Organic Process Research & Development **2005**, *9,* 499–507

Development of a Scalable Synthesis of Gastrazole (JB95008): A Potent CCK_2 Receptor Antagonist

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Abstract:

A practical and scalable synthesis was developed that was used to prepare multikilogram batches of gastrazole, a selective cholecystokinin-2 receptor antagonist. In addition, evidence was found to indicate an amide bond-forming reaction proceeded via the isoimide of a benzimidazoleamide acid derivative.

Introduction

Gastrazole (**JB95008**) is a potent and highly selective cholecystokinin-2 (CCK_2) receptor antagonist,[1−3] discovered in the James Black Foundation laboratories, that has been developed for the treatment of pancreatic cancer.[4] The discovery synthesis of **JB95008**, depicted in Scheme 1, is linear, and all intermediates were isolated as evaporation residues, a situation best avoided for large-scale synthesis. Furthermore, during the coupling of the acid **6** with cycloheptylmethylamine **7**, a significant quantity of imide impurity **9** (Scheme 1) was formed which required chromatographic purification for its complete removal. Also, isolation of the final drug substance **JB95008** had been previously carried out using a freeze-drying process. Although not impossible to scale up, we decided to investigate alternatives to this procedure. The discovery synthesis, whilst suitable for synthesis on relatively small scale, was difficult to apply on a large scale. In addition to the matters already mentioned, we also decided to address issues related to some of the solvents and reagents used.

Results and Discussion

The initial step of the synthesis was the peptide-coupling reaction between Boc-2-(L)-fluorophenylalanine **1** and the aniline **2**, leading to the Boc-protected aminoamide **3**. The use of 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) as activating agent was retained on scale-up as this uniquely avoided any racemisation of the amino acid, which had previously been observed when using a variety of other coupling reagents such as PyBroP in combination with Hünig’s base and 4-(dimethylamino)pyridine (DMAP). In the original procedure, the coupling agent EEDQ was stirred with amino acid **1** for 15 min before addition of the aniline **2**. When this reaction was performed in an RC1 reactor with an FTIR probe, it was noticed that during this 15 min “activation time” carbon dioxide was being given off from the reaction. From the mechanism[5] of activation with EEDQ, it was assumed that this carbon dioxide evolution was produced by ethanol (either generated during the reaction or from the 0.2% present in dichloromethane) reacting with the intermediate mixed anhydride to form the ethyl ester of **1**. This assumption was later confirmed by the detection of the ethyl ester of **1** in reaction mixtures. Furthermore, as much as 20% of this impurity was formed if the “activation time” was increased to 1 h. Fortunately, this was easily overcome by dissolving the amino acid **1** and aniline **2** in solvent followed by adding the coupling agent. This resulted in a robust reaction that always gave reproducible and high yields (92%). On completion of reaction the solvent was changed from dichloromethane to propylene glycol monomethyl ether (PGMME), a solvent from which the reaction product crystallizes. This resulted in product **3** that was also of high purity (99.6%).

Removal of the Boc protecting group of **3** was carried out in toluene using 3 equiv of hydrochloric acid in 2-propanol instead of the originally utilized 10 equiv of trifluoroacetic acid. On completion of the reaction, the acid was neutralized with aqueous sodium bicarbonate with separation of the two phases being performed at 40 °C. On cooling to room temperature the aminoamide **4** crystallizes (Scheme 2). Opening of the anhydride **5** with **4** was originally carried out in acetonitrile at reflux, from which the product **6** precipitates, followed by heating in methanol as a purification step. As a result of measurements which had shown the anhydride to be only sparingly soluble in methanol and, thus, possibly resistant to opening by this solvent, it was decided to attempt the reaction in methanol. To our satisfaction we observed that the reaction performed well at room temper-

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(1) Kalindjian, S. B.; Buck, I. M.; Cushnir, J. L.; Dunstone, D. J.; Hudson, M. L.; Low, C. M. R.; McDonald, I. M.; Pether, M. J.; Steel, K. I. M.; Tozer, M. J. *J. Med. Chem.* **1995**, *38*, 4294.

