Organic Process Research & Development **2005**, *9*, 663−669

An Efficient and Scalable Synthesis of the Endothelin Antagonists UK-350,926 and UK-349,862 Using a Dynamic Resolution Process

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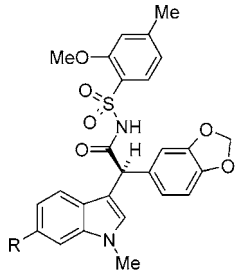
Abstract:

The development and scale-up of a potential manufacturing route to the endothelin antagonists UK-350,926 1 and UK-349,-862 2 are described. A key synthetic challenge in designing an efficient route to these molecules was the optical lability of the stereogenic centre during the construction of the acylsulfonamide functionality. In the discovery synthesis of UK-350,926 the chiral centre was introduced by classical resolution and the acylsulfonamide functionality synthesized by construction of the *N*-sulfonyl bond. An alternative more efficient process route was developed involving the preparation of racemic UK-350,-926 and final step dynamic resolution with (*S*)-(−)-1-phenylethylamine as the key step. The process route prepared the acylsulfonamide by construction of the *N*-carbonyl bond, eliminates a cryogenic reaction and a hazardous intermediate from the synthesis, improves the overall process yield, and allows access to both endothelin antagonists from common intermediates without the need for purification by chromatography. Full experimental details of the new five-step process to prepare UK-349,862 from commercially available starting materials are given for the first time.

Introduction

The endogenous endothelins[1] (ET-1, 2, and 3), a family of homologous 21-amino acid isopeptides, possess exceptionally potent vasoconstrictory activity and play an important role in the control of vascular smooth muscle tone and blood flow. Characterization of elevated endothelin levels in a variety of disease states has promoted an intense effort by a number of pharmaceutical companies to identify potent and selective non-peptide endothelin antagonists of different subtype selectivity for the two-endothelin receptors ET_A and ET_B. Indications that have been targeted include congestive heart failure, pulmonary hypertension, angina, renal dysfunction, restenosis, atherosclerosis, and prostate cancer.[2] The potent and ET_A selective endothelin antagonist UK-350,926 **1** was discovered at Pfizer's Sandwich Discovery Laboratories[3] and entered into development for the potential treatment and prophylaxis of acute renal failure. An orally bioavailable prodrug UK-349,862 **2**, containing a hydroxymethyl group at the 6-position of the indole, also was nominated as a development candidate at the same time for the restenosis indication. This contribution describes the development of an efficient and robust synthetic route capable of preparing kilogram quantities of UK-350,926 **1** and UK-349,862 **2** (Figure 1).



1 UK-350,926 R = -CO_2H
2 UK-349,862 R = -CH_2OH

Figure 1.

Results and Discussion

Review of the Discovery Chemistry Route. A key synthetic challenge of the early discovery routes[4,5] to this series of endothelin receptor antagonists was the construction of the acylsulfonamide functionality without loss of stereochemical integrity in compounds containing a labile diarylmethine stereogenic centre. A convergent synthesis of optically pure UK-350,926 **1** was developed by the Discovery chemists prior to the compound entering development, involving a classical resolution to access the desired (*S*)-enantiomer.[5] In the discovery chiral synthesis the acylsulfonamide functionality was introduced by constructing the *N*-sulfonyl bond (disconnection B in Scheme 1) by reaction of sulfonyl chloride **3** with carboxamide **4**.

The discovery synthesis[3,5] of UK-350,926 **1** is outlined in Scheme 2. The indole derivative **8** was alkylated at C-3 with the bromoacid **10** to give the diarylacetic acid derivative **11** in 57% yield and resolved in a classical chemical resolution process with the chiral amine (*R*)-(+)-1-phenylethylamine [*R*-(α)-methylbenzylamine] to give the desired (*R*),(*S*)-salt of **12** in 21% yield. Three successive recrystal-

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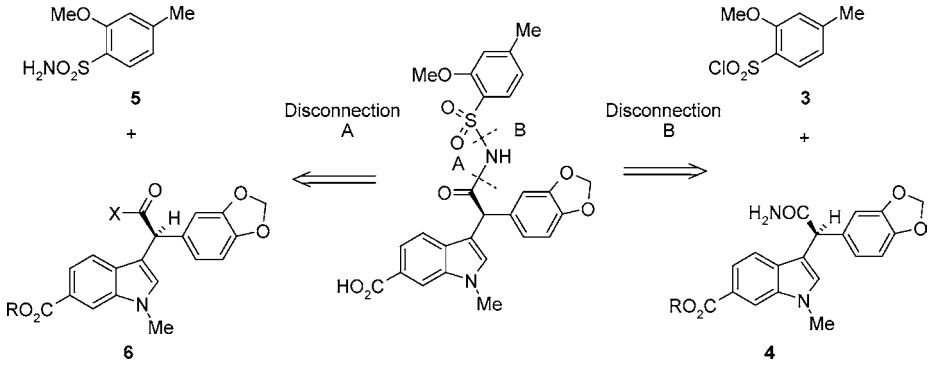
(1) Yanagisawa, M.; Kurihara, H.; Kimura, S.; Tomobe, Y.; Kobayashi, M.; Mitsui, Y.; Yazaki, Y.; Goto, K.; Masaki, T. *Nature* **1988**, *332*, 411−415.
(2) (a) Clark, W. M. *Curr. Opin. Drug Discovery Dev.* **1999**, *2*, 565−577. (b) Wu, C.; Holland, G. W.; Brock, T. A.; Dixon, R. A. F. *Investigational Drugs* **2003**, *6*, 232−239.
(3) Challenger, S.; Dack, K. N.; Derrick, A. M.; Dickinson, R. P.; Ellis, D.; Hajikarimian, Y.; James, K.; Rawson, D. J. WO 99/20623, 1999.
(4) (a) Rawson, D. J.; Dack, K. N.; Dickinson, R. P.; James, K. *Biorg. Med. Chem. Lett.* **2002**, *12*, 125−128. (b) Rawson, D. J.; Dack, K. N.; Dickinson, R. P.; James, K.; Long C.; Walker, D. *Med. Chem. Res.* **2004**, *13*, 149−157.
(5) Ellis, D. *Tetrahedron*: *Asymmetry* **2001**, *12*, 1589−1593.

