Organic Process Research & Development **1999**, *3*, 248−252

Multikilogram-Scale Synthesis of a Biphenyl Carboxylic Acid Derivative Using a Pd/C-Mediated Suzuki Coupling Approach

David S. Ennis,*[,†,1] Julie McManus,[†] Wladyslaw Wood-Kaczmar,[‡] John Richardson,[‡] Gillian E. Smith,[†] and Alexis Carstairs[†]

Synthetic Chemistry and Process Technologies, Chemical Development, SmithKline Beecham Pharmaceuticals, New Frontiers Science Park, Third Avenue, Harlow, Essex, CM19 5AW, U.K.

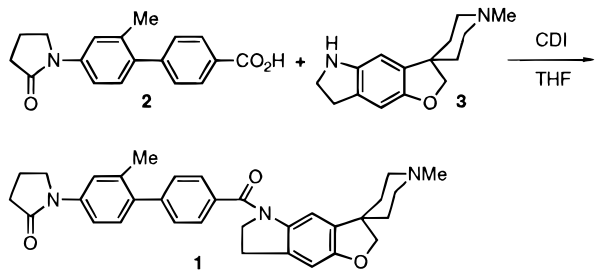
Abstract:

Reaction of 4-bromo-3-methylaniline with 4-chlorobutyryl chloride/TEA and subsequent treatment of the resulting secondary amide intermediate with KO*t*-Bu gives 1-(4-bromo-3-methylphenyl)pyrrolidin-2-one in 65% yield. This procedure has been optimised (74−76% overall yield) and has been carried out on 41 molar scale. In a variation of this process, we have employed NaOH as the ring-closing base under phase-transfer conditions. NaOH is added to a mixture of 4-bromo-3-methylaniline, 4-chlorobutyryl chloride, and catalytic TBAC in THF/H_2O. A further 2 equiv of aqueous NaOH is added, and the mixture is heated at 40−45 °C, providing access to cyclised product in an improved 86% yield. 1-(4-Bromo-3-methylphenyl)pyrrolidin-2-one is subsequently coupled with 4-carboxyphenylboronic acid under standard Suzuki coupling conditions [$Pd(PPh_3)_4$, Na_2CO_3, DME/H_2O] to give 2′-methyl-4′-(2-oxo-1-pyrrolidinyl)biphenyl-4-carboxylic acid in 64% yield, contaminated with 40−80 ppm of residual Pd. In a modification of this process, we have used Pd/C as the catalyst. Reaction in MeOH/H_2O gives an improved yield of the biphenylcarboxylic acid with residual Pd levels of <6 ppm. This process has been carried out on 24 molar scale. The synthesis of the arylpyrrolidinone and subsequent Suzuki coupling have been combined into a one-pot procedure, providing access to 2′-methyl-4′-(2-oxo-1-pyrrolidinyl)biphenyl-4-carboxylic acid in 82% overall yield from 4-bromo-3-methylaniline.

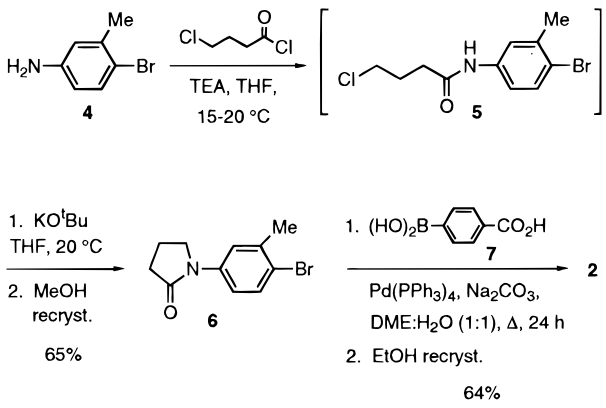
SB-245570 (**1**), in development for the treatment of depression, was prepared by the coupling of biphenylcarboxylic acid, SB-251475 (**2**), with indoline **3** (Scheme 1).

