Supporting information

The Synthesis of (–)-Isodomoic Acid C

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N-Benzyl-4-methoxy-N-(1-methyl-1-phenylethyl)benzamide 5. *p*-Anisoyl chloride (9.7 mL, 57.04 mmol) was added dropwise to a stirred solution of cumylamine (7.0 mL, 51.85 mmol) and triethylamine (10.8 mL, 77.78 mmol) in CH₂Cl₂ (120 mL) at 0 °C. The resulting solution was stirred for 18 hours under nitrogen. Water was added and the organics were extracted with CH₂Cl₂, washed with water and brine and evaporated under reduced pressure. Purification by recrystallisation (diethyl ether) afforded 4-methoxy-*N*-(1-methyl-1-phenylethyl)benzamide (13.9 g, 100 %) as a white solid, mp 170-172 °C; *m/z* (CI+) 270 (M+H⁺, 100 %); δ_H (300 MHz, CDCl₃) 7.75 (2H, d, *J* 9, H3, H5), 7.5-7.2 (5H, m, ArH), 6.93 (2H, d, *J* 9, H2, H6), 6.39 (1H, br s, NH), 3.86 (3H, s, OMe), 1.83 (6H, s, CH₃); δ_C (75 MHz, CDCl₃) 166.2, 162.3, 147.2, 128.9(x2), 128.7(x2), 127.9, 127.0, 125.0(x2), 113.9(x2), 56.4, 55.7, 29.5(x2); ν_{max}(film)/cm⁻¹ 3283 (NH), 1633 (C=O), 1609 (ArH), 1544, 1505.

A solution of this benzamide (12.56 g, 46.69 mmol) in dry DMF (150 mL) was added dropwise to dry NaH (3.74 g, 93.38 mmol) under nitrogen. After 12 hours, benzyl bromide was added to the reaction mixture. After a further 24 hours the reaction was quenched with water at 0 °C, extracted with ether, washed with brine, dried over MgSO₄, and evaporated under reduced pressure. Purification by recrystallisation (diethyl ether) afforded the title compound (12.75 g, 75 %) as a white solid, mp 117-119 °C; *m/z* (CI+) 360 (M+H⁺, 20 %), 242 (100 %); δ_H (300 MHz, CDCl₃) 7.5-7.2 (12H, m, ArH), 6.84 (2H, d, *J* 9, H2, H6), 4.83 (2H, s, CH₂), 3.81 (3H, s, OMe), 1.75 (6H, s, CH₃); δ_C (75 MHz, CDCl₃) 173.0, 160.7, 149.1,

140.1, 131.0, 129.0(x2), 128.8(x2), 128.5(x2), 127.4, 127.1(x2), 126.4, 124.(x2), 113.8(x2), 62.6, 55.5, 52.6, 28.8(x2); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 1637 (C=O), 1606 (ArH), 1506.

(3R, 3aR, 7aS)-2,3,3a,4-Tetrahydro-3-phenyl-2-(2-phenylpropan-2-yl)-7aH-isoindol-1,5-dione 7.[†] To a suspension of chiral amine **6**¹ (2.8 g, 13.93 mmol) in THF (150 mL) at $-78\text{ }^{\circ}\text{C}$, was added *n*-butyl lithium (11.14 mL, 27.86 mmol, 2.5 M in hexanes), dropwise. The resulting mixture was allowed to warm to room temperature over 15 minutes, resulting in a clear yellow solution. This was then re-cooled to $-78\text{ }^{\circ}\text{C}$, and a solution of amide **5** (2.5 g, 6.96 mmol) in THF (50 mL) was added dropwise. The mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 minutes before being slowly warmed to room temperature over 5 hours. The reaction was quenched with NH_4Cl , the layers separated and the aqueous layer extracted with ether. The combined organic fractions were washed with 3 x HCl (3 M) and brine, dried with MgSO_4 and concentrated under reduced pressure. Purification by flash chromatography (5:1 petrol:ethyl acetate) gave the title compound (1.50 g, 62 %) as a white solid. Mp $127\text{--}129\text{ }^{\circ}\text{C}$. Analytical HPLC (β -GEM, Regis), eluting with IPA and hexane (30:70), showed it to consist of a 7:93 mixture of two enantiomers, t_R 7.96 and 8.57 min (ee=86%). Recrystallisation from ethyl acetate afforded **7** (0.820 g, 34 %) of ee >99%, $[\alpha]_D^{26} = -224.0$ ($c = 1.05$ in CHCl_3). M/z (CI+) 346 ($M+H^+$, 20 %), 176 (100 %); δ_H (300 MHz, CDCl_3) 7.5–7.2 (10H, m, ArH), 6.94 (1H, dd, J 10, 5, H7), 6.17 (1H, dd, J 10, 2, H6), 4.48 (1H, d, J 2.5, H3), 3.70 (1H, m, H7a), 2.83–2.52 (3H, m, H4, H3a), 1.86 (3H, s, CH_3), 1.53 (3H, s, CH_3); δ_C (75 MHz, CDCl_3) 197.0, 171.9, 145.9, 144.7, 141.8, 130.6, 129.4(x2),

[†] Cyclisation of **5** gave the best yield of **7** when carried out in batches of 2.5 g.

128.5(x3), 127.3, 126.2(x2), 125.6(x2), 67.6, 60.3, 42.7, 41.8, 39.4, 28.6, 27.5;
 $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 2956 (CH), 1683 (C=O).

