Total Syntheses of Racemic, Natural (-) and Unnatural (+) Glyceollin I

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Supporting Information

(i) Experimental procedures.

(ii) NMR and CD studies including selected spectra.

(iii) Chiral HPLC chromatograms.

(iv) NMR spectra for new intermediates and final compounds (separately located in accompanying file).

(i) Experimental procedures

General Experimental Procedures

Chemical reactions were conducted under nitrogen in anhydrous solvents unless stated otherwise. Reagents obtained from commercial suppliers were used without further purification. Acetone was dried over 4 Å molecular sieves. Tetrahydrofuran (THF) was distilled under nitrogen over sodium-benzophenone. Thin-layer chromatography (TLC) was done on 250 μ fluorescent plates and visualized by using UV light or iodine vapor. Normal phase flash column chromatography was performed using silica gel (200-425 mesh 60 Å pore size) and ACS grade solvents. Melting points (mps) are uncorrected. NMR spectra were recorded on either a 600 MHz or a 400 MHz instrument. Peak locations were referenced using either tetramethyl silane (TMS) or residual non-deuterated solvent as an internal standard. Proton coupling constants are expressed in Hertz. In some cases, overlapping signals occurred in the ^{13}C NMR spectra. Spectroscopic data is in agreement with all known compounds.

2-Benzyloxy-4-methoxymethyloxy-acetophenone (2)
Oven-dried potassium carbonate (0.166 g, 1.2 mmol) was added to an ice cooled solution of 2,4-dihydroxy-acetophenone (0.152 g, 1 mmol) in 5 mL of acetone. MOMCl (0.15 mL, 2 mmol) was added drop-wise and the mixture was stirred at 0 ^{o}C for one hour. The temperature of the reaction was gradually allowed to come to RT and further stirred for 24 hours, afterwhich it was quenched with water (ca. 10 mL). The acetone was evaporated under vacuum. The remaining water layer was extracted with DCM (2 x 10 mL). The organic layers were combined, dried over sodium sulfate and evaporated to obtain 0.156 g (79 %) of oily product having a pink tinge. The crude product was used directly in the next step without further purification. The crude product (ca. 0.156 g) was dissolved in 10 mL of acetone. Oven dried potassium carbonate (0.166 g, 1.2 mmol) was added and the mixture stirred for 15 minutes. Benzylbromide (1.3 mL, 11 mmol) was added and the mixture was refluxed for 12 hours. After disappearance of starting material (TLC), the reaction was poured into ice water with vigorous stirring. A pinkish-white solid precipitated and it was recrystallized from methanol (ca. 2 mL) to obtain 0.203 g (71 %) of **2** as a white powder: mp 70-71 ^{o}C; TLC R_f 0.32 in hexanes:EtOAc (5:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (d, 1H, Ar-H6), 7.46-7.36 (m, 5H, C_6H_5), 6.69-6.66 (m, 2H, Ar-H5/Ar-H3).5.2,5.1 (2 x s.2 x 2H, $PhCH_2$, O-CH_2-O), 3.47 (s, 3H, OCH_3), 2.56 (s, 3H, CH_3CO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 162.2, 160.2, 136.2, 132.7, 128.9, 128.5, 127.9, 122.6, 108.3, 101.2, 94.5, 70.9, 56.5, 32.4; analysis calcd. for $C_{17}H_{18}O_4$: C 71.31, H 6.34.found: C 71.08, H 6.40.

4-Benzyloxy-2-hydroxy-benzaldehyde (4)
Anhydrous sodium bicarbonate (0.1 g, 1.2 mmol) was added to a solution of 2,4-dihydroxy-benzaldehyde (0.138 g, 1 mmol) in 10 mL of acetonitrile and the mixture was stirred for 1 hour at RT. Benzylbromide (0.13 mL, 1.1 mmol) was added and the mixture was refluxed for 6 hours. After disappearance of the reactant (TLC), the reaction was poured into ice water with vigorous stirring. A white solid precipitated and it was recrystallized from methanol (ca. 4 mL) to obtain 0.182 g (80 %) of **4** as a white powder:

mp[7] 78-80 °C; TLC R_f 0.88 in toluene:methanol (10:1); ^{1}H NMR (600 MHz, acetone-d_6) δ 11.41 (s, 1H, OH), 9.81 (s, 1H, CHO), 7.67 (d, 1H, J = 8.4 Hz, Ar-H6), 7.45-7.35 (m, 5H, C_6H_5), 6.70 (dd, 1H, ^2J = 8.4 Hz, ^3J = 2.4 Hz, Ar-H5), 6.56 (d, 1H, J = 1.8 Hz, Ar-H3), 5.24 (s, 2H, $PhCH_2$); ^{13}C NMR (100 MHz, acetone-d_6) 194.61, 166.1, 164.4, 135.9, 128.9, 128.6, 127.8, 115.5, 109.1, 101.8, 70.6; analysis calcd.. for $C_{14}H_{12}O_3$: C 73.67, H 5.30, found: C 73.62, H 5.35.

1-[2-Benzyloxy-4-(methoxy methyl) phenyl]-2-iodo-ethanone (5)

2-Benzyloxy-4-methoxymethyl-acetophenone (0.286 g, 1 mmol) was dissolved in 1 mL DCM and 5 mL of anhydrous methanol. Selectfluor™ (0.230 g, 0.6 mmol) and elemental iodine (0.126 g, 0.5 mmol) were added and the mixture stirred at room temperature for 12 hours. Then 15 mL of chloroform was added and an ash colored solid precipitated. The precipitate was filtered and the filtrate was extracted with 10% aqueous sodium thiosulfate solution (5 x 20 mL) until the organic layer became lemon yellow. The organic layer was evaporated under vacuum to obtain a yellowish oily residue which was redissolved in methanol:acetone (ca. 20 mL:2 mL) and refrigerated overnight. The desired product precipitated while the filtrate retained side products having iodination on the aromatic ring and di-iodination at the *alpha*-carbon. The product was filtered and dried to obtain 0.288 g (70 %) of **5** as a white powder which turned yellow on storage: mp 66-68 °C; TLC R_f 0.29 in hexanes:EtOAc (2:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (d, 1H, J = 9 Hz, Ar-H6), 7.50-7.38 (m, 5H, C_6H_5), 6.72-6.70 (m, 2H, Ar-H5/Ar-H3), 5.20-5.17 (2 x s, 2 x 2H, $PhCH_2$/O-CH_2-O), 4.4 (s, 2H, CH_2I), 3.48 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 163.0, 159.9, 135.7, 134.1, 129, 128.8, 128.3, 128.1, 118.5, 108.8, 101, 94.5, 71.3, 56.6; analysis calcd. for $C_{17}H_{17}O_4I$. C 49.53, H 4.16, I 30.79 ; found: C 49.41, H4.04, I 30.98.

4-Benzyloxy-salicylalcohol (6)

To an ice cooled suspension of 4-benzyloxy-2-hydroxy-benzaldehyde (0.228 g, 1 mmol) in 10 mL of methanol was slowly added sodium borohydride (0.038 g, 1 mmol). After addition of sodium borohydride, a clear solution was obtained. The reaction was stirred at 0 °C for 20 minutes followed by stirring at RT for 10 minutes. The solvent was evaporated under vacuum. To this solid residue was carefully added 0.1 N H_2SO_4 until the pH dropped to 6.5 with vigorous stirring. Additional water (ca. 40 mL) was added with continuous stirring which then caused the product to precipitate. The solid was filtered and copiously washed with water to remove all traces of acid (last wash pH ≥ 7). The solid was immediately vacuum dried to obtain 0.175 g (76 %) of **6** as a white solid**:** mp[8] 88-90 °C; TLC, R_f 0.29, in hexanes:EtOAc (2:1); ^{1}H NMR (600 MHz, DMSO-d_6) δ, 9.36 (s, 1H, Ph-OH), 7.43-7.32 (m, 5H, C_6H_5), 7.14-7.12 (d, 1H, J = 8.4 Hz, Ar-H6), 6.44-6.41 (m, 2H, Ar-H5/Ar-H3), 5.01 (s, 2H, $PhCH_2$), 4.8 (t, 1H, CH_2OH), 4.39 (s, 2H, CH_2OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.0, 155.2, 137.3, 128.5, 128.4, 128.3, 127.6, 127.5, 127.3, 121.2, 104.8, 101.8, 68.9, 57.9; analysis calcd. for $C_{14}H_{14}O_3$. C 73.03, H 6.13 found: C 73.16, H 5.94.

2-(5-Benzyloxy-2-hydroxy-phenoxy)-1-(2-benzyloxy-4-methoxymethyl-phenyl)-ethanone (7)

Potassium carbonate (0.165 g, 1.2 mmol) was added to a solution of

1-[2-benzyloxy-4-(methoxymethyl)phenyl]-2-iodo-ethanone (0.412 g, 1 mmol) and 4-benzyloxy-salicylalchohol (0.254 g, 1.1 mmol) in 10 mL of acetone and the mixture refluxed for 10 hours. After completion of the reaction (TLC), the solvent was evaporated and the residue extracted with EtOAc:water (2 x 20 mL:20 mL). The organic layers were combined, dried over sodium sulfate and evaporated. The residue was chromatographed over silica using hexanes: EtOAc (2:1). The organic fractions were evaporated to provide 0.371 g (72%) of **7** as a white solid: mp 115-118 ^{o}C; TLC R_f 0.16 in hexanes:EtOAc (2:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (d, 1H, *J* = 9 Hz, Ar-H5), 7.64-7.25 (m.10H, 2 x C_6H_5), 7.20 (d, 1H, *J* = 8.4 Hz, Ar-H6'), 6.92 (d, 1H, *J* = 2.4 Hz, Ar-H8), 6.77 (dd, 1H, ^{2}J = 9 Hz, ^{3}J = 2.4 Hz, Ar-H6), 6.55 (dd, 1H, ^{2}J = 8.4 Hz, ^{3}J = 2.4 Hz, Ar-H5'), 6.26 (d, 1H, *J* = 2.4 Hz, Ar-H3'), 5.30 (s, 4H, $PhCH_2$), 5.21 (s, 2H, O-CH_2-O), 4.98 (s, 2H, H-2), 4.57-4.56 (d, 2H, *J* = 6 Hz, CH_2OH), 4.13-4.11 (t, 1H, CH_2OH), 3.44 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 164.4, 162.2, 160.7, 158.6, 138.9, 137.6, 133.6, 130.2, 129.9, 129.8, 129.2, 125.1, 120.4, 110, 106.8, 102.5, 101.7, 95.6, 75.3, 72.4, 71.2, 61.5, 56.9; analysis calcd. for $C_{31}H_{30}O_7$. C 72.36, H 5.88, found: C 72.1, H 5.85.

