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Asymmetric Synthesis of an MMP-3 Inhibitor Incorporating a 2-Alkyl Succinate Motif

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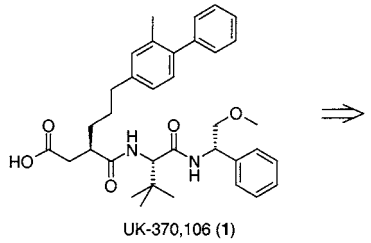
Abstract:

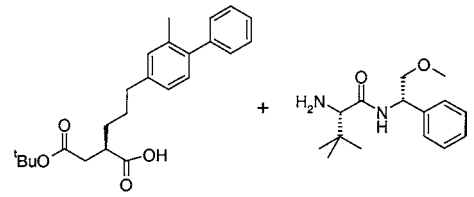
An efficient and practical synthesis is presented of the pharmaceutically active MMP-3 inhibitor UK-370,106 (1) via an olefination/catalytic asymmetric hydrogenation sequence. Commercially available 5-bromo-2-iodotoluene was converted in two steps to the biarylpropanal equivalent (11), which was reacted with the phosphonosuccinate (10) to selectively afford the *trans*-β-substituted itaconate (12). Catalytic asymmetric hydrogenation of the itaconate (12) was achieved in good conversion and with 86−96% enantiomeric excess with a range of phosphine-modified rhodium and ruthenium cationic complexes. The resulting enantiomerically enriched 2-alkyl succinate (2) was elaborated to the desired drug substance (1) in two steps. The synthesis benefits from several crystalline intermediates, allowing control of process impurities, and can be operated safely within parameters readily achievable on scale. Investigations into the polymorphic forms of (1) have shown that the compound crystallizes in planar sheets, based on a backbone of hydrogen-bonding amide and acid functionalities, with large hydrophobic pockets formed by the biarylpropyl groups. An understanding of this crystal-packing arrangement has aided the development of crystallization processes allowing complete control over solid form.

Introduction

Matrix metalloproteases (MMPs) are involved in the repair, degradation, and remodeling of extracellular matrix proteins. Since they have a destructive potential, failure to regulate MMP activity in physiological processes may underlie a number of pathological conditions, such as tissue destruction, as in venous and diabetic ulcers.[1] UK-370,106 (**1**), a potent and selective MMP-3 inhibitor discovered by chemists at Pfizer,[2] has been progressed into development as a candidate designed to treat pathological conditions involving tissue destruction. Retrosynthetic disconnection of (**1**) leads to a suitably protected key chiral 2-alkyl succinate building block (**2**) and the dipeptide (**3**). Initial quantities of (**1**) were prepared via these intermediates utilizing a modified



UK-370,106 (**1**)



(**2**) (**3**)

medicinal chemistry route, as outlined in Scheme 1. The dipeptide (**3**) was prepared from the coupling of BOC (*S*)-*tert*-leucine[3] with (*S*)-*O*-methyl-phenylglycinol,[4] followed by deprotection to the free amine. Assembly of the chiral succinate (**2**) began with a selective Suzuki coupling of 5-bromo-2-iodotoluene with phenylboronic acid to afford the biaryl bromide (**4**).[5] Formation of the Grignard reagent and subsequent addition to glutaric anhydride gave the keto acid (**5**), which was reduced to the biarylpentanoic acid (**6**). Conversion of the acid (**6**) to the acyl oxazolidinone (**7**) allowed installation of the key chiral succinate stereocenter via an asymmetric alkylation utilizing Evans' methodology.[6] Thus, treatment of the acyl oxazolidinone (**7**) with sodium bis(trimethylsilyl)amide, followed by addition of *tert*-butyl bromoacetate, afforded the 2-alkyl succinate derivative (**8**) with >98% diastereomeric excess. Cleavage of the chiral auxiliary afforded the mono-protected succinate (**2**) in good overall yield. The succinate (**2**) was then coupled with the dipeptide (**3**) and subsequently deprotected under acidic conditions to afford the desired product (**1**). Approximately 1 kg of UK-370,106 (**1**) was prepared in this manner.

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(5) Compound (**4**) has previously been prepared by a Gomberg−Bachmann−Hey reaction (4-bromo-2-methylaniline, isoamyl nitrite, benzene, reflux): Gomberg, M.; Pernet, J. C. *J. Am. Chem. Soc.* **1926**, *48*, 1372 and from the coupling of phenyldiazonium tetrafluoroborate with an arylboronic ester: Willis, D. M.; Strongin, R. M. *Tetrahedron Lett.* **2000**, *41*, 6271.

