Supporting Information for:

**An Enantioselective Synthesis of Imperanene via Enzymatic Asymmetrization of an
Intermediary 1,3-diol**

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General Procedures

Lipases PS-30 and AYS were generous gifts from Amano Enzymes and Novozyn-435 was donated by Novo Nordisk. ^1H -NMR and ^{13}C -NMR spectra were recorded on a Bruker 250 MHz spectrometer in CDCl_3 with TMS as the standard. Optical rotations were measured with a Rudolph Research Analytical AutoPol IV Automatic polarimeter. Thin-Layer chromatography (TLC) was performed on glass plates coated with 0.25mm thickness of silica-gel. All solvents were dried and distilled prior to use and organic solvent extracts dried over Na_2SO_4 .

4-formyl-2-methoxyphenyl 4-methylbenzenesulfonate (3). To a solution of vanillin (100g, 657 mmol) dissolved in dry acetone (500 ml) was added anhydrous K_2CO_3 (182g, 1314 mmol) and the mixture allowed stirring for 10 minutes at room temperature. To the solution was added tosyl chloride (251g, 1314 mmol) and the mixture refluxed for 24 hours. The solution was cooled to room temperature, filtered, and concentrated in vacuo. To the resulting solid was added hexane, the solution was warmed, then cooled to room temperature. The solid was vacuum-filtered and the solid washed with cold hexane to afford an off-white solid (191.5g, 657.2 mmol, 95%). ^1H NMR (250MHz, CDCl_3) δ : 2.46 (s, 3H, Ph-CH_3), 3.63 (s, 3H, $-\text{OCH}_3$), 7.28-7.77 (comp, 7H), 9.93 (s, 1H, C(O)H). ^{13}C NMR (62.5 MHz, CDCl_3) δ : 21.7, 55.7, 110.9, 124.3, 124.5, 128.5, 129.5, 132.7, 135.6, 142.9, 145.5, 152.5, 190.9.

4-(Hydroxymethyl)-2-methoxyphenyl 4-methylbenzenesulfonate (4). To a solution of protected vanillin **3** (75g, 245 mmol) in dry methanol (250 ml) cooled at 0°C was added sodium borohydride (23g, 612 mmol) portionwise over a 2 hr period. The reaction was brought to room temperature and allowed to stir for a further 12 hours. The mixture was concentrated under reduced pressure and to the resulting solid was added ethyl acetate (400 ml) followed by a solution of ammonium chloride (200 ml). The solution was extracted, the organic layer dried over sodium sulfate and concentrated under reduced pressure. Acetone was added to the resulting solid, cooled to 0°C and vacuum-filtered to afford a white solid (74.5g, 245 mmol, 99%), m.p. $84\text{--}87^\circ\text{C}$. IR (cm^{-1}) 2360, 1360, 1170, 1030, 843, 820. ^1H NMR (250MHz, CDCl_3) δ : 2.44 (s, 3H, Ph-CH_3), 3.54 (s, 3H, -

OCH₃), 4.63 (s, 2H, -CH₂OH), 6.81-7.09 (comp, 3H), 7.28-7.74 (dd, 4H, *J* = 8.2, 8.2 Hz, -OTs). ¹³C NMR (62.5 MHz, CDCl₃) δ: 21.6, 55.4, 64.4, 110.9, 118.5, 123.7, 128.5, 129.3, 133.0, 137.3, 141.2, 145.0, 151.7.

4-(Bromomethyl)-2-methoxyphenyl 4-methylbenzenesulfonate (5). To a solution of the alcohol **4** (36g, 117 mmol) in dry ether (250 ml) was added phosphorus tribromide (47g, 175 mmol) dissolved in dry ether (50 ml) and the reaction allowed to stir at room temperature for 45 minutes. The reaction was cooled to 0°C and ice water (approximately 100ml) was *carefully* added over a 30 minute period. The mixture was extracted and the organic layer dried over sodium sulfate and concentrated under reduced pressure. Hexane (100 ml) was added to the resulting solid and vacuum-filtered to afford an off-white solid (42.5g, 117 mmol, 98%), m.p. 69-71°C. IR (cm⁻¹) 1590, 1500, 1370, 1180, 1110, 1090, 1030, 866, 814. ¹H NMR (250MHz, CDCl₃) δ: 2.45 (s, 3H, Ph-CH₃), 3.57 (s, 3H, -OCH₃), 4.42 (s, 2H, -CH₂Br), 6.86-7.09 (comp, 3H), 7.27-7.76 (dd, 4H, *J* = 8.2, 8.2 Hz, -OTs). ¹³C NMR (62.5 MHz, CDCl₃) δ: 21.7, 32.7, 55.5, 113.2, 121.1, 124.0, 128.5, 129.4, 133.0, 137.7, 138.1, 145.1, 151.8.