(3-Iodopropoxy)triisopropylsilane 8. Imidazole (4.41 g, 64.83 mmol) and triisopropylsilyl chloride (5.55 mL, 25.93 mmol) were added to a solution of 3-bromo-1-propanol (3.6 g, 25.93 mmol) in CH_2Cl_2 (50 mL). The resulting mixture was stirred for 18 hours. Water was added and the organics were extracted with CH_2Cl_2 , dried over MgSO_4 and concentrated under reduced pressure to give (3-bromoethoxy)triisopropylsilane (8.1 g, 100 %) as a colourless oil. Found $M\text{-C}_3\text{H}_7$ 251.0452, $\text{C}_9\text{H}_{20}\text{OSiBr}$ requires M 251.0461; m/z (CI) 295 (M^+ , 25%), 69 (100 %); δ_{H} (300 MHz, CDCl_3) 3.87 (2H, t, J 6, H1), 3.60 (2H, t, J 6, H3), 2.11 (2H, qn, J 6, H2), 1.12 (21H, m, 3xCH, 6xCH₃); δ_{C} (75 MHz, CDCl_3) 61.0, 36.1, 31.1, 18.3(x6), 12.2 (x3); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 2942 (CH), 1463.

(3-Bromoethoxy)triisopropylsilane (8.0 g, 27.12 mmol) was added to a solution of sodium iodide (12.2 g, 81.36 mmol) in acetone (150 mL). The resulting solution was heated to reflux for 8 hours, in which time a precipitate of sodium bromide formed. The mixture was filtered and the product concentrated under reduced pressure. The resulting oil was dissolved in CH_2Cl_2 , washed with water and sodium thiosulphate solution, dried over MgSO_4 and concentrated under reduced pressure to give the title compound as a colourless oil. Found $M\text{-C}_3\text{H}_7$ 299.0323, $\text{C}_9\text{H}_{20}\text{OSiI}$ requires M 299.0323; m/z (CI) 343 (M^+ , 100%); δ_{H} (300 MHz, CDCl_3) 3.80 (2H, t, J 6, H1), 3.37 (2H, t, J 7, H3), 2.06 (2H, dt, J 6, 7, H2), 1.12 (21H, m, 3xCH + 3xCH₃); δ_{C} (75 MHz, CDCl_3) 62.9, 36.7, 18.3(x6), 12.2(x3); $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 2942 (CH), 1464.

(3*R*, 3*aR*, 7*R*, 7*aS*)-Hexahydro-7-(1-triisopropylsilyloxy)propyl-3-phenyl-2-(2-phenylpropan-2-yl) 6*H*-isoindole-1,5-dione **9.** To a slurry of copper(I) cyanide (1.14 g, 12.75 mmol) in dry ether at $-78\text{ }^{\circ}\text{C}$ was added methyl lithium (8.0 ml, 12.75 mmol, 1.6 M solution in ether) dropwise. The suspension was allowed to warm to room temperature. The resulting yellow solution was then re-cooled to $-78\text{ }^{\circ}\text{C}$. In a separate vessel, iodide **8** (4.36 g, 12.75 mmol) was dissolved in dry ether, cooled to $-78\text{ }^{\circ}\text{C}$, and *tert*-butyl lithium (19.3 ml, 25.51 mmol, 1.3 M solution in hexanes) was added dropwise. The solution was allowed to warm to room temperature and then added dropwise, via cannula, to the cuprate solution. A solution of enone **9** (4.00 g, 11.59 mmol), in dry ether was added dropwise to the cuprate mixture. The resulting orange solution was allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 2 hours. Saturated ammonium chloride was added, and the mixture allowed to warm to room temperature. Water was added and the organics extracted with diethyl ether. The combined organic fractions were washed with water, dried over MgSO_4 and evaporated under reduced pressure. Purification by flash chromatography (4:1 petrol:ethyl acetate), afforded the title compound (4.91 g, 79 %) as a colourless oil. $R_f = 0.52$ (3:1 Petrol:EtOAc). $[\alpha]_D^{26} = 13.6$ ($c = 1.00$ in CHCl_3) Found $M+H^+$ 562.3711, $\text{C}_{35}\text{H}_{52}\text{NO}_3\text{Si}$ requires M , 562.3711; m/z (ES+) 562 ($M+H^+$, 100 %); δ_H (300 MHz, CDCl_3) 7.45–7.25 (10H, m, ArH), 4.46 (1H, s, H3), 3.64 (2H, t, J 6, CH_2OSi), 2.92–2.02 (7H, m, H3a, 4, 6, 7, 7a), 1.89 (3H, s, CH_3), 1.57 (3H, s, CH_3), 1.55–1.30 (4H, m, $\text{SiOCH}_2\text{CH}_2\text{CH}_2$), 1.12–1.03 (21H, m, 3 x $i\text{Pr}$); δ_C (75 MHz, CDCl_3) 210.6, 175.4, 146.4, 142.1, 129.3 (x2), 128.5 (x2), 128.3, 127.7, 125.9 (x2), 125.6 (x2), 68.0, 63.4, 59.5, 44.0, 43.6, 43.1, 42.2, 34.5, 30.9, 30.6, 28.4, 27.2, 18.3 (x4), 18.0 (x2), 12.6, 12.2 (x2); $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 2941 (CH), 1715 (C=O), 1691 (C=O).

