798, found, 289.1795.

(+)-(3a''R,7a''S)-7a''-Methyl-5''-methylene-5'',6'',7'',7a''-tetrahydrodispiro[1,3-dioxolane-2,1'-cyclohexane-4',4''-inden]-1''(3a''H)-one (6):

To a solution of spiro cyclopentanone **11** (465 mg, 1.61 mmol) in MeOH (16 mL, 0.1M) at rt, was added a solution of NaOMe (0.5 M, 1.75 mL, 0.88 mmol, 0.54 eq) in MeOH. The reaction mixture was stirred at rt for overnight and was quenched with a saturated NH_4Cl solution, concentrated on a rotary evaporator, diluted with water and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified on CombiFlash silica gel column chromatography, eluted with gradient ethyl acetate-hexanes (10:90 to 45:55) to afford title product **6** (441 mg, 95 %) as light yellow oil. R_f (0.35, 30% EtOAc-hexanes); $[\alpha]_D^{22} +209.6$ (c 1.0, CH_2Cl_2); IR (neat) γ_{max} cm^{-1} 1708, 1106; ^1H NMR (400 MHz, CDCl_3): δ 7.53 (dd, $J = 5.9, 2.6$ Hz, 1 H); 6.15 (d, $J = 6.0$ Hz, 1 H); 4.88 (s, 1 H); 4.73 (s, 1 H); 3.93 (s, 4 H); 2.69 (s, 1 H); 2.37-2.27 (m, 1 H); 2.15-2.06 (m, 1 H); 1.95-1.81 (m, 4 H); 1.77-1.58 (m, 6 H); 1.07 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 213.6, 163.1, 147.1, 132.3, 111.5, 108.2, 64.1, 57.9, 47.3, 42.3, 34.3, 31.4, 30.9, 30.6, 29.8, 27.8, 25.5; HRMS (FAB^+) m/z calcd for $\text{C}_{18}\text{H}_{25}\text{O}_3[\text{M} + \text{H}]^+$ 289.1798, found, 289.1795.

(+)-(3''*R*,3*a*''*R*,7*a*''*S*)-3''-Isopropenyl-7*a*''-methyl-5''-methylenhexahydrodispiro[1,3-dioxolane-2,1'-cyclohexane-4',4''-inden]-1''(2''*H*)-one (**12**):

To a solution of 2-bromopropene (374 μ L, 4.27 mmol, 3 eq) in THF (4.3 mL) at -68°C , was added a solution of *n*-butyl lithium in hexanes (1.6 M, 5.33 mL, 8.53 mmol, 6.0 eq). The reaction mixture was stirred at -68°C for 55 min, it was transferred *via* cannula to a pre-cooled flask (-68°C) containing copper(I) cyanide (191 mg, 2.13 mmol, 1.5 eq) and the reaction mixture was placed in an ice-bath at 0°C and stirred for 25 min. The resultant black-purple reaction mixture was cooled back to -68°C and a solution of spiro *cis*-hydrindenone **6** (410 mg, 1.42 mmol) in THF (2.5 mL) was added. The reaction mixture was stirred at -68°C for 2 h (monitored on TLC), warmed up to -45°C , then quenched with saturated NH_4Cl solution (10 mL) and extracted with ethyl acetate (3 x 40 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated to minimum amount of solvent, the product was crashed out from the solution, solids were washed with hexanes to afford title product **12** (252 mg, 53.6%) as white solid, mother liquid was concentrated, purified on CombiFlash silica gel column chromatography, eluted with gradient ethyl acetate-hexanes (5:95 to 20:80) to afford additional product **12** (148 mg, 31.4%). R_f (0.5, 30% EtOAc-hexanes); m.p. $114.5\text{--}115.5^{\circ}\text{C}$; $[\alpha]_D^{22} +32.2$ (c 1.0, CH_2Cl_2); IR (thin film) $\gamma_{\text{max}} \text{ cm}^{-1}$ 1735, 1640, 1145, 940. ^1H NMR (400 MHz, CDCl_3): δ 5.14 (s, 1 H); 4.88 (s, 1 H); 4.83 (s, 1 H); 4.76 (d, $J = 1.75$ Hz, 1 H); 3.92 (s, 4 H); 2.89 (q, $J = 9.6$ Hz, 1 H); 2.67 (dd, $J = 19.7, 10.0$ Hz, 1 H); 2.43 (td, $J = 13.0, 5.0$ Hz, 1 H); 2.29–2.19 (m, 1 H); 2.17–1.97 (m, 4 H); 1.82–1.65 (m, 2 H); 1.75 (s, 3H); 1.61–1.47 (m, 5 H); 1.40–1.34 (m, 1 H); 1.32 (s, 3 H). ^{13}C NMR (100 MHz, CDCl_3): δ 219.8, 148.6, 148.2, 112.3, 112.0, 108.7, 64.1, 64.1, 56.6, 50.2, 43.1, 42.4, 41.2, 33.8, 33.6, 31.1, 30.4, 29.0, 23.4, 19.3; HRMS (FAB $^+$) m/z calcd for $\text{C}_{21}\text{H}_{31}\text{O}_3[\text{M} + \text{H}]^+$ 331.2268, found, 331.2263.