2-Methoxy-4-(triphenylphosphinomethyl bromide)phenyl 4-methylbenzenesulfonate (6). To a solution of the bromide **5** (25g, 67 mmol) in dry toluene was added freshly recrystallized triphenylphosphine (26g, 101 mmol) and the solution refluxed for 24 hours. The mixture was cooled to room temperature, filtered under reduced pressure, and washed with dry ether to afford a white solid (41.5g, 67.3 mmol, 97%), 235-238°C. IR (cm⁻¹) 1500, 1440, 1340, 1180, 1120, 843. ¹H NMR (250MHz, DMSO-d₆) δ: 2.39 (s, 3H, Ph-CH₃), 3.02 (s, 3H, -OCH₃), 5.26 (d, 2H, *J* = 15.6 Hz, Ph-CH₂), 6.56-6.99 (comp, 3H), 7.39-7.93 (comp, 19H). ¹³C-NMR (62.5 MHz, DMSO-d₆) δ: 21.2, 28.3, 55.2, 115.9, 116.8, 118.2, 123.2, 123.8, 128.3, 128.6, 129.7, 130.0, 130.2, 131.6, 134.1, 134.2, 135.2, 137.2, 145.7, 150.8.

Diethyl 2-(3-methoxy-4-(tosyloxy)benzyl)malonate (7). To a solution of distilled diethyl malonate (19g, 121 mmol) in dry THF (150 ml) at 0°C was added sodium hydride (2.9g, 121 mmol) portionwise under a nitrogen atmosphere. The reaction was allowed to stir for 20 minutes and a solution of bromide **5** (30g, 81 mmol) in dry THF (100 ml) was added dropwise over a 90 minute period. The solution was warmed to room temperature and allowed to stir for a further 12 hours. The solution was concentrated under reduced pressure and the viscous liquid taken up in ethyl acetate (400 ml) and extracted with aqueous sodium chloride (250 ml). The organic layer was dried over sodium sulfate and concentrated. The product was purified by silica gel chromatography using a gradient eluent of ethyl acetate: hexane (2:8) followed by ethyl acetate: hexane (3:7) to afford **7** (33g, 81 mmol, 91%) as light yellow viscous oil. IR (cm⁻¹) 2990, 1730, 1510, 1250, 1180, 1040, 839. ¹H NMR (250MHz, CDCl₃) δ: 1.21 (t, 6H, *J* = 7.1 Hz, -OCH₂CH₃), 2.44 (s, 3H, Ph-CH₃), 3.17 (d, 2H, *J* = 7.8 Hz, -CH₂CH), 3.53 (s, 3H, -OCH₃), 3.60 (t, 1H, *J* = 7.8 Hz, -CH₂CH), 4.16 (q, 4H, *J* = 7.1 Hz, -OCH₂CH₃), 6.69-7.04 (comp, 3H), 7.28-7.74 (dd, 4H, *J* = 8.2 Hz, OTs). ¹³C NMR (62.5 MHz, CDCl₃) δ: 13.9, 21.6, 34.4, 53.5, 55.4, 61.5, 113.2, 120.8, 123.8, 128.5, 129.2, 133.1, 137.0, 138.1, 145.0, 151.5, 168.6.

4-(3-Hydroxy-2-(hydroxymethyl)propyl)-2-methoxyphenyl-4-methylbenzene sulfonate (8).¹⁷

To a solution of **7** (20g, 44 mmol) in methanol:ether (1:3) cooled at 0°C was added lithium chloride (8g, 178 mmol) and the reaction stirred for an additional 10 minutes. Sodium borohydride (6.7g, 178 mmol) was then added portionwise over a 30 minute period and the reaction warmed to room temperature and allowed to stir for a further 8 hours. The solution was concentrated, the residue taken up in ethyl acetate (400 ml) and extracted with aqueous ammonium chloride solution (150 ml). The organic layer was dried over sodium sulfate and the resulting product was purified by silica gel chromatography using ethyl acetate as the eluent affording **8** (14.5g, yield = 89%) as a colorless viscous liquid. ¹H NMR (250MHz, CDCl₃) δ: 2.20 (m, 1H, -CH₂CH), 2.44 (s, 3H, Ph-CH₃), 2.54 (d, 2H, *J* = 7.6 Hz, -CH₂CH), 3.55 (s, 3H, -OCH₃), 3.72 (dd, 2H, *J* = 10 Hz and 3 Hz, -CH₂OH), 3.98 (dd, 2H, *J* = 10 Hz and 3 Hz, -CH₂OH), 6.61-6.68 (comp, 3H), 7.27-7.76 (dd, 4H, *J* = 8.2 Hz, OTs). ¹³C NMR (62.5 MHz, CDCl₃) δ: 14.1, 21.6, 34.0, 37.8, 55.5, 60.4, 66.6, 112.9, 120.7, 123.9, 128.5, 129.3, 133.1, 136.9, 138.7, 145.0, 151.7.