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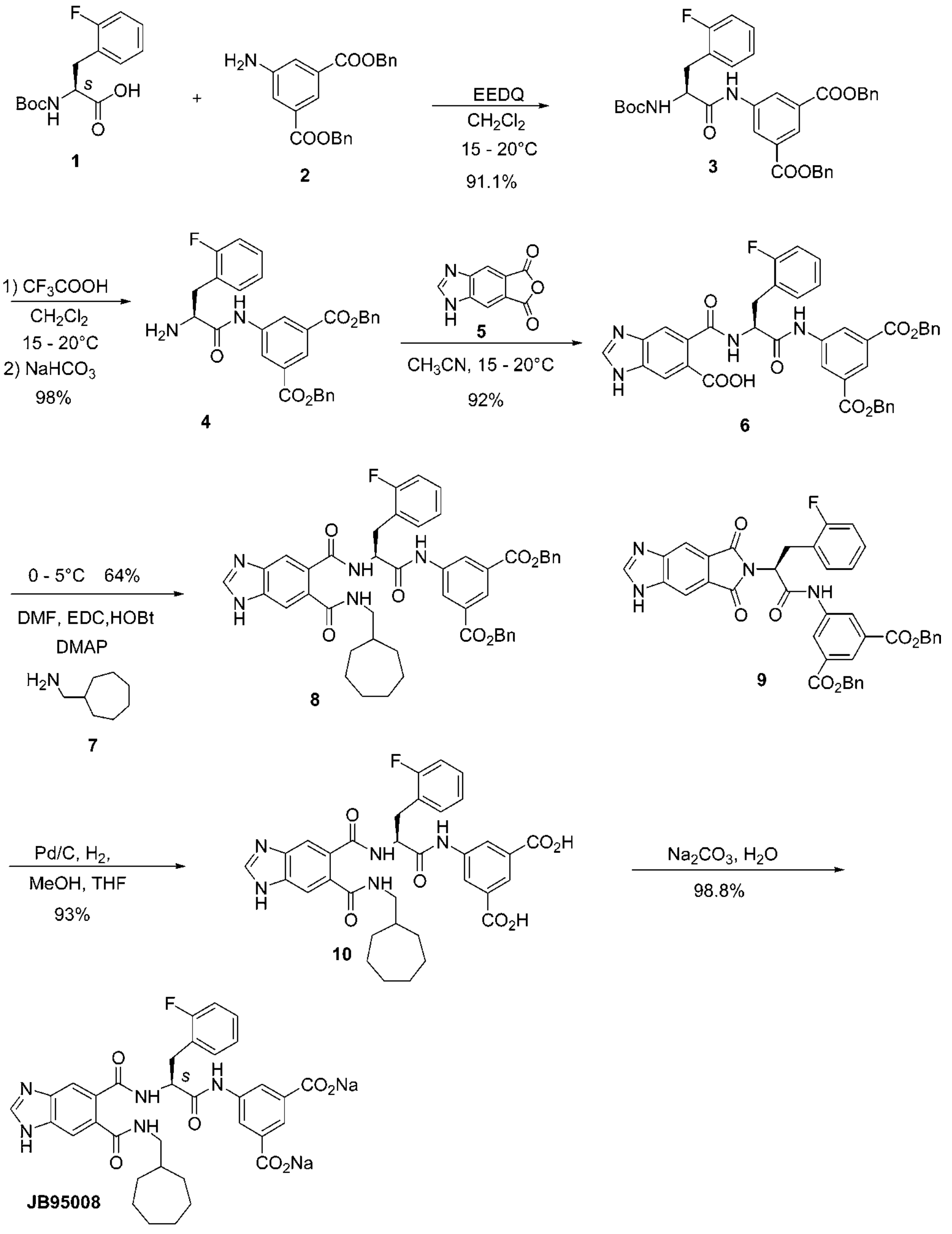
10.1021/op0500638 CCC: $30.25

Scheme 1. **Discovery synthesis of JB95008**



ature. Complete dissolution of starting materials occurred for a very short time (a matter of minutes) before the desired product **6** started to crystallize. Isolation by filtration gave **6** in acceptable (84%) yield and good quality. As expected, opening of the anhydride by methanol was not observed[6] under the reaction conditions employed. Formation of the second amide bond, however, with cycloheptylmethylamine **7** leading to **8**, proved to be far more problematic as it was accompanied with a competing ring-closure reaction to the imide **9** (Scheme 3). Some of the imide **9** may also have formed by elimination of cycloheptylmethylamine **7** from compound **8**, a process that is known to occur in solutions of **JB95008** under certain circumstances. In smaller-scale syntheses this impurity was formed in approximately 20% yield, and it had been demonstrated that its removal required column chromatography, after which the desired compound **8** could be isolated in 64% yield.