2',7-(Dibenzyloxy)-4'-(methoxymethyloxy)-isoflav-3-ene (9)

To a solution of 2-(5-benzyloxy-2-hydroxy-phenoxy)-1-(2-benzyloxy-4-methoxymethyl-phenyl)-ethanone (0.514 g, 1 mmol) in 5 mL of acetonitrile was added triphenyl phosphine hydrobromide (0.343 g, 1 mmol) and the suspension stirred at RT for ca. 4 hours. After disappearance of starting material (TLC), organic solvent was evaporated at 20 ^{o}C to provide a yellowish solid. The solid was redissolved in 5 mL of DCM and anhydrous ether was added with constant stirring. The white Wittig's ylide precipitated. This product was used directly in the next step without further purification. The crude product (ca. 0.80 g) was dissolved in 10 mL of methanol followed by addition of sodium methoxide (0.108 g, 2 mmol). The suspension was refluxed for ca. 12 hours afterwhich it was allowed to come to RT. A white solid precipitated. The precipitate was filtered and washed with water, then the filtrate was concentrated to ca. one-half the volume and again refluxed for 4 hours afterwhich it provided additional product upon cooling to RT. The combined product was recrystallized from methanol (ca. 30 mL) to obtain 0.374 g (78%) of **9** as a white solid**:** mp 132-134 ^{o}C; TLC R_f 0.43, in hexanes:EtOAc (5:1); ^{1}H NMR (600 MHz, acetone-d_6) δ 7.51-7.31 (m, 10H, 2 x C_6H_5), 7.27 (d, 1H, *J* = 8.4 Hz, Ar-H5), 7.00 (d, 1H, *J* = 7.8 Hz, Ar-H6'), 6.8 (d, 1H, *J* = 2.4 Hz, Ar-H8), 6.68 (dd, 1H, ^{2}J = 8.4 Hz, ^{3}J = 2.4 Hz, Ar-H6), 6.60 (s, 1H, Ar-H4), 6.56 (dd, 1H, ^{2}J = 8.4 Hz, ^{3}J = 2.4 Hz, Ar-H5'), 6.46 (d, 1H, *J* = 2.4 Hz, Ar-H3'), 5.2 (s, 2H, O-CH_2-O), 5.13 (s, 2H, $PhCH_2$), 5.09 (s, 2H, $PhCH_2$), 4.92 (s, 2H, H2), 3.42 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, acetone-d_6) δ 161.1, 159.9, 158.9, 156.3, 138.9, 138.5, 130.6, 130.5, 130, 129.9, 129.4, 129.3, 129.2, 129, 128.9, 123.2, 122.6, 118.8, 109.6, 103.6, 103.2, 95.8, 71.8, 71.1, 69.6, 56.7; analysis calcd. for $C_{31}H_{28}O_5$. C 77.01, H 5.80, found: C 77.0, H 5.80.

2',7-Dibenzyloxy-4'-(t-butyldimethylsilyl)-isoflav-3-ene (10)

a) 2',7-Dibenzyloxy-4'-hydroxy-isoflav-3-ene

To a solution of 2',7-dibenzyloxy-4'-methoxymethyl-isoflav-3-ene (0.480 g, 1 mmol) in acetonitrile:water (20 mL:1 mL) was added triphenyl phosphine hydrobromide (0.788 g, 2 mmol). The reaction was heated to 50 ^{o}C for ca. 2 hrs. After disappearance of the

starting material (TLC), the solvent was evaporated at 20 ^{o}C. The residue was extracted with EtOAc:water (3 x 10 mL:10 mL). The organic layers were combined, dried and evaporated. The residue was chromatographed over silica using hexanes:EtOAc (5:1). The organic fractions were evaporated to provide 0.374 g (78 %) of **2',7-Dibenzyloxy-4'-hydroxy-isoflav-3-ene (10a)** as an oil. Because of the instability of this intermediate, it was immediately used for the next step: TLC R_f 0.43, in hexanes:EtOAc (5:1); ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.66 (s, 1H, OH), 7.46-7.32 (m, 10H, 2 x C_6H_5), 7.13 (d, 1H, *J* = 8.4 Hz, Ar-H5), 7.0 (d, 1H, *J* = 7.8 Hz, Ar-H6') 6.57-6.55 (m, 2H, H4/Ar-H5'), 6.59 (d, 1H, *J* = 2.4 Hz, Ar-H8), 6.47 (d, 1H, *J* = 2.4 Hz, Ar-H3'), 6.40 (dd, 1H, ^{2}J = 8.4 Hz, ^{3}J = 2.4 Hz, Ar-H5'), 5.07 (s, 4H, $PhCH_2$), 4.85 (s, 2H, H2).

b) Product (10)

To a solution of 2',7-(dibenzyloxy)-4'-hydroxy-isoflav-3-ene (0.374 g, 0.8 mmol) in DCM was added TBDMSCl (0.180 g, 1.2 mmol) and triethylamine (0.2 mL, 1.5 mmol). The reaction mixture was stirred for 12 hours. After disappearance of reactant (TLC), the reaction was quenched with saturated ammonium chloride solution (10 mL) and the resulting mixture extracted with DCM:water (3 x 10 mL:10 mL) The organic layers were combined, dried over sodium sulfate and evaporated to give white product. The crude product was recrystallized from DCM:methanol (ca. 5:25 mL) to obtain 0.370 g (69 % for two steps) of **10** as white crystals: mp 106-107 ^{o}C; TLC R_f 0.75 in DCM:hexanes (2:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46-7.32 (m, 10H, 2 x C_6H_5), 7.21 (d, 1H, *J* = 8.4 Hz, Ar-H5), 7.02 (d, 1H, *J* = 8.4 Hz), 6.58-6.55 (m, 2H, Ar-H3'/H5), 6.49-6.46 (m, 2H, Ar-H6/8), 5.11 (s, 2H, Ph-CH_2), 5.07 (s, 2H, Ph-CH_2), 4.89 (s, 2H, OCH_2), 0.93{s, 9H, Si $(CH_3)_3$}, 0.17{s, 6H, Si $(CH_3)_2$}; ^{13}C NMR (100 MHz, DMSO-d_6) δ199.6, 159.7, 157.5, 156.8, 154.7, 137.7, 137.5, 129.7, 129.2, 129.1, 128.6, 128.5, 128.4, 128.3, 128.1, 121.5, 121.4, 1117.5, 112.8, 108.9.105.9, 102.8, 70.5, 69.9, 68.3, 26.3, 18.7; analysis calcd. for $C_{35}H_{38}O_4Si$ C 75.71, H 6.99; found: C 75.41, H 6.70.

(±) 4'-t-Butyl dimethylsilyloxy-2',7-(dibenzyloxy)isoflavan-3,4-diol (±) (11)

2',7-Dibenzyloxy-4'-t-butyldimethylsilyloxy-isoflav-3-ene (0.537 g, 1 mmol) was dissolved in 10 mL of acetone and 1 mL of water was added. Methane sulfonamide (0.095 g, 1 mmol) and 4-Methylmorpholine-4-oxide i.e. NMO (0.140 g, 1.2 mmol) were then added and the resulting mixture stirred at 0 ^{o}C for 30 minutes. Osmium tetroxide solution in water (1 mL = 0.004 mmol) was added slowly, upon which the reaction turned brownish-yellow. The reaction was gradually allowed to come to RT and stirred for 24 hours. After disappearance of the reactant (TLC), the reaction was quenched with 1 g of sodium bisulfate followed by evaporation of acetone. The residue was extracted with EtOAc:water (2 x 10 mL:10 mL). The organic layers were combined, dried over sodium sulfate, filtered and evaporated. The residue was chromatographed over silica with hexanes:EtOAc (5:1). The organic fractions were evaporated to provide 0.525 g (90 %) of (±)**11** as a fluffy, white solid**:** mp 110-112 ^{o}C; TLC R_f 0.25 in hexanes:EtOAc (5:1); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.46 (d, 1H, *J* = 8.4 Hz, Ar-H5), 7.46-7.28 (m, 10+1H, 2 x C_6H_5+Ar-H6'), 6.58-6.56 (m, 2H, Ar-H8/Ar-H5'), 6.48 (q, 1H, *J* = 8.4 Hz, *J* = 1.8 Hz, Ar-H6), 6.37 (d, 1H, *J* = 2.8 Hz, Ar-H3'), 5.51 (d, 1H, *J* = 7.2, H4), 5.19 (s, 2H, $PhCH_2$), 5.06 (s, 2H, $PhCH_2$), 4.72 (d, 1H, *J* = 11.4 Hz, H-2 eq), 4.23 (d, 1H, *J* = 7.24, 4-

OH), 4.19 (s, 1H, 3-OH), 4.02 (d, 1H, *J* = 11.4 Hz, H2 ax), 0.96{s, 9H, Si $(CH_3)_3$}, 0.17{s, 6H, Si $(CH_3)_2$}; ^{13}C NMR (100 MHz, acetone-d_6) δ 160.6, 158.2, 157.9, 156.4, 139.1, 138.6, 131.5, 130.8, 130.1, 129.9, 129.3, 129.1, 128.9, 128.8, 124.2, 119.1, 113.2, 109.4, 106.9, 102.8, 72.7, 71.6, 70.9, 68.3, 26.6, 19.3; analysis calcd. for $C_{35}H_{40}O_6Si$. C 71.89, H 6.89; found: C 71.72, H 6.81.