We sought an inexpensive and efficient synthesis of key intermediate **2**. The original route used to prepare **2** is outlined in Scheme 2. 4-Bromo-3-methylaniline (**4**)[2] was treated with 4-chlorobutyryl chloride and TEA in THF at 15−20 °C to give secondary amide **5** that, on reaction with KO*t*-Bu,[3] underwent cyclisation to form SB-249930 (**6**) in 65% isolated yield after recrystallisation from MeOH. A Pd(0)-mediated Suzuki coupling reaction of **6** with 4-carboxyphenylboronic acid (**7**) provided access to biphenylcarboxylic acid **2** in 64% yield after EtOH recrystallisation.

Scheme 1



Scheme 2



We now wish to describe the modification, optimisation, and scale-up of this approach to **2** in order to make supplies for Phases I and II clinical trials. Evaluation of alternative syntheses of SB-249930 (**6**) will also be discussed.

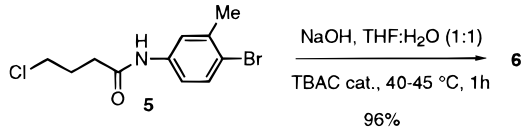
Multikilogram-Scale Synthesis of SB-249930 (6). As described in Scheme 2, arylpyrrolidinone **6** was prepared by a two-step process from aniline **4**. There were two potential problems associated with scaling-up the current procedure. First, KO*t*-Bu was added in solid portions, providing poor temperature control of the exothermic cyclisation; a more controlled addition was achieved with a preformed solution of base in THF. Second, crude product **6** was isolated after workup by evaporation of EtOAc to dryness. Subsequent recrystallisation from MeOH gave purified **6**. The latter purification procedure was achieved more efficiently by azeotropic replacement of EtOAc with MeOH.

With these problems addressed, we looked at improving the yield of cyclisation. At 20 °C, KO*t*-Bu-mediated cyclisation provided **6**, along with cyclopropyl impurity **8** [8−10% peak area ratio (PAR), HPLC], via a competitive

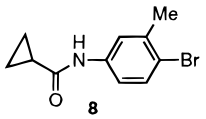
[†] Synthetic Chemistry.
[‡] Process Technologies.
(1) Current address: PR&D Loughborough, Astra Charnwood, Bakewell Road, Loughborough, Leicestershire, LE11 5RH, UK.
(2) Commercially available from Wychem Ltd., Newmarket, Suffolk, UK.
(3) At least 2 equiv of KO*t*-Bu was required.

 10.1021/op980079g CCC: $18.00
Published on Web 05/21/1999

Scheme 3



cyclisation pathway.[4] Reaction at 0−5 °C facilitated a more



efficient ring closure to give crude **6** contaminated with only 0.8−1.5% of impurity **8**. The latter was removed in the purification step, providing access to SB-249930 (**6**) (>99.5% PAR, HPLC) in 74−76% isolated yield.

Scale-up of the modified reaction proceeded smoothly. Crystallisation, however, was problematic; extremely rapid precipitation of **6** occurred at 20−25 °C, leading to an immobile suspension. By seeding the solution at 50−55 °C with an authentic sample of **6**, gradual crystallisation of product took place reproducibly, and the suspension was filtered without incident.

This method was successfully employed on the pilot plant to prepare 2 × 7.5 kg batches of SB-249930 (**6**) as part of the preparation of Phase I supplies of **1**.

Although this was an efficient transformation, we sought an alternative base to the expensive, air- and moisture-sensitive KO*t*-Bu in THF. We have found that NaOH can be employed to effect ring closure under phase-transfer type conditions. The results are reported below.

Initial reaction of secondary amide **5** with NaOH in THF/H_2O at 25 °C gave SB-249930 (**6**) (96% PAR, HPLC), albeit over a prolonged reaction time (24 h). In this example, however, we did not detect the formation of cyclopropyl impurity **8**.

