Syntheses and Stereochemical Revision of Pseudopterosin G-J Aglycone and Helioporin E

Scott E. Lazerwith, Ted W. Johnson and E. J. Corey*

Department of Chemistry and Chemical Biology
Harvard University, 12 Oxford Street, Cambridge, Massachusetts
02138

corey@chemistry.harvard.edu

Supporting Material

General Experimental Methods and Materials

All moisture and air sensitive reactions were performed in oven or flame dried glassware equipped with rubber septa under a positive pressure of nitrogen or argon. When necessary, solvents and reagents were distilled prior to use and were transferred using a syringe or cannula. Reaction mixtures were magnetically stirred, unless otherwise noted. Thin layer chromatography was performed on Merck precoated silica gel F-254 plates (0.25 mm). Concentration in vacuo was generally performed using a Büchi rotary evaporator. Kugelrohr distillation temperatures are reported as oven temperatures. Flash column chromatography was performed on Baker 230-400 mesh silica gel.

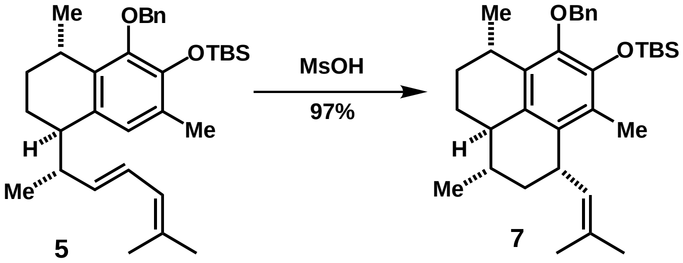
Physical Data. Melting points were determined using a Fisher-Johns hot stage apparatus and are reported uncorrected for all crystalline products. Optical rotations were determined using a Perkin-Elmer 241 polarimeter. Infrared spectra were recorded on a Nicolet 5ZDX FT-IR. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on an AM-500 (500 MHz), AM-400 (400 MHz), AM-300 (300 MHz) or AM-250 (250 MHz) Bruker nuclear magnetic resonance spectrometer, or a Unity/Inova-500 (500 MHz), Mercury-400 (400 MHz), or Mercury-300 (300 MHz) Varian nuclear magnetic resonance spectrometer, at the frequency indicated. Chemical shifts for ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane (δ 0.0) using the residual solvent signal as an internal standard: benzene-d_6 (δ 7.15, singlet), chloroform-*d* (δ 7.26, singlet). Multiplicities are given as: br (broad), s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet) or sept (septet) or m (multiplet). Coupling constants are reported as a *J* value in Hertz (Hz). The number of protons (n) for a given resonance is indicated by nH. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on an AM-400 (100 MHz), Mercury-400 (100 MHz), AM-500 (125 MHz), or Inova-500 (125 MHz) spectrometer at the frequency indicated. Chemical shifts for ^{13}C NMR spectra are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane (δ 0.0) using the residual solvent signal as an internal standard: benzene-d_6 (δ 128.0, triplet), chloroform-*d* (δ 77.07, triplet).

Electron impact (EI) with an electron beam energy of 70 eV, chemical ionization (CI) with ammonia as the reagent gas, or fast atom bombardment (FAB) in 3-nitrobenzyl alcohol (NBA) with NaI were used for the generation of the $[M]^+$, $[M+H]^+$, $[M+NH_4]^+$, or $[M+Na]^+$ ions. Low resolution EI and CI mass spectra were obtained using an AX-505H mass spectrometer (JEOL USA, Inc., Peabody, MA) using a mass resolution of 1,500. High resolution EI and CI mass spectra were obtained by using a SX-102A mass spectrometer (JEOL USA, Inc., Peabody, MA) using a mass resolution of 10,000 (EI) and 5,000 (CI). Low and high resolution FAB mass spectra were obtained by using a SX-102A mass spectrometer (JEOL USA, Inc., Peabody, MA) using a mass resolution of 3,000 (low resolution) and 10,000 (high resolution). Low and high resolution electrospray mass spectra (ESI) were obtained by using an LCT mass spectrometer (Micromass Inc., Beverly, MA) using a mass resolution of 5,000. All mass spectral analyses are reported in units of mass to charge (*m/e*).