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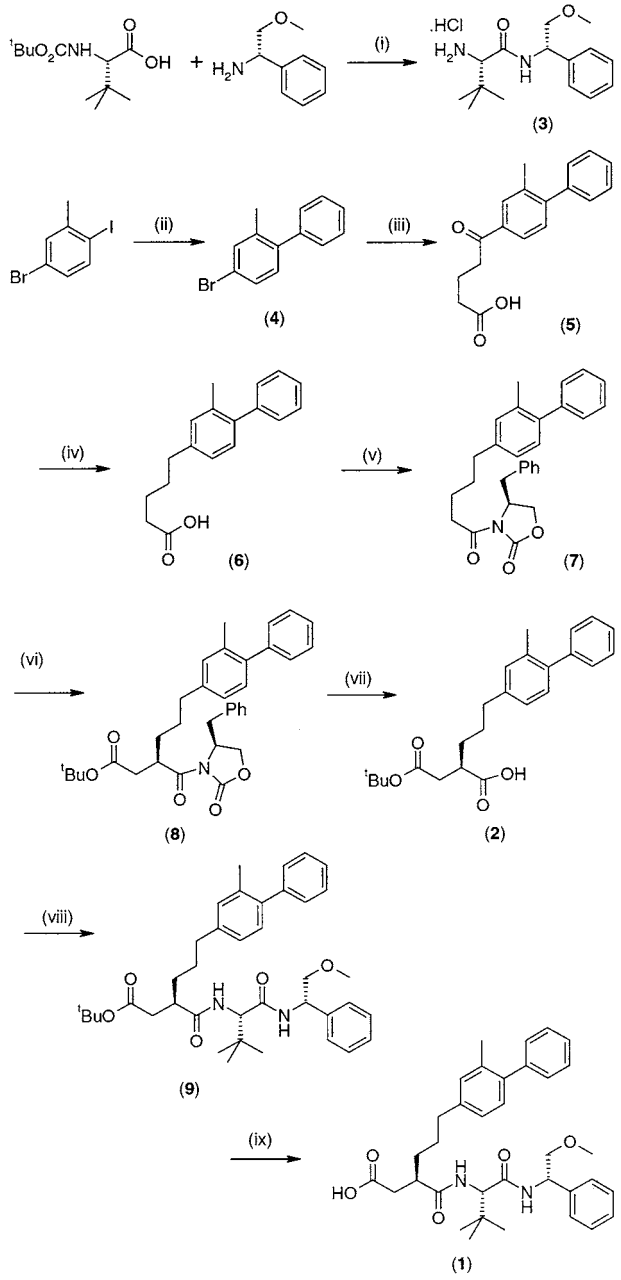
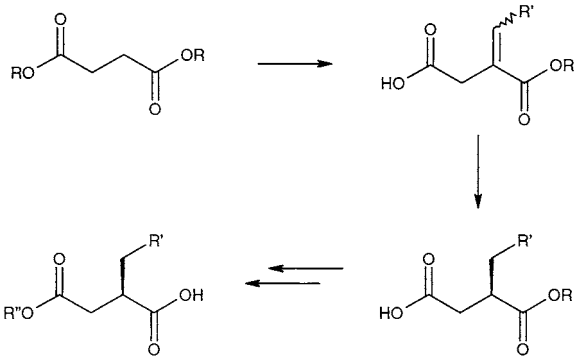
Scheme 1. **Medicinal Chemistry route to UK-370,106 (1)**[a]



[a] Conditions: (i) 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide·HCl, HOBT, NMM, CH_2Cl_2, rt; HCl, CH_2Cl_2, rt, 79%; (ii) $PhB(OH)_2$, Na_2CO_3, $Pd(OAc)_2$, PPh_3, acetone, H_2O, reflux, 80%; (iii) Mg, glutaric anhydride, THF, −40 °C, 73%; (iv) Et_3SiH, TFA, rt, 86%; (v) $(COCl)_2$, CH_2Cl_2, rt; (*S*)-4-benzyl-2-oxazolidinone, ^{n}BuLi, THF, −78 °C, 89%; (vi) NaHMDS, *tert*-butyl bromoacetate, THF, −78 °C, 65%; (vii) LiOH, H_2O_2, THF, H_2O, 0 °C, 85%; (viii) 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide·HCl, (**3**), HOBT, ^{i}Pr$_2$NEt, CH_2Cl_2, rt, 96%; (ix) TFA, CH_2Cl_2, rt, 59%

Opportunities to scale this chemistry further were limited by the lack of crystalline intermediates in the synthesis, leading to a lack of purification points and therefore inadequate control of the impurity burden. The route also suffered from two undesirable cryogenic reactions, the use of an expensive stoichiometric chiral auxiliary and safety concerns regarding the use of peroxide to cleave the chiral auxiliary. Key to the success of the clinical program, was the development of a scalable and cost-effective asymmetric synthesis of the 2-alkyl succinate (**2**), leading to drug substance (**1**) in good overall yield and with an appropriate purity profile.

Scheme 2. **Stobbe route to β-substituted itaconate derivatives and chiral 2-alkyl succinates**



Results and Discussion

A number of methods are known in the literature for the construction of enantiomerically pure 2-alkyl succinates.[7−9] The most appealing in terms of practicality and efficiency are those involving the asymmetric catalytic hydrogenation of β-substituted itaconate derivatives.[8] Of particular interest to us was the method described by Burk et al., involving the Stobbe condensation of an aldehyde or ketone with a dialkyl succinate, followed by asymmetric hydrogenation of the resulting itaconate products, catalyzed by a cationic rhodium complex in concert with a chiral diphosphine ligand.[9] Whilst this method affords rapid access to 2-alkyl succinates in good enantiomeric excess, further manipulation is required to afford succinates with an appropriate protecting-group alignment for our synthesis of (**1**) (Scheme 2). Our attention was therefore turned to the development of an olefination/asymmetric hydrogenation approach leading directly to the monoprotected succinate (**2**) without further manipulation of protecting groups.[10]

Towards this goal, the biaryl bromide (**4**) (Scheme 3) was reacted with allyl alcohol under Jeffery's conditions[11] to afford a biarylpropanal, which was conveniently isolated in a solid form as the sodium metabisulfite adduct (**11**). Concomitantly, we found that the phosphonosuccinate (**10**) could be readily prepared from triethyl phosphonoacetate and isolated as a crystalline solid. Treatment of the hydroxy sulfonate (**11**) and the phosphorus reagent (**10**) with an excess