Subsequent use of the automated STEM BLOCK[5] allowed us to rapidly optimise the reaction: in a series of experiments, we looked at the effect of (a) the proportion of H_2O, (b) temperature, (c) number of equivalents of NaOH, and (d) the presence of a phase-transfer catalyst. The study culminated in selection of the conditions described in Scheme 3. Reaction of **5** with NaOH (2 equiv) in THF/H_2O (1:1) in the presence of TBAC (1 mol %) at 40−45 °C for 1 h provided access to cyclised product **6** (98% PAR, HPLC) in 96% isolated yield.

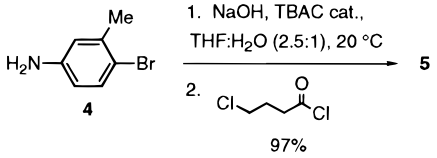
We have similarly shown that intermediate **5** can itself be formed under phase-transfer conditions (Scheme 4). Treatment of aniline **4** with NaOH (1.03 equiv) and 4-chlorobutyryl chloride (1.03 equiv) in the presence of TBAC (1 mol %) in THF/H_2O (2.5:1) gave **5** in 97% isolated yield (99% PAR, HPLC).

In an extension of this work, we have combined the two procedures into a "one-pot" preparation of **6** from aniline **4**. Thus, intermediate amide **5** was formed in THF/H_2O

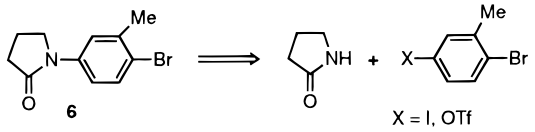
(4) Cyclopropyl impurity **8** was shown in a control experiment not to be formed from SB-249930 (**6**) in the presence of excess KO*t*-Bu.

(5) Anachem Synthesis Kit 233.

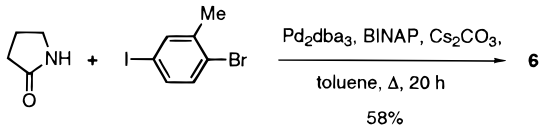
Scheme 4



Scheme 5



Scheme 6



(2.5:1), and the further 2 equiv of NaOH was added in H_2O (appropriate quantity to give a THF/H_2O ratio of 1:1). Only 1 mol % of TBAC was required in the reaction. A minor modification to the workup was required; TBME was used as the extraction solvent.[6] After the usual acid and H_2O washes, TBME was azeotropically replaced by MeOH, from which crystallisation was effected.

The new procedure was carried out on 100 g scale (with respect to **4**) to give **6** (PAR 100%, HPLC) in 86% yield.

Alternative Approaches to Arylpyrrolidinone 6. An alternative strategy to prepare **6** was considered involving a Pd(0)-mediated cross-coupling reaction (Scheme 5). Yamamoto and Kurata[7] have reported Ullmann type couplings of 2-pyrrolidinone with aryl halides. These reactions are, however, limited in scope, requiring stoichiometric copper and temperatures in excess of 240 °C. More recently, the pioneering work of Wolfe and Buchwald[8] has facilitated the coupling of primary and secondary amines with aryl halides or triflates using catalytic Pd(0) and lower temperatures (<112 °C).

We have successfully prepared **6** in 58% yield by the reaction of 5-iodo-2-bromotoluene (1 equiv) and 2-pyrrolidinone (1.2 equiv) in the presence of Pd_2dba_3 (5 mol %), BINAP (16 mol %), and Cs_2CO_3 (1.4 equiv) in toluene at reflux for 20 h (Scheme 6). Use of lower catalyst loadings led to prolonged reaction times. With NaO*t*-Bu as the base, no coupling was observed.

This procedure did not, however, compete in terms of overall yield and efficiency with the current supply route.

Ohta and co-workers[9] have reported the synthesis of *N*-substituted pyrrolidinones by the reaction of the appropri-

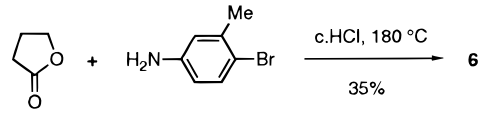
(6) With EtOAc as the extraction solvent, some degree of saponification was observed. The EtOH thus formed took some product into the aqueous layer, leading to lower recoveries of **6**. As TBME was successfully used as the extraction solvent, we also explored its use as the reaction solvent in place of THF. Although the preparation of intermediate **5** was possible, NaOH-mediated cyclisation to form **6** proved problematic; significant hydrolysis of **5** was observed under a variety of conditions.