Materials. Commercial solvents and reagents were used without further purification with the following exceptions.[1]

Solvents. Methylene chloride was distilled from calcium hydride or from phosphorous pentoxide under nitrogen. Tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl under nitrogen. Dimethylformamide (DMF) was distilled over activated molecular sieves.

Reagents. Methanesulfonic acid (MsOH) and iodomethane were distilled neat. Lithium di-*t*-butylbiphenylide was prepared by sonication of lithium metal in a solution of di*t*-butylbiphenyl in THF for 24 h. Boron tribromide was distilled over calcium hydride. Molecular sieves (m.s.) were dried by heating them in a microwave oven for 2 min, placing them at 1 mm Hg for 10 min, and repeating this procedure three additional times.

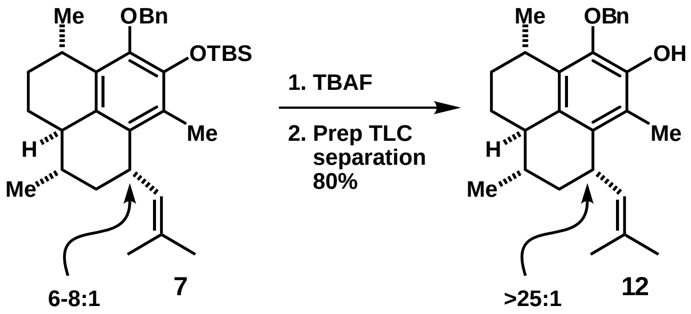


Tricycle 7. TBS ether **5** (0.0228 g, 0.045 mmol) was azeotropically dried with benzene (1 mL), dissolved in CH_2Cl_2 (4.5 mL) and cooled to -78 °C. The clear solution was treated dropwise with methanesulfonic acid (0.0088 mL, 0.14 mmol) in CH_2Cl_2 (0.1 mL) upon which the solution turned yellow. After warming to -50 °C, the mixture was stirred for 4 h and subsequently quenched by dropwise addition of triethylamine (0.2 mL). The resulting clear solution was warmed to ambient temperature and filtered through a small plug of silica gel (hexanes-Et_2O, 90:10), to afford after concentration 0.0222 g (97%) of desired tricycle **7** as a clear oil (6:1 mixture of inseparable diastereomers): R_f = 0.69 (hexanes-Et_2O, 50:50); FTIR (film) 2953, 2928, 2859, 1456, 1428, 840 cm^{-1}; ^1H NMR

---

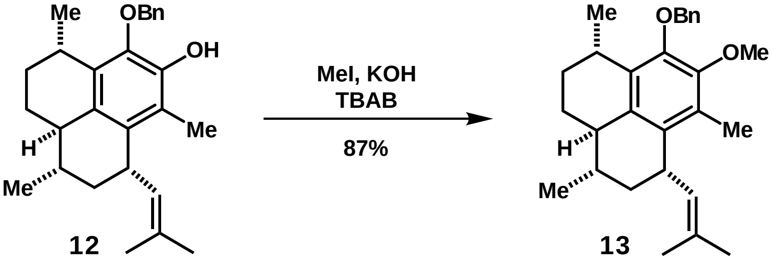
[1] For a compilation of methods for the purification of common laboratory substances, see: Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, Fourth ed.; Butterworth Heinemann: Oxford, 1996.

of the major diastereomer (400 MHz, $CDCl_3$) δ 7.18 (m, 5H), 5.12 (d, *J* = 8.0 Hz, 1H), 4.97 (br d, *J* = 9.2 Hz, 1H), 4.64 (d, *J* = 7.6 Hz, 1H), 3.67 (m, 1H), 3.08 (sext, *J* = 7.2 Hz, 1H), 2.08-1.98 (m, 3H), 2.03 (s, 3H), 1.95 (m, 1H), 1.72 (s, 3H), 1.68 (s, 3H), 1.28 (d, *J* = 7.2 Hz, 3H), 1.27-1.20 (m, 3H), 1.02 (d, *J* = 5.2 Hz, 3H), 0.96 (s, 9H), 0.85 (m, 1H), 0.11 (s, 3H), 0.04 (s, 3H); FABMS (NBA+NaI) 527 $[M+Na]^+$; HRMS calcd for $[C_{33}H_{48}O_2Si+Na]^+$: 527.3321, found: 527.3315.