(+)-(3''*S*,3*a*''*R*,5''*S*,7*a*''*S*)-3''-Isopropyl-5'',7*a*''-dimethylhexahydrodispiro[1,3-dioxolane-2,1'-cyclohexane-4',4''-inden]-1''(2''*H*)-one (**5a**) and (+)-(3''*S*,3*a*''*R*,5''*R*,7*a*''*S*)-3''-Isopropyl-5'',7*a*''-dimethylhexahydrodispiro[1,3-dioxolane-2,1'-cyclohexane-4',4''-inden]-1''(2''*H*)-one (**5b**):

To a solution of spiro 2-propenylalkenylketone **12** (320 mg, 0.968 mmol) in MeOH (22 mL, 0.044M) at rt, was added PtO_2 (37 mg, 0.15 mmol) in one portion. The reaction mixture was stirred at rt for 3 h under a hydrogen atmosphere. The mixture was filtered through a pad of celite and then washed with MeOH and

concentrated to afford ~ a 1:2 mixture of isomers (quant.). The residue was purified on silica gel column chromatography using ether-hexane (20:80 to 30:70) as eluent to afford title products **5b** (93 mg, 29 %) as a solid, and **5a** (209 mg, 65 %) as a colorless gum. For major isomer **5a**: R_f (0.3, 30% ether-hexanes); $[\alpha]_D^{22} +33.9$ (c 1.0, CH_2Cl_2); IR (neat) $\gamma_{\text{max}} \text{ cm}^{-1}$ 1734, 1111; ^1H NMR (400 MHz, CDCl_3): δ 3.94 (br s, 4 H); 2.33 (d, $J = 6.6$ Hz, 2 H); 2.14-2.05 (m, 1 H); 1.97 (s, 1 H); 1.95-1.18 (m, 14 H); 1.09 (s, 3 H); 1.00 (d, $J = 5.9$ Hz, 3 H); 0.96 (d, $J = 8.3$ Hz, 3 H); 0.94 (d, $J = 7.6$ Hz, 3 H); ^{13}C NMR (125 MHz, 75°C , $\text{C}_6\text{D}_5\text{CD}_3$): δ 217.2, 108.4, 63.9, 63.7, 48.6, 48.0, 39.8, 38.4, 37.3, 33.3, 30.5, 30.2, 29.4, 28.4, 27.9, 26.7, 26.4, 24.5, 21.6, 13.1; HRMS (FAB $^+$) m/z calcd for $\text{C}_{21}\text{H}_{35}\text{O}_3[\text{M} + \text{H}]^+$ 335.2581, found, 335.2577. For Minor Isomer **5b**: R_f (0.4, 30% ether-hexanes); m.p. 145-148 $^\circ\text{C}$; $[\alpha]_D^{22} +23.5$ (c 1.0, CH_2Cl_2); IR (thin film) $\gamma_{\text{max}} \text{ cm}^{-1}$: 1735, 1105; ^1H NMR (400 MHz, CDCl_3): δ 3.96 (s, 4 H); 2.64 (dd, $J = 18.8, 11.5$ Hz, 1 H); 2.40-2.32 (m, 1 H); 2.17-2.06 (m, 2 H); 2.03-1.87 (m, 4 H); 1.74-1.12 (m, 10 H); 1.21 (s, 3 H); 1.08 (d, $J = 7.4$ Hz, 3 H); 0.87 (d, $J = 6.8$ Hz, 3 H); 0.66 (d, $J = 6.8$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 221.8, 108.5, 64.2, 64.1, 55.0, 49.1, 38.8, 36.5, 36.1, 34.4, 32.1, 30.9, 30.8, 30.3, 28.5, 27.4, 24.0, 23.1, 22.5, 15.6, 14.3; HRMS (FAB $^+$) m/z calcd for $\text{C}_{21}\text{H}_{35}\text{O}_3[\text{M} + \text{H}]^+$ 335.2581, found, 335.2578.

