Total Synthesis of Hyperforin

Supporting Information

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General Procedures

Unless otherwise stated, all reactions were performed in oven-dried or flame-dried glassware under an atmosphere of dry nitrogen or argon. Dry tetrahydrofuran (THF), dichloromethane, toluene, hexane, acetonitrile, and diethyl ether were obtained by passing these previously degassed solvents through activated alumina columns. Amines and HMPA were distilled from calcium hydride prior to use. Diketene was freshly distilled immediately before use and was colorless. Copper(I) bromide dimethylsulfide complex was stored in a glovebox and small portions removed and manipulated on the benchtop. Lithium chloride was stored in a 160 °C oven and flame-dried under high vacuum before use. Reactions were monitored by thin layer chromatography (TLC) on Silicycle Siliaplate™ G TLC plates (250 µm thickness, 60 Å porosity, F-254 indicator) and visualized by UV irradiation and staining with *p*-anisaldehyde, phosphomolybdic acid, or potassium permanganate developing agents. Volatile solvents were removed under reduced pressure using a rotary evaporator. Flash column chromatography was performed using Silicycle F60 silica gel (60Å, 230-400 mesh, 40-63 µm). Proton nuclear magnetic resonance (¹H NMR) and carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded on Bruker AVQ-400, AV-500, or AV-600 spectrometers operating respectively at 400, 500, and 600 MHz for ¹H, and 100, 125, and 150 MHz for ¹³C. Chemical shifts are reported in parts per million (ppm) with respect to the residual solvent signal CDCl₃ (¹H NMR: δ = 7.26; ¹³C NMR: δ = 77.16). Peak multiplicities are reported as follows: s = singlet, bs = broad singlet, d = doublet, t = triplet, dd = doublet of doublets, td = triplet of doublets, m = multiplet. app = apparent. Melting points were determined using MEI-TEMP™ apparatus and are uncorrected. IR spectra were recorded on a Nicolet 380 FT-IR spectrometer. High-resolution mass spectra (HRMS) were obtained by the qb3 mass spectrometry facility at the University of California, Berkeley. X-ray crystallographic analyses were performed at the UC-Berkeley College of Chemistry X-ray crystallography facility.

Table 1. Synthesis of [3.3.1] bicycle **13** via oxidative rearrangement: Selected oxidant study.

Entry	Base/solvent	Oxidant	Yield (%) ^{a,b}
1	KOH/MeOH	PhI(OAc) ₂	92 ^{c,d,e,f}
2	LDA/THF	PhI(CN) ₂	40 ^c
3	LDA/THF	PhI(OTFA) ₂	23
4	LDA/THF	PhI(OAc) ₂	11
5	LDA/THF	I ₂	15
6	LDA/THF	NBS	9
7	LDA/THF	Fe(acac) ₃	6
8	LDA/THF	Cu(2-ethylhexanoate) ₂	0

^a Reactions performed on a 0.1 mmol scale. ^b yield determined by ¹H NMR. ^c isolated yield. ^d T = 25 °C. ^e [KOH] = 1.8 M. ^f yield on 1 mmol scale = 82%.

Ketone 7. *i.* A 1 L flame-dried flask was charged with anhydrous lithium chloride (6.6 g, 156 mmol, 1.2 equiv) and copper bromide dimethylsulfide complex (32.0 g, 156 mmol, 1.2 equiv). The reaction vessel was evacuated and backfilled with nitrogen and this process repeated for a total of three times. THF (600 mL) was added and the mixture was stirred for 5 minutes at 25°C and then cooled to -78 °C whereupon (3-methylbut-3-en-1-

yl)magnesium bromide (1 M in Et₂O), 130 mL, 130 mmol, 1 equiv) was added dropwise. The resulting dark brown solution was stirred for 30 minutes at -78 °C before adding TMSCl (20.0 mL, 156 mmol, 1.2 equiv) and 2-methylcyclopentenone (10.0 g, 104.1 mmol, 0.8 equiv) quickly in succession. The reaction mixture was stirred for 60 minutes at -78 °C and then triethylamine (20 mL) was added. The reaction vessel was slowly warmed to 25 °C over the course of 1 hour and then saturated *aq.* NH₄OH/saturated *aq.* NH₄Cl (9:1 v:v, 200 mL) added, resulting in a dark blue colored solution. The reaction mixture was filtered through Celite, and then extracted with ether (3 x 300 mL). The combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The crude residue was purified by column chromatography (1% → 2% Et₂O in hexanes) to afford the silyl enol ether product **SI-1** (18.1 g, 73% yield) as a colorless oil.

ii. A 250 mL flame-dried flask was charged with silyl enol ether **SI-1** (442 mg, 1.85 mmol, 1.0 equiv). The reaction vessel was evacuated and backfilled with nitrogen and this process repeated for a total of three times followed by the addition of THF (60 mL). After cooling the reaction flask to 0 °C, methyllithium lithium-iodide complex (1.0 M in ether, 2.2 mL, 2.20 mmol, 1.2 equiv) was added and the reaction mixture was stirred for 1 hr. HMPA (10 mL) was added at 0 °C followed by cooling to -78 °C and the addition of 5-iodo-2-methylpent-2-ene (1.3 mL, 9.25 mmol, 5.0 equiv). The colorless solution was warmed to 5 °C and stirred for 30 h at which point it was quenched with deionized H₂O (50 mL) and diluted with ether (100 mL). After organic layer was washed with deionized H₂O (2 x 50 mL). The combined aqueous layers were extracted with ether (2 x 100 mL), and the combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo* to afford a yellow oil. The crude material was dissolved in benzene (50 mL) under an atmosphere of nitrogen and *p*-toluenesulfonic acid monohydrate (35 mg, 0.185 mmol, 0.1 equiv) was added. The reaction mixture heated to 70 °C for 24 h, cooled to

room temperature, and the brown solution concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (1% → 2% Et₂O in hexanes) followed by chromatography on AgNO₃ impregnated silica gel (2% Et₂O in hexanes) to afford the ketone **7** (184 mg, 40% yield, 3:1 dr) as a yellow oil: ¹H NMR (600 MHz, CDCl₃-*d*) δ 5.17 (t, *J* = 7.2 Hz, 1H), 5.04 (t, *J* = 7.1 Hz, 1H), 2.33 (dd, *J* = 17.2, 8.4 Hz, 1H), 2.18 – 2.10 (m, 1H), 2.05 (m, 3H), 1.94 (m, 2H), 1.78 – 1.72 (m, 1H), 1.71 (s, 3H), 1.65 (s, 3H), 1.63 (s, 3H), 1.62 – 1.59 (m, 1H), 1.57 (s, 3H), 1.49 – 1.39 (m, 1H), 1.37 (ddd, *J* = 13.9, 11.7, 5.0 Hz, 1H), 0.85 (s, 3H); ¹³C NMR (150 MHz, CDCl₃-*d*) δ 223.76, 132.60, 131.76, 124.42, 122.70, 51.46, 43.28, 37.58, 36.11, 28.70, 25.93, 25.77, 25.10, 23.44, 17.99, 17.95, 17.71; IR (thin film) 2966, 2924, 2857, 1739, 1451, 1407 cm⁻¹; HRMS (EI) calcd for [C₁₇H₂₈O₁]: *m/z* 248.2140, found 248.2142.