10.1021/op050102f CCC: $30.25
Published on Web 08/19/2005

Scheme 1. **Synthetic strategies to construct the acylsulfonamide functionality**



lisations from ethyl acetate were necessary to achieve an acceptable optical purity (>98% de[6]). The key chiral acid intermediate **12** was available in five steps from the two commercially available starting materials **7** and **9** in 11% overall yield (four linear steps). This intermediate was then converted into the acylsulfonamide **14** in a two-step process involving the coupling of a carboxamide anion with sulfonyl chloride **3**.[7]

Although the Discovery group was able to demonstrate that a 1-hydroxy-7-azabenzotriazole (HOAt) active ester[8] of chiral acid **12** could be prepared without significant loss in optical purity (>98%[9]), it was critical that the basic urea byproduct from the dehydrating reagent, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), was completely removed with a citric acid wash prior to the addition of ammonia to avoid racemisation.[10] The synthesis of UK-350,926 **1** was completed with the deprotection of the benzyl ester **14** by hydrogenolysis.

The sequence developed by the Discovery chemists was capable of producing gram quantities of material for candidate nomination studies. It provided UK-350,926 **1** in a convergent manner and in approximately 4% overall yield for the sequence of seven linear steps (eleven steps in total from commercially available materials). There were a number of issues associated with the route for rapid scale-up and preparation of kilogram quantities. Our major concern with the synthesis was the sensitivity and lack of robustness in preparing the carboxamide **13**, with the potential to lose optical purity during the preparation of the HOAt active ester. On scale-up with increased processing times the potential optical sensitivity was more likely to become a significant problem. The discovery route also suffers from a low overall yield, largely due to an inherently inefficient classical resolution (unoptimised yield 21%). The preparation of the acylsulfonamide involved cryogenic conditions (−60 °C), and the synthesis required chromatography at three steps. In addition, bromoacid **10** was lachrymatory and showed hydrolytic and thermal sensitivity.

Process Route to UK-350,926 and UK-349,862. In designing a new route to this class of endothelin antagonists, a synthetic strategy that proceeds through common intermediates allowing access to both compounds was considered to be highly desirable. Early indications were that both candidates would be toxicologically bland, and it was estimated that a total of 7kg of API would be required to progress both candidates to Phase I clinical studies. Our target was to progress both candidates to Phase I studies within 12 months of candidate nomination. It was envisaged that UK-349,862 **2** would be available in a final step reduction of UK-350,926 **1**. An alternative strategy was developed, which was designed to overcome some of the limitations of the discovery route, and involved the preparation of racemic UK-350,926 and resolution in the final step. We considered a late stage resolution approach would be attractive on paper due to the perceived ease of racemate synthesis and the possibility of a crystallization-induced asymmetric transformation (dynamic resolution) process. In addition UK-350,-926 contains two acidic functional groups (acid pK_a = 5.01, acylsulfonamide pK_a = 5.38) and has the potential of forming mono- or disalts with chiral amines.

The process synthesis of UK-350,926 **1** is outlined in Scheme 3. Indole-6-carboxylic acid was converted in two steps to the *N*-methylindole derivative **15** in 73% overall yield. Methyl ester protection was chosen for the acid on the grounds of atom economy, crystallinity, and ease of deprotection by base hydrolysis. Carbonyl diimidazole (CDI) was used as an activating reagent instead of the more expensive carbodiimide (EDCI) in the esterification reaction, and on safety grounds a combination of potassium *tert*-butoxide and dimethyl sulfate was used instead of the discovery process using sodium hydride and iodomethane for the indole *N*-alkylation. The intermediate **15** is a crystalline compound and could be prepared without chromatography. Initially **15** was prepared in-house for the first two campaigns, but for the third Pilot Plant campaign it was purchased from external vendors.[11] The discovery conditions[3] were initially used to prepare the racemic acid **16** with some minor modifications. Concerns over the stability of bromoacid **10** (Scheme 2) (DSC showed mild exothermic

(6) Chiral HPLC conditions for (*R*)-(+)-1-phenylethylamine salt of **12**: Chiralpak AD 50 mm × 4.6 mm column, eluent 60% hexane, 40% 2-propanol + 0.1% glacial acetic acid.

(7) For the three-step preparation of sulfonyl chloride **3** from 4-bromo-3-methylanisole, see ref 3.