(7) Yamamoto, T.; Kurata, Y. *Can. J. Chem.* **1983**, *61*, 86.

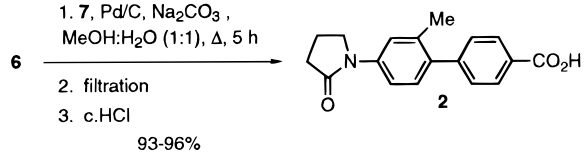
(8) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 6066 and references therein.

(9) Ohta, S.; Sano, A.; Yamashita, M.; Okamoto, M. *Heterocycles* **1993**, 743.

Scheme 7



Scheme 8



ate amine with γ-butyrolactone. In analogy to this work, we have prepared **6** in 35% yield by heating γ-butyrolactone (1 equiv) and aniline **4** (1.1 equiv) at 180 °C in the presence of catalytic concentrated HCl (0.3 equiv) for 4 h (Scheme 7). The purity profile (97.7% PAR, HPLC) and moderate isolated yield precluded further work in this area.

In summary, we have developed an inexpensive, efficient, and robust process for the preparation of SB-249930 (**6**).

Pd-Mediated Coupling of 6 and 4-Carboxyphenylboronic Acid (7). Typical Suzuki coupling conditions[10] were originally employed to prepare biphenyl acid **2** (Scheme 2). Although this was an efficient transformation on 4 molar scale, we preferred to avoid the use of the expensive and air-sensitive $Pd(PPh_3)_4$ catalyst that can vary in activity from batch to batch. In addition, material prepared using this catalyst was contaminated with residual Pd at levels of 40−80 ppm.

Recently, Pd_2dba_3,[11] $Pd(OAc)_2$,[12] and Pd/C[13] have been successfully employed as catalysts in Suzuki coupling reactions, significantly in the absence of organophosphorus ligands. Pd supported on charcoal is inexpensive and readily available and can be removed by Celite filtration at the end of the reaction. Its use, therefore, should overcome the Pd contamination problem. To this end, we have prepared SB-251475 (**2**) using modified and optimised Buchecker conditions,[13] as shown in Scheme 8. Arylpyrrolidinone **6** (1 equiv), boronic acid **7** (1.06 equiv), Na_2CO_3 (1.92 equiv), and Pd/C[14] (1.18 mol %) in MeOH/H_2O (1:1)[15] were heated at reflux for 5 h. The catalyst was removed by filtration through Celite, and the resulting solution was acidified with concentrated HCl, affording crude **2** (>98.5% PAR, HPLC) in 93−96% yield. The balance of material consisted of homocoupled diacid **9** (0.5% PAR, HPLC) and biphenyl derivative **10** (0.3% PAR, HPLC), the latter being derived from residual 4-tolylboronic acid in substrate (**7**).[16] Initially, purification of **2** was carried out by recrystallisation from EtOH. The voluminous nature of this method (approximately 60 volumes of EtOH was required to effect dissolution), however, led us to explore a purification by slurry in EtOH. It was found that heating a suspension of **2** in EtOH (25 volumes) at reflux for 1 h, cooling to ambient conditions, and isolating gave a 90−93% recovery of product (PAR > 99.3%, HPLC), identical in purity to that obtained by recrystallisation. EtOH was subsequently replaced by IMS as the solvent of choice. Both impurities **9** (0.3% PAR, HPLC) and **10** (0.2% PAR, HPLC) present in product **2** were removed in the final step (Scheme 1). In all cases, residual Pd levels in **2** were below the limit of detection (<4−6 ppm, ICP analysis).