Ketone 8. A 50 mL flame-dried flask was charged with ketone **7** (440 mg, 1.77 mmol, 1.0 equiv). The reaction vessel was evacuated and backfilled with nitrogen (three times in total) followed by the addition of THF (20 mL). After cooling the reaction vessel to -78 °C, a freshly prepared solution of lithium diisopropylamide (0.52 M in THF, 3.60 mL, 1.86 mmol, 1.1 equiv) was added dropwise via

syringe resulting in a light yellow solution. The reaction mixture was stirred for 30 minutes at -78 °C and then 30 minutes at 0 °C. Dry hexamethylphosphoramide was then added to the reaction mixture at 0 °C and the mixture re-cooled to -78 °C. Freshly distilled prenylbromide (0.22 mL, 1.95 mmol, 1.1 equiv) was added dropwise at -78 °C and the resulting pale yellow solution stirred for 15 minutes at this temperature and then warmed to 0 °C, stirred 15 minutes at this temperature, and then quenched with deionized water (20 mL). The reaction mixture was diluted with ether (100 mL), and the organic layer was washed with deionized water (2 x 20 mL). The combined aqueous layers were extracted with ether (2 x 50 mL). The combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The crude residue was purified by column chromatography (1% → 2% Et₂O in hexanes) to afford ketone **8** (498 mg, 89% yield, 13:1 mixture of diastereomers) as a colorless oil: ¹H NMR (600 MHz, CDCl₃-*d*) δ 5.14 (t, *J* = 6.7 Hz, 1H), 5.12 – 5.01 (m, 2H), 2.28 (tt, *J* = 9.0, 4.1 Hz, 1H), 2.22 (dt, *J* = 12.4, 5.9 Hz, 1H), 2.12 (dt, *J* = 12.9, 5.9 Hz, 1H), 2.09 – 1.99 (m, 2H), 1.94 (tt, *J* = 12.5, 5.8 Hz, 1H), 1.90 – 1.82 (m, 1H), 1.81 – 1.76 (m, 1H), 1.76 – 1.72 (m, 1H), 1.71 (s, 3H), 1.69 (s,

3H), 1.66 (s, 3H), 1.65 – 1.63 (m, 1H), 1.62 (s, 3H), 1.60 (s, 3H), 1.58 (s, 3H), 1.55 (dd, $J = 12.7$, 4.8 Hz, 1H), 1.33 (td, $J = 13.0$, 4.9 Hz, 1H), 0.88 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3 - d) δ 224.85, 133.57, 132.55, 131.73, 124.46, 122.90, 121.89, 52.35, 46.43, 41.08, 36.03, 29.98, 29.31, 28.71, 25.94, 25.93, 25.80, 23.41, 18.24, 17.99, 17.72; IR (thin film) 2966, 2916, 2858, 1734, 1451, 1376 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{22}\text{H}_{36}\text{O}_1]$: m/z 316.2766, found 316.2763.

Diketone 9. A 20 mL flame-dried reaction tube was charged with compound **8** (100 mg, 0.32 mmol, 1.0 equiv). The reaction vessel was evacuated and backfilled with nitrogen (three times in total) followed by the addition of degassed THF (5 mL) and Et_2O (5 mL). The reaction vessel was cooled to -78°C and freshly prepared lithium 2,2,6,6-tetramethylpiperidide (0.45 M in THF, 0.80 mL, 0.36 mmol,

1.2 equiv) was added dropwise resulting in a light yellow colored solution. The reaction mixture was stirred for 30 minutes at -78°C and then 60 minutes at 0°C . After this period, the reaction mixture was cooled to -40°C and freshly distilled diketene (30 μL , 0.38 mmol, 1.2 equiv) was rapidly in one portion resulting in a bright yellow solution. The reaction vessel was maintained at this temperature for 90 minutes and then quenched with saturated *aq.* NH_4Cl (20 mL) at this temperature. The reaction mixture was extracted with EtOAc (3 x 25 mL) and the combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The crude residue was purified by column chromatography (5% Et_2O in hexanes $\rightarrow$ 15% EtOAc in hexanes) to afford the annulated product **9** (44 mg, 35% yield) as a red/orange colored oil and recovered starting material **8** (22 mg, 22% yield). An analytically pure sample of compound **9** could be obtained by cooling a hexanes solution to -20°C wherein a white solid (mp = 99 – 101°C) precipitates: ^1H NMR (600 MHz, CDCl_3 - d) δ 5.11 – 5.00 (m, 2H), 4.95 – 4.89 (m, 1H), 3.66 (d, $J = 18.0$ Hz, 1H), 3.11 (d, $J = 18.0$ Hz, 1H), 2.79 – 2.68 (m, 2H), 2.49 (dd, $J = 15.2$, 7.0 Hz, 1H), 2.46 – 2.36 (m, 2H), 2.17 – 2.06 (m, 2H), 2.06 – 1.97 (m, 1H), 1.94 (s, 1H), 1.80 – 1.72 (m, 1H), 1.68 (s, 9H), 1.62 (s, 3H), 1.59 (s, 6H), 1.41 – 1.30 (m, 2H), 1.26 (t, $J = 12.9$ Hz, 1H), 1.17 (td, $J = 13.2$, 4.6 Hz, 1H), 1.02 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 206.4, 203.8, 135.2, 132.5, 132.3, 124.5, 122.8, 118.4, 84.3, 61.2, 52.0, 50.5, 50.4, 45.0, 37.5, 35.2, 34.7, 29.2, 26.2, 26.0, 25.8, 22.9, 18.3, 18.0, 18.0, 14.9; IR (thin film) 3520, 3375, 2968, 2923, 2878, 1733 cm^{-1} ; HRMS (ESI) calcd for $[\text{C}_{26}\text{H}_{39}\text{O}_3]^-$ (M-H) $^-$: m/z 399.2905, found 399.2904.

Vinylogous Esters 10 and 11. A flame-dried 50 mL flask was charged with compound **9** (200 mg, 0.50 mmol, 1 equiv). The reaction vessel was evacuated and backfilled with nitrogen (three times in total) followed by the addition of toluene (16 mL) and methanol (4

mL). A solution of trimethylsilyldiazomethane (2.0 M in hexanes, 0.40 mL, 0.75 mmol, 1.5 equiv) was added dropwise to the reaction mixture and the resulting yellow solution was stirred for 30 minutes. The reaction mixture was quenched with *aq.* acetic acid (1M solution, 10 mL) and extracted with ether (3 x 50 mL). The combined organic layers were washed with saturated sodium carbonate, dried over MgSO₄, and concentrated *in vacuo*. The crude residue was purified by column chromatography (10% → 20% EtOAc in hexanes) to afford compound **10** (100 mg, 48%) and compound **11** (100 mg, 48%) both as red/orange oils. Both compounds could be crystallized by cooling hexane solutions to – 20 °C, (compound **10**, white solid, mp = 83-84 °C; compound **11**, white solid, mp = 85-86 °C). **Regioisomer 11:** ¹H NMR (600 MHz, CDCl₃-*d*) δ 5.38 (s, 1H), 5.16 – 5.04 (m, 2H), 4.93 (t, *J* = 7.0 Hz, 1H), 3.68 (s, 3H), 2.64 (d, *J* = 17.9 Hz, 1H), 2.60 (dd, *J* = 13.2, 7.8 Hz, 1H), 2.48 (dd, *J* = 14.7, 6.5 Hz, 1H), 2.43 (d, *J* = 18.0 Hz, 1H), 2.36 (dd, *J* = 14.6, 8.4 Hz, 1H), 2.10 – 2.03 (m, 1H), 2.00 – 1.91 (m, 1H), 1.90 (s, 1H), 1.89 – 1.82 (m, 2H), 1.67 (s, 3H), 1.66 (s, 3H), 1.63 (s, 3H), 1.59 (s, 6H), 1.55 (s, 3H), 1.27 (dd, *J* = 13.6, 9.2 Hz, 1H), 1.13 (td, *J* = 12.5, 12.0, 4.4 Hz, 1H), 1.09 – 1.01 (m, 1H), 0.97 (s, 3H), 0.95 – 0.92 (m, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 202.7, 174.5, 134.3, 132.1, 131.6, 125.2, 124.2, 120.5, 102.9, 85.2, 59.2, 56.2, 52.1, 44.4, 40.0, 38.3, 37.5, 35.6, 32.1, 26.4, 26.2, 26.1, 23.9, 18.4, 18.3, 18.1, 15.0; IR (thin film) 3474, 2967, 2923, 2856, 1617, 1451 cm⁻¹; HRMS (EI) calcd for [C₂₇H₄₂O₃]: *m/z* 414.3134, found 414.3138. **Regioisomer 10:** ¹H NMR (600 MHz, CDCl₃-*d*) δ 5.44 (s, 1H), 5.04 (m, 2H), 4.94 (t, *J* = 7.1 Hz, 1H), 3.66 (s, 3H), 2.69 (d, *J* = 17.0 Hz, 1H), 2.59 (dd, *J* = 14.6, 9.1 Hz, 1H), 2.42 (dd, *J* = 15.0, 5.7 Hz, 1H), 2.39 (d, *J* = 17.1 Hz, 1H), 2.35 (dd, *J* = 13.4, 7.3 Hz, 1H), 2.10 – 2.04 (m, 1H), 2.03 – 1.98 (m, 1H), 1.97 (s, 1H), 1.93 – 1.84 (m, 2H), 1.67 (s, 3H), 1.62 (s, 3H), 1.61 (s, 3H), 1.59 (s, 3H), 1.59 (s, 3H), 1.53 (s, 3H), 1.52 – 1.46 (m, 1H), 1.42 (dd, *J* = 13.2, 10.0 Hz, 1H), 1.23 (td, *J* = 12.8, 12.3, 4.9 Hz, 1H), 1.17 (td, *J* = 13.0, 12.6, 4.9 Hz, 1H), 0.96 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 197.5, 180.3, 134.4, 131.9, 131.3, 124.9, 123.9, 120.6, 103.6, 84.8, 56.3, 53.8, 51.8, 46.6, 45.5, 40.3, 39.9, 35.9, 30.6, 26.1, 26.0,