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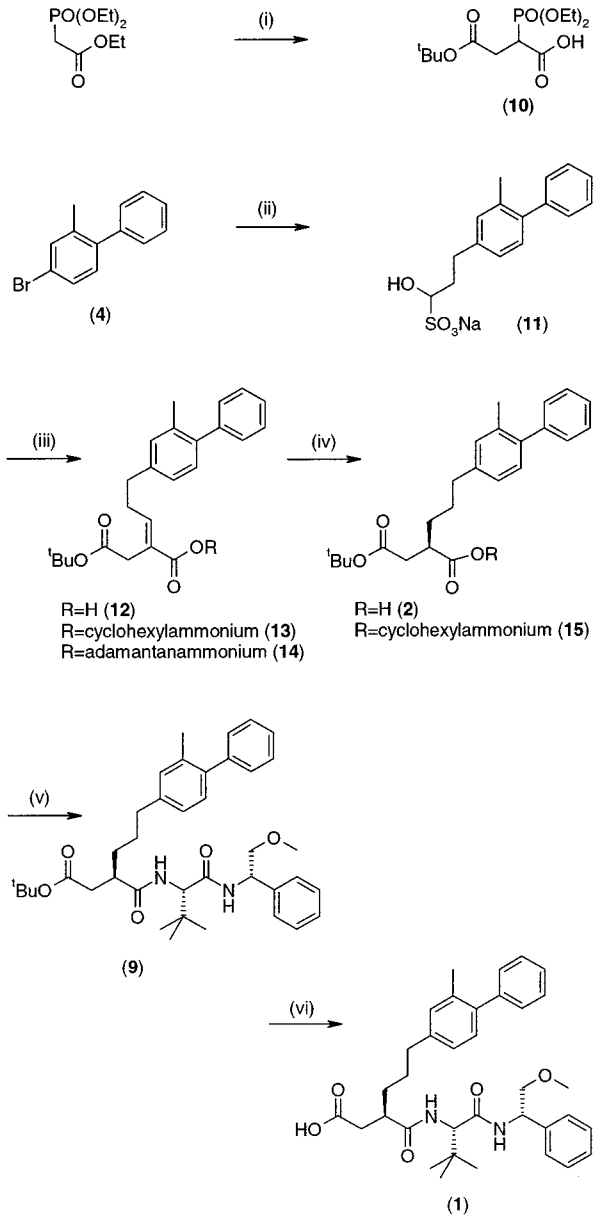
(9) Burk, M. J.; Bienewald, F.; Harris, M.; Zanotti-Gerosa, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 1931.
(10) Whilst the catalytic asymmetric hydrogenation of β-substituted itaconate half esters leading directly to succinic half esters such as **2** has not previously been reported, the corresponding reduction of unsubstituted itaconate half esters is known: Kawano, K.; Ishii, Y.; Ikariya, T.; Saburi, M.; Yoshikawa, S.; Uchida, Y.; Kumobayashi, H. *Tetrahedron Lett.* **1987**, *28*, 1905.
(11) Jeffery, T. *Tetrahedron Lett.* **1991**, *32*, 2121.

Scheme 3. **Process chemistry route to UK-370,106 (1)**[a]



[a] Conditions: (i) ^{t}BuOK, THF, *tert*-butyl bromoacetate, rt; KOH, H_2O, THF, −10 °C, 60%; (ii) allyl alcohol, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, Bu_4NCl, $NaHCO_3$, MeCN, reflux; $Na_2S_2O_5$, MeOH, H_2O, 64%; (iii) ^{t}BuOK, (**10**), THF, ^{t}BuOH, 0 °C; EtOAc, $C_6H_{11}NH_2$, 61%; **or** K_3PO_4, H_2O, $PhCH_3$, rt; ^{t}BuONa, (**10**), $PhCH_3$, 0 °C; adamantanamine, $PhCH_3$, rt, 67% (iv) [(*S*)-BINAP-Ru-(*p*-cymene)Cl]Cl, MeOH, H_2O, H_2 (60 psi), 60 °C, 65%; (v) 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide·HCl, (**3**), HOBT, ^{i}Pr$_2$NEt, CH_2Cl_2, rt, quantitative; (vi) TFA, CH_2Cl_2, rt; crystallized from EtOAc, 75%.

of potassium *tert*-butoxide, led smoothly and selectively to the *trans*-β-substituted itaconate (**12**), in around 61% yield following crystallization as the cyclohexylamine salt (**13**). The cis isomer was not observed by NMR spectroscopy. With quantities of the desired β-substituted itaconate (**12**) in hand, we were able to screen a range of catalytic asymmetric hydrogenation conditions for the preparation of the enantiomerically enriched target 2-alkyl succinate (**2**). This work was done both in-house and in collaboration with Chirotech Technology Limited. A range of chiral phosphine-modified rhodium and ruthenium complexes were screened, for the reduction of both the free acid and a number of salts of (**12**), under standard hydrogenation conditions. Both [(*S*,*S*)-Et-DUPHOS)Rh(COD)]BF_4[12] and [(*S*,*S*)-(Fc-4-Et)Rh(COD)]-BF_4[13] proved efficacious for the asymmetric reduction of the free carboxylic acid (**12**), giving the desired 2-alkyl succinate (**2**) in >98% conversion and 96% enantiomeric excess (100:1 substrate:catalyst ratio, 60 psi H_2, methanol, ambient temperature). Pleasingly, for the case of the [(*S*,*S*)-(Fc-4-Et)Rh-(COD)]BF_4 catalyst, the reaction proceeds in good conversion at a substrate:catalyst ratio of 1000:1, with an enantiomeric excess of 94%. When the cyclohexylamine salt (**13**) was utilized as substrate, both [(*S*)-BINAP-Ru-(*p*-cymene)Cl]Cl[14] and [(*S*)-Cl-OMe-BIPHEP-Ru(C_6H_6)Cl]Cl[15] proved effective, giving the desired succinate in 86% and 92% enantiomeric excess, respectively (100:1 substrate:catalyst ratio, 60 psi H_2, methanol, 60 °C). Similar enantioselectivities were observed for [(*S*)-BINAP-Ru-(*p*-cymene)Cl]Cl-catalyzed hydrogenations of inorganic salts (e.g., sodium) or other organic salts (e.g., 1-adamantanammonium) of (**12**), under identical conditions. Conversely, salts of (**12**) proved to be poor substrates for catalytic rhodium complexes, whilst the free acid (**12**) proved to be a poor substrate for cationic ruthenium complexes. Such observations are consistent with recently published mechanistic insights into ruthenium- and rhodium-catalyzed asymmetric hydrogenations.[16] Methanol was the solvent of choice for all catalysts described, since other solvents resulted either in poor enantioselectivity or poor conversion to the desired product. In general, increasing the temperature or pressure, or both, of the reactions led to a decrease in enantioselectivity, whilst a decrease in temperature or pressure led to extended reaction times and ultimately poor conversion. Significant quantities of the desired 2-alkyl succinate (**2**) have been prepared from the cyclohexylammonium itaconate (**13**) utilizing the readily available [(*S*)-BINAP-Ru-(*p*-cymene)Cl]Cl catalyst. The hydrogenation proceeds in good conversion and in 88% enantiomeric excess, giving a 65% yield of the cyclohexylamine salt (**15**) in >98% enantiomeric excess, after a single crystallization from ethyl acetate/methyl ethyl ketone.