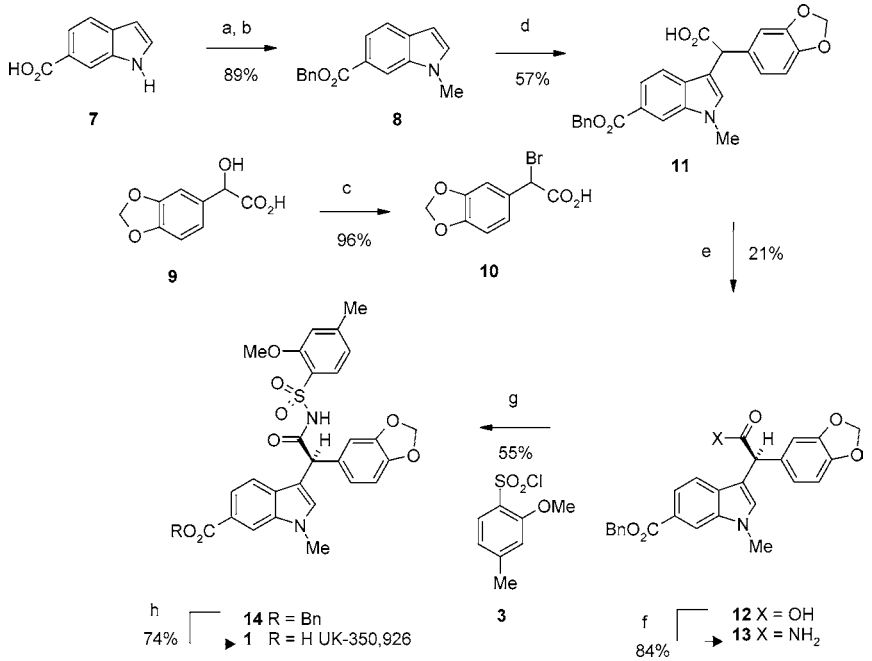
(8) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397−4398.

(9) Chiral HPLC conditions for **13**: Chiralpak AD 250 mm × 4.6 mm column, eluent 50% hexane, 50% 2-propanol, 0.3% trifluoroacetic acid (TFA), and 0.2% diethylamine (DEA).

(10) The Discovery Chemists reported an 8% loss in optical purity in one coupling reaction in which the basic urea byproduct was incompletely removed prior to the addition of ammonia.

(11) Peakdale Molecular and EMS-Dottikon AG supplied *N*-methylindole-6-carboxylic acid methyl ester.

Scheme 2. **Discovery synthetic route to UK-350,926**[a]



[a] Reagents and conditions: (a) **7**, BnOH (1.1 equiv), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 1.2 equiv), *N*,*N*-(dimethylamino)pyridine (1.3 equiv), CH_2Cl_2 , rt, 12 h, chromatography, 99%; (b) NaH, THF, 0 °C, 2 h, MeI (1.5 equiv), 0 °C, 12 h, 90%; (c) **9**, 62% Aq HBr, toluene, CH_2Cl_2 , rt, 4 h, 96%; (d) **8**, **10** (1.08 equiv), DMF, 90 °C, 4 h, chromatography, 57%; (e) **11**, (*R*)-(+)-1-phenylethylamine (1.0 equiv), EtOAc, 21%; (f) (i) (*R*,*S*)-salt **11** with (*R*)-(+)-1-phenylethylamine, 2 M aq HCl , EtOAc; (ii) **12**, 1-hydroxy-7-azabenzotriazole (HOAt, 1.3 equiv), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 1.5 equiv), CH_2Cl_2 , 0 °C, 90 min; (iii) aq NH_3 (3 equiv), 0 °C, 10 min, chromatography, 84%; (g) (i) **13**, NaHMDS (1.0 equiv), THF, −60 °C to −40 °C; (ii) **3** (1.0 equiv), −40 °C, 30 min, 55%; (h) **14**, 5% Pd/C, H_2 (60 psi), ethanol/water (9:1), recrystallisation 74%.

activity above 70 °C) led to the substitution of toluene in the original bromination process with the lower boiling solvent dichloromethane and the imposition of a temperature limit of 40 °C during the solvent strip.

The crude bromoacid **10** was used in the following alkylation reaction without further purification. In the methyl ester series the racemic acid **16** was isolated as a crystalline solid in 70% yield after an extractive workup and crystallization from dichloromethane, thus eliminating the need for purification by chromatography. This process was used to prepare approximately 22 kg of **16** from two scale-up campaigns. An alternative more efficient acid catalysed direct coupling of 3,4-methylenedioxymandelic acid **9** with indole **15** was developed in time for the third pilot plant campaign (Scheme 4). Reaction of an equimolar quantity of **9** and indole **15** in acetonitrile in the presence of trifluoroacetic acid gave the desired product **16** in 86% yield. The product was insoluble in the reaction mixture and was isolated by filtration in a direct drop process and used in the next step without further purification. This new process was successfully scaled-up in the Pilot Plant on a maximum scale of 24.9 kg of **9**, avoiding the need to prepare the lachrymatory and thermally labile bromoacid **10**. A total of 78 kg of **16** was produced using a combination of the two methods without the need for chromatography.