25.8, 23.6, 18.1, 18.0, 17.8, 15.3; IR (thin film) 3349, 2967, 2926, 2856, 1719, 1637 cm^{-1} ; HRMS (ESI) calcd for $[\text{C}_{27}\text{H}_{42}\text{O}_3\text{Na}]^+$ ($\text{M}+\text{Na}$) $^+$: m/z 437.3026, found 437.3028.

Procedure for the Basic Hydrolysis of 11 (Scheme SI-2). A 100 mL flame-dried reaction flask was charged with vinylogous ester **11** (450 mg, 1.09 mmol, 1 equiv) and sodium hydroxide (900 mg, 22.5 mmol, 21 equiv). The reaction vessel was evacuated and backfilled with nitrogen (three times in total) followed by the addition of dioxane (23 mL) and deionized water (23 mL). The reaction mixture was heated to 80°C and kept at this temperature for 18 h. The reaction mixture was then cooled to room temperature, acidified with 1 M HCl (pH 1-2), and extracted with EtOAc (3 x 40 mL). The combined organic washed with brine (5 mL), dried over MgSO_4 , and concentrated *in vacuo*. The crude residue was purified by column chromatography (20% EtOAc in hexanes) to afford diketone **9** (248 mg, 57% yield) as an orange oil.

Bicycle 13. A 25 mL flame-dried flask was charged with compound **10** (50 mg, 0.121 mmol, 1.0 equiv), (Diacetoxyiodo)benzene (100 mg, 0.311 mmol, 2.6 equiv), and potassium hydroxide (500 mg, 8.93 mmol, 74 equiv). The reaction vessel was evacuated and backfilled with nitrogen (a total of three times) followed by the addition of MeOH (5 mL). The reaction was stirred at room temperature for 2 h.

The resulting orange solution was concentrated *in vacuo*, diluted with EtOAc, washed with saturated *aq.* NH_4Cl (10 mL), and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The crude residue was purified by column chromatography (15% Et_2O in hexanes) to afford bicycle **13** (46 mg, 92% yield) as a yellow oil. ^1H NMR (600 MHz, CDCl_3) δ 5.71 (s, 1H), 5.07 (t, $J = 7.2$ Hz, 1H), 5.01 – 4.89 (m, 2H), 3.74 (s, 3H), 3.13 (s, 1H), 2.51 – 2.30 (m, 3H), 2.13 (m, 1H), 1.93 (dd, $J = 13.9, 3.8$ Hz, 1H), 1.90 – 1.81 (m, 1H), 1.69z (s, 3H), 1.67 (s, 6H), 1.65 (s, 3H), 1.64 (s, 3H), 1.61 – 1.58 (m, 1H), 1.56 (s, 3H), 1.51 (td, $J = 13.0, 4.3$ Hz, 1H), 1.45 – 1.37 (m, 1H), 1.26 (m, 2H), 0.84 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 207.2, 194.0, 177.6, 133.8, 133.3, 131.8, 124.5, 122.7, 119.6, 106.5, 70.7, 57.1, 56.9, 46.1, 41.0, 39.4, 38.7, 29.9, 27.8, 26.1, 26.0, 25.9, 22.0, 18.2, 18.1, 17.9, 17.8; IR (thin film) 2967, 2925, 2880, 1734, 1655, 1599 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{27}\text{H}_{40}\text{O}_3]$: m/z 412.2977, found 412.2978.

Procedure for Oxidative Ring Expansion using LDA as base (Table 1).

A 10 mL flame-dried flask was charged with compound **10** (50 mg, 0.121 mmol, 1.0 equiv). The reaction vessel was evacuated and backfilled with nitrogen (a total of three times) followed by the addition of THF (5 mL). The reaction was cooled to -78 °C and a freshly prepared solution of lithium diisopropylamide (0.52 M in THF, 0.80 mL, 0.42 mmol, 3.5 equiv) was added dropwise. The resulting orange colored solution was stirred for 15 minutes at -78 °C and then 30 minutes at 0 °C. During this time, a separate flame-dried 25 mL flask was charged with [bis(trifluoroacetoxy)iodo]benzene (94 mg, 0.218 mmol, 1.8 equiv) and the flask evacuated and backfilled with nitrogen (three times in total) followed by the addition of dichloromethane (5 mL). To the vessel containing PIFA was addition trimethylsilylcyanide (0.55 uL, 0.435 mmol, 3.6 equiv) at 0 °C and the mixture stirred at that temperature for 30 minutes. Both flasks were then cooled to -78 °C, and the dianion of compound **10** was cannula transferred into the flask containing the hypervalent iodine oxidant. The resulting yellow solution was stirred for 15 minutes at -78 °C and then 15 minutes at 0 °C. At this time, the reaction mixture was quenched with saturated *aq.* NaHCO₃ (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over MgSO₄, and concentrated *in vacuo*. The crude residue was purified by column chromatography (10% Et₂O in hexanes → 20% EtOAc in hexanes) to afford bicycle **13** (20 mg, 40% yield) as a yellow oil and recovered starting material **10** (8 mg, 15%) as a colorless oil.