(-) 4'-t-Butyl dimethylsilyloxy-2',7-(dibenzyloxy)isoflavan-3,4-diol (-) (11)
To a solution of 2',7-dibenzyloxy-4'-t-butyldimethylsilyl-isoflav-3-ene (0.537 g, 1 mmol) in 5 mL of DCM cooled at -78 °C was added chiral catalyst $(DHQD)_2$PHAL i.e. hydroquinidine-1,4-phthalazinediyl diether (0.78 g , 1 mmol), and the mixture stirred for 20 minutes. Osmium tetroxide (0.254g 1 mmol) was slowly added upon which the reaction turned brownish-yellow. The reaction was stirred for 24 hours. After disappearance of the reactant (TLC), the reaction was quenched with 2 g of sodium bisulfate followed by extraction with EtOAc:water (2 x 10 mL:10 mL). The organic layers were combined, dried over sodium sulfate, filtered and evaporated. The residue was chromatographed over silica with hexanes:EtOAc (5:1). The organic fractions were evaporated to provide 0.41g (70 %) of (-) **11** as a fluffy, white solid**:** mp 110-113 °C; TLC R_f 0.25 in hexanes:EtOAc (5:1) ; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.46 (d, 1H, *J* = 8.4 Hz, Ar-H5), 7.46-7.28 (m, 10+1H, 2 x C_6H_5+Ar-H6'), 6.58-6.56 (m, 2H, Ar-H8/Ar-H5'), 6.48 (q, 1H, *J* = 8.4 Hz, *J* = 1.8 Hz, Ar-H6), 6.37 (d, 1H, *J* = 2.8 Hz, Ar-H3'), 5.51 (d, 1H, *J* = 7.2, H4), 5.19 (s, 2H, $PhCH_2$), 5.06 (s, 2H, $PhCH_2$), 4.72 (d, 1H, *J* = 11.4 Hz, H-2 eq), 4.23 (d, 1H, *J* = 7.24, 4-OH), 4.19 (s, 1H, 3-OH), 4.02 (d, 1H, *J* = 11.4 Hz, H2 ax), 0.96{s, 9H, Si $(CH_3)_3$}, 0.17{s, 6H, Si $(CH_3)_2$}.

(+) 4'-t-Butyl dimethylsilyloxy-2',7(dibenzyloxy)isoflavan-3,4-diol (+) (11)
To a solution of 2',7-dibenzyloxy-4'-t-butyldimethylsilyl-isoflav-3-ene (0.532 g, 1 mmol) in 5 mL of DCM cooled at -78 °C was added chiral catalyst $(DHQ)_2$PHAL i.e. hydroquinine-1,4-phthalazinediyl diether (0.78 g, 1 mmol) and the mixture stirred for 20 minutes. Osmium tetroxide (0.254 g, 1 mmol) was added upon which the reaction turned brownish-yellow. The reaction was stirred for 24 hours. After disappearance of the reactant (TLC), the reaction was quenched with 2 g of sodium bisulfate followed by extraction with EtOAc:water (2 x 10 mL:10 mL). The organic layers were combined, dried over sodium sulfate, filtered and evaporated. The residue was chromatographed over silica with hexanes:EtOAc (5:1). The organic fractions were evaporated to provide 0.385 g (66 %) of (+) **11** as a fluffy, white solid**:** mp 110-112 °C; TLC R_f 0.25 in hexanes:EtOAc (5:1); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.46 (d, 1H, *J* = 8.4 Hz, Ar-H5), 7.46-7.28 (m, 10+1H, 2 x C_6H_5+Ar-H6'), 6.58-6.56 (m, 2H, Ar-H8/Ar-H5'), 6.48 (q, 1H, *J* = 8.4 Hz, *J* = 1.8 Hz, Ar-H6), 6.37 (d, 1H, *J* = 2.8 Hz, Ar-H3'), 5.51 (d, 1H, *J* = 7.2, H4), 5.19 (s, 2H, $PhCH_2$), 5.06 (s, 2H, $PhCH_2$), 4.72 (d, 1H, *J* = 11.4 Hz, H-2 eq), 4.23 (d, 1H, *J* = 7.24, 4-OH), 4.19 (s, 1H, 3-OH), 4.02 (d, 1H, *J* = 11.4 Hz, H2 ax), 0.96{s, 9H, Si $(CH_3)_3$}, 0.17{s, 6H, Si $(CH_3)_2$}.

General Procedure for Debenzylation

To a solution of 4'-t-butyldimethylsilyloxy-2',7-dibenzyloxyisoflavan-3,4-diol (0.584 g, 1 mmol) in 6 mL of acetone was added 10 % Pd-C (0.1 g) in 4 mL of cold acetone. This reaction mixture was hydrogenated at room temperature under 1 atm (15 psi) of H_2 pressure for ca. 4 hours. After the disappearance of starting material (TLC), the catalyst was filtered through a pad of celite. The celite-pad was washed with 10 x 2 mL of methanol. The solution was filtered once more through filter paper and evaporated to obtain the solids specified below.

(±) 4'-t-Butyldimethylsilyloxy-2',7-dihydroxyisoflavan-3,4-diol (±) (12)
white solid with red tinge: 0.360 g (89 %); mp decomposes at 142 °C; TLC R_f 0.23 in hexanes: EtOAc (2:1); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.20 (d, 1H, J = 8.4 Hz, Ar-H5), 7.17 (d, 1H, J = 8.4 Hz, Ar-H6'), 6.42 (dd, 1H, ^2J = 8.4 Hz, ^3J = 2.4 Hz, Ar-H6), 6.34 (d, 1H, J = 2.4 Hz, Ar-H8), 6.28 (dd, 1H, ^2J = 8.4 Hz, ^3J = 2.4 Hz, Ar-H5'), 6.26 (d, 1H, J = 2.4 Hz), 5.09 (s, 1H, H4), 4.35 (d, 1H, J = 11.4 Hz, H2 eq), 4.13 (d, 1H, J = 11.4 Hz, 4-OH), 4.19 (s, 1H, 3-OH), 4.02 (d, 1H, J = 11.4 Hz, H2 ax), 0.96{s, 9H, Si $(CH_3)_3$}, 0.18{s, 6H, Si $(CH_3)_2$},^{13}C NMR (100 MHz, acetone-d_6) δ 159.5, 150.8, 157.7, 155.9, 132.0, 129.0, 120.5, 116.7, 112.3, 110, 109.7, 103.4, 73.9, 70.1, 69.1, 26.5, 19.2; analysis calcd. for $C_{21}H_{28}O_6Si$. C 62.35, H 6.98; found: C 62.38, H 7.01.

(-) 4'-t-Butyldimethylsilyloxy-2',7-dihydroxyisoflavan-3,4-diol (-) (12)
White solid with red tinge: 0.34 g (84 %); mp decomposes at 144 °C; TLC R_f 0.23 in hexanes: EtOAc (2:1); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.20 (d, 1H, J = 8.4 Hz, Ar-H5), 7.17 (d, 1H, J = 8.4 Hz, Ar-H6'), 6.42 (dd, 1H, ^2J = 8.4 Hz, ^3J = 2.4 Hz, Ar-H6), 6.34 (d, 1H, J = 2.4 Hz, Ar-H8), 6.28 (dd, 1H, ^2J = 8.4 Hz, ^3J = 2.4 Hz, Ar-H5'), 6.26 (d, 1H, J = 2.4 Hz), 5.09 (s, 1H, H4), 4.35 (d, 1H, J = 11.4 Hz, H2 eq), 4.13 (d, 1H, J = 11.4 Hz, 4-OH), 4.19 (s, 1H, 3-OH), 4.02 (d, 1H, J = 11.4 Hz, H2 ax), 0.96{s, 9H, Si $(CH_3)_3$}, 0.18{s, 6H, Si $(CH_3)_2$}.

(+) 4'-t-Butyldimethylsilyloxy-2',7-dihydroxyisoflavan-3,4-diol (+) (12)
White solid with red tinge: 0.364 g (90 %); mp decomposes at 142 °C; TLC R_f 0.23 in hexanes: EtOAc (2:1); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.20 (d, 1H, J = 8.4 Hz, Ar-H5), 7.17 (d, 1H, J = 8.4 Hz, Ar-H6'), 6.42 (dd, 1H, ^2J = 8.4 Hz, ^3J = 2.4 Hz, Ar-H6), 6.34 (d, 1H, J = 2.4 Hz, Ar-H8), 6.28 (dd, 1H, ^2J = 8.4 Hz, ^3J = 2.4 Hz, Ar-H5'), 6.26 (d, 1H, J = 2.4 Hz), 5.09 (s, 1H, H4), 4.35 (d, 1H, J = 11.4 Hz, H2 eq), 4.13 (d, 1H, J = 11.4 Hz, 4-OH), 4.19 (s, 1H, 3-OH), 4.02 (d, 1H, J = 11.4 Hz, H2 ax), 0.96{s, 9H, Si $(CH_3)_3$}, 0.18{s, 6H, Si $(CH_3)_2$}.

General Procedure for Southern Benzofuran Ring Cyclization

To a solution of 4'-t-butyldimethylsilyloxy-2',7-dihydroxyisoflavan-3,4-diol (0.041 g, 0.1 mmol) in 20 mL of anhydrous ethanol was added (4 mg, 0.01 mmol) 1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine, polymer-bound and 4 Å molecular sieves (0.1 g). The reaction mixture was refluxed at 80 °C for 6 hours with continuous distillation of

the ethanol-water azeotrope. After disappearance of reactant (TLC), the molecular sieves and polymeric base were filtered. The filtrate was dried over sodium sulfate, filtered and solvent evaporated at 20 ^{o}C. The residue was chromatographed over silica using hexanes:EtOAc (4:1). The organic fractions were evaporated at 20 ^{o}C to provide the solids specified below.