(1R, 3aS, 4R, 7aR)-tert-Butyl hexahydro-3,6-dioxo-1-phenyl-1H-isoindole-4-(3-formyloxypropyl)-3(3H)-carboxylate 10.

Formic acid (18 ml) was added to isoindole **9** (1.44 g, 2.70 mmol), and heated to reflux for 30 minutes. The mixture was concentrated under reduced pressure and dissolved in DCM. The resulting solution was washed with 1M NaOH, dried over MgSO₄, and evaporated under reduced pressure. Purification by flash chromatograph (1:1 petrol:ethyl acetate) afforded 3-((3R, 3aR, 7R, 7aS)-octahydro-1,5-dioxo-3-phenyl-1H-isoindol-7-yl)propyl formate as a pale yellow oil (0.685 g, 90 %). $R_f = 0.26$ (1:2 Petrol:EtOAc). $[\alpha]_D^{25} = 45.7$ ($c = 0.84$ in CHCl₃). Found M^+ 315.1463, C₁₈H₂₁NO₄ requires M , 315.1465; m/z (CI) 316 ($M+H^+$, 100 %); δ_H (300 MHz, CDCl₃) 8.06 (1H, s, CHO), 7.5-7.2 (5H, m, ArH), 6.40 (1H, b, NH), 4.39 (1H, d, J 5, H3), 4.19 (2H, t, J 7, OCH₂), 2.9-2.1 (7H, m, H3a, 4, 6, 7, 7a), 2.0-1.4 (4H, m, OCH₂CH₂CH₂); δ_C (75 MHz, CDCl₃) 209.7, 177.9, 161.3, 140.3, 129.4 (x2), 128.7, 126.0 (x2), 63.8, 62.2, 45.2, 44.2, 43.6, 41.7, 35.2, 30.8, 25.9; $\nu_{max}(\text{film})/\text{cm}^{-1}$ 3348 (NH), 1711 (C=O).

Triethylamine (0.60 mL, 4.32 mmol), Boc-anhydride (0.22 g, 8.65 mmol) and DMAP (0.53 g, 4.32 mmol) were added to a solution of this formate ester (1.36 g, 4.32 mmol) in CH₂Cl₂ (60 mL). The mixture was stirred for 18 hours and concentrated under reduced pressure. The residue was purified by flash chromatography (2:1 petrol:ethyl acetate) to afford the title compound as a white solid (1.61 g, 90 %). $Mp = 128-129^\circ\text{C}$. $R_f = 0.22$ (2:1 Petrol:EtOAc). $[\alpha]_D^{25} = 48.0$ ($c = 0.70$ in CHCl₃). Found $M+NH_4^+$ 433.2337, C₂₃H₃₃N₂O₆ requires M , 433.2338; m/z (CI) 433 ($M+NH_4^+$, 2 %), 316 ($M-\text{Boc}$, 100%); δ_H (300 MHz, CDCl₃) 8.03 (1H, s, CHO), 7.5-7.2 (5H, m, ArH), 4.84 (1H, s, H1), 4.18 (2H, t, J 6, OCH₂), 2.9-2.1 (7H, m, H3a, 4, 5, 7, 7a), 1.9-1.3 (4H, m, OCH₂CH₂CH₂), 1.38 (9H, s, Boc); δ_C (75 MHz, CDCl₃) 209.0, 174.3, 161.2, 149.9, 139.8, 129.3 (x2), 128.4, 125.1 (x2),

83.9, 65.7, 63.7, 45.4, 42.9, 42.8, 40.9, 34.6, 30.8, 28.0 (x3). 26.0; $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 2956 (CH), 1781 (C=O), 1721 (C=O).

(1*R*, 3*aS*, 4*R*, 7*aR*)-2-*tert*-Butyl 1-methyl hexahydro-3,6-dioxo-1*H*-isoindole-4-(3-formyloxypropyl)-1,2(3*H*)-dicarboxylate 11. Sodium periodate (4.84 g, 22.61 mmol) and ruthenium chloride hydrate (80 mg, 0.40 mmol) were dissolved in a water (30 mL), acetonitrile (15 mL) mixture. A solution of isoindole **10** (0.55 g, 1.33 mmol) in ethyl acetate (15 mL) was added dropwise to the sodium periodate solution and left to stir for 18 hours at room temperature during which time a white precipitate formed. The mixture was filtered through Celite® with ethyl acetate and the filtrate was extracted with ethyl acetate, washed with brine and evaporated under reduced pressure. The crude oil was dissolved in a mixture of methanol (13 mL) and toluene (32 mL) and to it was added TMS Diazomethane (1 mL, 2.00 mmol, 2 M solution in ether) dropwise. After 5 minutes the reaction was quenched with acetic acid (1 drop) and the solvent removed under reduced pressure. Purification by flash chromatography (2:1 petrol:ethyl acetate) afforded the title compound as a colourless oil (0.34 g, 64 %). R_f = 0.13 (2:1 Petrol:EtOAc). $[\alpha]_D^{24}$ = 72.0 (c = 0.46 in CHCl_3). Found $M+\text{NH}_4^+$ 415.2082, $\text{C}_{19}\text{H}_{31}\text{N}_2\text{O}_8$ requires M , 415.2080; m/z (CI) 415 ($M+\text{NH}_4^+$, 15%), 298 ($M-\text{Boc}$, 100%); δ_{H} (300 MHz, CDCl_3) 8.07 (1H, s, CHO), 4.31 (1H, s, H1), 4.20 (2H, t, J 6, OCH_2), 3.84 (3H, s, OMe), 2.9-2.1 (7H, m, H3a, 4, 5, 7, 7a), 1.8-1.3 (4H, m, $\text{OCH}_2\text{CH}_2\text{CH}_2$), 1.55 (9H, s, Boc); δ_{C} (75 MHz, CDCl_3) 208.0, 173.0, 170.6, 161.3, 149.7, 84.6, 63.6, 63.0, 53.2, 46.1, 42.6, 35.1, 35.0, 34.1, 30.1, 28.2 (x3), 26.1; $\nu_{\max}(\text{film})/\text{cm}^{-1}$ 2956 (CH), 1790 (C=O), 1748 (C=O), 1721 (C=O).