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Chloride 14. A 25 mL flame-dried reaction flask was charged with compound **13** (110 mg, 0.267 mmol, 1.0 equiv). The reaction vessel was evacuated and backfilled with nitrogen (three times in total) followed by the addition of THF (10 mL). After cooling the reaction vessel to -78 °C, a solution of freshly prepared lithium 2,2,6,6-tetramethylpiperidide (0.50 M in THF, 1.25 mL, 0.625 mmol, 2.3 equiv) was added dropwise resulting in a light yellow colored

solution. The reaction mixture was stirred for 60 minutes at -78 °C and then *p*-toluenesulfonyl chloride (120 mg, 0.628 mmol, 2.3 equiv) added as a solution in THF. The reaction mixture was maintained at -78 °C for 15 minutes, warmed to 0 °C for 15 minutes, and then quenched with saturated *aq.* NaHCO₃ solution (5 mL). The reaction mixture was extracted with EtOAc (3 x 20

mL) and the combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The crude residue was purified by column chromatography (10% CH_2Cl_2 in hexanes $\rightarrow$ 5% ether in hexanes) affording **14** (106 mg, 89% yield) as a yellow oil: ^1H NMR (600 MHz, CDCl_3 -*d*) δ 5.06 (t, $J = 7.4$ Hz, 1H), 4.97 (t, $J = 5.9$ Hz, 1H), 4.93 (t, $J = 6.9$ Hz, 1H), 4.20 (s, 3H), 3.34 (s, 1H), 2.48 (dd, $J = 14.9, 5.6$ Hz, 1H), 2.41 – 2.31 (m, 2H), 2.14 (dd, $J = 13.6, 5.8$ Hz, 1H), 2.02 (dd, $J = 14.0, 4.1$ Hz, 1H), 1.85 (tt, $J = 12.8, 5.3$ Hz, 1H), 1.70 (s, 3H), 1.68 – 1.64 (m, 12H), 1.64 – 1.59 (m, 1H), 1.56 (s, 3H), 1.51 (dd, $J = 12.8, 4.5$ Hz, 1H), 1.42 (ddd, $J = 13.8, 11.7, 3.4$ Hz, 1H), 1.22 (tt, $J = 13.1, 5.9$ Hz, 1H), 1.01 – 0.91 (m, 1H), 0.85 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 205.2, 187.9, 172.3, 134.2, 133.7, 132.0, 124.2, 122.4, 119.4, 115.7, 70.6, 62.8, 60.2, 46.9, 41.1, 39.5, 38.6, 30.7, 27.7, 26.0, 26.0, 25.9, 21.9, 18.2, 18.2, 17.9, 17.8; IR (thin film) 2967, 2925, 2878, 1735, 1673, 1579 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{27}\text{H}_{39}\text{ClO}_3]$: m/z 446.2588, found 446.2587.

Chloride 15. Two 20 mL flame-dried reaction tubes were charged with compound **14** (2 x 46 mg, 0.206 mmol, 1.0 equiv). The reaction vessels were evacuated and backfilled with nitrogen (three times in total) followed by the addition of THF (1 mL). The reaction mixtures were cooled to -78°C and a freshly prepared solution of lithium 2,2,6,6-tetramethylpiperidide (0.50 M in THF, 0.62 mL, 0.31 mmol, 3.2 equiv) was added dropwise to each vessel resulting in a light brown colored solution. The reaction mixtures were stirred for 10 minutes at -78°C , warmed to 0°C and stirred 5 minutes, and then re-

cooled to -78°C . Isobutyryl cyanide (50 μL , 0.49 mmol, 5 equiv) was added dropwise to both vessels at -78°C . The reaction mixtures were slowly warmed to -35°C over the course of 30 minutes at which point they were quenched with saturated *aq.* NaHCO_3 solution (5 mL). The two reaction mixtures were combined and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The crude residue was purified by column chromatography (2% ether in hexanes) to afford the chloride product **15** (75 mg, 70% yield) as a yellow oil: ^1H NMR (400 MHz, CDCl_3 -*d*) δ 5.02 (t, $J = 7.1$ Hz, 1H), 4.99 – 4.89 (m, 2H), 4.25 (s, 3H), 2.52 (dd, $J = 14.6, 5.4$ Hz, 1H), 2.42 (dd, $J = 14.6, 7.9$ Hz, 1H), 2.16 – 2.03 (m, 3H), 2.03 – 1.96 (m, 1H), 1.94 (dd, $J = 13.6, 4.0$ Hz, 1H), 1.88 – 1.81 (m, 2H), 1.81 – 1.73 (m, 1H), 1.70 (s, 3H), 1.68 (m, 6H), 1.64 (s, 3H), 1.59 (s, 3H), 1.56 (s, 3H), 1.47

(t, $J = 5.4$ Hz, 1H), 1.45 – 1.39 (m, 1H), 1.13 (d, $J = 6.5$ Hz, 3H), 1.06 (d, $J = 6.5$ Hz, 3H), 1.02 (d, $J = 2.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 208.0, 205.2, 187.2, 172.0, 134.7, 133.9, 131.5, 124.5, 122.3, 119.1, 116.1, 84.4, 63.0, 60.6, 50.2, 43.0, 39.6, 36.6, 30.6, 27.4, 26.1, 26.0, 25.9, 25.0, 21.6, 20.6, 18.3, 18.2, 17.8, 13.9; IR (thin film) 2924, 2869, 2852, 1734, 1663, 1582 cm^{-1} ; HRMS (EI) calcd for $[\text{C}_{31}\text{H}_{45}\text{ClO}_4]$: m/z 516.3006, found 516.2999.

SI-2

O-methylhyperforin (SI-2). A 10 mL flame-dried flask was charged with compound **15** (50 mg, 0.10 mmol, 1.0 equiv). The reaction vessel was evacuated and backfilled with nitrogen (three times in total) followed by the addition of THF (5 mL). The solution was cooled to 0 °C and *i*-PrMgCl•LiCl solution (1.3 M in Et_2O , 0.26 mL, 0.34 mmol, 3.4 equiv) was added dropwise. After 15 minutes at 0 °C, the reaction mixture was warmed to room temperature and stirred for 75 minutes. The reaction vessel was

then cooled to -78 °C, and freshly prepared lithium diisopropylamide (0.52 M in THF, 0.73 mL, 0.38 mmol, 3.8 equiv) was added dropwise. After stirring for 20 minutes at this temperature, 2-thienyl(cyano)copperlithium (0.25 M in THF, 2.7 mL, 0.68 mmol, 7 equiv) was added dropwise. The reaction mixture was stirred for 5 minutes at -78 °C and then warmed to -40 °C and stirred an additional 30 minutes. The mixture was then re-cooled to -78 °C and freshly distilled prenyl bromide (190 μL , 1.7 mmol, 17 equiv) was added. The reaction mixture was warmed to -30 °C over the course of 90 minutes and then quenched with saturated *aq.* NH_4Cl and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over MgSO_4 , and concentrated *in vacuo*. The crude residue was purified by column chromatography (2% Et_2O in hexanes) affording *O*-methylhyperforin (39 mg, 73% yield) as a colorless oil: ^1H NMR (400 MHz, CDCl_3 -*d*) δ 5.09 – 5.02 (m, 2H), 5.02 – 4.97 (m, 1H), 4.97 – 4.92 (m, 1H), 3.92 (s, 3H), 3.18 (d, $J = 6.5$ Hz, 2H), 2.50 (dd, $J = 14.8, 6.1$ Hz, 1H), 2.40 (dd, $J = 14.7, 7.4$ Hz, 1H), 2.09 (t, $J = 14.1$ Hz, 2H), 1.98 (septet, $J = 6.4$ Hz, 1H), 1.93 – 1.84 (m, 3H), 1.79 – 1.71 (m, 1H), 1.69 – 1.65 (m, 15H), 1.64 (s, 3H), 1.63 – 1.60 (m, 1H), 1.59 (s, 3H), 1.56 (s, 3H), 1.46 – 1.40 (m, 1H), 1.40 – 1.35 (m, 1H), 1.11 (d, $J = 6.5$ Hz, 3H), 1.02 (d, $J = 6.5$ Hz, 3H), 0.99 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 209.3, 207.3, 194.1, 174.1, 134.0, 133.5, 133.2, 131.2, 127.7, 125.0, 122.7, 121.9, 119.9, 84.3, 62.6, 58.9, 49.4, 43.4, 42.8, 39.1, 36.7, 30.3, 27.3, 26.1, 26.0, 25.9, 25.8, 25.1,

23.7, 21.5, 20.6, 18.3, 18.14, 18.13, 17.9, 13.8; IR (thin film) 2967, 2926, 2873, 1730, 1720, 1646 cm^{-1} ; HRMS (ESI) calcd for $[\text{C}_{36}\text{H}_{54}\text{O}_4\text{Na}]^+$ ($\text{M}+\text{Na}$) $^+$: m/z 573.3914 found 573.3913.