With an efficient and practical synthesis of the 2-alkyl succinate (**2**) in hand, significant quantities of the active pharmaceutical (**1**) were prepared by utilizing a modified medicinal chemistry protocol. Thus, the cyclohexylamine salt (**13**) was broken to the free acid, which was coupled with the dipeptide (**3**) by the action of 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride, in the presence of 1-hydroxybenzotriazole and Hunig's base. The amide product (**9**) is an oil and was therefore deprotected directly by the action of TFA in dichloromethane, giving 75% yield

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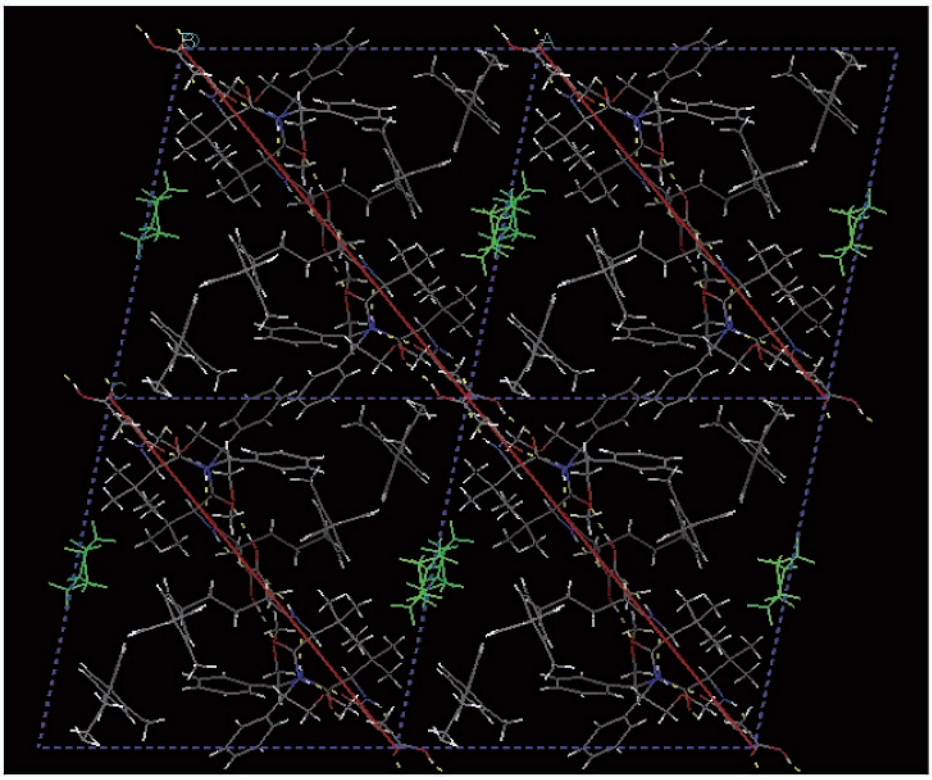

Figure 1. **X-ray crystal structure of the cyclohexane in situ solvate of UK-370,106 (1), illustrating the planar framework and large hydrophobic pores running through the structure.**

of the desired material (**1**), over two steps, following crystallization from ethyl acetate. The material was isolated as a single diastereoisomer, in good purity, and with no entrainment of heavy metals derived from the asymmetric hydrogenation.

Subsequent modifications and process improvements are ongoing in readiness for further scale-up. First, the olefination reaction is heterogeneous in nature, leading to concerns of scale-up effects in the future. In a revised process, the hydroxy sulfonate (**11**) was broken to the corresponding free aldehyde by the action of aqueous potassium phosphate in toluene. The free aldehyde was then reacted with the phosphonosuccinate (**10**) to provide the *trans*-β-substituted itaconate (**12**) in a homogeneous reaction promoted by sodium *tert*-butoxide. The itaconate product was isolated as the 1-adamantanamine salt (**14**) in an improved 67% yield. Preliminary studies suggest that asymmetric hydrogenation of the 1-adamantanamine salt (**14**) proceeds smoothly to yield the desired 2-alkyl succinate (**2**), in good conversion and high enantiomeric excess. This reduction will be further developed to identify optimal conditions for a commercial process. In addition, the coupling and deprotection protocols for the preparation of (**1**) will be changed to a more economic process. 1,1′-Carbonyl diimidazole has shown some promise as a reliable and cost-effective reagent for the coupling of the 2-alkyl succinate (**2**) and the dipeptide (**3**), whilst an aqueous hydrochloric acid deprotection of the amide (**9**) is likely to be preferable to the current trifluoroacetic acid conditions.