(+)-(3''S,3a''R,5''S,7a''S)-2''-Phenylthio-3''isopropyl-5'',7a''-dimethylhexahydrodispiro[1,3-dioxolane-2,1'-cyclohexane-4',4''-inden]-1''(2''H)-one (13):

To a cold (-68°C) solution of LDA [prepared from diisopropylamine (70 μL , 0.49 mmol, 4.5 eq) in THF (0.9 mL) and n-Butyllithium 1.6M hexanes (245 μL , 0.392 mmol, 3.6 eq)] was added dropwise a solution of spiro tricyclic intermediates **5a** (36.4 mg, 0.11 mmol) in THF (0.6 mL). The mixture was stirred at -70°C for 1 h, and a solution of *S*-phenyl benzenethiosulfonate (98 mg, 0.392 mmol, 3.6 eq) in THF (0.5 mL) was added. The reaction was stirred for 1.5 h, the cooling bath removed, and the reaction was warmed to rt over 30 min. The mixture was then quenched with a saturated NH_4Cl solution, extracted with ethyl acetate (3 x 10 mL), combined extracts were washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified on CombiFlash silica gel column chromatography, eluted with gradient ethyl acetate-hexanes (10:90 to 15:85) to afford the title product **13** (41.5 mg, 86 %) as white foam. ^1H NMR spectra confirmed single isomer and the absolute stereochemistry of phenyl sulfide was not confirmed as it will be destroyed later in the sequence. R_f (0.5, 20%, ethyl acetate-hexanes); $[\alpha]_D^{22} +179.0$ (c 1.0, CH_2Cl_2); IR (neat) $\gamma_{\text{max}} \text{ cm}^{-1}$ 1740, 1106; ^1H NMR (400 MHz, CDCl_3): δ 7.57-7.53 (m, 2 H); 7.31-7.2 (m, 3 H); 3.99-3.89 (m, 4 H); 3.52 (d, $J = 5.8$ Hz, 1 H); 2.11-2.04 (m, 2 H); 1.98-1.80 (m, 3 H); 1.67-1.51 (m, 6 H); 1.42-1.21 (m, 5 H); 1.17 (s, 3 H); 1.048 (d, $J = 6.6$ Hz, 3 H); 1.031 (d, $J = 7.2$ Hz, 3 H), 0.92 (d, $J = 7.1$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 218.5, 136.8, 131.3, 128.8, 126.9, 108.5, 64.23, 64.16, 54.7, 48.5,

48.0, 47.5, 37.1, 34.6, 30.3, 29.9, 29.5, 29.2, 28.2, 27.0, 26.7, 24.2, 22.3, 20.7, 13.3; HRMS (FAB⁺) *m/z* calcd for C₂₇H₃₈O₃S[M + K]⁺ 481.2178, found, 481.2179.

(+)-(3'S,3a'R,5'S,7a'S)-3'-Isopropyl-5',7a'-dimethyl-2'-(phenylthio)hexahydro-4H-spiro[cyclohexane-1,4'-indene]-1',4(2'H)-dione (**13**):