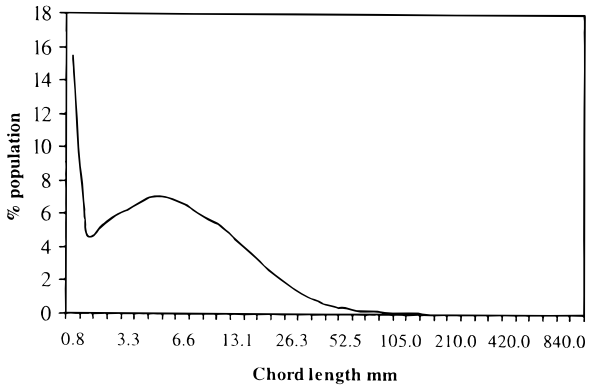
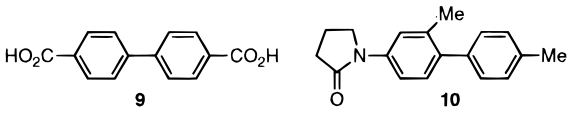


Figure 1. **Particle size distribution of SB-251475 (2) after acidification at 20 °C.**



This Pd/C-mediated Suzuki coupling procedure was successfully carried out in the pilot plant to prepare 2 × 6.3 kg batches of **2**.

A processing problem encountered in the plant campaign to make Phase I supplies had to be addressed. The acidification step produced a thick suspension of fine material that was extremely slow to filter, even with the use of a centrifuge.

In the laboratory, with the aid of a Lasentec crystallisation monitor,[17] we were able to compare the particle size distributions in suspensions of **2** formed under different conditions and, therefore, obtain tangible evidence for improved filtration. The results of this study are summarised below.

Figure 1 shows the mean chord length (8.26 μm) of particles obtained by acidification under standard conditions. The fines constituted 66% of the suspension, and as a consequence filtration was slow.

(10) (a) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513. (b) Suzuki, A. *Pure Appl. Chem.* **1994**, *66*, 213.

(11) (a) Moreno-Manas, M.; Pajuelo, F.; Pleixats, R. *J. Org. Chem.* **1995**, *60*, 2396. (b) Wallow, T. I.; Novak, B. M. *J. Org. Chem.* **1994**, *59*, 5034.

(12) Campi, E. M.; Jackson, W. R.; Maruccio, S. M.; Naeslund, C. G. M. *J. Chem. Soc., Chem. Commun.* **1994**, 2395.

(13) (a) Marck, G.; Villiger, A.; Buchecker, R. *Tetrahedron Lett.* **1994**, *35*, 3277. (b) Gala, D.; Stamford, J. J.; Kugelman, M. *Org. Process Res. Dev.* **1997**, *1*, 163.

(14) The type of Pd/C catalyst used was significant: intermediate catalyst type 487 (from Johnson Matthey), in which the Pd is distributed in the pores and on the surface, proved much less efficient than type 58 catalyst (eggshell, from Johnson Matthey), in which the Pd is entirely distributed on the carbon surface. No other sources of catalyst were investigated at this stage. Lower loadings (<1.18 molar %) of Pd/C catalyst were studied, but significant reductions in the rate of reaction were observed.

(15) The ratio of MeOH:H_2O was critical. Optimum yields of **2** were obtained with a 1:1 ratio. The reaction was less efficient in EtOH:H_2O mixtures of varying ratio, failing to proceed to completion. In DME:H_2O (1:1), no reaction took place.

(16) 4-Carboxyphenylboronic acid (**7**) (from MDA) was contaminated with 4-tolylboronic acid (0.9%). The former was prepared by $KMnO_4$ oxidation of 4-tolylboronic acid.

(17) Lasentec M400L, Lasentec, Redmond, WA.