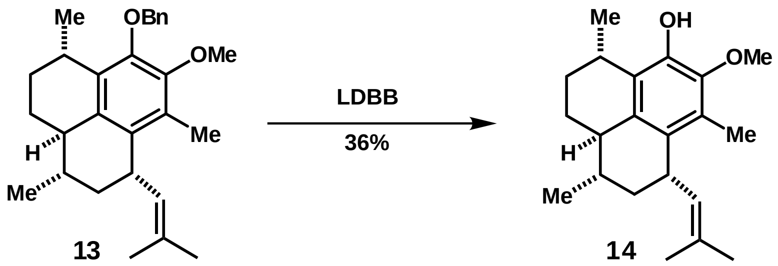


Phenol 12. A solution of TBS ether **7** (0.0222 g, 0.0440 mmol, 6:1 mixture of diastereomers) in THF (2 mL) was treated dropwise with tetrabutylammonium fluoride (0.053 mL, 1.0 M in THF, 0.053 mmol). After five minutes at 23 °C, the orange solution was concentrated onto a small amount of silica gel and purified by flash chromatography (hexanes-Et_2O, 95:5) to afford 0.0167 g of crude phenol **12** as a clear oil (6:1 mixture of diastereomers). A second careful purification using preparative TLC (hexanes-CH_2Cl_2, 75:25, allowing the compound to run up 4 times) afforded 0.0137 (80%) phenol **12** as a ≥25:1 mixture of diastereomers (as determined by ^{1}H NMR analysis): R_f = 0.43 (hexanes-Et_2O, 85:15); $[\alpha]^{24}_{D}$ +103 (*c* 0.20, $CHCl_3$); FTIR (film) 3526, 2920, 2862, 1452, 1050 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (m, 5H), 5.51 (s, 1H), 4.97 (d, *J* = 11.2 Hz, 2H), 4.73 (d, *J* = 11.2 Hz, 1H), 3.74 (m, 1H), 3.24 (sext, *J* = 7.3 Hz, 1H), 2.10 (m, 3H), 2.06 (s, 3H), 2.01 (m, 1H), 1.74 (s, 3H), 1.67 (s, 3H), 1.36 (m, 1H), 1.34 (d, *J* = 6.8 Hz, 3H), 1.25 (m, 2H), 1.03 (d, *J* = 5.9 Hz, 3H), 0.97 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 142.3, 137.3, 135.1, 131.8, 131.2, 131.0, 128.7, 128.5, 128.3, 127.9, 121.0, 75.3, 43.8, 40.2, 37.1, 34.6, 31.6, 29.3, 27.8, 25.6, 23.8, 20.1, 17.7,

12.1; CIMS (NH_3) 408 $[M+NH_4]^+$, 391 $[M+H]^+$; HRMS calcd for $[C_{27}H_{34}O_2+H]^+$: 391.2637, found: 391.2622.