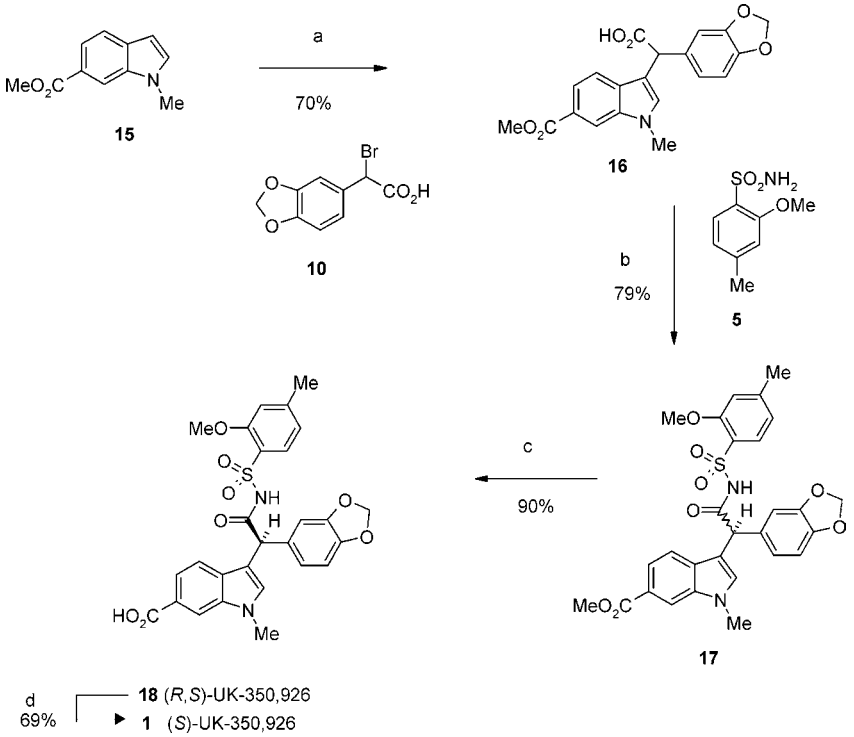
A literature method[12] was used to prepare the acylsulfonamide **17** involving the coupling of an acyl imidazolide derived from acid **16** with sulfonamide **5** in a one-pot process. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was required to catalyse the reaction. The acylsulfonamide product **17** was obtained in 79% yield after an acidic workup and crystallization from acetonitrile. This crystallization was a key purification point in the synthesis and produced material of high purity. Hydrolysis of the methyl ester **17** with excess sodium hydroxide in aqueous methanol completed the synthesis of racemic UK-350,926 **18**. The racemate was highly crystalline, and crystallization from dichloromethane gave high quality material containing the ester **17** (0.1−0.5%) as the only significant impurity. A total of 18.5 kg of racemic acid **18** was prepared in the first two scale-up campaigns.

Initial results on the attempted resolution screen of racemic UK-350,926 with our in-house collection of chiral amines were not encouraging due to the propensity of the highly crystalline racemic free acid to preferentially precipitate from solution. The only success in the initial screen was with the chiral amine brucine hydrate **19**. Crystallisation of a stoichiometric brucine salt from hot acetone (11 mL/g) gave the desired diastereoisomer in 92% recovery and 40% de (Scheme 5).

During the first campaign 4.77 kg of racemic acid and 3.82 kg of brucine hydrate were converted to 7.65 kg of salt. The optical purity of the salt could not be upgraded by recrystallisation, but advantage was taken of the highly crystalline nature of the racemic free acid. The brucine salt was broken, and the minor *R*-enantiomer of the free acid was removed by preferential crystallization of the racemate from ethyl acetate (5 mL/g). Concentration of the mother liquors and crystallization from dichloromethane gave the desired *S*-enantiomer **1** in acceptable optical purity (>94% ee) and in 28% step yield. Although this process to upgrade

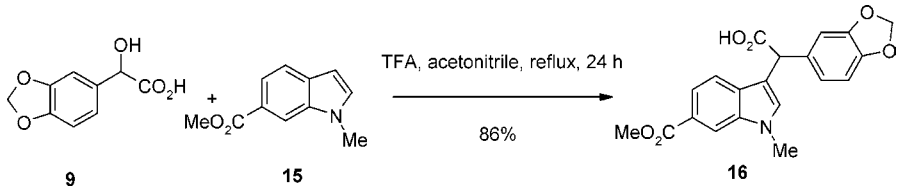
(12) Drummond, J. T.; Johnson, G. *Tetrahedron Lett.* **1988**, *29*, 1653.

Scheme 3. **Process synthetic route to UK-350,926**[a]

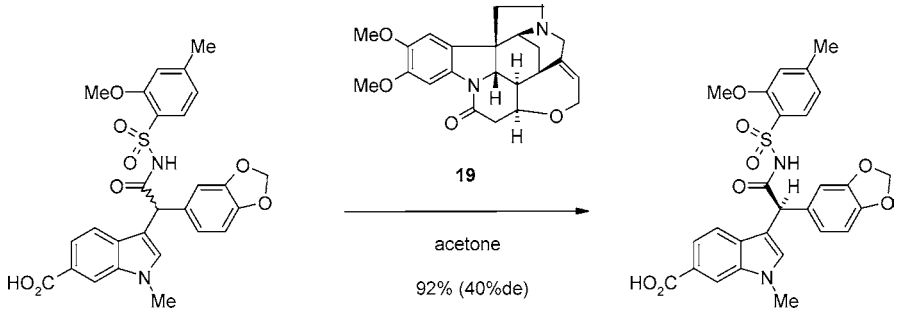


[a] Reagents and conditions: (a) **15**, **10** (1.1 equiv), DMF, 80 °C 4 h, 70%; (b) (i) **16**, 1,1′-carbonyldiimidazole (CDI, 1.1 equiv), THF, refux 1.5 h; (ii) **5** (1.1 equiv), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.1 equiv), THF reflux 4.5 h, 79%; (c) **17**, NaOH (7 equiv), MeOH, water, 90%; (d) (i) **18**, (*S*)-(−)-1-phenethylamine (2.0 equiv), THF, DME 60 to 45 °C, 72 h, 76%; (ii) 1 M aq HCl , EtOAc, THF, *n*-hexane, 91%.