Hyperforin (1). [Note: The following procedure was conducted in the dark. Solvents used were degassed with argon for 10 minutes prior to use]. A 10 mL flame-dried reaction tube was charged with compound *O*-methylhyperforin (53 mg, 0.096 mmol, 1 equiv) and dry lithium chloride (40 mg, 0.95 mmol, 10 equiv). The reaction vessel was evacuated and backfilled with nitrogen three times followed by the addition of DMSO (2 mL).

The reaction mixture was heated to 120 °C and kept at this temperature for 30 minutes. The reaction mixture was then cooled to room temperature, diluted with H_2O , and extracted with 1:1 hexane:EtOAc (3 x 20 mL). The combined organic layers extracts were washed with H_2O (3 x 5 mL), washed with brine (5 mL), dried over Na_2SO_4 , and concentrated *in vacuo* to afford a yellow oil. The crude residue was purified by column chromatography (2% $\rightarrow$ 5% EtOAc in hexanes) to afford hyperforin (29 mg, 56% yield) as an oil: ^1H NMR (600 MHz, $\text{MeOD}-d_4$) δ 5.12 (t, J = 6.4 Hz, 1H), 5.04 – 4.96 (m, 3H), 3.16 (dd, J = 14.8, 7.2 Hz, 1H), 3.10 (dd, J = 14.8, 6.9 Hz, 1H), 2.52 (dd, J = 14.9, 6.8 Hz, 1H), 2.43 (dd, J = 14.6, 7.1 Hz, 1H), 2.14 – 2.12 (m, 1H), 2.11 – 2.04 (m, 1H), 2.04 – 1.97 (m, 1H), 1.97 – 1.89 (m, 2H), 1.80 – 1.74 (m, 4H), 1.73 (s, 3H), 1.71 (s, 6H), 1.68 (s, 3H), 1.67 (s, 3H), 1.65 (s, 3H), 1.62 (s, 3H), 1.60 (s, 3H), 1.41 (t, J = 12.7 Hz, 1H), 1.11 (d, J = 6.5 Hz, 3H), 1.06 (d, J = 6.5 Hz, 3H), 1.00 (s, 3H); ^{13}C NMR (150 MHz, $\text{MeOD}-d_4$) δ 212.2, 209.3, 134.9, 134.5, 133.8, 132.1, 126.4, 124.1, 123.0, 122.3, 121.3, 49.9, 43.4, 43.3, 41.1, 38.3, 31.0, 29.0, 26.4, 26.3, 26.3, 26.2, 25.8, 22.9, 22.3, 21.4, 18.5, 18.4, 18.4, 18.1, 15.6; IR (thin film) 3314, 2968, 2927, 2874, 1723, 1602 cm^{-1} ; HRMS (ESI) calcd for $[\text{C}_{35}\text{H}_{51}\text{O}_4]^-$ ($\text{M}-\text{H}$) $^-$: m/z 535.3793 found 535.3783.

^1H and ^{13}C NMR comparison of natural and synthetic hyperforin

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C	600 MHz ¹	500 MHz ²	500 MHz ³	600 MHz ⁴	500 MHz ⁵	600 MHz (this work)
27	5.18 (tt, $J = 7.2$, 1.2 Hz, 1H)	5.15-5.11 (m, 1H)	5.12 (t, $J = 7.0$ Hz, 1H)	5.10-5.00 (m, 1H)	5.09 (tt, $J = 7.1$, 1.3 Hz, 1H)	5.12 (t, $J = 6.4$ Hz, 1H)
22	5.11 (tt, $J = 7.2$, 1.2 Hz, 1H)	5.07-4.97 (m, 3H)	5.04-4.95 (m, 3H)	5.00-4.88 (m, 3H)	5.03-4.94 (m, 3H)	5.04-4.96 (m, 3H)
32	4.76 (tq, $J = 7.2$, 1.2 Hz, 1H)					
17	4.76 (tq, $J = 7.2$, 1.2 Hz, 1H)					
26a	3.20 (septet, $J = 7.2$ Hz, 2 H)	3.17 (dd, $J = 14.7$, 7.0 Hz, 1 H)	3.12 (dd, $J = 14.6$, 7.2 Hz, 1 H)	3.10 (dd, $J = 14.4$, 7.2 Hz, 1 H)	3.13 (dd, $J = 14.9$, 6.9 Hz, 1 H)	3.16 (dd, $J = 14.8$, 7.2 Hz, 1H)
26b		3.11 (dd, $J = 14.7$, 6.7 Hz, 1 H)	3.07 (dd, $J = 14.7$, 7.1 Hz, 1 H)	3.05 (dd, $J = 14.4$, 7.2 Hz, 1 H)	3.07 (dd, $J = 14.9$, 6.9 Hz, 1 H)	3.10 (dd, $J = 14.8$, 6.9 Hz, 1H)
31a	2.49 (dd, $J = 7.2$, 4.8 Hz, 2H)	2.54 (dd, $J = 14.1$, 6.7 Hz, 1H)	2.49 (dd, $J = 14.4$, 6.9 Hz, 1H)	2.47 (dd, $J = 14.4$, 6.6 Hz, 1H)	2.50 (dd, $J = 14.6$, 6.9 Hz, 1H)	2.52 (dd, $J = 14.9$, 6.8 Hz, 1H)
31b		2.44 (dd, $J = 14.1$, 7.0 Hz, 1H)	2.40 (dd, $J = 14.6$, 6.8 Hz, 1H)	2.37 (dd, $J = 14.4$, 6.6 Hz, 1H)	2.41 (dd, $J = 14.6$, 7.1 Hz, 1H)	2.43 (dd, $J = 14.6$, 7.1 Hz, 1H)
11	2.11 (m, 1H)	2.19-1.90 (m, 5H)	2.14 (septet, $J = 6.5$ Hz, 1H)	2.20-2.11 (m, 2H)	2.11-2.02 (m, 2H)	2.14-2.12 (m, 1H)
16a	2.02 (m, 2H)		2.10-2.02 (m, 1H)			2.11-2.04 (m, 1H)
6a			2.02-1.87 (m, 3H)	2.01-1.91 (m, 1H)	2.01-1.86 (m, 3H)	2.04-1.97 (m, 1H)
21a	2.02 (m, 1H)			1.97 (dd, $J = 13.2$, 4.8 Hz, 1 H)		1.97-1.89 (m, 2H)
21b	1.92 (m, 2H)			1.88 (dd, $J = 13.2$, 4.2 Hz, 1 H)		
7	1.80 (m, 2H)	1.79-1.66 (m, 4H)	1.78-1.72 (m, 3H)	1.75-1.62 (m, 4H)	1.77-1.70 (m, 3H)	1.80-1.74 (m, 4H)
15a						
16b	1.80 (m, 1H)					
15b	1.75 (m, 1H)		1.66-1.63 (m, 1H)		1.68-1.63 (m, 1H)	
6b	1.27 (m, 1H)	1.47-1.38 (m, 1H)	1.37 (dd, $J = 13.3$, 12.2 Hz, 1H)	1.42-1.34 (m, 1H)	1.39 (dd, $J = 13.3$, 12.2, 1H)	1.41 (t, $J = 12.7$ Hz, 1H)
30	1.70 (s, 3H)	1.74 (s, 3H)	1.71 (s, 3H)	1.69 (s, 3H)	1.70 (s, 3H)	1.73 (s, 3H)
19	1.64 (s, 3H)	1.72 (s, 6H)	1.68 (s, 6H)	1.67 (s, 6H)	1.68 (s, 6H)	1.71 (s, 6H)
34	1.60 (s, 6H)					
35		1.69 (s, 3H)	1.66 (s, 3H)	1.64 (s, 3H)	1.65 (s, 3H)	1.68 (s, 3H)
24	1.50 (s, 3H)	1.68 (s, 3H)	1.64 (s, 3H)	1.62 (s, 3H)	1.64 (d, $J = 0.8$ Hz, 3H)	1.67 (s, 3H)
29	1.50 (s, 3H)	1.66 (s, 3H)	1.63 (s, 3H)	1.62 (s, 3H)	1.62 (d, $J = 0.8$ Hz, 3H)	1.65 (s, 3H)
25	1.50 (s, 3H)	1.62 (s, 3H)	1.59 (s, 3H)	1.58 (s, 3H)	1.59 (s, 3H)	1.62 (s, 3H)
20	1.47 (s, 3H)	1.61 (s, 3H)	1.58 (s, 3H)	1.57 (s, 3H)	1.58 (s, 3H)	1.60 (s, 3H)
12	1.15 (dd, 6H)	1.12 (d, $J = 6.4$ Hz, 3H)	1.09 (d, $J = 6.5$ Hz, 3H)	1.08 (d, $J = 6.6$ Hz, 3H)	1.09 (d, $J = 6.4$ Hz, 3H)	1.11 (d, $J = 6.5$ Hz, 3H)
13		1.06 (d, $J = 6.4$ Hz, 3H)	1.04 (d, $J = 6.5$ Hz, 3H)	1.03 (d, $J = 6.6$ Hz, 3H)	1.03 (d, $J = 6.6$ Hz, 3H)	1.06 (d, $J = 6.5$ Hz, 3H)
14	0.98 (s, 3H)	1.01 (s, 3H)	0.97 (s, 3H)	0.96 (s, 3H)	0.97 (s, 3H)	1.00 (s, 3H)