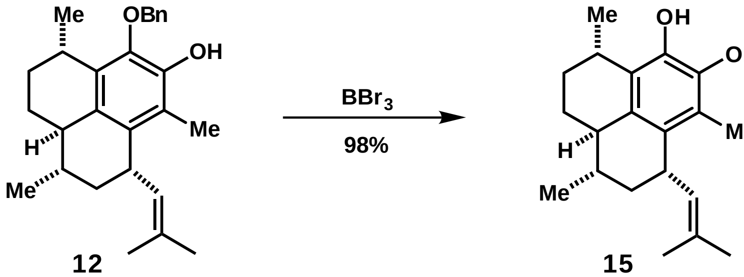
Methyl ether 13. A solution of phenol **12** (0.0020 g, 0.0051 mmol) in THF (0.5 mL) was treated with iodomethane (0.003 mL, 0.05 mmol), potassium hydroxide (0.006 g, 0.1 mmol), tetrabutylammonium bromide (0.002 g, 0.005 mmol) and stirred at 23 °C for 1 h. The reaction mixture was concentrated onto a small amount of silica gel and purified by flash chromatography (hexanes-Et_2O, 95:5) to afford 0.0018 g (87%) of desired product **13** as a clear oil: $R_f = 0.51$ (hexanes-Et_2O, 90:10); $[\alpha]^{23}_{D}$ +28 (*c* 0.18, $CHCl_3$); FTIR (film) 2925, 2862, 1453, 1315, 1063, 1025 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.8 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 1H), 5.08 (d, *J* = 11.2 Hz, 1H), 4.98 (br d, *J* = 9.8 Hz, 1H), 4.94 (d, *J* = 11.2 Hz, 1H), 3.79 (s, 3H), 3.72 (m, 1H), 3.25 (sext, *J* = 7.3 Hz, 1H), 2.10 (s, 3H), 2.05 (m, 3H), 1.96 (m, 1H), 1.74 (s, 3H), 1.69 (s, 3H), 1.36-1.20 (m, 3H), 1.26 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 5.9 Hz, 3H), 0.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 147.8, 138.5, 135.5, 134.3, 133.6, 130.9, 128.6, 128.4, 128.3, 127.7, 127.6, 74.3, 60.3, 44.1, 40.2, 37.5, 34.2, 31.2, 28.5, 27.7, 25.6, 24.6, 20.6, 17.7, 12.3; EIMS 404 $[M]^+$; HRMS calcd for $[C_{28}H_{36}O_2]^+$: 404.2715, found: 404.2722.



Methyl ether 14. A solution of methyl ether **13** (0.0018 g, 0.0044 mmol) in THF (0.5 mL) was cooled to -78 °C and treated with a solution of lithium-di-*tert*-butylbiphenylide (0.450 mL, ~0.25 M in THF, 0.11 mmol) until the color stayed dark green. After five minutes the reaction mixture was quenched with NH_4Cl (saturated aq, 1 mL) and warmed to ambient temperature. Water was added and the mixture was extracted twice with ether. The combined organic extracts were dried over $MgSO_4$ (anhyd), filtered and concentrated in vacuo. Flash chromatography (hexanes → hexanes-Et_2O, 95:5) afforded 0.0005 g (36%) of desired product **14** as a clear film: R_f = 0.36 (hexanes-EtOAc, 90:10); $[\alpha]_D^{25}$ +90 (*c* 0.05, $CHCl_3$); FTIR (film) 3419, 2953, 2923, 2862, 1455, 1298, 1260, 1119, 1058, 1018 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.66 (s, 1H), 4.95 (br d, *J* = 9.3 Hz, 1H), 3.74 (s, 3H), 3.67 (m, 1H), 3.16 (m, 1H), 2.16 (m, 1H), 2.08 (s, 3H), 2.07-1.99 (m, 2H), 1.96 (m, 1H), 1.73 (s, 3H), 1.67 (s, 3H), 1.67 (s, 3H), 1.36-1.18 (m, 3H), 1.29 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 5.9 Hz, 3H), 0.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.1, 128.4, 60.8, 44.8, 40.3, 37.1, 34.1, 32.2, 28.9, 27.9, 25.6, 23.1, 20.1, 17.7, 12.6;[2] EIMS 314 $[M]^+$, 258, 243, 201; HRMS calcd for $[C_{21}H_{30}O_2]^+$: 314.2246, found: 314.2242.

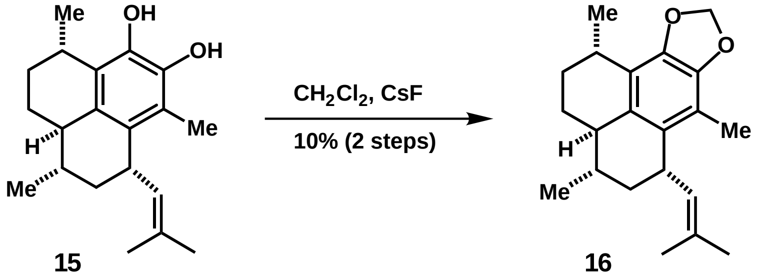
---

[2] Six carbon resonances (all quaternary carbons) were unresolved due to the small amount of compound. The fifteen carbon resonances reported matched the data gathered for the methyl ether **14** derived from pseudopterosin I.