(±) 9-(-t-Butyl dimethyl silyloxy)-glycinol (±) (13)
Pinkish-white solid: 0.023 g (60 %)**;** mp 197-199 ^{o}C; TLC R_f 0.38 in hexanes:EtOAc (2:1); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.55 (s.1H, -OH), 7.30 (d, 1H, *J* = 8.4 Hz, Ar-H1), 7.24 (d, 1H, *J* = 8.4, Ar-H7), 6.55 (dd, 1H, ^{2}J = 8.4 Hz, ^{3}J = 2.4 Hz, Ar-H-2), 6.45 (dd, 1H, ^{2}J = 8.4 Hz, ^{3}J = 2.4 Hz, Ar-H8), 6.3 (d, 1H, *J* = 2.4 Hz, ArH-4), 6.26 (d, 1H, *J* = 2.4 Hz, Ar H-10), 5.26 (s, 1H, 11a-H), 5.01 (s, 1H, 6a-OH), 4.14 (d, 1H, *J* = 12 Hz, H6 eq), 4.02 (d, 1H, *J* = 12 Hz, H6 ax), 0.96{s, 9H, Si $(CH_3)_3$}, 0.19{s, 6H, Si $(CH_3)_2$}; ^{13}C NMR (100 MHz, acetone-d_6) δ 162.4, 160.3, 159.3, 157.7, 133.8, 125.6, 124.3, 114.1, 113.8, 111.4, 104.5, 103.9, 86.6, 77.4, 71.3, 26.6, 19.3; analysis calcd. for $C_{21}H_{26}O_5Si$. C 65.26, H 6.78 found: C 65.10, H 6.67.

(-) 9-(-t-Butyl dimethyl silyloxy)-glycinol (-) (13)
Pinkish-white solid: 0.025 g (64 %)**;** mp 198-200 ^{o}C; TLC R_f 0.38 in hexanes:EtOAc (2:1); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.55 (s.1H, -OH), 7.30 (d, 1H, *J* = 8.4 Hz, Ar-H1), 7.25 (d, 1H, *J* = 8.4, Ar-H7), 6.55 (dd, 1H, ^{2}J = 8.4 Hz, ^{3}J = 2.4 Hz, Ar-H-2), 6.45 (dd, 1H, ^{2}J = 8.4 Hz, ^{3}J = 2.4 Hz, Ar-H8), 6.3 (d, 1H, *J* = 2.4 Hz, ArH-4), 6.26 (d, 1H, *J* = 2.4 Hz, Ar H-10), 5.26 (s, 1H, 11a-H), 5.01 (s, 1H, 6a-OH), 4.14 (d, 1H, *J* = 12 Hz, H6 eq), 4.02 (d, 1H, *J* = 12 Hz, H6 ax), 0.96{s, 9H, Si $(CH_3)_3$}, 0.19{s, 6H, Si $(CH_3)_2$}.

(+) 9-(-t-Butyl dimethyl silyloxy)-glycinol (+) (13)
Pinkish-white solid: 0.023 g (60 %)**;** mp 198-201 ^{o}C; TLC R_f 0.38 in hexanes:EtOAc (2:1); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.55 (s.1H, -OH), 7.30 (d, 1H, *J* = 8.4 Hz, Ar-H1), 7.25 (d, 1H, *J* = 8.4, Ar-H7), 6.55 (dd, 1H, ^{2}J = 8.4 Hz, ^{3}J = 2.4 Hz, Ar-H-2), 6.45 (dd, 1H, ^{2}J = 8.4 Hz, ^{3}J = 2.4 Hz, Ar-H8), 6.3 (d, 1H, *J* = 2.4 Hz, ArH-4), 6.26 (d, 1H, *J* = 2.4 Hz, Ar H-10), 5.26 (s, 1H, 11a-H), 5.01 (s, 1H, 6a-OH), 4.14 (d, 1H, *J* = 12 Hz, H6 eq), 4.02 (d, 1H, *J* = 12 Hz, H6 ax), 0.96{s, 9H, Si $(CH_3)_3$}, 0.19{s, 6H, Si $(CH_3)_2$}.

General Procedure for Northern Chromene Ring Cyclization

To a solution of 9-(t-butyldimethylsilyloxy)glycinol (0.040 g, 0.1 mmol) in 5 mL of xylene was added 1,1-diethoxy-3-methyl-2-butene (0.2 mmol in 0.2 mL of xylene) and 3-picoline (0.025 mmol in 0.3 mL xylene). The reaction mixture was refluxed at 130 ^{o}C for 18 hours. After disappearance of reactant (TLC), the solvent was evaporated and the residue was chromatographed over silica using DCM as eluant. The organic fractions were evaporated to provide two yellowish oils: a major fraction that elutes first and represents desired isomer; and a second fraction that contains minor amounts of the isomer corresponding to protected glyceollin II.

(±) 9-(t-Butyldimethylsilyloxy) glyceollin I (±) (14a)
Major yellow oil: 0.022 g (50 %)**;** TLC R_f 0.46 in toluene:methanol (10:1); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.27 (d, 1H, *J* = 8.4 Hz, Ar-H1), 7.24 (d, 1H, *J* = 8.4 Hz, Ar-H7), 6.57 (d, 1H, *J* = 9.6 Hz, H12), 6.48-6.45 (m, 2H, Ar-H7/Ar-H8), 6.3 (d, 1H, Ar-10H), 5.65 (d, 1H, *J* = 10.2 Hz, H13), 5.27 (s, 1H, 11a-H), 5.09 (s, 1H, 6a-OH), 4.20 (d, 1H, *J* = 11.4 Hz, H6 eq), 4.08 (d, 1H, *J* = 11.4 Hz, H6 ax), 1.38,1.35 (2 s, 2 x 3H, H15/H16), 0.96{s, 9H, Si $(CH_3)_3$}, 0.19{s, 6H, Si $(CH_3)_2$}; ^{13}C NMR (100 MHz, acetone-d_6) δ 162.3, 159.3, 155.4, 152.2, 132.7, 130.7, 125.6, 124, 117.6, 114.7, 114.1, 111.7, 111.2, 103.9, 86.5, 77.3, 77.2, 71.5, 28.6, 26.6, 19.3; HRMS Calc. (M^+ +Na) 475.1917, found 475.1923

A 10 % yield of the racemic form of TBDMS-GLY II (**14b**) was obtained, after silica gel chromatography.

(-) 9-(t-Butyldimethylsilyloxy) glyceollin I (-) (14a)
Major yellow oil: 0.027 g (61 %)**;** TLC R_f 0.46 in toluene:methanol (10:1); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.27 (d, 1H, *J* = 8.4 Hz, Ar-H1), 7.24 (d, 1H, *J* = 8.4 Hz, Ar-H7), 6.57 (d, 1H, *J* = 9.6 Hz, H12), 6.48-6.45 (m, 2H, Ar-H7/Ar-H8), 6.3 (d, 1H, Ar-10H), 5.65 (d, 1H, *J* = 10.2 Hz, H13), 5.27 (s, 1H, 11a-H), 5.09 (s, 1H, 6a-OH), 4.20 (d, 1H, *J* = 11.4 Hz, H6 eq), 4.08 (d, 1H, *J* = 11.4 Hz, H6 ax), 1.38-1.35 (2x s, 2x3H, H15/H16), 0.96{s, 9H, Si $(CH_3)_3$}, 0.19{s, 6H, Si $(CH_3)_2$}.

The other material obtained during this reaction, (-) 9-(t-butyldimethylsilyloxy)glyceollin II (14b), eluted as an inseparable mixture with additional side-products. No attempts were made to further isolate this isomer.

(+) 9-(t-Butyldimethylsilyloxy) glyceollin I (+) (14a)
Major yellow oil: 0.025 g (57 %)**;** TLC R_f 0.46 in toluene:methanol (10:1); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.27 (d, 1H, *J* = 8.4 Hz, Ar-H1), 7.24 (d, 1H, *J* = 8.4 Hz, Ar-H7), 6.57 (d, 1H, *J* = 9.6 Hz, H12), 6.48-6.45 (m, 2H, Ar-H7/Ar-H8), 6.3 (d, 1H, Ar-10H), 5.65 (d, 1H, *J* = 10.2 Hz, H13), 5.27 (s, 1H, 11a-H), 5.09 (s, 1H, 6a-OH), 4.20 (d, 1H, *J* = 11.4 Hz, H6 eq), 4.08 (d, 1H, *J* = 11.4 Hz, H6 ax), 1.38-1.35 (2x s, 2x3H, H15/H16), 0.96{s, 9H, Si $(CH_3)_3$}, 0.19{s, 6H, Si $(CH_3)_2$}.

The other material obtained during this reaction, (+)9-(t-butyldimethylsilyloxy)glyceollin II (14b), eluted as an inseparable mixture with additional side-products. No attempts were made to further isolate this isomer.

General Procedure for Deprotection of the TBDMS Group
9-(t-Butyldimethylsilyloxy)-glyceollin I (0.043 g, 0.1 mmol) was dissolved in 1 mL of acetonitrile and the solution was cooled to -20 ^{o}C. $N(Et)_3 \cdot 3HF$ in acetonitrile (1.2 mL, 0.12 mmol) was added and the mixture stirred for 8 hours at 4 ^{o}C. After disappearance of reactant (TLC), the pH was adjusted to 7-8 by addition of triethylamine and the mixture filtered through a silica column using DCM:MeOH (10:1). Evaporation of the solvent at 20 ^{o}C provided a brownish oily residue which was chromatographed over silica using hexanes:DCM:MeOH (10:10:1). The organic fractions were evaporated at 20 ^{o}C to provide the solids specified below.

(±) Glyceollin I (15)
White solid with red tinge: 0.023 g (69 %); TLC R_f 0.22 in hexanes:DCM:methanol (10:10:1); ^{1}H NMR (400 MHz, methanol-*d*$_4$) δ 7.20 (d, 1H, *J* = 8.4 Hz, Ar-H1), 7.07 (d, 1H, *J* = 8.4 Hz, Ar-H7), 6.59 (d, 1H, *J* = 10.2 Hz, H12), 6.46 (d, 1H, *J* = 8.4 Hz, Ar-H2), 6.39 (dd, 1H, ^2J = 8.4 Hz, ^3J = 2.4 Hz, Ar-H8), 6.22 (d, 1H, *J* = 2.4 Hz, Ar-H10), 5.61 (d, 1H, *J* = 10.2 Hz, H13), 5.16 (s, 1H, 11a-H), 4.90 (s, 1H, 6a-OH), 4.16 (d, 1H, *J* = 11.4 Hz, H6 eq), 3.93 (d, 1H, *J* = 11.4 Hz, H6 ax), 1.38,1.37 (2 s, 2 x 3H, H15/H16); ^{13}C NMR (100 MHz, Methanol *d*$_4$) δ 162.3, 161.3, 155.4, 151.9, 132.4, 130.5, 125.3, 121.3, 117.7, 114.3, 111.7, 111.4, 109.5, 99.1, 86.1, 77.3, 77.2, 71.3, 28.2; HRMS Calc. (M^+ +Na) 361.1052, found: 361.1052.