¹³ C	150 MHz ¹	125 MHz ²	125 MHz ³	150 MHz ⁴	125 MHz ⁵	150 MHz (this work)
10	209.64	na	211.7	na	211.8	212.2
9	208.35	na	208.8	na	208.9	209.3
2	183.18	na	na		na	na
4	181.59	na	na	na	na	na
33	133.36	135.44	134.6	134.1	134.7	134.9
23	133.19	134.04	134.2	134.0	134.3	134.5
28	132.93	132.63	133.5	132.4	133.6	133.8
18	131.61	na	131.8	131.6	131.9	132.1
17	126.61	126.98	126.0	126.4	126.1	126.4
22	122.71	124.73	123.8	124.1	123.9	124.1
27	122.31	123.66	122.6	123.6	122.6	123.0
3	121.21	122.82	122.1	121.7	122.1	122.3
32	120.25	121.90	120.9	121.6	120.9	121.3
1	82.42	na	82.6	na	na	na
5	58.27	na	60.7	na	na	na
8	47.81	na	49.5	na	49.5	49.9
11	42.57	43.94	43.1	43.3	43.1	43.4
7	41.57	43.68	43.0	42.8	43.0	43.3
6	40.27	41.68	40.8	40.7	40.8	41.1
15	37.68	38.81	37.9	38.0	37.9	38.3
31	30.03	31.59	30.7	30.9	30.7	31.0
21	27.66	29.52	28.6	28.7	28.7	29.0
34	25.01	27.02	26.2	26.2	26.2	26.4
29	24.99	26.90	26.1	26.1	26.1	26.3
24	24.90	26.83	26.0	26.0	26.0	26.3
19	24.88	26.74	25.9	25.9	25.9	26.2
16	24.00	26.33	25.4	25.6	25.5	25.8
26	22.40	23.43	22.5	22.9	22.6	22.9
12	20.44	22.86	22.0	22.2	22.0	22.3
13	19.36	22.01	21.2	21.2	21.2	21.4
35	18.14	19.10	18.3	18.3	18.3	18.5
25	18.10	19.01	18.2	18.2	18.2	18.4
20	18.01	18.94	18.1	18.1	18.1	18.4
30	17.92	18.70	17.9	17.9	17.9	18.1
14	15.80	16.13	15.3	15.3	15.3	15.6

X-ray Crystallography of 11

A colorless plate 0.060 x 0.040 x 0.010 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 60 mm and exposure time was 20 seconds per frame using a scan width of 2.0°. Data collection was 99.8% complete to 67.000° in θ . A total of 36801 reflections were collected covering the indices, $-7 \leq h \leq 8$, $-24 \leq k \leq 24$, $-18 \leq l \leq 20$. 4502 reflections were found to be symmetry independent, with an R_{int} of 0.0657. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21/n (No. 14). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Crystal data and structure refinement for compound **11**

Empirical formula	C ₂₇ H ₄₂ O ₃	
Formula weight	414.60	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 2 ₁ /n	
Unit cell dimensions	a = 6.9326(2) Å	α = 90°.
	b = 20.5641(5) Å	β = 94.577(2)°.
	c = 17.2667(5) Å	γ = 90°.
Volume	2453.74(12) Å ³	
Z	4	
Density (calculated)	1.122 Mg/m ³	
Absorption coefficient	0.549 mm ⁻¹	
F(000)	912	
Crystal size	0.060 x 0.040 x 0.010 mm ³	
Theta range for data collection	3.348 to 68.975°.	
Index ranges	-7 ≤ h ≤ 8, -24 ≤ k ≤ 24, -18 ≤ l ≤ 20	
Reflections collected	36801	
Independent reflections	4502 [R(int) = 0.0657]	
Completeness to theta = 67.000°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.929 and 0.860	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	4502 / 0 / 280	
Goodness-of-fit on F ²	1.019	
Final R indices [I > 2σ(I)]	R ₁ = 0.0437, wR ₂ = 0.1054	
R indices (all data)	R ₁ = 0.0678, wR ₂ = 0.1166	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.232 and -0.190 e.Å ⁻³	

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **11**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
C(1)	5312(2)	7285(1)	6547(1)	22(1)
C(2)	5177(2)	6576(1)	6910(1)	24(1)
C(3)	3575(2)	6648(1)	7502(1)	24(1)
C(4)	2984(2)	7366(1)	7492(1)	25(1)
C(5)	3343(2)	7606(1)	6683(1)	22(1)
C(6)	1767(2)	7377(1)	6077(1)	23(1)
C(7)	2256(2)	7274(1)	5285(1)	25(1)
C(8)	4105(2)	7221(1)	5115(1)	23(1)
C(9)	5784(2)	7319(1)	5699(1)	23(1)
C(10)	7177(2)	6374(1)	7286(1)	28(1)
C(11)	4495(3)	6056(1)	6302(1)	27(1)
C(12)	4360(3)	5363(1)	6619(1)	33(1)
C(13)	3527(3)	4886(1)	6031(1)	33(1)
C(14)	1763(3)	4624(1)	5981(1)	36(1)
C(15)	241(3)	4774(1)	6522(2)	52(1)
C(16)	1167(3)	4131(1)	5365(1)	50(1)
C(17)	4041(3)	6394(1)	8333(1)	28(1)
C(18)	2288(3)	6426(1)	8789(1)	27(1)
C(19)	1146(3)	5938(1)	8962(1)	26(1)
C(20)	-590(3)	6048(1)	9412(1)	33(1)
C(21)	1467(3)	5245(1)	8755(1)	46(1)
C(22)	3379(2)	8360(1)	6623(1)	25(1)
C(23)	1618(3)	8686(1)	6899(1)	27(1)
C(24)	146(3)	8946(1)	6469(1)	30(1)
C(25)	-59(3)	8947(1)	5598(1)	42(1)
C(26)	-1500(3)	9267(1)	6834(1)	41(1)
C(27)	3295(3)	6996(1)	3773(1)	36(1)
O(1)	6732(2)	7657(1)	7002(1)	25(1)
O(2)	85(2)	7310(1)	6248(1)	28(1)
O(3)	4727(2)	7084(1)	4412(1)	28(1)

Table 3. Bond lengths [$\text{\AA}$] and angles [$^\circ$] for **11**.