12 **15**

Pseudopterosin G-J Aglycone 15. A solution of phenol **12** (0.0024 g, 0.0061 mmol) in CH_2Cl_2 (1 mL) was cooled to 0 °C and treated dropwise with a solution of BBr_3 (0.00087 mL, 0.0092 mmol) in CH_2Cl_2 (0.050 mL). After five minutes, the reaction mixture was concentrated onto a small amount of silica gel and purified by flash chromatography (hexanes:EtOAc, 90:10 → hexanes:EtOAc, 50:50) to afford 0.0018 g (98%) of desired catechol **15** as a light yellow film, which was taken immediately on to the next step: R_f = 0.26 (hexanes-EtOAc, 80:20); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.05 (s, 1H), 4.94 (br d, *J* = 9.3 Hz, 1H), 4.79 (s, 1H), 3.69 (m, 1H), 3.12 (m, 1H), 2.20 (m, 1H), 2.08-1.94 (m, 3H), 2.04 (s, 3H), 1.73 (d, *J* = 1.0 Hz, 3H), 1.67 (d, *J* = 1.0 Hz, 3H), 1.38-1.18 (m, 3H), 1.28 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 5.9 Hz, 3H), 0.92 (m, 1H).



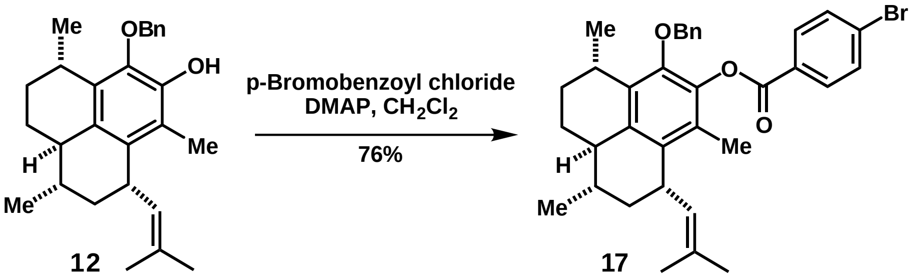
15 **16**

Helioporin E (16). Catechol **15** (0.0018 g, 0.0060 mmol) was dissolved in DMF (0.25 mL)[3] and treated with CsF (0.049 g, 0.32 mmol) and CH_2Cl_2 (0.0045 mL, 0.070 mmol). The reaction mixture was flushed with nitrogen, sealed in a screw-top glass vial, and heated to 110 °C. After stirring for 40 minutes, the reaction mixture was passed through a small plug of silica gel (hexanes-Et_2O, 90:10) and purified by preparative TLC

---

[3] Deoxygenated by the freeze-pump-thaw method (three times).

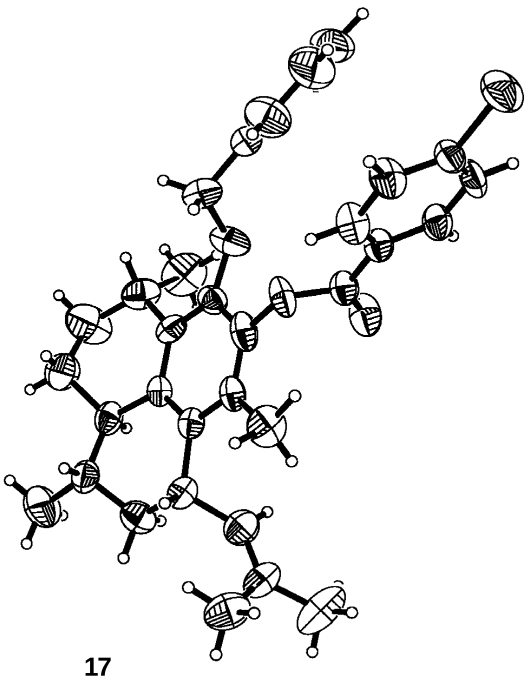
(hexanes-Et_2O, 99:1, run up twice) to afford 0.0002 g (10%) of desired tetracycle **16** as a clear film: R_f = 0.53 (hexanes-Et_2O, 95:5); FTIR (film) 2955, 2921, 2856, 1453, 1421, 1085, 1027 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.90 (d, *J* = 1.5 Hz, 1H), 5.84 (d, *J* = 1.5 Hz, 1H), 4.94 (br d, *J* = 9.3 Hz, 1H), 3.71 (br q, *J* = 8.8 Hz, 1H), 2.96 (m, 1H), 2.15-1.97 (m, 4H), 2.03 (s, 3H), 1.72 (s, 3H), 1.67 (s, 3H), 1.30 (d, *J* = 6.8 Hz, 3H), 1.30-1.11 (m, 3H), 1.00 (d, *J* = 5.4 Hz, 3H), 1.00 (m, 1H); EIMS 312 $[M]^+$, 256, 241; HRMS calcd for $[C_{21}H_{28}O_2]^+$: 312.2090, found: 312.2091.