2-(Hydroxymethyl)-3-(3-methoxy-4-(tosyloxy)phenyl)propyl acetate (9). To a solution of **8** (10g, 27 mmol) in dry THF (30 ml) was added PS-30 (5g) followed by vinyl acetate (3.5g, 41 mmol). The reaction was allowed to stir at 40°C for 48 hours and the reaction was filtered under vacuum with subsequent concentration of the filtrate. The product was purified by wet column chromatography using ethyl acetate: hexane (2:1) to afford a clear viscous liquid (7.5g, 27 mmol, 62%). $[\alpha]_D^{25} = +7.9^\circ$ (CHCl₃, *c* = 0.027). IR (cm⁻¹) 3440, 2930, 1740, 1510, 1240, 1030, 862. ¹H-NMR (250MHz, CDCl₃) δ: 1.85 (m, 1H, -CH₂CH), 2.08 (s, 3H, -C(O)CH₃), 2.44 (s, 3H, Ph-CH₃), 2.54 (dd, 2H, *J* = 7.6 Hz and 18.9 Hz, -CH₂CH), 3.55 (m, 5H, -OCH₃, -OCH₂OH), 4.06 (dd, 2H, *J* = 11.3 Hz and 4.8 Hz, -CH₂C(O)CH₃), 6.65-6.71 (comp, 3H), 7.27-7.76 (dd, 4H, *J* = 8.2 Hz, OTs). ¹³C NMR (62.5 MHz, CDCl₃) δ: 20.6, 21.3, 34.3, 38.7, 55.5, 63.5, 113.1, 120.9, 124.0, 128.5, 129.3, 133.1, 136.7, 139.2, 145.6, 151.6, 171.0.

2-Formyl-3-(3-methoxy-4-(tosyloxy)phenyl)propyl acetate (10). To a solution of **9** (1g, 2.4 mmol) in dry dichloromethane (30 ml) at 0°C was added Dess-Martin Periodinane (5ml, 15% w/v). The reaction was allowed to stir at 0°C for a further 90 minutes then allowed to warm to room temperature and stirred for an additional 2 hours. A solution of sodium thiosulfate (15ml) was added and the solution stirred for an additional 15 minutes, then vacuum-filtered over celite. An additional 30 ml of dichloromethane was added and extracted with aqueous sodium chloride (20 ml). The organic layer was dried over sodium sulfate, concentrated, and the product (amber liquid, 0.750g, 2.4 mmol, 75%) used immediately in the next reaction without further purification. IR (cm⁻¹) 2930, 1740, 1510, 1230, 1040, 845. ¹H-NMR (250MHz, CDCl₃) δ: 2.04 (s, 3H, -C(O)CH₃), 2.45 (s, 3H, Ph-CH₃), 2.77 (dd, 2H, *J* = 7.8 Hz and 13.6 Hz, -CH₂CH), 2.91 (m, 1H, -CH₂CH), 3.53 (s, 3H, -OCH₃), 4.2 (dd, 2H, *J* = 11.3 Hz and 4.8 Hz, -CH₂C(O)CH₃), 6.65-6.71 (comp, 3H), 7.27-7.76 (dd, 4H, *J* = 8.2 Hz, OTs), 9.66 (s, 1H, -C(O)H).

(E)-2-(3-methoxy-4-(tosyloxy)benzyl)-4-(3-methoxy-4-(tosyloxy)phenyl)but-3-enyl acetate (11). To a solution of the Wittig reagent (9.7g, 15 mmol) **6** in dry THF under a