Scheme 4. **Direct coupling to prepare racemic acid 16**



Scheme 5. **Resolution of racemic UK-350,926 with brucine hydrate**



optical purity was inefficient, it did allow for the preparation of the first batch of UK-350,926 **1** (1.34 kg) to support initial toxicology studies. The overall yield for the first laboratory campaign using the new synthesis was approximately 10% (six linear steps), which compared favourably with the original discovery synthesis (4%) and vindicated our decision to switch routes early in the development programme. The high toxicity of brucine hydrate and the sacrificial nature of the final step dictated that we needed an alternative resolution process in time for the second Kilo Laboratory campaign.

A solvent screen indicated that ethers and, in particular, tetrahydrofuran (THF) were good solvents for solubilising the racemic acid. This information led us to complete a salt screen using optically pure (*S*)-enantiomer **1** and our in-house collection of chiral amines (1 molar equiv) in THF, which gave two crystalline salts, one with (1*R*,2*R*)-2-amino-1-(4-nitrophenyl)-1,3-propanediol and the other with (*S*)-(−)-1-phenylethylamine [*S*-(α)-methylbenzylamine]. Interestingly the stoichiometry of the precipitated (*S*)-(−)-1-phenylethylamine salt was 1:1.5 (acid/amine) by ^{1}H NMR analysis. In

Table 1. **Resolution of racemic UK-350,926 with (*S*)-(−)-1-phenylethylamine**

entry	scale	conditions	yield	optical purity[13] (%de)
1	1 g	(*S*)-(−)-1-phenylethylamine (1.5 equiv) THF	55	80
2	1.174 kg	(*S*)-(−)-1-phenylethylamine (2 equiv) THF/DME, 55−45 °C	84	94
3	6.52 kg	(*S*)-(−)-1-phenylethylamine (2 equiv) THF/DME, 55−45 °C	82	90

view of the low cost and bulk availability of (*S*)-(−)-1-phenylethylamine we focused all our development efforts on this salt. Resolution of the racemic acid of **1** with (*S*)-(−)-1-phenylethylamine (1.5 molar equiv) in THF (20 mL/g) gave the desired (*S*,*S*)-salt in 55% yield and 80% de.[13] This was the starting point for further development work on this process, which led to the discovery of an efficient dynamic resolution process. The key parameters were found to be solvent composition, crystallization temperature, and amine stoichiometry. A mixture of THF and 1,2-dimethoxyethane (DME), temperatures in the 45−55 °C range, and an excess of the chiral amine were found to be optimal for this process. (*S*)-(−)-1-Phenylethylamine (2 molar equiv) was added to the racemic acid in THF (5.5 mL/g) and DME (5.5 mL/g), and the mixture was heated to 55 °C for 24 h, 50 °C for 24 h, and 45 °C for 24 h. The temperature gradient and heavy seeding were essential to prevent material oiling-out during the initial phase of the crystallization. This process was successfully scaled-up twice in laboratory glassware on a 1 kg scale and twice in the Kilo Laboratory on 6.25 and 7.0 kg scales as part of the second bulk campaign (Table 1, Scheme 6) to give 9.66 kg of UK-350,926 **1** (>90% ee). The laboratory pilot on a 1 kg scale gave the desired *S*,*S*-salt in 84% yield and acceptable optical purity (94% de). In the Kilo Laboratory the yields and optical purity were slightly lower than those of the laboratory batches (Table 1, entries 2 and 3). Fortunately we were able to upgrade the optical purity of material of 90% ee to greater than 98% by crystallization of a disodium salt of the free acid from aqueous ethanol. The overall yield for the second campaign was increased to approximately 22% as a result of the improvements to the resolution step. During the third pilot plant campaign the development of both endothelin antagonists **1** and **2** was stopped due to adverse toxicology before the dynamic resolution process could be scaled further. Had the compounds continued in development further work on the dynamic resolution would have focused on optimizing the selectivity to deliver the desired optical purity without the need for the salt upgrade and to reduce the unacceptable processing time.

In the discovery chemistry route to racemic UK-349,862 **2** a benzyl ester derivative of racemic acid **1** was reduced with lithium aluminium hydride (LAH). An alternative literature method,[14] avoiding LAH, was used to reduce **1** to the alcohol **2** involving the in situ formation of an intermediate acyl imidazole with 1,1-carbonyldiimidazole (CDI) followed by reduction with sodium borohydride in aqueous THF (Scheme 7). On a pilot scale in laboratory glassware this gave UK-349,862 **2** in 86% yield and without significant loss in optical purity. However on scale-up to a 0.5 kg scale this process resulted in 10% loss in optical purity. Quenching the reaction at the intermediate imidazolide stage and chiral purity assay of the recovered acid by HPLC indicated that optical purity was lost during the activation stage. Two reductions in laboratory glassware were successfully completed on a 0.75 and 1.5 kg scale. Provided the activation step was restricted to 1 h, the loss in optical purity could be minimized. A significant issue in this process was the stability of **2** to acid during the quench and subsequent solvent strip. A symmetrical ether dimer impurity was observed when dilute hydrochloric acid was used to quench the reaction. The level of this dimer could be controlled to less than 5% by switching to a citric acid quench (pH = 3) and restricting the temperature in the solvent strip to less than 45 °C. Optical purity in this series could also be upgraded by selectively removing the unwanted (*R*)-enantiomer as the racemate by crystallization from methanol. The modified reduction process was used to prepare 2 kg of UK-349,862 **2**, which was sufficient for initial toxicological evaluation.