To a solution of phenyl sulfide **13** (14.8 mg, 0.033 mmol) in THF (0.3 mL) at rt, was added aq. 1N HCl (250 μ L, 0.1 mmol, 2.9 eq). The reaction mixture was stirred at rt for 3 h, an additional amount of aq. 1N HCl (250 μ L, 2.88 eq) and THF (250 μ L) was added. The reaction was stirred overnight, concentrated, diluted with a saturated NaHCO₃ solution and extracted with methylene chloride. The combined organic layers were dried (Na₂SO₄) and concentrated to afford title product **14** (13.1 mg, quant.) as white foam. ¹H NMR of the crude product was very clean and the crude material was used in the next step without further purification. *R_f* (0.3, 20% ethyl acetate-hexanes); [α]_D²² +187.0 (*c* 1.0, CH₂Cl₂); IR (neat) $\gamma_{\max}$ cm⁻¹ 1740, 1712; ¹H NMR (400 MHz, CDCl₃): δ 7.54 (br d, *J* = 7.6 Hz, 2 H); 7.32-7.20 (m, 3 H); 3.55 (d, *J* = 5.9 Hz, 1 H); 2.46-2.22 (m, 4 H); 2.22-2.13 (m, 2 H); 2.04 (s, 1 H); 1.95-1.24 (m, 9 H); 1.20 (s, 3 H); 1.06-1.00 (m, 9 H); ¹³C NMR (100 MHz, CDCl₃): δ 217.9, 211.2, 136.2, 131.6, 128.9, 127.2, 55.0, 48.5, 47.9, 37.2, 37.0, 36.4, 35.0, 32.1, 29.6, 29.0, 28.6, 26.2, 24.0, 22.3, 21.1, 13.2; HRMS (FAB⁺) *m/z* calcd for C₂₅H₃₄O₂S[M + K]⁺ 437.1916, found, 437.1917.

(+)-(1*S*,3*a'**R*,5'*S*,7*a'**S*)-3'-Isopropyl-5',7*a'*-dimethyl-5',6',7',7*a'*-tetrahydro-4H-spiro[cyclohex-2-ene-1,4'-indene]-1',4(3*a'*H)-dione (**4a**) and (+)-(1*R*,3*a'**R*,5'*S*,7*a'**S*)-3'-Isopropyl-5',7*a'*-dimethyl-5',6',7',7*a'*-tetrahydro-4H-spiro[cyclohex-2-ene-1,4'-indene]-1',4(3*a'*H)-dione (**4b**):

Step 1: To a solution of cyclohexanone phenyl sulfide **14** (11 mg, 0.028 mmol) in toluene-dimethylsulfoxide (0.9 mL, 2:1, 0.06 M) at rt, was added IBX (17.9 mg, 0.064 mmol, 2.3 eq). The reaction mixture was stirred at 65°C for 7 h, diluted with ether and washed with a saturated NaHCO₃ solution, water, brine, dried (Na₂SO₄), concentrated and purified by silica gel column chromatography to afford ~1.2:1 mixture of enones (9.5 mg, 86%) as an oil. *R_f* (0.3, 20% ethyl acetate-hexanes). **Step 2:** To a solution of the enones, obtained in step 1, (8 mg, 0.02 mmol) in ethanol (0.4 mL) was added magnesium