Glyceollin I (15)
White solid with red tinge: 0.026 g (77 %); TLC R_f 0.22 in hexanes:DCM:methanol (10:10:1); Chiral HPLC showed an essentially one peak chromatogram ; ^{1}H NMR (400 MHz, methanol-*d*$_4$) δ 7.20 (d, 1H, *J* = 8.4 Hz, Ar-H1), 7.07 (d, 1H, *J* = 8.4 Hz, Ar-H7), 6.50 (d, 1H, *J* = 10.2 Hz, H12), 6.37 (d.1H, *J* = 8.4 Hz, Ar-H7), 6.30 (dd, 1H, ^2J = 8.4 Hz, ^3J = 2.4 Hz, Ar-H8), 6.13 (d, 1H, *J* = 2.4 Hz, Ar-H7), 5.52 (d, 1H, *J* = 10.2 Hz, H13), 5.06 (s, 1H, 11a-H), 4.81 (s, 1H, 6a-OH), 4.07 (d, 1H, *J* = 11.4 Hz, H6 eq), 3.93 (d, 1H, *J* = 11.4 Hz, H 6ax), 1.38-1.35 (2 s, 2x3H, H15/H16); HRMS Calc. [M^+ +Na] 361.1052, found: 361.1059; analysis calcd. for $C_{20}H_{18}O_5$.·0.5 H_2O, C 69.16, H 5.51 found: C 68.97, H 5.58

(+) Glyceollin I (15)
White solid with yellow tinge: 0.025 g (75 %); TLC R_f 0.22 in hexanes:DCM:methanol (10:10:1); Chiral HPLC showed an essentially one peak chromatogram ; ^{1}H NMR (400 MHz, methanol-*d*$_4$) δ 7.21-7.19 (d, 1H, *J* = 8.4 Hz, Ar-H1), 7.07 (d, 1H, *J* = 8.4 Hz, Ar-H7), 6.51-6.49 (d, 1H, *J* = 10.2 Hz, H12), 6.38-6.36 (d.1H, *J* = 8.4 Hz, Ar-H7), 6.31-6.29 (dd, 1H, ^2J = 8.4 Hz, ^3J = 2.4 Hz, Ar-H8), 6.13 (d, 1H, *J* = 2.4 Hz, Ar-H7), 5.53-5.51 (d, 1H, *J* = 10.2 Hz, H13), 5.06 (s, 1H, 11a-H), 4.81 (s, 1H, 6a-OH), 4.08-4.06 (d, 1H, *J* = 11.4 Hz, H6 eq), 3.94-3.92 (d, 1H, *J* = 11.4 Hz, H6 ax), 1.38-1.35 (2 s, 2 x 3H, H15/H16); HRMS Calc. [M^+ +Na] 361.1052, found: 361.1059.

(ii) Discussion of NMR and CD studies including selected spectra

Natural Stereochemistry of the 6a-hydroxy group

There are two asymmetric centers in glyceollin, namely at positions 6a and 11a. It has been shown by computational studies that the *cis* ring junction is energetically favored over the *trans.*[1] The majority of the known natural pterocarpans have a *cis* ring junction and are levorotatory.[2] Ferreira et al., has synthesized a *trans* pterocarpan.[3] They observed that the C-11a proton is axially oriented in the *trans* isomer and this results in its conspicuous shielding (δ = 1 ppm) as compared to the *cis* isomer. In the glyceollin NMR spectra, such shielding was absent indicating that there is a *cis* ring junction. The diagnostic protons at the C-6 position appear as two separate doublets with the C-6 equatorial proton appearing downfield compared to the C-6 axial proton. The *cis* ring junction for the glyceollins is also confirmed by the W coupling between the C-11a proton and the lower field C-6 equatorial proton.

The negative optical rotation of the glyceollins also suggests an S,S configuration at the 6a,11a ring junction by analogy to all of the other natural Pterocarpans.[4] Circular Dichroism (CD) and Optical Rotatory Dispersion (ORD) studies also corroborate the absolute configuration at these stereocenters. The ORD curves of the glyceollins show a large negative trough in the region of 240 nm which is consistent with other pterocarpans having the same absolute configuration at the 6a-11a ring junction.[4] The CD features of the pterocarpans have been used historically for determining their absolute configuration. The CD of pterocarpans is characterized by two bands, namely a high energy/low wavelength (220-240 nm) ^1L_a and a low energy/high wavelength (260-310 nm) ^1L_b band, contributed by the chroman ring and benzofuran ring chromophores. According to Antus et al.[5] and Slade et al.,[2] the negative Cotton effect in the 220-240 nm range and positive Cotton effect in the 260-310 nm range confirms the (6aS,11aS) configuration at the junction of the chroman and benzofuran rings within the *cis* 6a-hydroxy pterocarpans. These assignments are further shown in Table 1. Table 2 provides actual data for several of the natural pterocarpans. The optical rotation of the 6a-hydroxypterocarpans is solely determined by the absolute configurations at the 6a and 11a ring carbons. Thus, in the 6a-hydroxypterocarpan family, all the levorotatory compounds can be associated with a (6aS,11aS)-*cis* configuration and all the dextrorotatory compounds with a (6aR,11aR)-*cis* configuration.

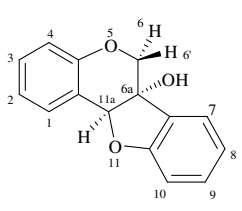
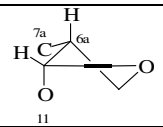
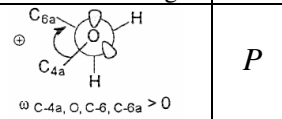
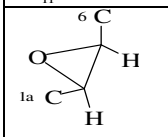
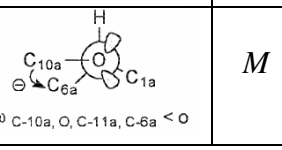
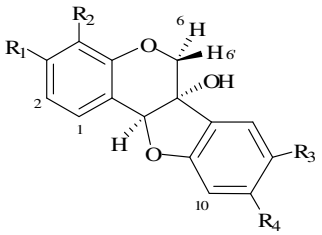
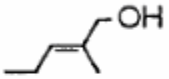
Compound	Standard projection	Newman projection and torsional angle	Helicity	Sign of ^1L_b band CD	Sign of ^1L_a band CD
			*P*	Positive	Negative
			*M*	Negative	Negative

Table1. Circular dichroism: helicity and Cotton effects of pterocarpans.[5]

Table2. CD data for natural pterocarpans. Adapted from Antus et al.[5a]



R^1	R^2	R^3	R^4	^1L_b band CD	^1L_a band CD
H	H	H	H	287 (+4.8) 269 (-1.1)	229 (-5.9)
OH		–OCH$_2$O–		302 (+3.1) 293 (+2.3)	238 (-9.8)
OMe	H	H	OMe	287 (+5.4)	236 (-11.9)
OH	H	H	OMe	287 (+5.3)	236 (-13.2)
OMe	H	H	OH	287 (+9.8)	236 (-23.1)
OH	H	–OCH$_2$O–		310 (+0.8) 290 (+0.9)	237 (-2.9)

New chiral shift reagent NMR studies for diols

We also deployed lanthanide shift reagents to establish the optical purity of the diols. We observed no doubling of the peaks in the NMR spectra for the enantiopure diols, in contrast to the NMR spectrum of the racemate. The racemate diol forms diastereomeric complexes with europium chiral shift reagents, namely europium(III) tris[3-(heptafluoropropylhydroxymethylene)-*l*-camphorate], which can be clearly observed as separate NMR resonances. Thus, NMR spectra of each stereoisomer indicated the presence of only one enantiomer. Successful asymmetric dihydroxylation was achieved using dihydroqunidine (DHQD) ligand for synthesis of levorotatory (-) diol and dihydroquinine (DHQ) ligand for synthesis of dextrorotatory (+) diol. The effect of chiral shift reagents was not observed on the C-3 and C-4 hydroxy NMR shifts due to a broadening effect. However, their effect was conspicuously seen on the NMR shifts of the C-4 proton and the C-8 aromatic proton, suggesting the proximity of europium agent to both of these protons. The complex of (-) diol and (+) chiral shift reagent europium(III) tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorate] is an enantiomer to the complex of (+) diol and (-) chiral shift reagent europium(III) tris[3-(heptafluoropropylhydroxymethylene)-*l*-camphorate], and this pair appropriately provides identical NMR spectra. However, the complex of (-) diol and (+) chiral shift reagent europium(III) tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorate] is in a diastereomeric relation with the complex of (+) diol and (+) chiral shift reagent europium(III) tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorate], and this pair thus provides different NMR spectra. These observations support the opposite stereochemistry of the diols for each enantiomer. This situation is depicted in Figures 1 and 2. The most relevant NMR shift data is summarized below in Table 3

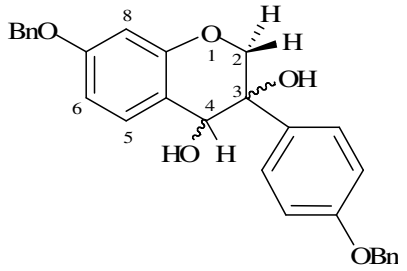
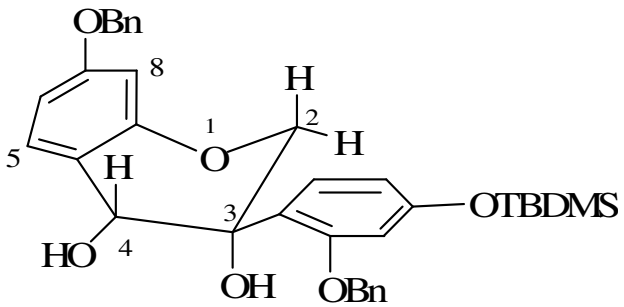