Although a number of reagents and reaction conditions were tried, none resulted in any reduction in the quantity of impurity **9** (Table 1). Furthermore, to prevent the formation of even higher quantities of **9** a slight excess of the expensive cycloheptylmethylamine synthon was required.

Thus, at this point it was decided that we needed to adopt a somewhat different approach. We reasoned that the relatively bulky amino amide moiety of **6** was, via steric hindrance, slowing the intermolecular reaction sufficiently to allow intramolecular imide formation. To overcome this problem we decided to introduce the smaller cycloheptylmethylamine group first (Scheme 4). The opening of the anhydride **5** was again carried out in methanol. However,

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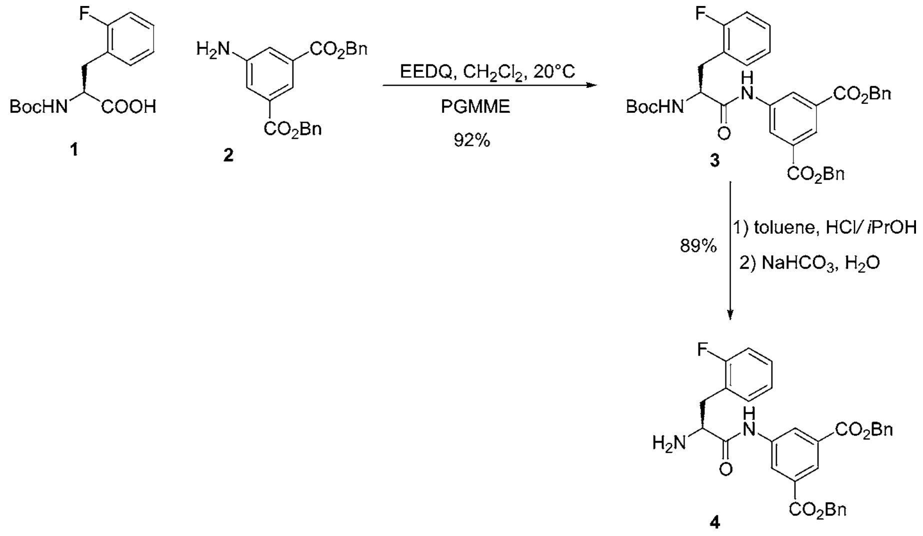
(6) The anhydride was shown to be stable in methanol at room temperature for up to 2 h.