Conclusions

We have developed an efficient scalable route, which allows access to the two endothelin antagonists UK-350,926 and UK-349,862 from three common commercially available starting materials. The key step involves a dynamic resolution of a late stage intermediate with (*S*)-(−)-1-phenylethylamine. Furthermore the new process avoids handling optically sensitive intermediates, a hazardous intermediate, expensive coupling reagents, and a cryogenic step. All of the intermediates are crystalline solids removing the need for purification by chromatography in the original discovery synthesis. The new process has been implemented on a kilogram scale to prepare approximately 12.5 kg of UK-350,926 and 2 kg of UK-349,862. The overall process yield for the four-step synthesis of UK-350,926 **1** from commercially available indole **15** was improved from approximately 4% for the discovery synthesis to 42% through a combination of outsourcing (two steps) and improved synthetic efficiency.

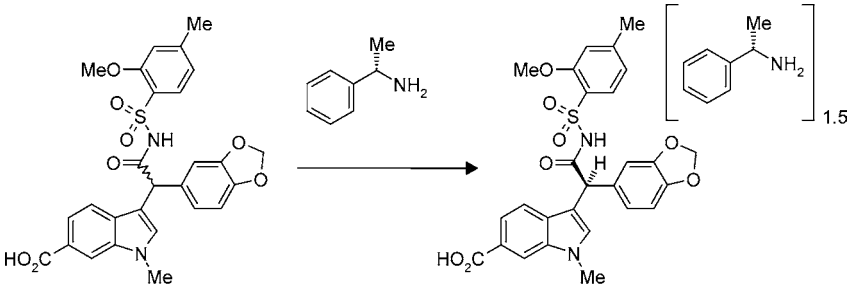
Experimental Section

All reactions involving air-sensitive reagents were performed under dry nitrogen. Melting points are uncorrected. 300 MHz ^{1}H NMR and 75 MHz ^{13}C NMR spectra were recorded using $CDCl_3$ as the solvent unless otherwise indicated. Chemical shifts are reported in ppm (δ) relative to residual protons in the deuterated solvent. All materials obtained from commercial suppliers were used without further purification.

(13) Chiral HPLC conditions for **20** and **1**: Chiralpak AD 250 mm × 4.6 mm column, eluent 50% *n*-hexane/ethanol (80:20) and 0.1% trifluoroacetic acid (TFA), flow rate 1.0 mL/min (*S*-enantiomer retention time 13.21 min, *R*-enantiomer retention time 16.87 min).

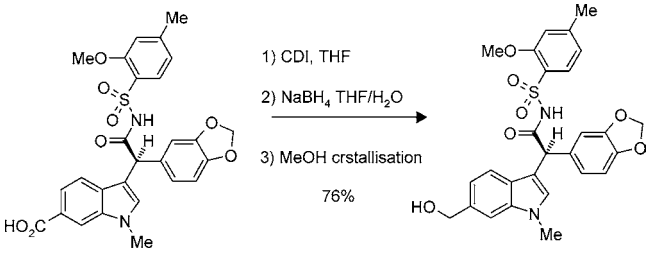
(14) Sharma, R.; Voynov, G. H.; Ovaska, T. V.; Marquez, V. E. *Synlett* **1995**, 839−840.

Scheme 6. **Dynamic resolution of racemic UK-350,926 with (*S*)-(−)-1-phenylethylamine**



18 20

Scheme 7. **Conversion of UK-350,926 to UK-349,862**



1 UK-350,926 2 UK-349,862

2-(6-Methoxycarbonyl-1-methyl-1*H*-indol-3-yl)-2-(3,4-methylenedioxyphenyl)acetic Acid (16). To a stirred suspension of methyl 1-methyl-1*H*-indole-6-carboxylate **15** (24 kg, 126.8 mol) and 2-hydroxy-2-(3,4-methylenedioxyphenyl)acetic acid **9** (24.9 kg, 126.8 mol) in acetonitrile (240 L) was added trifluoroacetic acid (28.9 kg, 253.6 mol). The suspension was heated to reflux for 24 h, allowed to cool to room temperature, and granulated for 16 h. The precipitated product was filtered, washed with acetonitrile (2 × 24 L), and vacuum dried (45 °C) to give **16** (40.2 kg, 86%) as an off-white crystalline solid. Mp: 194−198 °C. ^{1}H NMR δ: 3.83 (s, 3H), 3.94 (s, 3H), 5.19 (s, 1H), 5.93 (s, 2H), 6.76 (d, 1H), 6.87−6.90 (m, 2H), 7.26 (s, 1H), 7.44 (d, 1H), 7.76 (d, 1H), 8.07 (s, 1H). ^{13}C NMR (DMSO-d_6) δ: 42.7, 57.8, 62.0, 111.1, 118.1, 118.9, 122.0, 123.0, 128.9, 129.6, 131.7, 132.6, 140.3, 141.9, 143.4, 146.0, 156.3, 157.4, 177.3, 183.9. Anal. Calcd for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66; N, 3.81%. Found: C, 65.34; H, 4.61; N, 3.81.