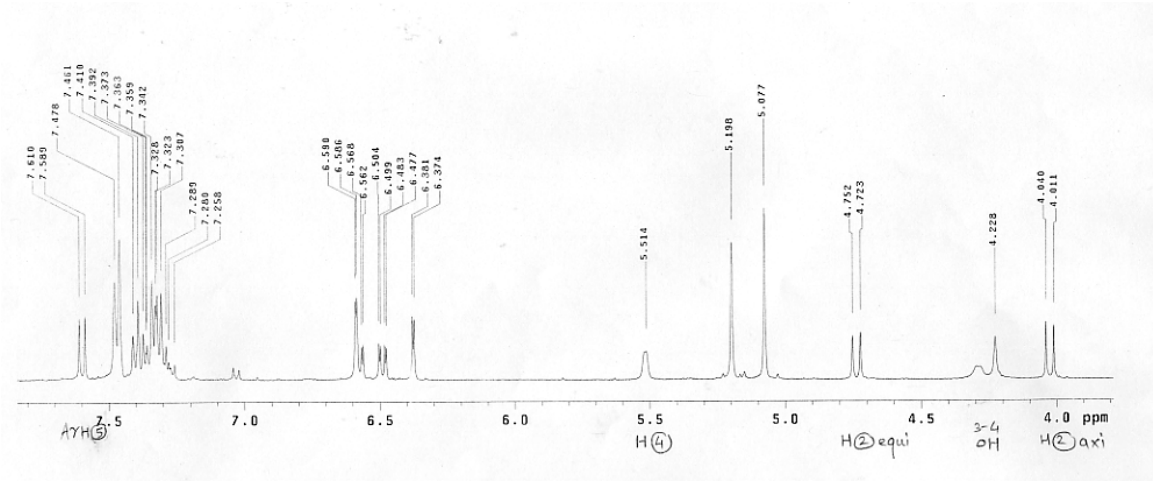
Table 3. NMR shift (PPM) for enantiomeric diols and their diastereomeric complexes with chiral shift reagent (CSR). The molar ratio of diol:CSR is 5:1.

Compound	Ar-H 8	H 4	H 2 equatorial	H 2 axial
(-) Diol	6.59	5.51	4.74	4.03
(-) Diol (+) CSR	6.61	5.75	4.88	4.25
(-) Diol (-) CSR	6.62	5.94	5.0	4.45
(+) Diol	6.59	5.52	4.74	4.03
(+) Diol (-) CSR	6.61	5.78	4.90	4.28
(+) Diol (+) CSR	6.62	5.91	4.85	4.41



(-) Diol (3*S* 4*R*)

NMR spectrum before addition of chiral shift reagent:



NMR spectrum after addition of (+) chiral shift reagent:

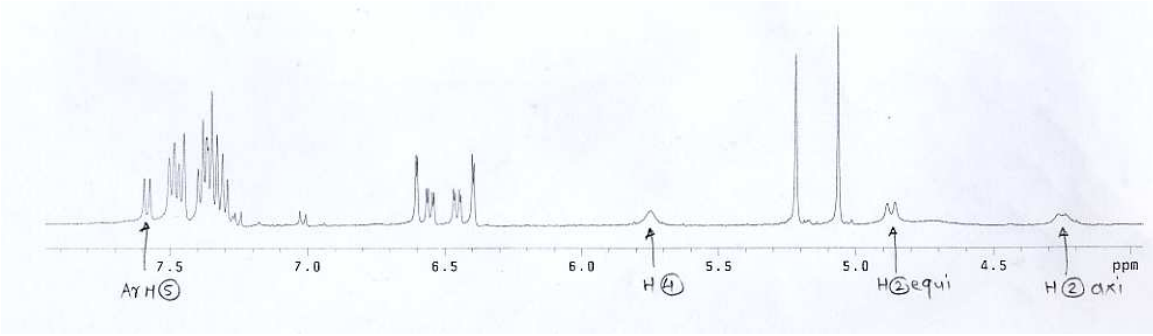
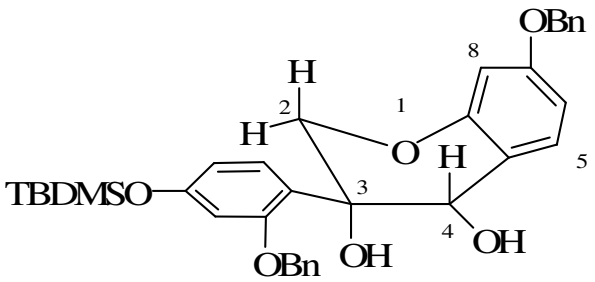
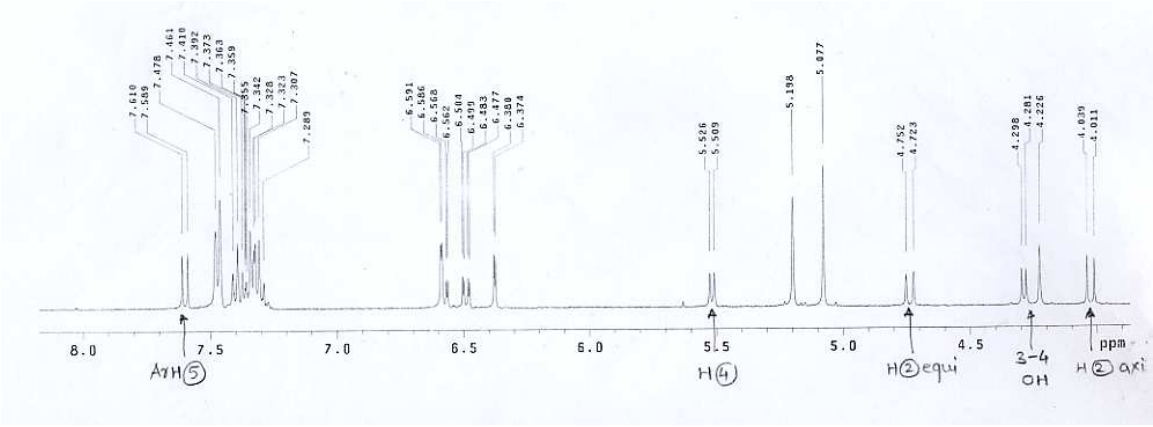


Figure 1. Chiral Shift Reagent NMR studies for (-) Diol.



(+) Diol (3*R* 4*S*)

NMR spectrum before addition of chiral shift reagent:



NMR spectrum after addition of (+) chiral shift reagent:

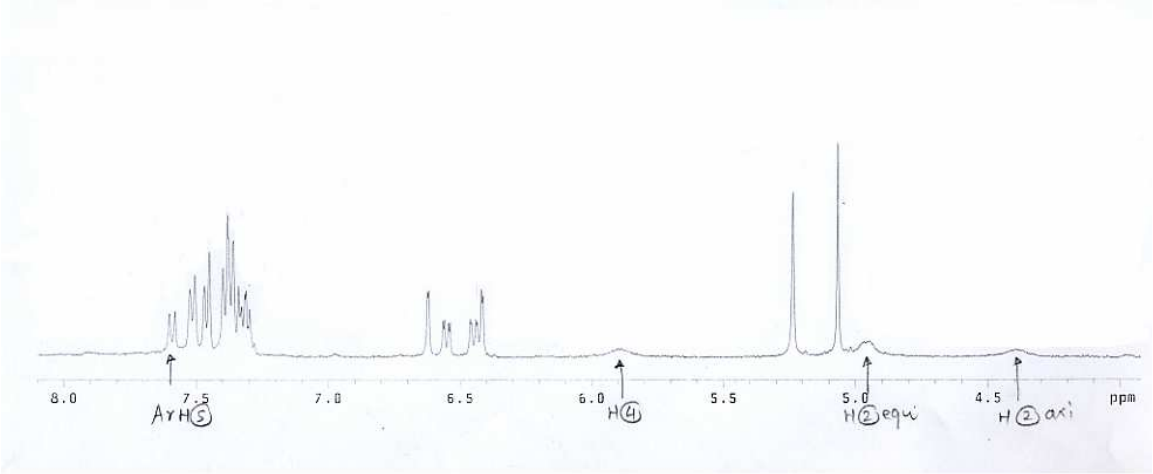


Figure 2. Chiral Shift Reagent NMR studies for (+) Diol.

CD studies of Diols

The absolute stereochemical assignments for the diols were made by relying upon well established CD studies. T.G van Aardt et al. describe the diol intermediate for the synthesis of the variabilins in which the CD spectra of the levorotatory isomer shows a negative Cotton effect in the region of 220-250 nm, and then it shows a positive Cotton effect in the region of 270-290 nm.[3] Similar types of Cotton effects were observed by Mori and Kisida for the diol intermediates synthesized on route to unnatural (-) pisatin.[6] They also used the CD spectra to establish the absolute stereochemistry of the diol intermediate. The CD spectrum of the (-) diol intermediate for the synthesis of (-) pisatin, the CD spectrum of our (-) diol intermediate for the synthesis of the (-) glyceollins, and the CD spectrum of our (+) diol intermediate for the synthesis of the (+) glyceollins, are compared in Figures 3 and 4.