C(1)-O(1)	1.431(2)	C(15)-H(15A)	0.9800
C(1)-C(9)	1.528(2)	C(15)-H(15B)	0.9800
C(1)-C(5)	1.551(2)	C(15)-H(15C)	0.9800
C(1)-C(2)	1.593(2)	C(16)-H(16A)	0.9800
C(2)-C(10)	1.539(2)	C(16)-H(16B)	0.9800
C(2)-C(11)	1.546(2)	C(16)-H(16C)	0.9800
C(2)-C(3)	1.576(2)	C(17)-C(18)	1.502(2)
C(3)-C(4)	1.532(2)	C(17)-H(17A)	0.9900
C(3)-C(17)	1.536(2)	C(17)-H(17B)	0.9900
C(3)-H(3)	1.0000	C(18)-C(19)	1.327(3)
C(4)-C(5)	1.521(2)	C(18)-H(18)	0.9500
C(4)-H(4A)	0.9900	C(19)-C(21)	1.491(3)
C(4)-H(4B)	0.9900	C(19)-C(20)	1.501(2)
C(5)-C(6)	1.527(2)	C(20)-H(20A)	0.9800
C(5)-C(22)	1.554(2)	C(20)-H(20B)	0.9800
C(6)-O(2)	1.234(2)	C(20)-H(20C)	0.9800
C(6)-C(7)	1.451(2)	C(21)-H(21A)	0.9800
C(7)-C(8)	1.342(2)	C(21)-H(21B)	0.9800
C(7)-H(7)	0.9500	C(21)-H(21C)	0.9800
C(8)-O(3)	1.350(2)	C(22)-C(23)	1.503(2)
C(8)-C(9)	1.491(2)	C(22)-H(22A)	0.9900
C(9)-H(9A)	0.9900	C(22)-H(22B)	0.9900
C(9)-H(9B)	0.9900	C(23)-C(24)	1.325(3)
C(10)-H(10A)	0.9800	C(23)-H(23)	0.9500
C(10)-H(10B)	0.9800	C(24)-C(25)	1.499(3)
C(10)-H(10C)	0.9800	C(24)-C(26)	1.500(3)
C(11)-C(12)	1.533(3)	C(25)-H(25A)	0.9800
C(11)-H(11A)	0.9900	C(25)-H(25B)	0.9800
C(11)-H(11B)	0.9900	C(25)-H(25C)	0.9800
C(12)-C(13)	1.495(3)	C(26)-H(26A)	0.9800
C(12)-H(12A)	0.9900	C(26)-H(26B)	0.9800
C(12)-H(12B)	0.9900	C(26)-H(26C)	0.9800
C(13)-C(14)	1.332(3)	C(27)-O(3)	1.435(2)
C(13)-H(13)	0.9500	C(27)-H(27A)	0.9800
C(14)-C(15)	1.495(3)	C(27)-H(27B)	0.9800
C(14)-C(16)	1.504(3)	C(27)-H(27C)	0.9800

O(1)-H(1)	0.8400		
O(1)-C(1)-C(9)	108.11(13)	C(8)-C(7)-H(7)	119.4
O(1)-C(1)-C(5)	105.28(13)	C(6)-C(7)-H(7)	119.4
C(9)-C(1)-C(5)	112.55(14)	C(7)-C(8)-O(3)	126.31(16)
O(1)-C(1)-C(2)	109.49(13)	C(7)-C(8)-C(9)	123.34(16)
C(9)-C(1)-C(2)	116.32(14)	O(3)-C(8)-C(9)	110.35(14)
C(5)-C(1)-C(2)	104.53(13)	C(8)-C(9)-C(1)	115.22(14)
C(10)-C(2)-C(11)	108.44(14)	C(8)-C(9)-H(9A)	108.5
C(10)-C(2)-C(3)	114.19(14)	C(1)-C(9)-H(9A)	108.5
C(11)-C(2)-C(3)	108.22(14)	C(8)-C(9)-H(9B)	108.5
C(10)-C(2)-C(1)	109.46(14)	C(1)-C(9)-H(9B)	108.5
C(11)-C(2)-C(1)	112.95(14)	H(9A)-C(9)-H(9B)	107.5
C(3)-C(2)-C(1)	103.62(13)	C(2)-C(10)-H(10A)	109.5
C(4)-C(3)-C(17)	111.96(15)	C(2)-C(10)-H(10B)	109.5
C(4)-C(3)-C(2)	106.57(14)	H(10A)-C(10)-H(10B)	109.5
C(17)-C(3)-C(2)	117.87(14)	C(2)-C(10)-H(10C)	109.5
C(4)-C(3)-H(3)	106.6	H(10A)-C(10)-H(10C)	109.5
C(17)-C(3)-H(3)	106.6	H(10B)-C(10)-H(10C)	109.5
C(2)-C(3)-H(3)	106.6	C(12)-C(11)-C(2)	115.08(15)
C(5)-C(4)-C(3)	105.11(14)	C(12)-C(11)-H(11A)	108.5
C(5)-C(4)-H(4A)	110.7	C(2)-C(11)-H(11A)	108.5
C(3)-C(4)-H(4A)	110.7	C(12)-C(11)-H(11B)	108.5
C(5)-C(4)-H(4B)	110.7	C(2)-C(11)-H(11B)	108.5
C(3)-C(4)-H(4B)	110.7	H(11A)-C(11)-H(11B)	107.5
H(4A)-C(4)-H(4B)	108.8	C(13)-C(12)-C(11)	113.48(16)
C(4)-C(5)-C(6)	111.62(14)	C(13)-C(12)-H(12A)	108.9
C(4)-C(5)-C(1)	102.16(13)	C(11)-C(12)-H(12A)	108.9
C(6)-C(5)-C(1)	110.76(14)	C(13)-C(12)-H(12B)	108.9
C(4)-C(5)-C(22)	113.00(14)	C(11)-C(12)-H(12B)	108.9
C(6)-C(5)-C(22)	106.07(13)	H(12A)-C(12)-H(12B)	107.7
C(1)-C(5)-C(22)	113.36(13)	C(14)-C(13)-C(12)	127.68(19)
O(2)-C(6)-C(7)	120.46(16)	C(14)-C(13)-H(13)	116.2
O(2)-C(6)-C(5)	120.55(16)	C(12)-C(13)-H(13)	116.2
C(7)-C(6)-C(5)	118.89(14)	C(13)-C(14)-C(15)	124.5(2)
C(8)-C(7)-C(6)	121.11(15)	C(13)-C(14)-C(16)	121.10(19)