Scheme 2. **Development synthesis of fragment 4**



Scheme 3. **Synthesis of 8 from 6 and 7**

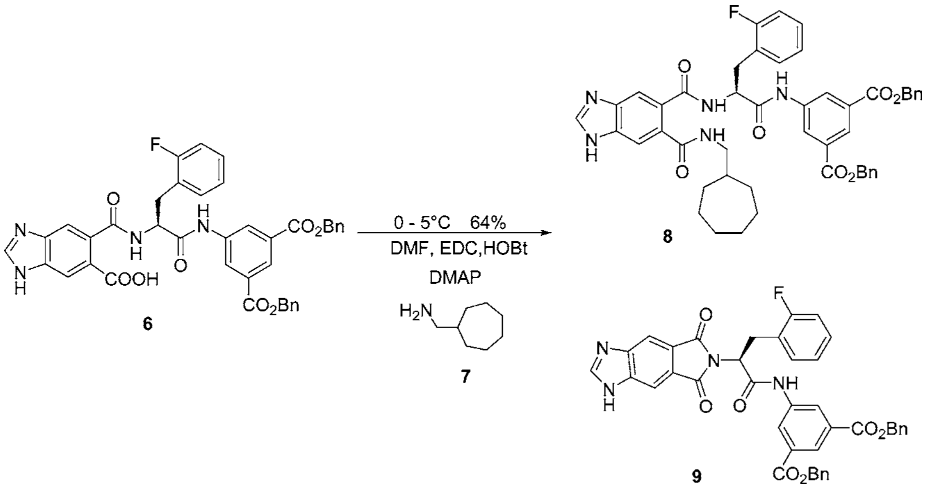


Table 1. **Composition of the reaction mixture, coupling 6 and 7**

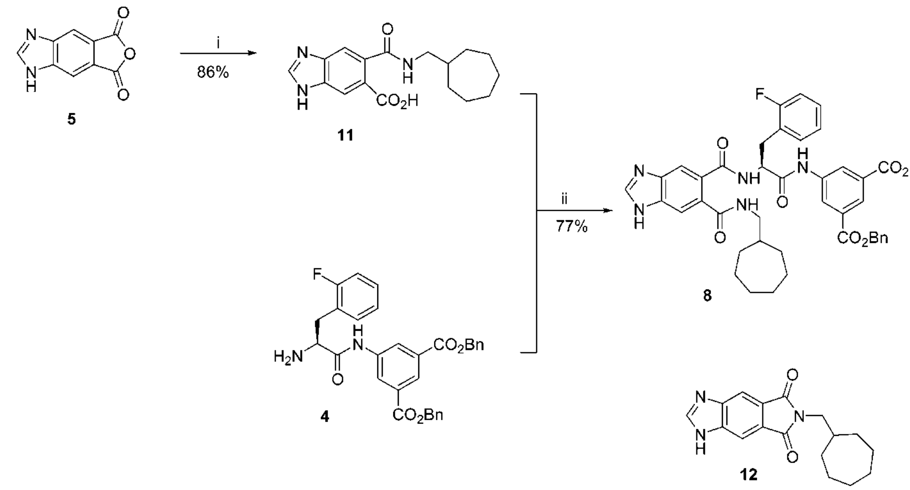
				LC profile		
	coupling reagent	solvent	temp (°C)	product **8** (area %)	imide **9** (area %)	unreacted **6** (area %)
1	EEDQ	DMF	24	/	/	100
2	EEDQ	THF	24	11	8	60
3	CDI	THF	0−24	15	25	46
4	EDC/HOBt/DMAP	DMF	0−24	80	20	/
5	EDC/HOBt/DMAP	THF	0−24	68	32	/
6[a]	EDC/HOBt/DMAP	DMF	0−24	60	40	/
7[b]	EDC/HOBt/DMAP	DMF	0−24	78	22	/
8	DDC/HOBt/DMAP	DMF	0−24	80	20	/
9	EDC/DMAP	DMF	0−24	72	28	/
10	EDC/HOBt/4-PAP[c]	DMF	0−24	50	19	/

[a] Triethylamine added to reaction mixture to neutralize the HCl associated with EDC. [b] 20% DMAP used instead of the usual 10%. [c] 4-PAP = 4-pyrrolidino pyridine.

unlike for the formation of **6**, the reaction product **11** did not crystallize directly from the reaction mixture, but it was found that precipitation of the product occurred by pouring the reaction mixture into water. Indeed, the solubility of the product in methanol could be used as a visual indication that the reaction was complete or very near to completion. The reaction of **7** with anhydride **5** was also found to be somewhat temperature sensitive. If work-up of the reaction was carried out after 2 h at room temperature, then analysis showed that only 0.5% of imide impurity **12** was formed. However, if the reaction mixture was stirred at room temperature for 48 h, then the quantity of **12** rose to 25%. In contrast, if the reaction mixture was kept between 0° and 5 °C, even after 20 h the quantity of imide did not rise above 0.5%, and the desired product could be isolated in 86% yield with good chemical purity.