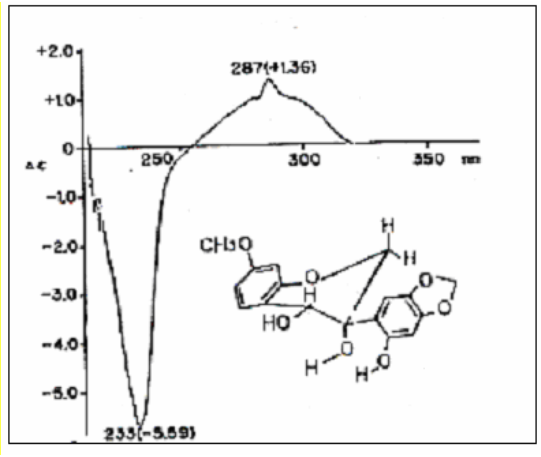


Figure 3. Diol needed for (-) Pisatin. Copied from reference.[6]

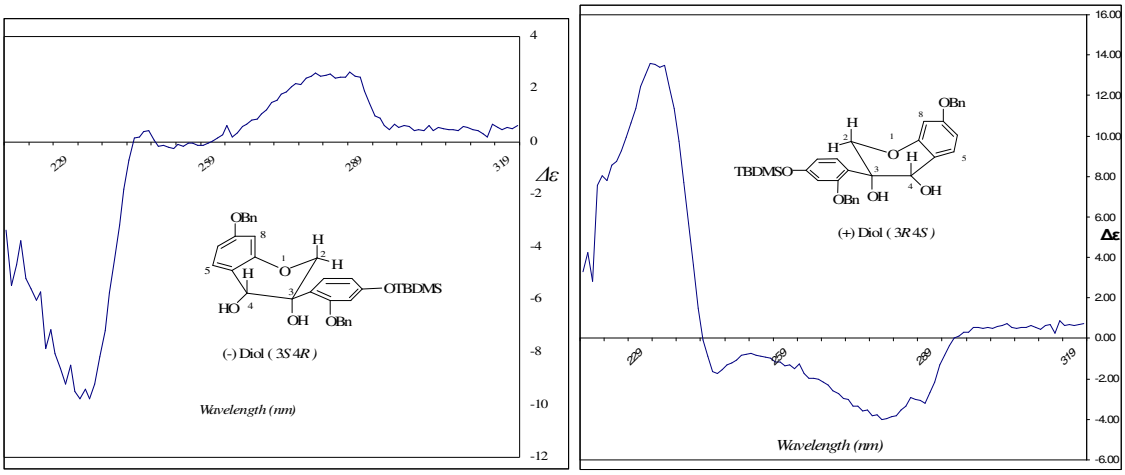


Figure 4. CD spectra of diols prepared herein for (-) glyceollin and (+) glyceollin.

NMR and CD studies of TBDMS protected glycinols

The absolute stereochemistry and *cis* ring junction of the benzofuran and chromene ring systems were confirmed by NMR spectroscopic methods combined with CD analysis. As indicated, T.G. van Aardt et al. previously synthesized the *cis* and *trans* pterocarpan skeletons and characterized the ring junction by using extensive NMR studies.(3) The NMR shift of the C-11a proton is clearly diagnostic for the *cis* versus *trans* isomers. In the *trans* isomer, the C-11a proton is oriented axial relative to both aromatic rings. This relationship causes an up-field shift of about 1 ppm for the C-11a proton in the *trans* isomer compared to the *cis* isomer.(3) The NMR spectra of the synthesized glycinol derivative showed a C-11a proton at about 5.2 ppm which correlates with the shift reported for the *cis* isomer of variabilin by T.G. van Aardt et al., and for the *cis* isomer of pisatin as separately reported by Mori et al.(6) It has been previously established that the natural glyceollins have a *cis* ring junction between rings C and D. The proton NMR spectra of the glyceollins show the C-6 protons as two separate doublets, namely a downfield equatorial *alpha*-proton, and an upfield axial *beta*-proton. The COSY spectra of our glycinol derivative showed the same correlation between the C-11a proton and the downfield equatorial proton, the C-6 due to W coupling (Figure 5). This effect would not be possible in the *trans* isomer.

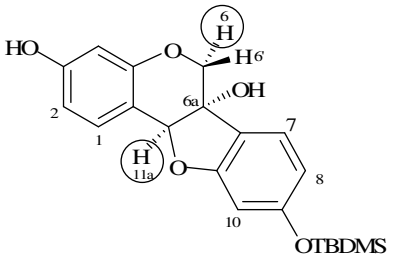


Figure 5. NMR COSY relationship between the equatorial C-6 and C-11a proton.

These assignments were further supported by CD studies. The CD spectra of the *cis* and *trans* isomers of other 6a-hydroxy-pterocarpans have been previously reported. Depending upon the observed Cotton effects, the configuration can be similarly assigned for our closely analogous system. The assignment of absolute configuration for other 6a-hydroxy-pterocarpan structures and the Cotton effects observed in their CD spectra have been summarized by Slade et al.(2) These are shown in Table 4 and Figure 6. The measured CD spectra of our synthesized glycinol derivative match with those for the *cis* fused 6a-hydroxy Pterocarpans. Our results are shown in Figure 7.

Table 4.Correlation of absolute configuration and cotton effects for 6a-hydroxy pterocarpans. Copied from reference.(2)

Cotton Effect (CE) observed for 6a-Hydroxypterocarpans

CE at ^1L_b (ca. 270–300 nm)	CE at ^1L_a (ca. 220–250 nm)	Helicity	$[\alpha]_D$	Absolute configuration
Negative	Positive	*P*	+	(6a*R*,11a*R*)-*cis*
Positive	Negative	*M*	–	(6a*S*,11a*S*)-*cis*
Negative	Negative	*M*	+	(6a*S*,11a*R*)-*trans*
Positive	Positive	*P*	–	(6a*R*,11a*S*)-*trans*

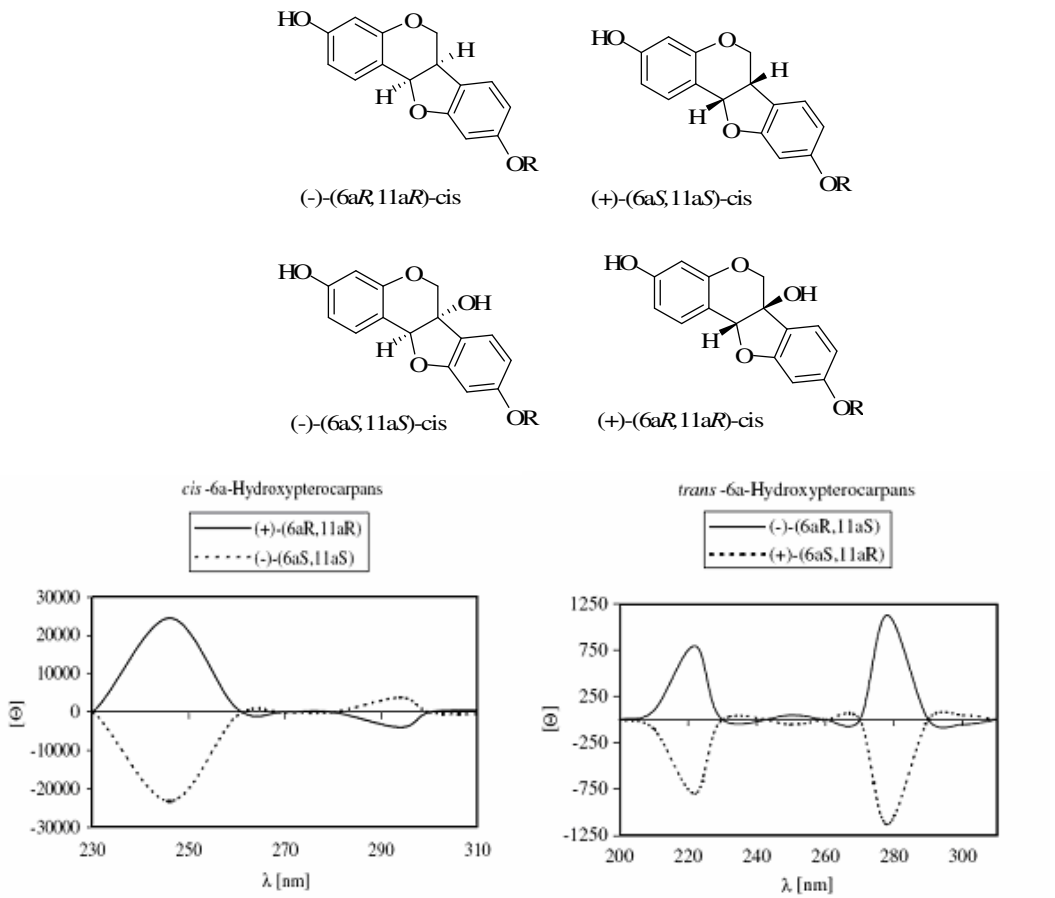
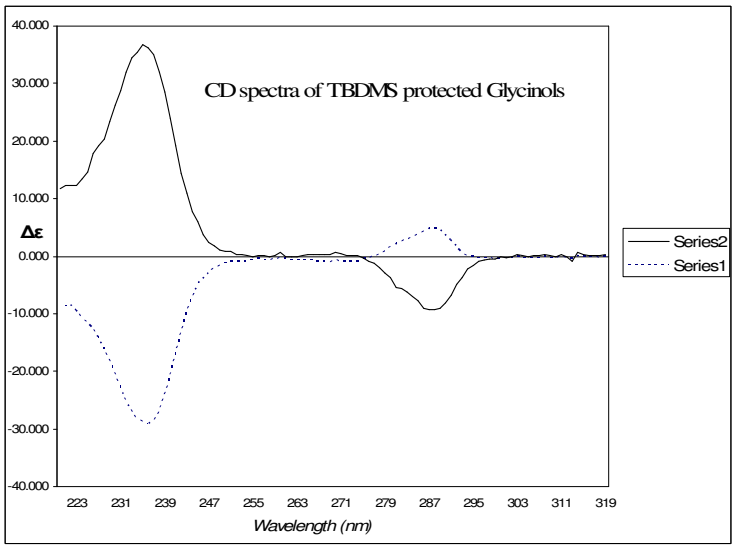


Figure 6. Stereochemistry and absolute configuration of *cis* and *trans* pterocarpans accompanied by their CD spectra. Adapted from reference.[11].



- - - - Series1 (-) (6a-*S*,11a-*S*) Glycinol TBDMS.
____ Series2 (+) (6a-*R*,11a-*R*) Glycinol TBDMS.

Figure 7. Measured CD spectra of glycinol derivatives synthesized herein.

Final Assignment of Structure for the Synthesized Glyceollins

High resolution mass spectral data is in accord with the correct empirical formula $C_{20}H_{18}O_5$. These results are summarized in Table 5.

Table 5. High resolution mass spectral data.

Compound	Theoretical Mass (amu) $[M^+ + Na]$	Observed Mass (amu) $[M^+ + Na]$	Δ PPM
(±) Glyceollin I	361.1052	361.1052	0
(-) Glyceollin I	361.1052	361.1059	+ 1.9
(+) Glyceollin I	361.1052	361.1065	+ 3.6

The CD spectral data is in accord with all of the previous literature, as well as with our prior data for the asymmetric intermediates. The CD spectra for the glyceollin enantiomers are shown in Figure 8.