In addition to the synthetic challenges encountered within the UK-370,106 (**1**) program, we also modified the final crystallization process to gain control of solid form. The compound exhibits several polymorphic forms, which are similar in lattice energy, with a characteristic melting point of 188−191 °C. Crystallization of (**1**) from ethyl acetate was shown to lead to a drug substance of inconsistent form. An X-ray structure of (**1**) was elucidated from a single crystal grown from acetone/cyclohexane (Figure 1). The data indicate that the compound crystallizes in planar sheets, based on a backbone of hydrogen bonding amide and acid functionalities, with large hydrophobic pockets formed by the biarylpropyl groups. Within the hydrophobic space, large pores exist as channels down the crystal framework. In the case of the single crystal grown from acetone/cyclohexane, cyclohexane molecules occupy (or are entrained within) this space. This has been observed for a number of solvents, which can be easily driven from the pores by gentle heating. We have therefore termed such composites “in situ solvates”. The several polymorphic forms of (**1**), which can be generated by crystallization from different solvents, can putatively all be characterized by the same planar structure, but differ in the distance between planes and therefore the size of the hydrophobic pores. Some level of control may be gained from the initial in situ solvate generated in solution, which determines the size of the hydrophobic cavity prior to a de-solvation process upon isolation and drying of the compound. In support of this theory, we have observed that recrystallization from ethyl acetate/methanol mixtures leads consistently to a single form, with a characteristic powder X-ray diffraction (PXRD) pattern. Conversely, recrystallization from ethyl acetate/tetrahydrofuran mixtures leads consistently to a different form, again with a characteristic PXRD pattern. In this manner, the final polymorphic form

of (**1**) can be controlled in the final crystallization process. A further insight into the behavior of UK-370,106 (**1**) solid forms can be gleaned from the X-ray crystal structure (Figure 1). The crystal planes are aligned such that a "greasy" hydrophobic plane, with very little noncovalent bonding (no hydrogen bonds), can allow the planes to slip, leading to a degree of plasticity. This has been observed empirically by compaction simulation and nanoindentation studies, which illustrate very low hardness and a low yield stress.

In summary, an efficient and practical asymmetric synthesis of UK-370,106 (**1**) has been demonstrated, expedited by an olefination/hydrogenation strategy used to access quantities of the enantiomerically enriched 2-alkyl succinate (**2**). Whilst the revised process is of similar overall yield to that of the original Medicinal Chemistry synthesis, the route benefits from several crystalline intermediates, allowing control of process impurities, and can be operated safely within parameters readily achievable on scale. This has facilitated the preparation of bulk quantities of (**1**) for use in toxicology and clinical trials, with complete control over solid form.

Experimental Section

(2*S*)-Amino-3,3-dimethyl-*N*-[(1*S*)-2-methoxy-1-phenylethyl]butanamide Hydrochloride (3). 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (25.4 g, 0.13 mol) was added in one portion to a stirred mixture of 1-hydroxy-1,2,3-benzotriazole (20.2 g, 0.13 mol), *N*-methylmorpholine (14.4 mL, 0.13 mol), (*S*)-(2-methoxy-1-phenyl)ethylamine (19.1 g, 0.13 mol), and BOC-(*S*)-*tert*-leucine (27.8 g, 0.12 mol) in dichloromethane (600 mL), at 4 °C, under nitrogen. The mixture was allowed to warm to room temperature, where it was stirred for 3 h. The mixture was washed with 5% aqueous citric acid (2 × 500 mL) and saturated aqueous sodium bicarbonate (2 × 500 mL) and then concentrated to a volume of 250 mL. Dioxane (250 mL) was added, and the mixture was cooled to 0 °C. Hydrogen chloride gas was bubbled through for 1 h, until the solution was saturated. The mixture was allowed to warm to room temperature where it was stirred for 1 h. The mixture was concentrated in vacuo, and the residue was re-stripped from diethyl ether (3 × 200 mL) to give the dipeptide (36.3 g, 79%) as a colorless solid; mp 197−199 °C. ^{1}H NMR (300 MHz, d_6-DMSO) δ = 8.87 (1H, br d, J = 9 Hz), 8.06 (3H, br s), 7.41 (2H, d, J = 7 Hz), 7.33 (2H, t, J = 7 Hz), 7.28 (1H, d, J = 7 Hz), 5.12 (1H, m), 3.61 (1H, d, J = 9 Hz), 3.52 (2H, m), 3.24 (3H, s), 1.03 (9H, s) ppm. ^{13}C NMR (100 MHz, d_6-DMSO) δ = 163.38, 136.16, 124.78, 123.94, 123.79, 71.57, 57.08, 54.80, 49.09, 29.81, 23.36 ppm. Anal. Calcd for $C_{15}H_{25}N_2O_2Cl$: C, 59.89; H, 8.38; N, 9.31. Found: C, 59.84; H, 8.34; N, 9.29. MS (thermospray) m/z = 265.1907 (MH^+). FTIR ν_{max} 1682, 1559, 1507, 1125, 870, 705 cm^{-1}.