(1R, 3aS, 4R, 7aR)-2-tert-Butyl 1-methyl hexahydro-4-((3-tert-butyl diphenylsilyloxy)propyl)-3,6-dioxo-1H-isoindole-1,2(3H)-dicarboxylate 12.

Sodium methoxide (12.09 mmol, 1 M in methanol) was added dropwise over 0.5 hours to a solution of isoindole **11** (1.20 g, 3.02 mmol) in methanol (120 mL) at -78°C . The reaction mixture was stirred for 1 hour. Saturated ammonium chloride solution was added and the mixture was extracted with ethyl acetate, washed with brine, dried over MgSO_4 and evaporated under reduced pressure to afford the crude product. Purification by flash chromatography (1:2 petrol:ethyl acetate) gave (1R, 3aS, 4R, 7aR)-2-tert-Butyl 1-methyl hexahydro-4-(3-hydroxypropyl)-3,6-dioxo-1H-isoindole-1,2(3H)-dicarboxylate (0.79 mmol, 71%) as a white solid. $\text{Mp} = 135 - 136^{\circ}\text{C}$. $R_f = 0.17$ (1:2 Petrol:EtOAc). $[\alpha]_D^{23} = 91.8$ ($c = 0.51$ in CHCl_3). Found $\text{M} + \text{NH}_4^+$ 387.2134, $\text{C}_{18}\text{H}_{31}\text{N}_2\text{O}_7$ requires M , 387.2131; m/z (CI) 387 ($\text{M} + \text{NH}_4^+$, 60%), 370 (M^+ , 15%), 270 ($\text{M} - \text{Boc}$, 100%); δ_{H} (300 MHz, CDCl_3) 4.31 (1H, s, H1), 3.84 (3H, s, OMe) 3.68 (2H, t, J 6, OCH_2), 2.9-2.1 (7H, m, H3a, 4, 5, 7, 7a), 1.8-1.3 (5H, m, $\text{OCH}_2\text{CH}_2\text{CH}_2$, OH), 1.54 (9H, s, Boc); δ_{C} (75 MHz, CDCl_3) 208.3, 173.4, 170.6, 149.8, 84.6, 63.1, 62.5, 53.2, 46.1, 42.8, 42.6, 35.0, 34.1, 30.8, 29.8, 28.2 (x3); $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 3443 (OH), 2932, 1787 (C=O), 1748 (C=O), 1717 (C=O).

To a solution of this alcohol (0.79 g, 2.13 mmol) and imidazole (0.17 g, 2.56 mmol) in CH_2Cl_2 (150 mL) was added *tert*-butyl diphenylsilylchloride (0.66 mL, 2.56 mmol). The mixture was stirred for 18 hours. Water was added and the organics extracted with CH_2Cl_2 , dried over MgSO_4 and evaporated under reduced pressure. Purification by flash chromatography (3:1 petrol:ethyl acetate) gave the title compound (1.16 g, 90 %) as a colourless oil. $R_f = 0.35$ (3:1 Petrol:EtOAc). $[\alpha]_D^{23} = 36.4$ ($c = 0.56$ in CHCl_3). Found $\text{M} + \text{Na}^+$ 630.2865, $\text{C}_{34}\text{H}_{45}\text{NO}_7\text{NaSi}$ requires M , 630.2863; m/z (ES+) 629 ($\text{M} + \text{Na}^+$, 100%); δ_{H} (300 MHz, CDCl_3) 7.7-7.3 (10H, m, ArH), 4.30 (1H, s, H1), 3.83 (3H, s, OMe) 3.68

(2H, t, J 6, OCH₂), 2.9-2.0 (7H, m, H3a, 4, 5, 7, 7a), 1.7-1.3 (4H, m, OCH₂CH₂CH₂), 1.56 (9H, s, Boc), 1.07 (9H, s, *t*-Butyl); δ_C (75 MHz, CDCl₃) 208.2, 173.1, 170.6, 149.9, 135.8 (x4), 134.1, 129.9 (x2), 127.9 (x5), 84.5, 63.7, 63.1, 53.1, 46.0, 42.8, 42.8, 35.1, 34.3, 30.7, 30.0, 28.2 (x3), 27.1 (x3), 19.4; $\nu_{\max}$ (film)/cm⁻¹ 2953, 1792 (C=O), 1752 (C=O), 1720 (C=O).