Methyl 3-(1-{[(2-Methoxy-4-methylphenyl)sulfonyl]-carbamoyl}-1-(3,4-methylenedioxyphenyl)methyl)-1-methyl-1*H*-indole-6-carboxylate (17). 1,1′-Carbonyldiimidazole-(22.7 kg, 119 mol) was added to a stirred solution of 2-(6-methoxycarbonyl-1-methyl-1*H*-indol-3-yl)-2-(3,4-methylenedioxyphenyl)acetic acid **16** (39.8 kg, 108 mol) in dry tetrahydrofuran (398 L) at room temperature. The suspension was heated to reflux for 1.5 h, allowed to cool to room temperature, and treated sequentially with 2-methoxy-4-methylbenzenesulfonamide **5** (24 kg, 119 mol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 18.1 kg, 119 mol). The mixture was heated to reflux for 4.5 h, cooled to room temperature, and diluted with dichloromethane (318 L) and demineralised water (270 L), and 2 M hydrochloric acid (46.5kg, 54.9 L) was added. The phases were separated, and the organic phase was washed with dilute hydrochloric acid (2 M, 46.5 kg, 54.9 L) in water (270 L). The phases were separated, the organic phase was concentrated to low volume (approximately 180 L) and diluted with acetonitrile (740 L), and the distillation continued at constant volume until the refractive index of the distillate was below 1.345. The mixture was allowed to cool to 10 °C, and the precipitated product was granulated for 16 h, collected by filtration, washed with acetonitrile (2 × 41.1 kg, 52.5 L), and dried at 45 °C under vacuum to give **17** (47.1 kg, 79%) as a white crystalline solid. Mp: 184−185 °C. ^{1}H NMR δ: 2.40 (s, 3H), 3.44 (s, 3H), 3.74 (s, 3H), 3.94 (s, 3H), 5.04 (s, 1H), 5.90 (d, 2H), 6.57 (s, 1H), 6.57−6.73 (m, 3H), 6.87 (d, 1H), 7.04 (s, 1H), 7.22 (d, 1H), 7.64 (dd, 1H), 7.92 (d, 1H), 8.02 (s, 1H), 8.80 (brs, 1H). ^{13}C NMR (DMSO-d_6) δ: 31.5, 42.7, 57.8, 61.9, 65.8, 111.1, 118.1, 118.7, 121.9, 123.1, 128.5, 129.7, 130.7, 131.7, 132.7, 133.4, 140.1, 141.1, 142.1, 145.9, 156.5, 156.8, 157.4, 166.6, 177.3, 180.4.

3-(1-{[(2-Methoxy-4-methylphenyl)sulfonyl]carbamoyl}-1-(3,4-methylenedioxyphenyl)methyl)-1-methyl-1*H*-indole-6-carboxylic Acid (18). Aqueous sodium hydroxide (41.5 kg, 415 L of a 40% aqueous solution, 415 mol) was added to a stirred suspension of methyl 3-(1-{[(2-methoxy-4-methylphenyl)sulfonyl]carbamoyl}-1-(3,4-methylenedioxyphenyl)methyl)-1-methyl-1*H*-indole-6-carboxylate **17** (31.9 kg, 57.9 mol) in methanol (160 L) and demineralised water (140 L). The suspension was warmed to 45 °C for 1.5 h, cooled to room temperature, and diluted with dichloromethane (180 L). The pH of the aqueous phase was adjusted to 3 with the addition of concentrated hydrochloric acid (42.5 kg, 36 L of a 35% aqueous solution), and the phases were separated. The organic phase was concentrated to approximately 100 L by distillation at atmospheric pressure and cooled to 20 °C, and the precipitated product was granulated for 1 h. The product was filtered, washed with dichloromethane (40 kg, 30 L), and dried at 50 °C under vacuum to give **18** (28.4 kg, 90%) as a white crystalline solid. Mp: 199 °C. ^{1}H NMR δ: 2.41 (s,3H), 3.40 (s, 3H), 3.75 (s, 3H), 5.07 (s, 1H), 5.92 (d, 2H), 6.51 (s, 1H), 6.68−6.73 (m, 3H), 6.89 (d, 1H), 7.11 (s, 1H), 7.23 (d, 1H), 7.66 (dd, 1H), 7.93 (d, 1H), 8.06 (s, 1H), 9.06 (brs, 1H). ^{13}C NMR (DMSO-d_6) δ: 31.5, 42.7, 57.9, 65.9, 111.2, 118,2, 118.7, 121.8, 122.1, 123.3, 128.3, 130.0, 130.8, 131.7, 133.3, 133.8, 139.9, 141.1, 141.7, 142.1, 146.0, 156.5, 156.9, 157.4, 166.6, 178.4, 180.5.