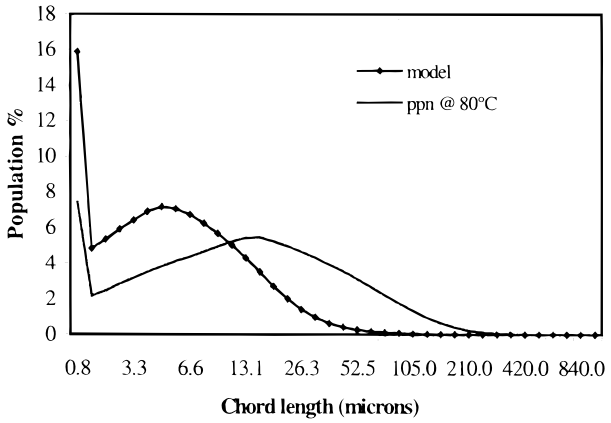
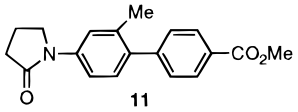


Figure 2. **Particle size distribution of SB-251475 (2) after acidification at 80 °C.**

The rate of addition of concentrated HCl and the use of different acids (concentrated H_2SO_4 and AcOH) had no effect. Increasing the alcohol:H_2O ratio caused a decrease in the percentage of fines, and the filtration rate was improved, but recovered yields of **2** dropped by 4−6%. Decreasing the alcohol:H_2O ratio did not improve the filterability.

The temperature of acidification was shown to be crucial (Figure 2). Acidification at 80 °C in MeOH/H_2O (1:3) led to particles with a mean chord length of 26.3 μm, and the percentage of fines was significantly reduced to 34% (cf. 66% in control reaction). Subsequent filtration proceeded rapidly, and recoveries were 91−93%. No esterification to form **11** was observed under these conditions.



11

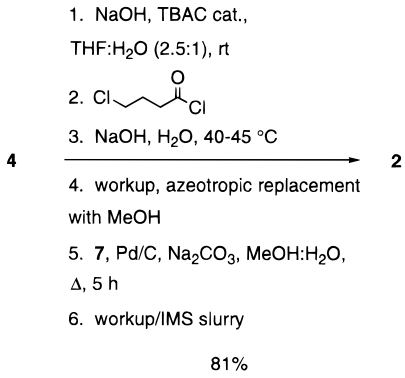
The modified acidification procedure was successfully scaled-up (2 molar scale) and safety tested in preparation for the next plant campaign.

With regard to the coupling reaction, the level of Na_2CO_3 was reduced to 1.2 equiv (with respect to **6**). Further reduction in the catalytic amount of Pd/C catalyst, however, proved unsuccessful, as reaction times increased significantly.

One-Pot Preparation of Biphenyl Acid 2 from Aniline 4. We have further optimised the preparation of **2** into a "one-pot" procedure from bromoaniline **4**, summarised in Scheme 9. The latter was transformed to SB-249930 (**6**). Usual extractive workup into TBME followed by azeotropic replacement with MeOH gave a methanolic solution of **6** (96% PAR, HPLC). To the solution were added phenylboronic acid **7**, Pd/C (1.18 mol %), Na_2CO_3 (1.2 equiv), and H_2O (appropriate volume to give a 1:1 ratio of MeOH:H_2O), and the coupling reaction was carried out in the normal manner. Purification (IMS slurry) gave **2** of typical purity (99.3% PAR, HPLC) in 81% overall yield from **4**, comparing favourably with the stepwise process (72% overall yield from **4**).

In conclusion, we have developed an inexpensive, efficient, robust, and environmentally friendly synthesis of biphenylcarboxylic acid **2** free of Pd contamination.

Scheme 9



Experimental Section

General. Melting points were recorded on a capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker 250-MHz instrument. Chemical shifts for ^{1}H NMR are reported in ppm downfield (δ) relative to TMS as an internal standard in $CDCl_3$ or DMSO-d_6. Mass spectra were recorded on a Perkin-Elmer Sciex API-III instrument. Residual heavy metal levels were measured by inductively coupled plasma atomic emission spectroscopy (ICP-AES) on a Jobin Yvon 24 spectrometer.

Reactions were monitored by HPLC analysis: RP Select B column, 3:2 ratio of aqueous TFA (0.1%):MeCN mobile phase at 1 mL/min; UV detection at 215 nm.