(1*R*, 3*aR*, 4*S*, 8*aR*)-2-*tert*-Butyl 1-methyl hexahydro-4-((3-*tert*-butyl diphenylsilyloxy)propyl)-3,7-dioxo-1*H*-oxepino[4,5-*c*]pyrrole-1,2(7*H*)-dicarboxylate 13. mCPBA (70 %) (0.15 g, 0.61 mmol) was added in one portion to a stirred solution of ketone **12** (0.18 g, 0.30 mmol) in CH₂Cl₂ (5 mL). The mixture was stirred for 72 hours. Sodium sulfite (5 mL of saturated aqueous solution) was added and the mixture was extracted with CH₂Cl₂. The combined organic extracts were washed with sodium hydrogen carbonate (5 mL of saturated aqueous solution), water (10 mL), dried over MgSO₄ and evaporated under reduced pressure. Purification by flash chromatography (4:1 petrol:ethyl acetate) gave the title lactone (0.19 g, 100 %) as a colourless oil. R_f = 0.58 (2:1 Petrol:EtOAc). $[\alpha]_D^{24}$ = 13.7 (c = 1.02 in CHCl₃). Found $M+NH_4^+$ 641.3259, C₃₄H₄₉N₂O₈Si requires M , 641.3258; m/z (CI) 641 ($M+NH_4^+$, 20%), 624 ($M+H^+$, 12%), 541 (M -Boc, 100%); δ_H (300 MHz, CDCl₃) 7.7-7.4 (10H, m, ArH), 4.28 (1H, s, H1), 4.19 (2H, bs, H5), 3.81 (3H, s, CO₂Me), 3.67 (2H, b, OCH₂), 2.9-2.5 (5H, m, H3a, 4, 8, 8a), 1.7-1.3 (4H, m, OCH₂CH₂CH₂), 1.52 (9H, s, Boc), 1.04 (9H, s, *t*-Butyl); δ_C (75 MHz, CDCl₃) 171.9, 171.5, 170.0, 149.6, 135.8 (x3), 135.8 (x2), 134.0, 129.9 (x2), 127.9 (x4), 84.7, 67.2, 63.5, 63.4, 53.3, 49.0, 37.0, 34.8, 33.1, 29.9, 28.1 (x3), 27.1 (x3), 26.2, 19.4; $\nu_{\max}$ (film)/cm⁻¹ 2932, 1794 (C=O), 1746 (C=O).

(2*R*, 3*R*, 4*R*)-1-*tert*-Butyl 2-methyl 3-((methoxycarbonyl)methyl)-4-[(1*S*)-2-hydroxy-1-((3-*tert*-butyldiphenylsilyloxy)propyl)]-5-oxopyrrolidine-1,2-

dicarboxylate 14. Sodium methoxide (4.77 mmol, 1 M in methanol) was added dropwise over 0.5 hours to a solution of isoindole **13** (0.59 g, 0.95 mmol) in methanol (10 mL) at -78°C . The reaction mixture was stirred for 1 hour. Saturated ammonium chloride solution was added and the mixture was extracted with ethyl acetate, washed with brine, dried over MgSO_4 and evaporated under reduced pressure to afford the crude product. Purification by flash chromatography (1:1 petrol:ethyl acetate) gave the title compound (0.37 mmol, 60%) as a colourless oil. $R_f = 0.37$ (1:1 Petrol:EtOAc); $[\alpha]_D^{23} = -3.2$ ($c = 0.50$ in CHCl_3): Found $M+\text{Na}^+$ 678.3065, $\text{C}_{35}\text{H}_{49}\text{NO}_9\text{SiNa}$ requires M , 678.3069; m/z (ES $^-$) 700 ($M-H+2\text{Na}$, 100%), 654 ($M-H^+$, 17%); δ_{H} (300 MHz, CDCl_3) 7.7–7.4 (10H, m, ArH), 4.35 (1H, d, J 5, H2), 3.81 (3H, s, CO_2Me), 3.72 (3H, s, CO_2Me), 3.68 (4H, m, SiOCH_2 , CH_2OH), 3.10 (1H, dd, J 5, 9, H4), 2.95 (1H, ddd, J 6, 9, 11, H3), 2.65 (1H, dd, J 6, 17, CO_2MeCH_2), 2.60 (1H, b, OH), 2.52 (1H, dd, J 9, 17, CO_2MeCH_2), 1.8–1.3 (5H, m, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}$), 1.49 (9H, s, Boc), 1.06 (9H, s, *t*-Butyl); δ_{C} (75 MHz, CDCl_3) 174.7, 171.8, 170.9, 149.4, 135.8 (x4), 134.0, 133.9, 129.9 (x2), 127.9 (x4), 84.4, 63.9, 63.8, 63.2, 53.0, 52.4, 47.3, 38.6, 35.5, 33.4, 30.4, 28.1 (x3), 27.1 (x3), 23.7, 19.4; ν_{max} (film)/ cm^{-1} 3532 (OH), 2954, 1788 (C=O), 1744 (C=O).

(2*R*, 3*R*, 4*S*)-1-*tert*-Butyl 2-methyl 3-((methoxycarbonyl)methyl)-4-(5-(*tert*-butyldiphenylsilyloxy)pent-1-en-2-yl)-5-oxopyrrolidine-1,2-dicarboxylate 15.