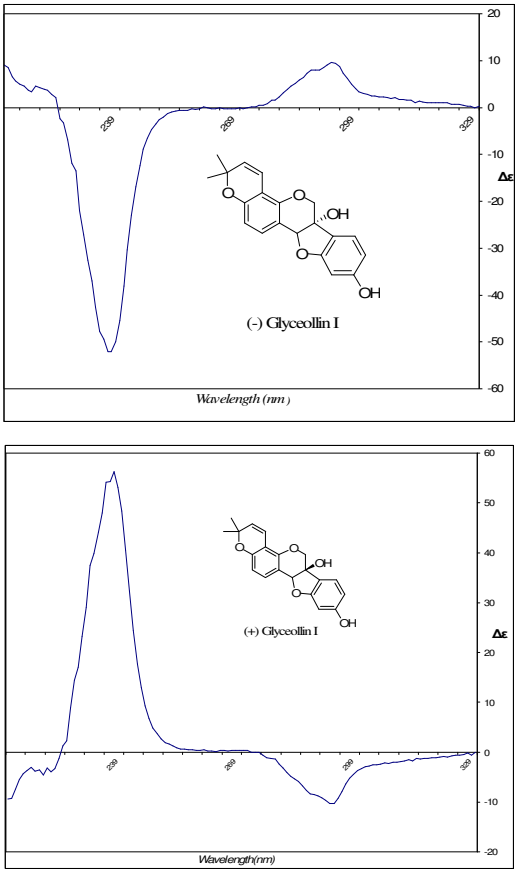


Figure 8. CD spectra of (-)-glyceollin and (+)-glyceollin.

(iii) **Chiral HPLC chromatograms**

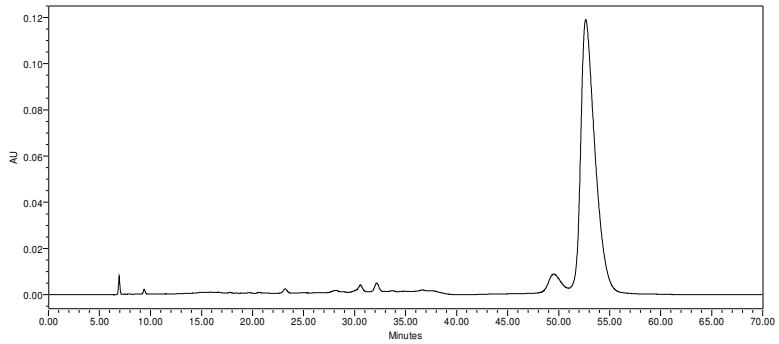
Method: Chiral Cyclobond^{TM} (ASTEC) column; Temperature 35 ^{o}C; Flow rate 0.5 mL/minutes; Gradient solvent system having water:methanol:acetonitrile as shown below.

Time (minutes)	% Water	% CH_3CN	% MeOH
0	60	0	40
30	45	0	55
31	60	1	39
48	60	10	30
49	60	0	40
60	60	0	40

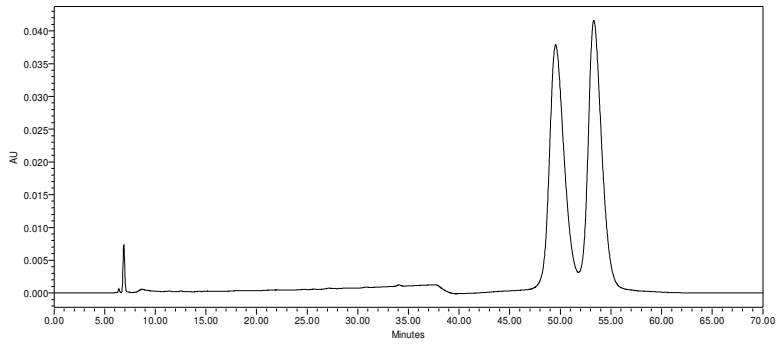
Compound	Retention Time (Minutes)
(±) Synthetic Glyceollin I	Peak one 49.5 Peak two 53.3
(-) Natural Glyceollin I	52.7
(-) Synthetic Glyceollin I	53.2
(+) Synthetic Glyceollin I	49.4

Representative HPLC Chromatograms:

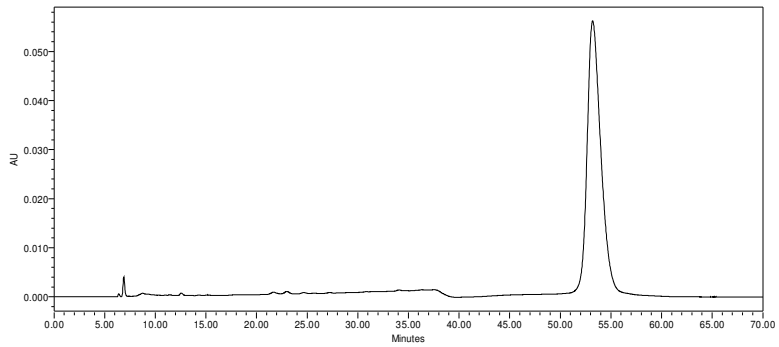
Natural (-) glyceollin I



Synthetic racemic mixture (±) glyceollin



Synthetic (-) glyceollin



Synthetic (+) glyceollin

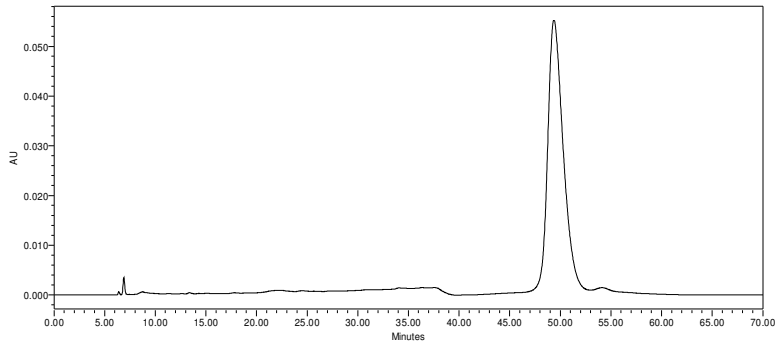
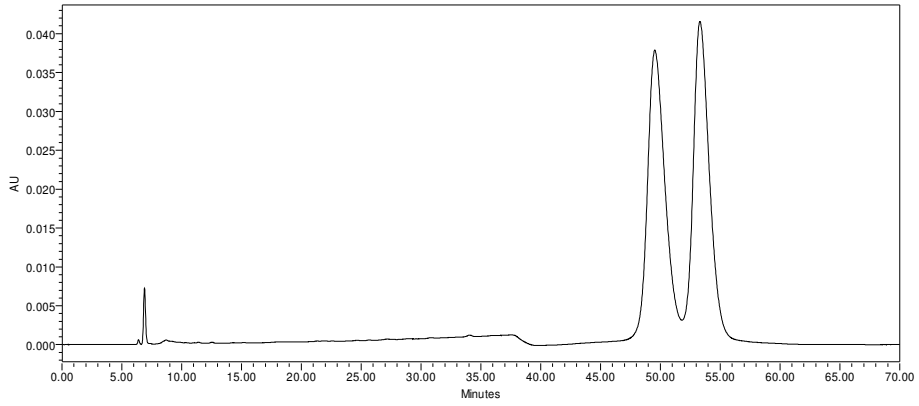
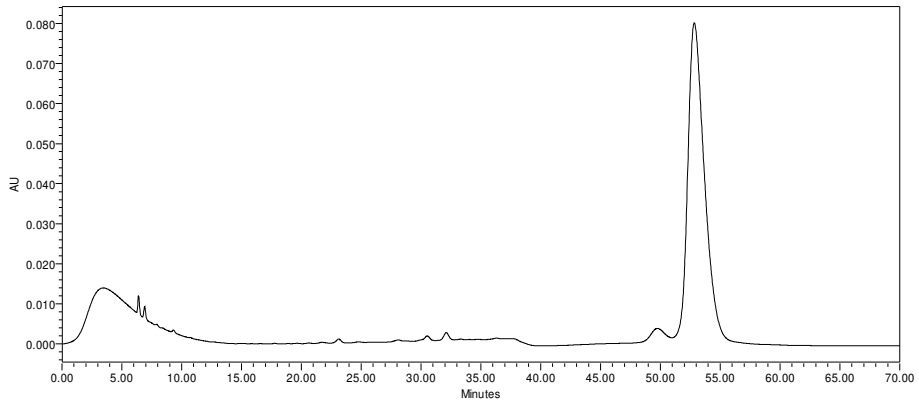


Figure 9. Glyceollin I chiral HPLC fingerprinting. Column: Cyclobond™ (astec). Gradient solvent system utilizing water:methanol:acetonitrile (see preceding table).

Synthetic racemic mixture (±) glyceollin



Synthetic (-) glyceollin spiked with natural (-) glyceollin



Synthetic (+) glyceollin spiked with natural (-) glyceollin

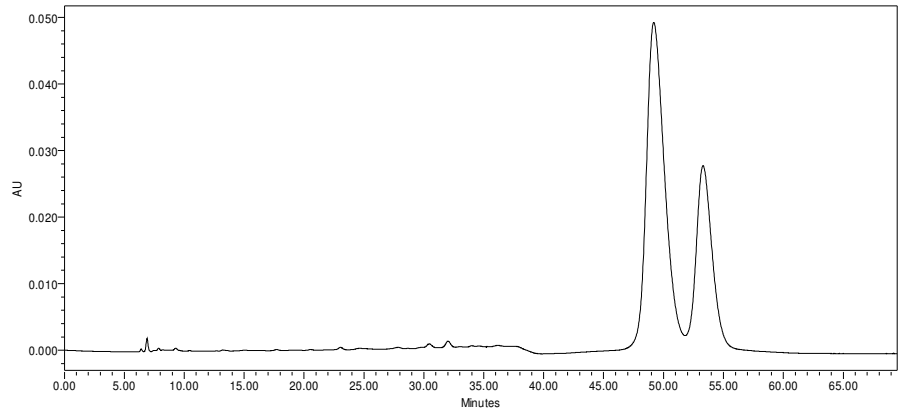


Figure 10. Chiral HPLC spiking studies. Column: Cyclobond^{TM} (astec).
Gradient solvent system utilizing water:methanol:acetonitrile (see preceding table).

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