nitrogen atmosphere at 0°C was added *n*-butyl lithium (0.98g, 15 mmol). The reaction was allowed to stir for an additional 30 minutes and a solution of the aldehyde **10** (2.5g, 6.2 mmol) in dry THF (10 ml) was added to the sanguineous solution at 0°C. The reaction was allowed to warm to room temperature and stirred for an additional 19 hours. The solution was then concentrated, and the residue taken up in ethyl acetate (50 ml) and extracted with brine (20 ml). Purification over wet silica chromatography using ethyl acetate: hexane (2:8) provided compound **11** as a viscous, amber liquid (3.58g, 6.15 mmol, 88%). IR (cm⁻¹) 2960, 1740, 1370, 1170, 1090, 852, 810. ¹H NMR (250MHz, CDCl₃) δ: 1.98 (s, 3H, C(O)CH₃), 2.43 (s, 6H, Ph-CH₃), 2.61 (m, 3H, Ph-CH₂-CH-), 3.37 (s, 3H, -OCH₃), 3.44 (s, 3H, -OCH₃), 4.01 (m, 2H, -CH₂OAc), 5.84 (dd, 1H, *J* = 7.9, 15.8 Hz), 6.27 (d, 1H, *J* = 15.8 Hz), 6.33-7.15 (comp, 6H), 7.19-7.70 (comp, 8H); ¹³C- NMR (62.5 MHz, CDCl₃) δ: 14.1, 21.6, 37.8, 43.8, 55.5, 60.5, 66.2, 110.0, 113.3, 118.2, 121.0, 123.5, 124.0, 128.5, 129.3, 130.6, 131.0, 133.0, 136.3, 136.7, 137.1, 139.2, 145.0, 151.3, 151.6, 170.5.

3-(3-methoxy-4-(tosyloxy)phenyl)-2-((tosyloxy)methyl)propyl acetate (12). To a solution of the monoacetate **9** (2.17g, 5.31 mmol) in dry dichloromethane (30 ml) was added triethyl amine (0.81g, 8 mmol) and DMAP (100mg) at 0°C. Tosyl chloride (1.52g, 8.0 mmol) was then added and allowed to stir at r.t. for 8 hours. The solution was then concentrated and ethyl ether was added and the solution filtered. The filtrate was concentrated under reduced pressure and purified by flash column chromatography using EA/hexane (4:6) to afford a viscous colorless liquid (2.79g, 5.31 mmol, 93%). [α]_D²⁵ = -11.3° (CHCl₃, *c* = 0.035). IR (cm⁻¹) 3560, 2960, 1740, 1600, 1510, 1370, 1170, 852, 810. ¹H-NMR (250MHz, CDCl₃) δ: 1.88 (s, 3H, C(O)CH₃), 2.45 (m, 1H, CH), 2.38 (s, 3H, Ph-CH₃), 2.39 (s, 3H, Ph-CH₃), 2.54 (d, 2H, *J* = 7.4 Hz, Ph-CH₂), 3.45 (s, 3H, -OCH₃), 3.85 (m, 4H, -CH₂OAc, -CH₂OTs), 6.50-7.12 (comp, 3H, -Ph), 7.25-7.77 (m, 8H, -OTs); ¹³C-NMR (62.5 MHz, CDCl₃) δ: 20.6, 21.6, 33.7, 39.3, 55.5, 62.9, 68.5, 113.3, 120.8, 124.0, 127.8, 128.5, 129.3, 129.9, 132.5, 133.1, 145.0, 151.7, 170.5.

3-(3-methoxy-4-(tosyloxy)phenyl)-2-(hydroxymethyl)-1-(tosyloxy)propane (13). To a solution of the monoacetate **12** (2.5g, 4.4 mmol) in dry methanol (20 ml) was added anhydrous potassium carbonate (1.2g, 8.8 mmol). The reaction was allowed to stir at room temperature for 3 hours upon which it was concentrated and purified by flash column chromatography using ethyl acetate: hexane (4:6) affording a viscous colorless liquid **13** (2.0g, 4.4 mmol, 86%). [α]_D²⁵ = -9.7° (CHCl₃, *c* = 0.020). ¹H NMR (250MHz, CDCl₃) δ: 1.98 (m, 1H, CH), 2.37 (s, 6H, Ph-CH₃), 2.52 (dd, 2H, *J* = 6.3, 5.9 Hz, Ph-CH₂), 3.44 (s, 3H, -OCH₃), 3.47 (m, 2H, -CH₂OH), 3.94 (m, 2H, -CH₂OTs), 6.53-6.94 (comp, 3H), 7.19-7.70 (comp, 8H); ¹³C- NMR (62.5 MHz, CDCl₃) δ: 21.6, 33.4, 42.4, 55.5, 69.2, 113.3, 120.9, 127.8, 128.5, 129.3, 132.6, 133.2, 136.8, 139.0, 145.0, 151.6.