Tri-*n*-butylphosphine (0.22 mL, 0.91 mmol) was added dropwise to a stirred

solution of pyrrolidinone **14** (0.20 g, 0.30 mmol) and o-nitrophenylselenocyanate (0.21 g, 0.91 mmol) in THF (10 mL) at room temperature. After 2 hours, the solution was cooled to -40 °C. Pyridine (30 μ L) was added followed by dropwise addition of an aqueous solution of hydrogen peroxide (0.3 mL). The mixture was allowed to warm to room temperature and stirred for 12 hours. A saturated solution of sodium bisulfite (4 mL) was added and the reaction mixture was extracted with ethyl acetate, washed with water, dried over MgSO₄ and evaporated under reduced pressure. Purification by flash chromatography (10:1 petrol:ethyl acetate) afforded the title alkene (0.11 g, 60 %) as a colourless oil. R_f = 0.32 (3:1 Petrol:EtOAc). $[\alpha]_D^{25}$ = -21.8 (c = 0.22 in CHCl₃). Found $M+Na^+$ 660.2969, C₃₅H₄₇NO₈SiNa requires M , 660.2963; m/z (ES+) 660 ($M+Na$, 100%); δ_H (300 MHz, CDCl₃) 7.7-7.4 (10H, m, ArH), 5.19 (1H, s, =CH_aCH_b), 5.09 (1H, s, =CH_aCH_b), 4.39 (1H, d, J 3, H₂), 3.85 (3H, s, CO₂Me), 3.82-3.73 (2H, m, SiOCH₂), 3.72 (3H, s, CO₂Me), 3.51 (1H, b d, J 8, H₃), 2.96 (1H, m, H₄), 2.54-2.29 (3H, m, CO₂MeCH₂ + SiOCH₂CH₂CH_a), 2.12-1.60 (3H, m, SiOCH₂CH₂CH_b), 1.53 (9H, s, ^{*t*}Bu-Boc), 1.08 (9H, s, ^{*t*}Bu-TBDPS); δ_C (75 MHz, CDCl₃) 171.9, 171.6, 171.1, 140.8, 135.8 (x4), 134.1, 129.9 (x2), 127.9 (x4), 124.4, 116.4, 110.0, 84.3, 63.4, 62.2, 53.1, 52.3, 51.2, 35.2, 34.5, 32.7, 30.4, 28.2 (x3), 27.1 (x3), 19.5; ν_{max} (film)/cm⁻¹ 2954, 1793 (C=O), 1743 (C=O), 1719 (C=O).

(2*R*, 3*R*, 4*S*)-1-*tert*-Butyl 2-methyl 3-((methoxycarbonyl)methyl)-4-(5-(*tert*-butyldiphenylsilyloxy)pent-1-en-2-yl)pyrrolidine-1,2-dicarboxylate **16.** A solution of DIBALH (0.95 mmol, 1 M in toluene) was added dropwise over 15 minutes to a stirred solution of **15** (0.07 g, 0.11 mmol) in THF (10 mL) at -78 °C. After 1 hour, methanol was added and the mixture was allowed to warm to room temperature. Saturated potassium tartrate solution and ethyl acetate were added the mixture was stirred for 15 minutes. The layers were separated and the organics extracted with ethyl acetate, washed with brine, dried over MgSO₄ and

evaporated under reduced pressure. The crude product was used without further purification. Dry CH_2Cl_2 was added and the mixture was cooled to $-78\text{ }^\circ\text{C}$. Triethylsilane (19 μL , 0.12 mmol) and boron trifluoride etherate (14 μL , 0.11 mmol) were added dropwise. After 30 minutes, further triethylsilane (19 μL , 0.12 mmol) and boron trifluoride etherate (14 μL , 0.11 mmol) were added. After 2 hours the reaction was quenched with saturated aqueous NaHCO_3 , extracted with CH_2Cl_2 , dried over MgSO_4 and evaporated under reduced pressure. Purification by flash chromatography (4:1 petrol:ethyl acetate) gave the title compound (0.028 g, 41 %) as a colourless oil. $R_f = 0.61$ (3:1 Petrol:EtOAc). $[\alpha]_D^{23} = -4.1$ ($c = 0.68$ in CHCl_3). Found $M+\text{Na}^+$ 646.3159, $\text{C}_{35}\text{H}_{49}\text{NO}_7\text{SiNa}$ requires M , 646.3171; m/z (ES+) 646 ($M+\text{Na}$, 60%); δ_{H} (300 MHz, CDCl_3) 7.7-7.4 (10H, m, ArH), 4.95 (1H, s, $=\text{CH}_a\text{CH}_b$), 4.76 (1H, s, $=\text{CH}_a\text{CH}_b$), 4.19 (1H, d, J 3, H2), 3.79 (3H, s, CO_2Me), 3.76-3.64 (3H, m, SiOCH_2 , H5a), 3.72 (3H, s, CO_2Me), 3.45 (1H, m, H5b), 3.06 (1H, m, H3), 2.86 (1H, m, H4), 2.54-1.94 (4H, m, $\text{CO}_2\text{MeCH}_2 + \text{SiOCH}_2\text{CH}_2\text{CH}_2$), 1.80-1.60 (2H, m, $\text{SiOCH}_2\text{CH}_2$), 1.44 (9H, s, $^t\text{Bu-Boc}$), 1.08 (9H, s, $^t\text{Bu-TBDPS}$); δ_{C} (75 MHz, CDCl_3) 172.7, 172.6, 154.1, 145.0, 135.8 (x4), 134.1 (x2), 129.9 (x2), 127.9 (x4), 112.1, 80.6, 64.3, 63.5, 52.5, 52.2, 47.8, 44.1, 41.9, 33.3, 32.2, 30.8, 28.7 (x3), 27.1 (x3), 19.5; $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 2950, 1743 (C=O), 1704 (C=O).