(*S*)-(+)-3-(1-{[(2-Methoxy-4-methylphenyl)sulfonyl]-carbamoyl}-1-(3,4-methylenedioxyphenyl)methyl)-1-methyl-1*H*-indole-6-carboxylic Acid UK-350,926 (1). (*S*)-(−)-1-Phenethylamine (2.94 kg, 24.3 mol) was added over a period

of 15 min to a stirred suspension of 3-(1-{[(2-methoxy-4-methylphenyl)sulfonyl]carbamoyl}-1-(3,4-methylenedioxyphenyl)methyl)-1-methyl-1*H*-indole-6-carboxylic acid **18** (6.52kg, 12.15 mol) in tetrahydrofuran (35.8 L, 5.5 mL/g) and 1,2-dimethoxyethane (35.8 L, 5.5 mL/g) at 60 °C. The resulting solution was allowed to cool over a period of 1 h to 55 °C, seeded with (*S*)-(−)-1-phenethylamine salt (65 g) of the subtitle compound, and stirred for 24 h. The resulting suspension was allowed to cool to 50 °C over a period of 5 h and stirred for a total of 24 h. At this point the suspension was cooled to 45 °C and stirred at this temperature for an additional 24 h. The suspension was allowed to cool to room temperature, and the precipitated product of the subtitle compound was collected by filtration, washed with DME (13.0 L), and dried at 45 °C under vacuum to give the (*S*)-(−)-1-phenethylamine salt (7.2 kg, 82%, ratio of (*S*)-(−)-1-phenethylamine to compound 1.5:1) of the subtitle compound **20**. The salt (7.2 kg, 10.02 mol) was partitioned between ethyl acetate (36 L), tetrahydrofuran (7.2 L), and dilute hydrochloric acid (1 M, 36 L, 3.6 L of concentrated HCl in 32.4 L of water), and the organic phase was separated and then washed with 1 M hydrochloric acid (3 × 4.46 L) and water (3.6 L). The organic phase was dried by azeotropic distillation with ethyl acetate at constant volume and concentrated to a volume of approximately 18 L, and then *n*-hexane (18 L) was added. The precipitated product was granulated at 0 °C for 1 h, filtered, washed with *n*-hexane (7.2 L), and dried at 45 °C under vacuum to give **1** (4.88 kg, 91%) as a white crystalline solid. Mp: 250 °C. The enantiomeric excess of the compound was found to be >94% using chiral stationary phase HPLC.

^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s,3H), 3.40 (s, 3H), 3.75 (s, 3H), 5.07 (s, 1H), 5.92 (d, 2H), 6.51 (s, 1H), 6.68−6.73 (m, 3H), 6.89 (d, 1H), 7.11 (s, 1H), 7.23 (d, 1H), 7.66 (dd, 1H), 7.93 (d, 1H), 8.06 (s, 1H), 9.06 (brs, 1H). Anal. Calcd for $C_{27}H_{24}N_2O_8S$: C, 60.43; H, 4.51; N, 5.22. Found: C, 60.44; H, 4.47; N, 5.16.

(*S*)-(+)-2-(6-Hydroxymethyl-1-methyl-1*H*-indol-3-yl)-*N*-[(2-methoxy-4-methylphenyl)sulfonyl]-2-(3,4-methylenedioxyphenyl)acetamide (2). 1,1′-Carbonyldiimidazole (271 g, 1.67 mol) was added to a stirred slurry of (*S*)-(+)-3-(1-{[(2-methoxy-4-methylphenyl)sulfonyl]carbamoyl}-1-(3,4-methylenedioxyphenyl)methyl)-1-methyl-1*H*-indole-6-carboxylic acid **1** (748.3 g, 1.39 mol, 90% ee by chiral HPLC) in anhydrous THF (2.25 L) at room temperature. A solution was obtained after approximately 5 min. The mixture was stirred at room temperature for 1 h and transferred over a period of 30 min to a solution of sodium borohydride (158.8 g, 4.19 mol) in a mixture of THF (1.5 L) and water (0.94 L) at 0 °C. The addition was exothermic, and the temperature rose to 18 °C over the course of the addition. The reaction mixture was stirred for an additional 1 h at room temperature and quenched into a stirred mixture of ethyl acetate (3.75 L) and aqueous citric acid (2.15 kg of citric acid in 3.75 L of water). The phases were separated, and the organic phase was washed with water (2 × 1.88 L), concentrated to low volume under reduced pressure (temperature maintained below 45 °C during the concentration), replaced with methanol (3.0 L), and allowed to cool to room temperature. The precipitated product was granulated for 16 h, collected by filtration, washed with methanol (360 mL), and dried at 50 °C under vacuum to give **2** (560.2 g, 76%) as a white crystalline solid. The enantiomeric excess of the product was 84% [92(*S*):8(*R*) by chiral HPLC] ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.45 (s, 3H), 3.55 (s, 3H), 3.75 (s, 3H), 4.75 (s, 2H), 5.15 (s, 1H), 5.95 (d, 2H), 6.70 (s, 1H), 6.75 (m, 3H), 6.85 (s, 1H), 6.95 (d, 1H), 7.00 (d, 1H), 7.25 (d, 1H), 7.35 (s, 1H), 7.85 (d, 1H).

Acknowledgment

We thank Dr. Nick Haire and his analytical team and our discovery colleagues David Rawson and David Ellis for excellent support during this project. We would also like to thank Dr. Mike Williams (Pfizer, Sandwich) and Professor Steven V. Ley (University of Cambridge) for their helpful discussions.

Received for review June 20, 2005.

OP050102F