3-(3-methoxy-4-(tosyloxy)phenyl)-2-((tosyloxy)methyl)propanal (14). To a solution of **13** (1.5g, 2.4 mmol) in dry dichloromethane (30 ml) at 0°C was added Dess-Martin Periodinane (5ml, 15%w/v). The reaction was allowed to stir at 0°C for a further 90 minutes then allowed to warm to room temperature and stirred for an additional 2 hours. A solution of sodium thiosulfate (15ml) was added and the solution stirred for an

additional 15 minutes, then vacuum-filtered over celite. An additional 30 ml of dichloromethane was added and extracted with aqueous sodium chloride (20 ml). The organic layer was dried over sodium sulfate, concentrated, and the product **14** (amber liquid, 1.25g, 2.88 mmol, 83%) used immediately in the next reaction without further purification. IR (cm⁻¹) 1700, 1600, 1360, 1290, 1150, 1110, 1030, 841, 818. ¹H-NMR (250MHz, CDCl₃) δ: 2.45 (s, 6H, Ph-CH₃), 2.77 (dd, 2H, *J* = 7.8 Hz and 13.6 Hz, -CH₂CH), 2.97 (m, 1H, -CH₂CH), 3.45 (s, 3H, -OCH₃), 4.2 (dd, 2H, *J* = 11.3 Hz and 4.8 Hz, -CH₂OTs), 6.47-6.91 (comp, 3H), 7.13-8.25 (m, 8H, -OTs), 9.60 (s, 1H, -C(O)H)

Pertosylated Imperanene (15). To a solution of the Wittig reagent (3.66g, 5.78 mmol) **6** in dry THF under a nitrogen atmosphere at 0°C was added *n*-butyl lithium (0.37g, 5.8 mmol). The reaction was allowed to stir for an additional 30 minutes and a solution of the aldehyde **14** (1g, 2 mmol) in dry THF (10 ml) was added to the sanguineous solution at 0°C. The reaction was allowed to warm to room temperature and stirred for an additional 19 hours. The solution was then concentrated, and the residue taken up in ethyl acetate (50 ml) and extracted with brine (20 ml) to afford a viscous, amber liquid **15** (1.1g, 1.93 mmol, 72%) which was taken onto the next step without further purification. IR (cm⁻¹) 2940, 1740, 1510, 1240, 1020, 796, 739. ¹H-NMR (250MHz, CDCl₃) 2.44 (s, 9H, Ph-CH₃), 2.54 (m, 3H, Ph-CH₂-CH-), 3.35 (s, 3H, -OCH₃), 3.45 (s, 3H, -OCH₃), 3.87 (m, 2H, -CH₂OTs), 5.84 (dd, 1H, *J* = 7.9, 15.8 Hz), 6.27 (d, 1H, *J* = 15.8 Hz), 6.49-7.01 (comp, 6H), 7.1-7.75 (m, 12H, -OTs); ¹³C- NMR (62.5 MHz, CDCl₃) δ: 21.6, 37.2, 43.8, 55.5, 71.5, 110.2, 112.6, 113.5, 118.3, 120.0, 121.1, 123.8, 124.0, 127.8, 128.5, 129.0, 129.3, 129.9, 131.7, 132.5, 133.1, 136.7, 136.8, 137.7, 138.5, 145.1, 151.5, 151.7.

Imperanene (1). To a solution of **11** or **15** dissolved in ethanol was added aqueous potassium hydroxide solution. The mixture was brought to reflux for 3 hours after which they were concentrated under vacuum. The viscous liquid was taken up in ethyl acetate then extracted with brine. The organic layer was dried over sodium sulfate and concentrated. Purification by flash column chromatography using ethyl acetate: hexane (15:85) provided the *R* (60%) and *S* (56%) isomers, respectively. The optical rotations were as followed for both (-)-*R*-[α]_D²⁵ = -102.9° (CHCl₃, *c* = 0.011) and (+)-*S*-imperanene- [α]_D²⁵ = +104° (CHCl₃, *c* = 0.010). IR (cm⁻¹) 3430, 2970, 1600, 1510, 1270, 1030, 810, 754. ¹H-NMR (250MHz, CDCl₃) δ: 2.61 (m, 3H, Ph-CH₂-CH-), 3.48 (m, 2H, -CH₂OH), 3.74 (s, 3H, -OCH₃), 3.80 (s, 3H, -OCH₃), 5.51-5.65 (comp, 2H, Ph-OH), 5.84 (dd, 1H, *J* = 7.9, 15.8 Hz), 6.27 (d, 1H, *J* = 15.8 Hz), 6.59-6.76 (comp, 6H). ¹³C NMR (75 MHz, CDCl₃) δ: 37.6, 47.6, 55.8, 65.2, 108.2, 111.7, 114.1, 114.4, 119.7, 121.8, 128.3, 129.7, 131.5, 132.1, 143.8, 145.2, 146.3, 146.6.