1-(4-Bromo-3-methylphenyl)pyrrolidin-2-one (6). (i) KO*t*-Bu-Mediated Cyclisation Procedure. 4-Bromo-3-methylaniline (**4**) (7.75 kg, 40.82 mol, 98%) in THF (116 L) was treated with TEA (4.25 kg, 42.04 mol) at 20−25 °C under a nitrogen atmosphere. The solution was then cooled to 15 °C, and 4-chlorobutyryl chloride (5.98 kg, 42.04 mol, 99.2%) was added slowly over 1 h, maintaining the reaction temperature between 15 and 20 °C. The resulting suspension was stirred at 15−20 °C for 1 h.

The reaction mixture was cooled to 0−5 °C, and a solution of KO*t*-Bu (11.05 kg, 98.01 mol, 99.5%) in THF (93 L) (prepared at ambient under nitrogen) was added over 1 h, maintaining the reaction temperature between 0 and 5 °C. The suspension was then stirred at this temperature for a further 15 min.

On completion, the reaction mixture was diluted with H_2O (51 L) and EtOAc (67 L). The aqueous layer was separated, and the organic layer was washed sequentially with 2 N HCl (51 L) and brine (39 L). The THF/EtOAc was then evaporated to low volume (approximately 230 L removed, atmospheric distillation). The remaining EtOAc in the concentrate was replaced by MeOH by a series of azeotropic distillations. The methanolic solution was then cooled to 50−55 °C, seeded with an authentic sample of arylpyrrolidinone **6**, and cooled to 15−20 °C (crystallisation occurred at 44 °C). The suspension was filtered, and the solid cake was washed with MeOH (9 L, 0−5 °C) and dried in vacuo (1 mmHg) at 40 °C to constant weight to give SB-249930 (**6**) (7.5 kg, 74%) as a white solid: mp 107 °C; δ ($CDCl_3$) 1.57 (s, 3H), 2.15 (m, 2H), 2.60 (t, 2H, J = 7.9 Hz), 3.84 (t, 2H, J = 6.6 Hz), 7.30 (dd, 1H, J = 1.7 and 6.6 Hz), 7.50 (d, 1H, J = 7.9 Hz), 7.52 (d, 1H, J = 1.7 Hz); MS *m*/*z* (relative

intensity) 255 (MH^+, 100), 253 (MH^+, 100); HPLC, 100% peak area ratio (PAR).

(ii) NaOH-Mediated Cyclisation Procedure. To a solution of 4-bromo-3-methylaniline (**4**) (100.0 g, 0.54 mol) in THF (800 mL, 8 volumes) were added NaOH (22.14 g, 0.55 mol) in H_2O (320 mL, 3.2 volumes) and tetrabutylammonium chloride (TBAC, 1.60 g, 1 mol %) at 20−25 °C. 4-Chlorobutyryl chloride (62.53 mL, 0.55 mol, 99.2%) was added to the biphasic mixture over 0.5 h, maintaining the reaction temperature at 20−25 °C. After the mixture was stirred at 20−25 °C for a further 15 min, NaOH (43.0 g, 1.07 mol) in H_2O (480 mL, 4.8 volumes) was added over 10 min, and the resulting reaction mixture was heated at 40−45 °C for 2 h.

On completion, the reaction mixture was cooled to 20−25 °C, TBME (900 mL, 9 volumes) was added, and the solution was stirred for 15 min. The organic layer was isolated and was washed sequentially with 2 N HCl (200 mL) and brine (400 mL). The organic layer was then concentrated to 360 mL (3.6 volumes), and the residual solvent (THF) was replaced with MeOH by a series of azeotropic distillations (3 × 500 mL). The MeOH solution was cooled to 20−25 °C, with seeding at 50 °C (to ensure gradual crystallisation of product). After a further 1 h at 20−25 °C, the suspension was filtered, and the solid cake was washed with MeOH (5 mL, 1 volume) and dried in vacuo (1 mmHg) at 40 °C to give **6** (117.4 g, 86%) as a white solid: HPLC, 100% PAR.