(2R, 3R, 4S)-1-tert-Butyl 2-methyl 3-((methoxycarbonyl)methyl)-4-(4-formylbut-1-en-2-yl)pyrrolidine-1,2-dicarboxylate 17. To a solution of **16** (0.042 g, 0.067 mmol) in THF (3 mL) was added TBAF (0.073 mL, 0.073 mmol, 1 M solution in THF) dropwise at room temperature. After 2 hours at room temperature water was added and the solution stirred for 30 minutes. The organics were extracted with ethyl acetate, washed with brine, dried with MgSO_4 and concentrated under reduced pressure to give the crude product. Purification by flash chromatography (1:1 petrol:ethyl acetate) afforded (2R, 3R, 4S)-1-tert-

butyl 2-methyl 3-((methoxycarbonyl)methyl)-4-(5-hydroxypent-1-en-2-yl)pyrrolidine-1,2-dicarboxylate (0.021 g, 80 %) as a colourless oil. $R_f = 0.19$ (1:1 Petrol:EtOAc). $[\alpha]_D^{20} = -9.0$ ($c = 0.67$ in CHCl_3). Found $M+H^+$ 386.2171, $\text{C}_{19}\text{H}_{32}\text{NO}_7$ requires M , 386.2173; m/z (ES+) 403 ($M+\text{NH}_4$, 100%), 386 ($M+H^+$, 70%); δ_H (300 MHz, CDCl_3) 5.00 (1H, s, $=\text{CH}_a\text{CH}_b$), 4.81 (1H, s, $=\text{CH}_a\text{CH}_b$), 4.21 (1H, d, J 3, 33% H_2), 4.12 (1H, d, J 2, 66% H_2), 3.79 (3H, s, OMe), 3.78-3.64 (3H, m, H5a, CH_2OH), 3.73 (3H, s, OMe), 3.46 (1H, m, H5b), 3.09 (1H, m, H3), 2.87 (1H, m, H4), 2.54-1.94 (5H, m, $\text{CO}_2\text{MeCH}_2 + \text{SiOCH}_2\text{CH}_2\text{CH}_2$, OH), 1.80-1.60 (2H, m, $\text{SiOCH}_2\text{CH}_2$), 1.47 (9H, s, ^tBu); δ_C (75 MHz, CDCl_3) 172.9, 172.8, 154.1, 145.0, 112.1, 80.6, 64.3, 62.5, 52.6, 52.2, 47.8, 44.5, 41.9, 33.4, 32.2, 30.7, 28.5 (x3); $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 3451 (OH), 2953, 1741 (C=O), 1702 (C=O).

A solution of this alcohol (14.9 mg, 0.039 mmol) in CH_2Cl_2 (1 mL) was added to a solution of Dess-Martin periodinane² (0.13 g, 0.045 mmol, 15 w/w% in CH_2Cl_2) in CH_2Cl_2 (1 mL). The resulting solution was stirred for 30 minutes. Ether was added and the solution was poured into an aqueous solution of NaOH (1.3 M) and stirred for 10 minutes. The layers were separated and the aqueous layer extracted with ether. The combined organic extracts were washed with brine, dried over MgSO_4 and concentrated under reduced pressure to afford the crude product. Purification by flash chromatography (2:1 petrol:ethyl acetate) afforded the title compound (12 mg, 80%) as colourless oil. $R_f = 0.26$ (2:1 Petrol:EtOAc). $[\alpha]_D^{21} = -6.0$ ($c = 0.67$ in CHCl_3). Found $M+\text{Na}^+$ 406.1837, $\text{C}_{19}\text{H}_{29}\text{NO}_7\text{Na}$ requires M , 406.1836; m/z (ES-) 406 ($M+\text{NH}_4$, 100%), 384 ($M+H^+$, 10%); δ_H (300 MHz, CDCl_3) 9.82 (1H, s, CHO), 4.94 (1H, s, $=\text{CH}_a\text{CH}_b$), 4.85 (1H, s, $=\text{CH}_a\text{CH}_b$), 4.23 (1H, d, J 2, 33% H_2), 4.14 (1H, d, J 3, 66% H_2), 3.80 (3H, s, OMe), 3.74 (3H, s, OMe), 3.68 (1H, m, H5a), 3.48 (1H, m, H5b), 3.09 (1H, m, H3), 2.90 (1H, m, H4), 2.70-2.20 (6H, m, $\text{CO}_2\text{MeCH}_2 + \text{CHOCH}_2\text{CH}_2$), 1.57 (9H, s, ^tBu); δ_C (75 MHz, CDCl_3) 201.4, 172.9, 172.6, 151.0, 143.7, 112.4, 80.7, 64.3, 52.6, 52.2, 47.8, 44.5, 41.7, 33.3, 30.0, 28.5 (x3), 27.9; $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$ 2955, 1741 (C=O), 1699 (C=O).