C(15)-C(14)-C(16)	114.37(18)	H(21B)-C(21)-H(21C)	109.5
C(14)-C(15)-H(15A)	109.5	C(23)-C(22)-C(5)	113.98(14)
C(14)-C(15)-H(15B)	109.5	C(23)-C(22)-H(22A)	108.8
H(15A)-C(15)-H(15B)	109.5	C(5)-C(22)-H(22A)	108.8
C(14)-C(15)-H(15C)	109.5	C(23)-C(22)-H(22B)	108.8
H(15A)-C(15)-H(15C)	109.5	C(5)-C(22)-H(22B)	108.8
H(15B)-C(15)-H(15C)	109.5	H(22A)-C(22)-H(22B)	107.7
C(14)-C(16)-H(16A)	109.5	C(24)-C(23)-C(22)	127.66(18)
C(14)-C(16)-H(16B)	109.5	C(24)-C(23)-H(23)	116.2
H(16A)-C(16)-H(16B)	109.5	C(22)-C(23)-H(23)	116.2
C(14)-C(16)-H(16C)	109.5	C(23)-C(24)-C(25)	124.70(18)
H(16A)-C(16)-H(16C)	109.5	C(23)-C(24)-C(26)	121.28(19)
H(16B)-C(16)-H(16C)	109.5	C(25)-C(24)-C(26)	114.01(17)
C(18)-C(17)-C(3)	110.88(14)	C(24)-C(25)-H(25A)	109.5
C(18)-C(17)-H(17A)	109.5	C(24)-C(25)-H(25B)	109.5
C(3)-C(17)-H(17A)	109.5	H(25A)-C(25)-H(25B)	109.5
C(18)-C(17)-H(17B)	109.5	C(24)-C(25)-H(25C)	109.5
C(3)-C(17)-H(17B)	109.5	H(25A)-C(25)-H(25C)	109.5
H(17A)-C(17)-H(17B)	108.1	H(25B)-C(25)-H(25C)	109.5
C(19)-C(18)-C(17)	127.39(17)	C(24)-C(26)-H(26A)	109.5
C(19)-C(18)-H(18)	116.3	C(24)-C(26)-H(26B)	109.5
C(17)-C(18)-H(18)	116.3	H(26A)-C(26)-H(26B)	109.5
C(18)-C(19)-C(21)	124.46(18)	C(24)-C(26)-H(26C)	109.5
C(18)-C(19)-C(20)	121.36(17)	H(26A)-C(26)-H(26C)	109.5
C(21)-C(19)-C(20)	114.16(16)	H(26B)-C(26)-H(26C)	109.5
C(19)-C(20)-H(20A)	109.5	O(3)-C(27)-H(27A)	109.5
C(19)-C(20)-H(20B)	109.5	O(3)-C(27)-H(27B)	109.5
H(20A)-C(20)-H(20B)	109.5	H(27A)-C(27)-H(27B)	109.5
C(19)-C(20)-H(20C)	109.5	O(3)-C(27)-H(27C)	109.5
H(20A)-C(20)-H(20C)	109.5	H(27A)-C(27)-H(27C)	109.5
H(20B)-C(20)-H(20C)	109.5	H(27B)-C(27)-H(27C)	109.5
C(19)-C(21)-H(21A)	109.5	C(1)-O(1)-H(1)	109.5
C(19)-C(21)-H(21B)	109.5	C(8)-O(3)-C(27)	117.81(14)
H(21A)-C(21)-H(21B)	109.5		
C(19)-C(21)-H(21C)	109.5		
H(21A)-C(21)-H(21C)	109.5		

Symmetry transformations used to generate

equivalent atoms:

Table 4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **11**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	20(1)	22(1)	24(1)	0(1)	2(1)	-2(1)
C(2)	20(1)	24(1)	27(1)	3(1)	1(1)	1(1)
C(3)	20(1)	23(1)	29(1)	3(1)	1(1)	-1(1)
C(4)	23(1)	25(1)	26(1)	1(1)	4(1)	1(1)
C(5)	19(1)	23(1)	26(1)	1(1)	3(1)	-1(1)
C(6)	20(1)	18(1)	32(1)	4(1)	3(1)	1(1)
C(7)	22(1)	24(1)	27(1)	2(1)	-3(1)	-2(1)
C(8)	26(1)	18(1)	26(1)	1(1)	2(1)	-3(1)
C(9)	18(1)	22(1)	28(1)	0(1)	3(1)	-1(1)
C(10)	22(1)	29(1)	33(1)	6(1)	2(1)	1(1)
C(11)	27(1)	24(1)	30(1)	2(1)	4(1)	1(1)
C(12)	34(1)	25(1)	38(1)	4(1)	3(1)	0(1)
C(13)	36(1)	24(1)	42(1)	-1(1)	12(1)	1(1)
C(14)	37(1)	28(1)	43(1)	-1(1)	9(1)	-1(1)
C(15)	39(1)	63(2)	57(1)	-14(1)	11(1)	-5(1)
C(16)	49(1)	42(1)	61(2)	-14(1)	15(1)	-13(1)
C(17)	27(1)	26(1)	30(1)	4(1)	1(1)	-1(1)
C(18)	34(1)	24(1)	24(1)	2(1)	4(1)	3(1)
C(19)	28(1)	25(1)	26(1)	3(1)	1(1)	2(1)
C(20)	35(1)	32(1)	33(1)	5(1)	9(1)	1(1)
C(21)	48(1)	29(1)	64(2)	0(1)	23(1)	-3(1)
C(22)	20(1)	23(1)	32(1)	1(1)	1(1)	-2(1)
C(23)	29(1)	20(1)	32(1)	-1(1)	6(1)	-3(1)
C(24)	25(1)	20(1)	43(1)	-2(1)	2(1)	-5(1)
C(25)	37(1)	40(1)	46(1)	5(1)	-10(1)	3(1)
C(26)	29(1)	25(1)	69(2)	-5(1)	6(1)	1(1)
C(27)	33(1)	45(1)	29(1)	-4(1)	-3(1)	-3(1)
O(1)	18(1)	28(1)	29(1)	-3(1)	-1(1)	-2(1)
O(2)	19(1)	30(1)	37(1)	2(1)	4(1)	-1(1)
O(3)	27(1)	33(1)	23(1)	-1(1)	1(1)	-2(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for maimone55.

	x	y	z	U(eq)
H(3)	2423	6398	7280	29
H(4A)	1602	7413	7589	30
H(4B)	3777	7613	7894	30
H(7)	1251	7244	4879	29
H(9A)	6362	7750	5606	27
H(9B)	6774	6986	5612	27
H(10A)	7091	5939	7514	42
H(10B)	7600	6686	7693	42
H(10C)	8112	6368	6889	42
H(11A)	3205	6184	6062	32
H(11B)	5399	6055	5886	32
H(12A)	5671	5216	6812	39
H(12B)	3548	5368	7066	39
H(13)	4353	4754	5647	40
H(15A)	677	5134	6864	78
H(15B)	10	4389	6836	78
H(15C)	-960	4897	6220	78
H(16A)	2183	4093	5004	75
H(16B)	-41	4270	5080	75
H(16C)	972	3708	5609	75
H(17A)	4496	5938	8313	33
H(17B)	5093	6658	8595	33
H(18)	1958	6843	8975	33
H(20A)	-402	5827	9915	50
H(20B)	-1744	5873	9119	50
H(20C)	-758	6515	9496	50
H(21A)	2628	5211	8469	69
H(21B)	345	5084	8430	69
H(21C)	1640	4984	9230	69
H(22A)	4539	8525	6933	30

H(22B)	3499	8483	6075	30
H(23)	1552	8709	7445	32
H(25A)	1075	8738	5401	63
H(25B)	-157	9396	5409	63
H(25C)	-1229	8707	5414	63
H(26A)	-1310	9224	7400	62
H(26B)	-2719	9058	6647	62
H(26C)	-1546	9729	6694	62
H(27A)	2442	6634	3887	54
H(27B)	3937	6899	3301	54
H(27C)	2529	7394	3696	54
H(1)	7834	7580	6854	38

7

—223.80

7

132.64
131.80
124.46
122.74

—51.50

—43.32

37.62

36.15

28.74

25.97

25.81

25.14

23.48

18.03

17.99

17.75

9

11

10

10

134.42
131.88
131.32
124.90
123.94
120.57

103.62

84.84

56.28
53.84
51.76
46.59
45.54
40.30
39.94
35.91
30.56
26.11
25.96
25.76
23.62
18.09
17.98
17.79
15.26

hyperforin, 1

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134.93
134.49
133.76
132.10
126.39
124.14
122.99
122.34
121.28

49.87
43.41
41.13
38.27
31.02
28.96
26.42
26.32
26.27
26.25
26.17
25.77
22.86
22.28
21.44
18.53
18.45
18.37
18.14
15.56