(iii) Pd(0)-Mediated Coupling Procedure. 2-Bromo-5-iodotoluene (500 mg, 1.68 mmol), 2-pyrrolidinone (172 mg, 2.02 mmol), Pd_2dba_3 (77 mg, 5 mol %), BINAP (168 mg, 16 mol %), and Cs_2CO_3 (770 mg, 2.36 mmol) in toluene (3 mL) were heated at 110 °C for 20 h under a nitrogen atmosphere. The reaction mixture was cooled to ambient, diluted with Et_2O, and filtered. The filtrate was concentrated under vacuum to give crude product as an orange solid. Purification by column chromatography (silica gel, Et_2O) gave **6** (247 mg, 58%) as a beige solid: HPLC, 98.2% PAR.

Condensation of γ-Butyrolactone with Aniline 4. γ-Butyrolactone (2.5 g, 29 mmol), aniline **4** (5.94 g, 32 mmol), and concentrated HCl (0.83 mL, 9.6 mmol, 11.6 M) were heated at 200 °C for 4 h. On cooling, the product set solid. The latter was extracted with EtOAc (3 × 80 mL), and the organic fractions were combined and washed sequentially with 1 N HCl (10 mL) and brine (20 mL). The organic layer was then dried ($MgSO_4$) and the EtOAc removed in vacuo to give crude product **6** (6.9 g). Purification by recrystallisation from MeOH (30 mL) gave **6** (2.05 g, 35%) (97.7% PAR, HPLC).

2′-Methyl-4′-(2-oxo-1-pyrrolidinyl)biphenyl-4-carboxylic Acid (2). SB-249930 (**6**) (6.20 kg, 24.40 mol), 4-carboxyphenylboronic acid (**7**) (4.35 kg, 25.86 mol, 98.6%), Na_2CO_3 (4.97 kg, 46.84 mol, 99.5%), and Pd/C (1.3 kg, 1.18 mol %) in MeOH (31 L) and H_2O (31 L) were heated at reflux (approximately 77.8 °C) for 5 h under a nitrogen atmosphere.

On completion, the reaction mixture was filtered through Celite (packed with H_2O) at 60 °C, the bed was washed with warm H_2O (40 L, 50 °C), and the filtrate was cooled to 20−25 °C. Acidification to pH 2 by addition of concentrated HCl over 1 h gave a thick white precipitate that was stirred at 20−25 °C for 0.5 h. The suspension was filtered (slow) and the solid cake washed with H_2O (140 L) to give the crude product that was dried in vacuo (1 mmHg) at 40−45 °C to give **2** (6.89 kg, 96%). Biphenyl acid **2** was suspended in IMS (172 L) and was heated at reflux for 1 h. The suspension was then cooled to 20−25 °C and was stirred for 0.5 h at this temperature. The suspension was filtered, and the solid cake was washed with chilled IMS (21 L, 0−5 °C) and then dried in vacuo (1 mmHg) at 40−45 °C, providing **2** (6.28 kg, 91%) as a white solid: mp 253 °C; δ (DMSO-d_6) 2.08 (m, 2H), 2.25 (s, 3H), 2.53 (t, 2H, 6.6 Hz), 3.86 (t, 2H, J = 6.6 Hz), 7.23 (d, 1H, J = 7.3 Hz), 7.46 (d, 2H, J = 7.3 Hz), 7.58 (s, 1H), 7.60 (d, 1H, J = 7.3 Hz), 7.98 (d, 2H, J = 7.3 Hz), 12.98 (bs, 1H); MS m/z (relative intensity) 296 (MH^+, 100); HPLC, 99.3% PAR, 99.7% assay; ICP, <6 ppm Pd,[18] <4 ppm B.[18]

Acknowledgment

We are indebted to Martin Teasdale, Mark Blower, and Adrian Bateman of Analytical Sciences for their help with the measurement of residual Pd levels and the development of HPLC systems. Special thanks also to Steve Buchwald for a personal communication with regard to the intermolecular coupling of 2-pyrrolidinone.

Received for review October 7, 1998.

OP980079G

(18) Below limit of detection.