***p*-Bromobenzoate 17**. A solution of phenol **12**[4] (0.001 g, 0.003 mmol) in CH_2Cl_2 was treated with *p*-dimethylaminopyridine (excess, approx. 0.005 g) and *p*-bromobenzoyl chloride (excess, approx. 0.005 g). After stirring for 20 min, the reaction mixture was purified by preparative TLC (hexanes-Et_2O, 90:10) to afford 0.001 g (70%) of desired product **17**, which after concentration from methanol solidified to a white powder. Clear X-ray quality crystals were grown by slow evaporation from methanol: mp 140-144 °C; R_f = 0.39 (hexanes-Et_2O, 90:10); FTIR (film) 1741, 1265, 1115, 1075, 1011 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.3 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 1H), 7.19 (s, 5H), 5.03 (br s, 1H), 4.88 (br s, 2H), 3.74 (m, 1H), 3.21 (br s, 1H), 2.26-1.95 (m, 4H), 1.98 (s, 3H), 1.71 (s, 3H), 1.66 (s, 3H), 1.45-1.22 (m, 4H), 1.26 (d, 3H), 1.05 (d, 5.9 Hz, 3H), 0.98 (m, 1H); FABMS (NBA+NaI) 597 $[M+Na+2]^+$, 595 $[M+Na]^+$; HRMS calcd for $[C_{34}H_{37}BrO_3+Na]^+$: 595.1824, found: 595.1832.

---

[4] Purified by preparative TLC to ≥ 99:1 as judged by ^1H NMR.



17

Empirical Formula	$C_{34}H_{37}BrO_3$
Formula Weight	573.55
Temperature	213 (2) °K
Wavelength	0.71073 Å
Crystal System, Space Group	Monoclinic
Space Group	$P2_1$
Unit Cell Dimensions	a = 10.1336 (11) Å, α = 90°
	b = 10.1759 (10) Å, β = 96.054 (2)°
	c = 14.6073 (15) Å, γ = 90°
Volume	1497.9 (3) Å^3, 2
Calculated Density	1.272 Mg/m^3
Absorption Coefficient	1.404 mm^{-1}
F(000)	600
Crystal Size	0.22 x 0.05 x 0.025 mm
Theta Range for Data Collection	1.40 to 28.31°
Index Ranges	$-13 \leq h \leq 12$, $-13 \leq k \leq 7$, $-18 \leq l \leq 19$
Reflections Collected (Unique)	10287/5942 (R_{int} = 0.1657)
Completeness to 2Θ = 28.39	98.5%

Refinement Method	Full-Matrix Least-Squares on F^2
Data/Restraints/Parameters	5942/1/343
Goodness-of-Fit on F^2	0.921
Final R Indices [$I > 2\sigma(I)$]	$R_1 = 0.0607$, $wR_2 = 0.1199$
R Indices (all data)	$R_1 = 0.2085$, $wR_2 = 0.2001$
Absolute Structure Parameter	0.000 (17)
Largest Difference Peak	0.652 eÅ^{-3}
Largest Difference Hole	-0.735 eÅ^{-3}