monoperoxyphthalate hexahydrate (MMPP) (5 mg, 0.01 mmol, 0.5 eq) at rt, after stirring for 1 h, the reaction mixture was concentrated, diluted with water and extracted with methylene chloride (3 x 10 mL). The combined extracts were washed with a NaHCO₃ solution, brine, dried (Na₂SO₄), purified on silica gel chromatography using automatized gradient pump system CombiFlash, eluted with ethyl acetate-hexanes (20:80 to 50:50) to afford mixture of sulfoxides (7.4 mg, 90 %) as a colorless oil. *R_f* (0.15, 20% ethyl acetate-hexanes). **Step 3:** In a sealed microwave flask, the mixture of sulfoxide, obtained in step 2, (7.4 mg, 0.018 mmol) and potassium carbonate, 325 mesh (25 mg, 0.18 mmol, 10 eq) in toluene (1 mL) was heated at 120°C for 4 h and cooled to rt. The potassium carbonate was filtered off and the remaining solution was concentrated and then purified by chromatography on silica gel using ethyl acetate-hexanes (20:80 to 50:50) to afford ~1.2:1 mixture of title products **4a** and **4b** (4.2 mg, 83 %) as a colorless oil. *R_f* (0.3, 30% ethyl acetate-hexane). Analytical HPLC was carried out on chiralpak-AD, using isopropanol-hexane (5:95) as eluent, flow rate, 1.0 mL/min and detection at 254 nM. Retention times for **4a** and **4b** are 11.2 and 14.9 min, respectively. Semi-preparative HPLC was carried out on chiralpak-AD, 250 mm x 20 mm, flow rate, 5 mL/min, 5% isopropanol-hexanes, 254 nM, to afford spiro dienones **4a** (2.5 mg, 48%) and **4b** (1.7 mg, 33%). **Spiro dienone 4a:** [α]_D²² +42.6 (*c* 0.5, CH₂Cl₂); IR (neat) $\gamma_{\max}$ cm⁻¹ 1703, 1606, 1461, 1385, 1219; ¹H NMR (400 MHz, CDCl₃): δ 6.33 (dd, *J* = 10.4, 1.3 Hz, 1 H); 6.04 (s, 1 H); 5.95 (d, *J* = 10.3 Hz, 1 H); 2.87 (s, 1 H); 2.63-2.46 (m, 3 H); 2.26-1.95 (m, 3 H); 1.73-1.45 (m, 3 H), 1.27-1.19 (m, 1 H); 1.18 (d, *J* = 6.6 Hz, 3 H); 1.09 (d, *J* = 7.0 Hz, 3 H); 1.06 (s, 3 H); 0.81 (d, *J* = 6.6 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 212.6, 198.8, 185.7, 158.0, 128.0, 126.3, 55.7, 50.6, 41.9, 33.1, 32.3, 31.2, 29.7, 28.0, 25.5, 25.1, 22.3, 19.9, 16.3; HRMS (FAB⁺) *m/z* calcd for C₁₉H₂₆O₂[M + H]⁺ 287.2010, found, 287.2011. **Spiro dienone 4b:** [α]_D²² +192.5 (*c* 0.4, CH₂Cl₂); IR (neat) $\gamma_{\max}$ cm⁻¹ 1703, 1606, 1461, 1385, 1219; ¹H NMR (400 MHz, CDCl₃): δ 6.99 (d, *J* = 10.3 Hz, 1 H); 5.98 (d, *J* = 10.3 Hz, 1 H); 5.92 (s, 1 H); 2.90 (s, 1 H); 2.51-2.11 (m, 5 H); 1.71-1.57 (m, 2 H); 1.54-1.32 (m, 3 H); 1.18-1.132 (2 x d, *J* = ~6.7 Hz, 6 H), 1.16 (s, 3 H), 1.07 (d, *J* = 7.0 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃): δ 211.6, 198.2, 185.7, 161.2, 128.7, 125.0, 55.9, 48.1, 41.7, 34.4, 33.3, 32.4, 30.7, 29.8, 25.4, 23.6, 20.7, 19.9, 14.5; HRMS (FAB⁺) *m/z* calcd for C₁₉H₂₆O₂[M + H]⁺ 287.2010, found, 287.2011.

(+)-(1*S*,3*a'**R*,4*R*,5*S*,7*a'**S*)-3'-Isopropyl-4-hydroxy-4,5',7*a'*-trimethyl-5',6',7',7*a'*-tetrahydrospiro[cyclohex-2-ene-1,4'-inden]-1'(3*a'*H)-one (Cyanthiwigin AC, **2**) and (+)-(1*S*,3*a'**R*,4*S*,5*S*,7*a'**S*)-3'-Isopropyl-4-hydroxy-4,5',7*a'*-trimethyl-5',6',7',7*a'*-tetrahydrospiro[cyclohex-2-ene-1,4'-inden]-1'(3*a'*H)-one (12-Epicyanthiwigin AC, **15**):