3-(Diethoxyphosphoryl)succinic Acid 1-*tert*-Butyl Ester (10). Triethyl phosphonoacetate (12.0 kg, 53.5 mol) was added over 30 min to a stirred solution of potassium *tert*-butoxide (7.20 kg, 64.2 mol) in THF (118 L), between 0 and 5 °C, under nitrogen. The mixture was warmed to 25−30 °C where it was stirred for 1 h and then added over 45 min to a solution of *tert*-butyl bromoacetate (11.5 kg, 59.0 mol) in THF (28 L), between 0 and 5 °C, under nitrogen. The mixture was stirred at 0−5 °C for 1 h, and then demineralised water (6.1 L) and ethanol (30 L) were added. A solution of potassium hydroxide (4.2 kg, 75.0 mol) in demineralised water (84 L) was added over 2 h, between −5 and 0 °C, and the mixture was stirred at −10 °C for 16 h. A solution of citric acid (16.5 kg, 85.8 mol) in demineralised water (32 L) was added, and the mixture was concentrated in vacuo to a volume of 180 L. Ethyl acetate (90 L) was added, the organic phase was separated, and the aqueous phase was re-extracted with ethyl acetate (30 L). The combined organic phases were washed with water (30 L) and then stripped and replaced with cyclohexane by distillation at atmospheric pressure, at a constant volume of 72 L. *tert*-Butyl methyl ether (18 L) was added, and the mixture was stirred at ambient temperature for 12 h and then filtered. The residue was washed with a mixture of cyclohexane (16 L) and *tert*-butyl methyl ether (3.6 L), and then dried in vacuo for 16 h to give the phosphonoacetate as a colorless solid (10.0 kg, 60%); mp 120−122 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.20−4.10 (4H, m), 3.49−3.36 (1H, m), 3.00−2.85 (1H, m), 2.72−2.60 (1H, m), 1.20 (9H, s), 1.37−1.27 (6H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.78, 170.06, 81.83, 63.90, 41.66 (d), 32.88, 28.37, 16.68 ppm. FTIR ν_{max} 2990, 1726, 1147, 1019, 756 cm^{-1}.

4-Bromo-2-methyl-1,1′-biphenyl (4).[5] A stirred solution of 5-bromo-2-iodotoluene (668 g, 2.25 mol), phenylboronic acid (302 g, 2.47 mol), palladium (II) acetate (25 g, 0.11 mol), and triphenylphosphine (59 g, 0.22 mol) in acetone (8 L) and aqueous sodium carbonate (2 M, 3.3 L) was heated to reflux for 12 h, under nitrogen. The mixture was allowed to cool to room temperature, and then toluene (7 L) and deionised water (7 L) were added; the mixture was stirred at room temperature for 12 h. Further toluene (2 L) was added, and the organic layer was separated. The aqueous fraction was re-extracted with toluene (2 × 1 L). To the combined organic phases were added deionised water (4 L) and concentrated hydrochloric acid, with stirring, until the solution reached pH 1. The organic layer was separated, washed with water (4 L), and then concentrated in vacuo to leave a brown oil. Hexane (10 mL/g) was added to give a brown slurry, and the mixture was stirred at room temperature for 20 min and then filtered. The filtrate was concentrated in vacuo to leave a brown oil. Purification by distillation gave the title compound (446 g, 80%) as a colorless oil; bp 120−127 °C/1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ= 7.42−7.26 (7H, m), 7.09 (1H, d, J = 8 Hz), 2.25 (1H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 141.06, 140,97, 137.82, 133.20, 131.49, 129.22, 129.01, 128.42, 127.33, 121.31, 20.79 ppm. Anal. Calcd for $C_{13}H_{11}Br$: C, 63.18; H, 4.49. Found: C, 63.36; H, 4.50. FTIR ν_{max} 1472, 1008, 763, 670 cm^{-1}.

Sodium 1-Hydroxy-3-(2-methyl-1,1′-biphenyl-4-yl)-1-propanesulfonate (11). A stirred solution of (**4**) (20 g, 81 mmol), allyl alcohol (14 mL, 0.20 mol), tetrabutylammonium chloride (22 g, 81 mmol), sodium bicarbonate (17 g, 0.20 mol), palladium acetate (0.91 g, 4.0 mmol), and tri-*o*-

tolylphosphine (2.5 g, 8.1 mmol) in acetonitrile (200 mL) was heated to reflux for 1 h, under nitrogen, and then cooled. Ethyl acetate (200 mL) was added, and the mixture was washed with water (2 × 200 mL), aqueous citric acid solution (10%, 100 mL), and brine (100 mL). Magnesium sulfate (20 g) and charcoal (2 g) were added, and the mixture was filtered and concentrated to low volume. Methanol (100 mL) was added, and a solution of sodium metabisulfite (11.2 g) in water (20 mL) was added dropwise, over 10 min, at room temperature. The resulting mixture was stirred at room temperature for 16 h and then filtered. The residue was washed with ethyl acetate (3 × 20 mL) and dried in vacuo to leave the hydroxy sulfonate as a colorless solid (15.9 g, 64%); mp 170−178 °C. ^{1}H NMR (400 MHz, d_6-DMSO) δ = 7.49−7.30 (5H, m), 7.11−7.04 (3H, m), 5.26 (1H, br d), 3.84−3.78 (1H, m), 2.81−2.70 (1H, m), 2.20 (3H, s), 2.12−1.99 (1H, m), 1.85−1.74 (1H, m) ppm. ^{13}C NMR (100 MHz, d_6-DMSO) δ = 141.94, 141.80, 139.28, 134.96, 131.08, 130.03, 129.61, 128.77, 127.29, 126.64, 82.71, 34.49, 31.95, 21.10 ppm. Anal. Calcd for $C_{16}H_{17}NaO_4S$: C, 58.53; H, 5.22. Found: C, 57.93; H, 5.25. Sulfate ashes 21.35% (expected 21.6%). FTIR ν_{max} 1214, 1180, 1033, 767, 702 cm^{-1}.