(2R, 3R, 4S)-1-tert-Butyl 2-methyl 4-((E)-6-(ethoxycarbonyl)hepta-1,5-dien-2-yl)-3-((methoxycarbonyl)methyl)pyrrolidine-1,2-dicarboxylate 19. Following the method of Masamune,³ triethyl 2-phosphonopropionate (8 μ L, 0.031 mmol), DBU (4 μ L, 0.026 mmol) and aldehyde **17** (10 mg, 0.026 mmol) were added to a stirred suspension of LiCl (1.3 mg, 0.031 mmol) in dry acetonitrile (1 mL). The mixture was stirred at room temperature for 1 hour. Water was added and the product was extracted with ethyl acetate, dried over MgSO_4 and concentrated under reduced pressure. Purification by flash chromatography (4:1 petrol:ethyl acetate) gave the title compound (6.0 mg, 50 %) as a colourless oil. R_f = 0.60 (2:1 Petrol:EtOAc): Found $M+H^+$ 468.2587, $\text{C}_{24}\text{H}_{38}\text{NO}_8$ requires M , 468.2592; m/z (ES+) 958 ($2M+H^++Na^+$, 100%), 490 ($M+Na^+$, 75%), 468 ($M+H^+$, 40%); δ_H (300 MHz, CDCl_3) 6.73 (1H, t, J 7, CH), 5.01 (1H, s, $=\text{CH}_a\text{CH}_b$), 4.85 (1H, s, $=\text{CH}_a\text{CH}_b$), 4.23 (2H, q, J 7, $\text{CO}_2\text{CH}_2\text{CH}_3$), 4.22 (1H, d, J 2, 33% H_2), 4.13 (1H, d, J 3, 66% H_2), 3.80 (3H, s, OMe), 3.74 (3H, s, OMe), 3.68 (1H, m, H5a), 3.48 (1H, m, H5b), 3.09 (1H, m, H3), 2.87 (1H, m, H4), 2.60–2.00 (6H, m, $\text{CO}_2\text{MeCH}_2 + \text{CHCH}_2\text{CH}_2$), 1.86 (3H, s, Me), 1.48 (9H, s, ^tBu), 1.33 (3H, t, J 7, $\text{CO}_2\text{CH}_2\text{CH}_3$); δ_C (75 MHz, CDCl_3) 172.9, 172.6, 165.2, 159.0, 150.5, 140.9, 128.8, 110.0, 80.6, 64.3, 60.8, 52.5, 52.2, 47.7, 44.9, 41.7, 34.4, 30.0, 28.7 (x3), 22.6, 14.6, 12.7; ν_{max} (film)/ cm^{-1} 2930, 1741 (C=O), 1707 (C=O), 1650 (C=O).

isodomoic acid C **1**

(–)-Isodomoic acid C 1. Following the method of Hanessian,⁴ compound **19** (6.0 mg, 0.013 mmol) was dissolved in a mixture of THF (0.5 mL) and 2 M aqueous LiOH (0.5 mL) and stirred at room temperature for 12 hours. A solution of HCl (2 M) was added until pH 2 had been reached. The mixture was extracted with ethyl acetate, dried over MgSO_4 and evaporated under reduced pressure. CH_2Cl_2 (0.5

mL) and TFA (0.5 mL) were added and the reaction mixture was heated to reflux for 2 hours. Following removal of the solvent, the crude product was dissolved in water and added to a column containing Dowex-50 H⁺ (WX8-200, 8% cross-linking, 100-200 wet mesh). The product was eluted with NH₄OH (1M). Evaporation, followed by passage through a column of Amberlite CG-50 with water afforded, after evaporation, (–)-isodomoic acid C (3 mg, 86 %) as a yellow solid. The product was further purified by HPLC (Rainin Dynamax ODS column, 21.2 x 250 mm, 90:10:0.1 H₂O:MeCN:CF₃CO₂H, detecting at 255 nm), neutralised with NH₄OH, dissolved in water and passed through a polydivinylbenzene SPE cartridge (Waters Oasis) eluting with methanol, and evaporated to yield a pure sample of isodomoic acid C **1** (0.2 mg), spectroscopically identical with a sample of naturally-derived isodomoic acid C **1** [Table], $[\alpha]_{\text{D}}^{20} = -30 \pm 10$ (c = 0.02 in H₂O) (lit.⁵ $[\alpha]_{\text{D}}^{25} = -30$ (c = 0.015 in H₂O)).

Table: Spectroscopic comparison of natural and synthetic (–)-isodomoic acid C.**

α_{H} (D ₂ O)		α_{C} (D ₂ O)	
Natural (400 MHz)	Synthetic (300 MHz)	Natural (100 MHz)	Synthetic (75 MHz)
6.56 (1H, t, J 7)	6.57 (1H, t, J 7)	178.0	178.3
4.99 (1H, s)	4.97 (1H, s)	173.9	173.4
4.76 (1H, s)	4.79 (1H, s)	173.4	173.0
3.99 (1H, d, J 3)	3.97 (1H, d, J 3)	142.8	142.1
3.51 (2H, dd, J 11.5, 7.5)	3.50 (2H, dd, J 11.5, 7)	142.0	142.0
3.36 (1H, t, J 11.5)	3.33 (1H, t, J 11.5)	129.2	128.5
2.95 (2H, m)	2.90 (2H, m)	112.7	112.3
2.40–2.10 (6H, m)	2.30–2.00 (6H, m)	66.0	*
1.70 (3H, s)	1.69 (3H, s)	46.6	46.1
		44.3	43.8
		41.3	40.6
		35.1	34.5
		34.4	33.9
		26.2	25.7
		12.0	11.4

*Peak obscured by noise

**Spectra kindly supplied by Prof. Alistair Wilkins of Waikato University, Hamilton, New Zealand

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