To a stirred solution of spiro dienone **4a** (8.6 mg, 0.03 mmol) in THF (0.6 mL) was added a solution of methylmagnesium chloride (120 μ L, 0.036 mmol, 1.2 eq, 0.3M) in THF at -100°C (ether + liq. N₂). After

stirring for 30 min, additional methylmagnesium chloride (120 μ L, 0.036 mmol, 1.2 eq, 0.3M) was added twice at 30 min time intervals. The solution was slowly warmed to -80°C during 1 h (TLC monitored), quenched with a saturated NH_4Cl solution, extracted with ethyl acetate (3 x 5 mL), dried (Na_2SO_4) and concentrated to afford ~2:1 mixture of cyanthiwigin-AC (**2**) and 12-epicyanthiwigin (**15**). Purification on preparative silica gel TLC using ethyl acetate-hexanes (35:65) as eluent (eluted thrice to get better separation) afforded 12-epicyanthiwigin-AC (**15**, 2.5 mg, 28%) and Cyanthiwigin-AC (**2**, 5.8mg, 63%). For **15**: R_f (0.25, 30% ethyl acetate-hexane); $[\alpha]_D^{22} +69.3$ (c 0.15, CH_2Cl_2); IR (neat) γ_{max} cm^{-1} , 3412, 2867, 1705, 1603, 1462 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3): δ 5.97 (s, 1 H); 5.66 (dd, $J = 10.1, 1.3$ Hz, 1 H); 5.02 (dd, $J = 10.2, 1.5$ Hz, 1 H); 2.74-2.63 (m, 1 H); 2.67 (s, 1 H); 2.18-2.08 (m, 1 H); 1.93-1.6 (m, 3 H); 1.58-1.25 (m, 5 H); 1.33 (s, 3 H); 1.17 (d, $J = 6.6$ Hz, 3 H); 1.066 (d, $J = 7.0$ Hz, 3 H); 0.982 (s, 3 H); 0.681 (d, $J = 6.64$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 213.3, 187.1, 137.7, 132.2, 125.2, 66.3, 57.0, 50.7, 41.4, 33.2, 32.1, 29.5, 29.2, 25.6, 25.0, 23.4, 22.2, 19.5, 16.2; For Cyanthiwigin-AC (**2**):³ R_f (0.2, 30% ethyl acetate-hexane), $[\alpha]_D^{22} +40.0$ (c 0.1, CH_2Cl_2), Optical rotation for the natural product was not measured due to minute quantities of material for comparison; IR (neat) γ_{max} cm^{-1} 3435, 1686, 1600, 1125; ^1H NMR (400 MHz, CDCl_3): δ 5.96 (s, 1 H); 5.57 (d, $J = 10.2$ Hz, 1 H); 4.95 (d, $J = 10.2$ Hz, 1 H); 2.84-2.74 (m, 1 H); 2.68 (s, 1 H); 2.17-2.08 (m, 1 H); 1.83 (t, $J = 6.1$ Hz, 2 H); 1.75-1.56 (m, 3 H); 1.51-1.31 (m, 3 H); 1.28 (s, 3 H); 1.17 (d, $J = 6.6$ Hz, 3 H); 1.10 (d, $J = 7.0$ Hz, 3 H); 1.00 (s, 3 H); 0.69 (d, $J = 6.7$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3): δ 213.5, 187.8, 135.6, 133.4, 125.2, 68.8, 58.2, 50.8, 41.5, 34.3, 32.2, 30.0, 29.8, 28.3, 26.4, 25.7, 25.2, 22.4, 19.8, 16.2.

References:

- ¹Isaacs, R.; Di Grandi, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 3938-3941.
- ²Wasylishen, R. E.; Rice, K. C.; Weiss U. *Can. J. Chem.* **1975**, *53*, 414-417.
- ³Peng, J.; Avery M. A.; Hamann, M. T. *Org. Lett.* **2003**, *5*, 4575-4578.

2 (400 MHz, CDCl₃)

Avance 400 East "Ash"

2 (100 MHz, CDCl₃)

4a (400 MHz, CDCl₃)

4a (100 MHz, CDCl₃)

4b (400 MHz, CDCl₃)

4b (100 MHz, CDCl₃)

Inova 500 (Maple) Tritium Probe
 1-J. Reddy sample 219155-181-8
 in CDCl₃ @ 25C
 (LAT book 71711-045)

Data Collected on:
 mltm4-inova500
 Archive directory:
 /export/home/cp22/vnmrsys/data
 Sample directory:

File: NOESY

Pulse Sequence: NOESY

Solvent: CDCl₃

Temp: 25.0 C / 298.1 K

Relax. delay 1.000 sec

Mixing 1.000 sec

Acq. time 0.150 sec

Width 5049.2 Hz

2D Width 5049.2 Hz

16 repetitions

2 x 256 increments

OBSERVE H1, 499.7335867 MHz

DATA PROCESSING

Gauss apodization 0.069 sec

F1 DATA PROCESSING

Gauss apodization 0.094 sec

FT size 4096 X 4096

Total time 4 hr, 58 min

NOESY SPECTRUM

4b (500 MHz, CDCl₃)

NOE interaction

4 & 16 - H (strong)
 4 & 20 - H (strong)
 4 & 17 - H (strong)
 4 & 19 - H (very weak)

Inova 500 (Maple) Tritium Probe
T.J. Reddy sample 219155-181-B
in CDCl₃ @ 25C
(LAT book 71711-045)

Data Collected on:
mlnmr4-inova500
Archive directory:
/export/home/cp22/vnmrsys/data
Sample directory:

File: NOESY

Pulse Sequence: NOESY
Solvent: CDCl₃

Temp. 25.0 C / 298.1 K

Relax. delay 1.000 sec
Mixing 1.000 sec
Acq. time 0.150 sec
Width 5049.2 Hz
2D Width 5049.2 Hz
16 repetitions
2 x 256 increments
OBSERVE H1, 499.7335867 MHz
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.094 sec
F1 size 4096 x 4096
Total time 4 hr, 58 min

NOESY SPECTRUM

4b (500 MHz, CDCl₃)

NOE interaction

14 & 16 - H (strong)
14 & 20 - H (strong)
14 & 18 - H (strong)
14 & 4 - H (strong)
14 & 6 - H (very weak)

Inova 500 (Maple) Tritium Probe
T.J. Reddy sample 219155-181-B
in CDCl₃ @ 25C
(LAT book 71711-045)

Data Collected on:
mtlmr-4-inova500
Archive directory:
/export/home/cp22/vnmrsys/data
Sample directory:

File: ghsqc

Pulse Sequence: ghsqc

Solvent: CDCl₃

Temp. 25.0 C / 298.1 K

Relax. delay 1.000 sec

Acq. time 0.150 sec

Width 5049.2 Hz

2D Width 21361.8 Hz

4 repetitions

2 x 256 increments

OBSERVE H1, 499.735867 MHz

DECOUPLE C13, 125.6675324 MHz

Power 45 dB

on during acquisition

off during delay

W40 3shiftfile modulated

DATA_PROCESSING

Gauss apodization 0.069 sec

F1 DATA PROCESSING

Gauss apodization 0.022 sec

F1 size 2048 x 4096

Total time 41 min

HSQC SPECTRUM

4b (500 MHz, CDCl₃)

Inova 500 (Maple) Tritium Probe
T.J. Reddy sample 219155-181-B
in CDCl₃ @ 25C
(LAT book 71711-045)

Data Collected on:
ml1mr4-inova500
Archive directory:
/export/home/cp22/vnmrsys/data
Sample directory:

File: gc05Y

Pulse Sequence: gc05Y

Solvent: CDCl₃

Temp. 25.0 C / 298.1 K

Relax. delay 1.000 sec
Acq. time 0.150 sec
Width 5049.2 Hz
2D Width 5049.2 Hz
2 repetitions
256 increments
OBSERVE H1, 499.7335867 MHz
DATA PROCESSING
Sq. sine bell 0.075 sec
F1 DATA PROCESSING
Sq. sine bell 0.101 sec
F1 size 4096 x 2048
Total time 10 min

COSY SPECTRUM

4b (500 MHz, CDCl₃)

5a (400 MHz, CDCl₃)

5a (125 MHz, 75°C, Toluene-D₈)

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5b (400 MHz, CDCl₃)

5b (100 MHz, CDCl₃)

Inova 600 (Mahogany) - Cryoprobe
219155-151 in CDCl₃ @ 25C
(LAT book 71711-013)

Data collected on:
mltmr5-inova600
Archive directory:
/export/home/cp22/vnmrSYS/data
Sample directory:

File: NOESY_CDCl3

Pulse Sequence: NOESY
Solvent: CDCl₃

Temp. 25.0 C / 298.1 K

Relax. delay 1.000 sec
Mixing 1.000 sec
Acq. time 0.150 sec
Width 3055.8 Hz
2D Width 3055.8 Hz
16 repetitions
2 x 256 increments
OBSERVE H1, 599.9391966 MHz
DATA PROCESSING
Gauss apodization 0.069 sec
F1 DATA PROCESSING
Gauss apodization 0.118 sec
F1 size 4096 x 4096
Total time 5 hr, 1 min

NOESY SPECTRUM

5b (600 MHz, CDCl₃)

NOE interaction

3 & 16 - H (strong)
3 & 4 - H (very weak)
3 & 19 - H (strong)
4 & 20 - H (strong)
4 & 17 - H (strong)
17 & 20 - H (medium)
19 & 20 - H (strong)

Inova 600 (Mahogany) - Cryoprobe
219155-151 in CDCl₃ @ 25C
(LAT book 71711-013)

Data Collected on:
mtnmr5-inova600
Archive directory:
/export/home/cp22/vnmrSYS/data
Sample directory:

File: ghmhbc

Pulse Sequence: ghmhbc
Solvent: CDCl₃

Temp. 25.0 C / 298.1 K

Relax. delay 1.000 sec

Acq. time 0.150 sec

Width 3055.8 Hz

2D Width 36199.1 Hz

32 repetitions

1024 increments

OBSERVE H1 509.9391966 MHz

DATA PROCESSING

Sine bell 0.075 sec

F1 DATA PROCESSING

Sine bell 0.057 sec

FT size 1024 x 8192

Total time 11 hr, 24 min

HMBC SPECTRUM

5b (600 MHz, CDCl₃)

Inova 600 (Mahogany) - Cryoprobe
 21915-151 in CDCl₃ @ 25C
 (LAT book 7/11-013)

Data Collected on:
 m1nmr5-inova600
 Archive directory:
 /export/home/cp22/vnmrSYS/data
 Sample directory:

File: ghsqc_CDC13

Pulse Sequence: ghsqc
 Solvent: CDC13

Temp. 25.0 C / 298.1 K

Relax. delay 1.000 sec
 Acq. time 0.150 sec
 Width 3055.8 Hz
 2D Width 25649.2 Hz
 4 repetitions
 2 x 256 increments
 OBSERVE H1, 599.9391966 MHz
 DECOUPLE C13, 150.8661411 MHz
 Power 41 dB
 on during acquisition
 off during delay
 W40.ch1176.cp22 modulated
 DATA PROCESSING
 Gauss apodization 0.069 sec
 F1 DATA PROCESSING
 Gauss apodization 0.018 sec
 FT size 1024 x 4096
 Total time 41 min

HSQC SPECTRUM

5b (600 MHz, CDCl₃)

Inova 600 (Mahogany) - Cryoprobe
219155-151 in CDC13 @ 25C
(LAT book 71711-013)

Data Collected on:
mt1mr5-inova600

Archive directory:
/export/home/cn2

Sample directory:

File: gcosy

Pulse Sequence: gCOSY

Solvent: CDCl₃

Temp. 25.0 C / 298.1 K

Relax. delay 1.000 sec
Arch. time 0.150 sec

Width	3055.8	HZ
2D Width	3055.8	HZ

2 repetitions

OBSERVE H1, 599.9391966 MHZ

Sq. sine bell 0.075 sec

Sq. sine bell 0.168 sec

Total time 10 min

Total time 10 min

COSY SPECTRUM

5b (600 MHz, CDCl₃)

6 (400 MHz, CDCl₃)

6 (100 MHz, CDCl₃)

7b (400 MHz, CDCl₃)

USER: redyhtu
 BOOK: 219155-076
 EXPNO: 4
 ACQUIRED: 15-Jun-2005 01:33:30
 SOLVENT: CDCl3
 FILENAME: /rmc_archive/data/redyhtu/rmc/219155-076/4/fid

7b (100 MHz, CDCl₃)

10 (400 MHz, CDCl₃)

10 (100 MHz, CDCl₃)

11 (400 MHz, CDCl₃)

11 (100 MHz, CDCl₃)

12 (400 MHz, CDCl₃)

12 (100 MHz, CDCl₃)

15 (400 MHz, CDCl₃)

15 (100 MHz, CDCl₃)