(*E*)-2-[2-(*tert*-Butoxy)-2-oxoethyl]-5-(2-methyl-1,1′-biphenyl-4-yl)-2-pentenoic Acid Cyclohexylamine Salt (13). A solution of potassium *tert*-butoxide (6.6 kg, 59 mol) in THF (22 L) was added over 1 h to a stirred solution of (**11**) (4.55 kg, 13.8 mol) and (**10**) (4.94 kg, 15.9 mol) in THF (5.2 L) and *tert*-butyl alcohol (18.3 L), between −5 and 0 °C, under nitrogen. The mixture was stirred between −5 and 0 °C for 4 h, and then a solution of citric acid (12.0 kg, 62 mol) in demineralised water (28 L) was added in one portion. The pH was adjusted to pH 4−5 by the addition of aqueous sodium hydroxide solution (40%), and the organic phase was separated. The organic phase was concentrated in vacuo to a volume of approximately 25 L and then recombined with the aqueous phase. Ethyl acetate (28 L) was added, and the organic phase was separated and then washed with a solution of sodium bicarbonate (3.18 kg) in demineralised water (45 L). Demineralised water (15 L) was added, and the pH was adjusted to pH 4−5 by the addition of a solution of citric acid (2.27 kg) in demineralised water (23 L). The organic phase was separated, washed with demineralised water (14 L), and then azeotropically dried by distillation at atmospheric pressure at a constant volume of 56 L. The mixture was cooled to 35 to 40 °C, and cyclohexylamine (1.10 kg, 11.1 mol) was added in one portion. The mixture was cooled to ambient temperature where it was stirred for 18 h. The mixture was then cooled to 0 °C where it was stirred for 2 h and then filtered. The residue was washed with ethyl acetate (5 L) and then dried in vacuo at 40−45 °C to leave the itaconate as a colorless solid (4.1kg, 61%); mp 133−135 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42−7.30 (5H, m), 7.16 (1H, d, J = 7.6 Hz), 7.15−7.05 (2H, m), 6.83 (1H, t, J = 7.2 Hz), 3.29 (2H, s), 2.50−2.43 (2H, m), 2.26 3H, s), 2.03−1.98 (2H, m), 1.78−1.71 (2H, m), 1.61−1.57 (1H, m), 1.44 (9H, s), 1.30−1.10 (5H, m) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.37, 171.14, 142.00, 140.84, 139.86, 139.17, 135.45, 132.21, 130.45, 130.06, 129.42, 128.20, 126.81, 125.83, 80.20, 50.46, 35.34, 34.98, 31.73, 31.46, 28.58, 25.47, 25.12, 20.90 ppm. Anal. Calcd for $C_{30}H_{41}NO_4$: C, 75.12; H, 8.62; N, 2.92. Found: C, 75.02; H, 8.59; N, 2.91. FTIR ν_{max} 2980, 1721, 1695, 1160, 702 cm^{-1}.

(*E*)-2-[2-(*tert*-Butoxy)-2-oxoethyl]-5-(2-methyl-1,1′-biphenyl-4-yl)-2-pentenoic Acid Adamantanamine Salt (14). A solution of potassium phosphate (32.0 g, 0.152 mol) in water (100 mL) was added dropwise over 20 min to a suspension of (**11**) (25.0 g, 76.1 mmol) in toluene (300 mL) and water (200 mL) at room temperature. The mixture was stirred at room temperature for 16 h, and the organic phase was separated, washed with water (100 mL), and concentrated to a volume of approximately 50 mL. The resulting solution was added dropwise over 30 min to a solution of sodium *tert*-butoxide (22.4 g, 0.233 mol) and (**10**) (22.2 g, 71.5 mmol) in toluene (150 mL) between −10 and 0 °C, under nitrogen. The mixture was stirred between −10 and 0 °C for 3 h, and then aqueous citric acid solution (10%, 150 mL) was added in one portion. The organic phase was separated, washed with water (150 mL), and dried by azeotropic distillation at a volume of 300 mL toluene. The reaction was cooled to 35 to 40 °C, and a solution of 1-adamantanamine (10.6 g, 70.4 mmol) in toluene (100 mL) was added over 5 min. The mixture was cooled to ambient temperature where it was stirred for 18 h. The mixture was then cooled to 5 °C where it was stirred for 1 h and then filtered. The residue was dried in vacuo at 40−45 °C to leave the itaconate as a colorless solid (27.0 g, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41−7.05 (9H, m), 3.28 (2H, s), 2.80−2.76 (2H, m), 2.58−2.52 (2H, m), 2.26 (3H, s), 2.15−2.11 (3H, m), 2.00−1.98 (6H, m), 1.70−1.66 (6H, m), 1.45 (9H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.79, 170.95, 142.01, 140.81, 139.85, 135.45, 131.90, 130.46, 130.05, 129.42, 128.20, 126.81, 125.84, 125.49, 80.14, 51.29, 41.12, 36.16, 35.33, 34.95, 31.47, 29.56, 28.56, 20.89 ppm. Anal. Calcd for $C_{34}H_{45}NO_4$: C, 76.80; H, 8.53; N, 2.63. Found: C, 76.90; H, 8.53; N, 2.51. MS (thermospray) m/z = 532.3422 (MH^+). FTIR ν_{max} 2909, 2853, 1731, 1521, 1388, 1145, 704 cm^{-1}.

(*R*)-2-[2-(*tert*-Butoxy)-2-oxoethyl]-5-(2-methyl-1,1′-biphenyl-4-yl)-pentanoic Acid Cyclohexylamine Salt (15). A stirred solution of (**13**) (1.1 kg, 2.3 mol) and [(*S*)-2,2′-bis(diphenylphosphino-1,1′-binaphthyl]chloro(*p*-cymene)ruthenium chloride (2.2 g, 2.4 mmol) in methanol (8.2 L) and water (2.8 L) was heated to 60 °C, under hydrogen (60 psi), for 40 h and then allowed to cool to room temperature (enantiomeric excess = 88%). The mixture was concentrated in vacuo to a volume of 3 L, and then ethyl acetate (5 L) was added. The mixture was distilled at constant volume of ethyl acetate until water droplets appeared in the distillate. The mixture was then cooled to ambient temperature, and then demineralised water (2.9 L) and citric acid (485 g, 2.5 mol) were added. The organic phase was separated and washed with demineralised water (1.1 L) and then dried azeotropically by distillation at a constant volume of 8.25 L. Methylethyl ketone (8.25 L) was added, and the mixture was warmed to 40 °C. Cyclohexylamine (228 g, 2.28 mol) was added in one portion, and the mixture was allowed to

cool to ambient temperature where it was stirred for 16 h. The mixture was filtered, and the residue was washed with a mixture of ethyl acetate (55 mL) and methyl ethyl ketone (55 mL) and then dried in vacuo at 45 °C to leave the succinate as a colorless solid (0.71 kg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.42−7.25 (5H, m), 7.11 (1H, d, J = 7.6 Hz), 7.08−7.00 (2H, m), 2.90−2.82 (1H, m), 2.67−2.58 (4H, m), 2.30 (1H, br dd), 2.23 (3H, s), 2.00−1.86 (2H, m), 1.80−1.50 (7H, m), 1.41 (9H, s), 1.38−1.09 (5H, m) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ =181.40, 172.54, 142.18, 141.59, 139.54, 135.17, 130.58, 129.93, 129.42, 128.20, 126.75, 125.98, 80.08, 50.51, 44.93, 38.99, 36.27, 32.89, 31.76, 30.06, 28.62, 25.47, 25.10, 20.92 ppm. Anal. Calcd for $C_{30}H_{43}NO_4$: C, 74.81; H, 9.00; N, 2.91. Found: C, 74.83; H, 9.02; N, 3.01. MS (thermospray) m/z = 482.3261 (MH^+). Enantiomeric excess, 98.4% by HPLC (Chiralpak AD 250 mm × 4.6 mm, rt, 95% hexane/5% IPA containing 0.1% TFA, 1 mL/min, detection 220 nm). FTIR ν_{max} 2931, 2860, 1732, 1573, 1406, 1135, 705 cm^{-1}.

(*3R*)-3-{(*1S*)-1-[(*1S*)-2-Methoxy-1-phenyl-1-ethyl]carbamoyl-2,2-dimethyl-1-propyl}carbamoyl-6-(2-methyl-1,1′-biphenyl-4-yl) Hexanoic Acid (1). A solution of (**15**) (3.0 kg, 6.23 mol) in dichloromethane (15 L) was washed with aqueous citric acid solution (10%, 2 × 15 L) and water (15 L) and then dried by azeotropic distillation at constant volume of dichloromethane. The mixture was cooled to 0−5 °C, and the dipeptide (**3**) (1.97 kg, 6.55 mol), 1-hydroxybenzatriazole hydrate (1.05 kg, 7.77 mol), and di-isopropylethylamine (1.65 kg, 12.8 mol) were added. 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (1.31 kg, 6.83 mol) was added, and the mixture was allowed to warm to room temperature where it was stirred for 16 h. The mixture was washed with a solution of sodium bicarbonate (0.44 kg, 5.25 mol) in water (12.5 L), aqueous citric acid solution (10%, 12.5 L), and demineralised water (12.5 L) and then dried by azeotropic distillation at constant volume. The mixture was combined with a second batch to give a solution of (**9**) in dichloromethane (assumed quantitative yield, 13.91 mol in 33.5 L). To this mixture was added trifluoroacetic acid (8.74 L) over 15 min, at 20−25 °C, under nitrogen. The mixture was stirred at 20−25 °C for 16 h, and then dichloromethane (22 L), THF (10.9 L) and demineralised water (22 L) were added. The pH was adjusted to 2−3 by the addition of aqueous sodium hydroxide solution (5 M, 13 L). The organic phase was separated, washed with demineralised water (22 L), and dried by azeotropic distillation at a constant volume of 32 L, replacing the solvent with THF. The mixture was filtered to remove any specks, and then the solvent was stripped and replaced to ethyl acetate by distillation at atmospheric pressure, at a volume of 55 L. The mixture was allowed to cool to ambient temperature over 10 h, and the resulting suspension was filtered. The precipitate was washed with ethyl acetate (5.5 L) and then dried in vacuo at 40 °C to leave the acid (**1**) (6.0 kg, 75% over two steps) as a colorless crystalline solid; mp 178−180 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39−7.16 (13H, m), 7.09−7.04 (2H, m), 6.94 (1H, s), 5.16−5.12 (1H, m), 4.42 (1H, d, J = 8 Hz), 3.63 (2H, d, J = 4 Hz), 3.34 (3H, s), 2.75−2.69 (2H, m), 2.51−2.39 (3H, m), 2.19 (3H, s), 1.69−1.41 (4H, m), 1.03 (9H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 172.70, 171.12, 167.98, 139.16, 137.99, 136.44, 136.42, 131.71, 127.24, 126.46, 126.04, 125.24, 124.88, 124.15, 123.60, 123.45, 122.71, 72.13, 57.89, 54.93, 50.07, 39.61, 33.99, 32.36, 31.55, 29.60, 25.83, 23.33, 16.82 ppm. MS (thermospray) m/z = 573.3323 (MH^+); Anal. Calcd for $C_{35}H_{44}N_2O_5$: C, 73.40; H, 7.74; N, 4.89. Found: C, 73.42; H, 7.70; N, 4.92. FTIR ν_{max} 3300, 2960, 2930, 1711, 1639, 1543, 700 cm^{-1}.

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