Formation of the second amide bond to give **8** was found to work well using 1-hydroxybenzotriazole (HOBt), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC), and DMAP as coupling agents in *N*,*N*-dimethylacetamide (DMA) as solvent. As we had hoped, this did lead to substantially lower quantities of imide **9**, with the small quantity that was formed arising presumably from the cycloheptylmethylamine-elimination pathway. The crude reaction product contained typically 2−4% of imide **9** which was successfully removed by recrystallization from 4-methyl-2-pentanone, product **8** being isolated in 75% yield with chemical purity of 96% and optical purity >99.7%. Although this reaction was working well, it did suffer from the fact that the filtration proved to be difficult. The solid that precipitated by pouring

Scheme 4. **Synthesis of 8 from 4 and 11**[a]



[a] Reagents and conditions: i) cycloheptylmethylamine **7**, MeOH, 0−5 °C; ii) EDC, HOBt, DMAP, DMA, 0−5 °C.

the reaction mixture into water was somewhat sticky and tended to block the filter, a complication which, it was felt, might lead to problems on a plant scale. Numerous experiments were performed to overcome this. The result of this investigation was that the coupling of **4** and **11** could be carried out with EDC alone while still maintaining the low levels of imide formation. Indeed under these conditions and after recrystallization from 4-methyl-2-pentanone, the product **8** was isolated in 77% yield with chemical purity of 96%. Also, the filtration of the crude product after the reaction mixture had been added to aqueous base was no longer found to be a problem as the HOBt that tended to make the solid sticky was no longer present. We also observed that, during the reactions that used just EDC as coupling agent, an intermediate was formed that was consumed as the reaction proceeded. Mass spectral analysis showed this intermediate to have the same mass as imide **12**, but it did not have the same retention time on HPLC. We postulated that the most probable structure of the intermediate was the isoimide **15** (Scheme 5). Although attempts to isolate and fully characterize this isoimide were unsuccessful, we feel there is sufficient indirect evidence to indicate its presence in the reaction. Isoimides are known compounds;[7] indeed, those with an aromatic group on nitrogen have been isolated. Furthermore, if the reaction mixture containing this intermediate **15** was allowed to warm to room temperature without the addition of a second nucleophile, the imide **12** was formed in quantitative yield. Imide **12** also proved resistant to ring opening with amino amide **4**. Although the intermediate **15** can be formed using other reagents such as 1,1-carbonyldiimidazole (CDI), we found that the use of EDC gave the most reproducible yields and quality of product **8**. Dehydration of the benzimidazoleamide acid **11** can lead to either the isoimide or the imide. We found that at low (0−5 °C) temperature in DMA this occurred almost exclusively in favor of the isoimide, a situation that was not the case in THF as under similar conditions 31% of the imide was formed. As this intermediate **15** was not observed in the reactions in which HOBt was also used, it would appear that these reactions proceed via a pathway involving an activated ester intermediate such as **16** (Scheme 5). An issue identified with the reactions that proceeded via the isoimide was that the reaction temperature had to be maintained between 0 and 5 °C to prevent rearrangement to imide. This also had the consequence that the reactions were found to be somewhat slower than when HOBt was also used.

In contrast to the above results, treatment of **17**, the isoimide of **6**, with cycloheptylmethylamine **7** at a temperature of −5 °C led to formation of **9** in 70% yield (Scheme 6), further underlining the steric influence of the amino amide side chain. Imide **9** was also shown to be resistant to ring opening with cycloheptylmethylamine **7**.

The next step of the sequence was the deprotection of the benzoic acid groups in **8**. This seemingly simple transformation was complicated by the low solubility of the di-acid product **10** in most organic solvents. Although numerous methods are known for the removal of benzyl ester protecting groups,[8] the mild and efficient catalytic hydrogenation method was chosen. This was originally carried out on discovery scale in a rather large volume (11 L/mol) of a mixture of THF and methanol at room temperature. After filtration to remove the catalyst, the reaction product was isolated by evaporation to dryness followed by stirring in acetone. Our initial efforts were directed towards avoiding the need to evaporate the reaction mixture to dryness. As we had discovered that 2-propanol was a suitable recrystallization solvent, we decided to isolate **10** by performing a solvent switch to this solvent, after the catalyst had been removed by filtration, and allowing the product to crystallize. The reaction was then attempted in other solvent systems as described in Table 2. As both starting material and reaction product were less soluble in 2-propanol than in methanol, these reactions required heating to 50 °C. Unfortunately, this resulted in ring closure and therefore formation of some

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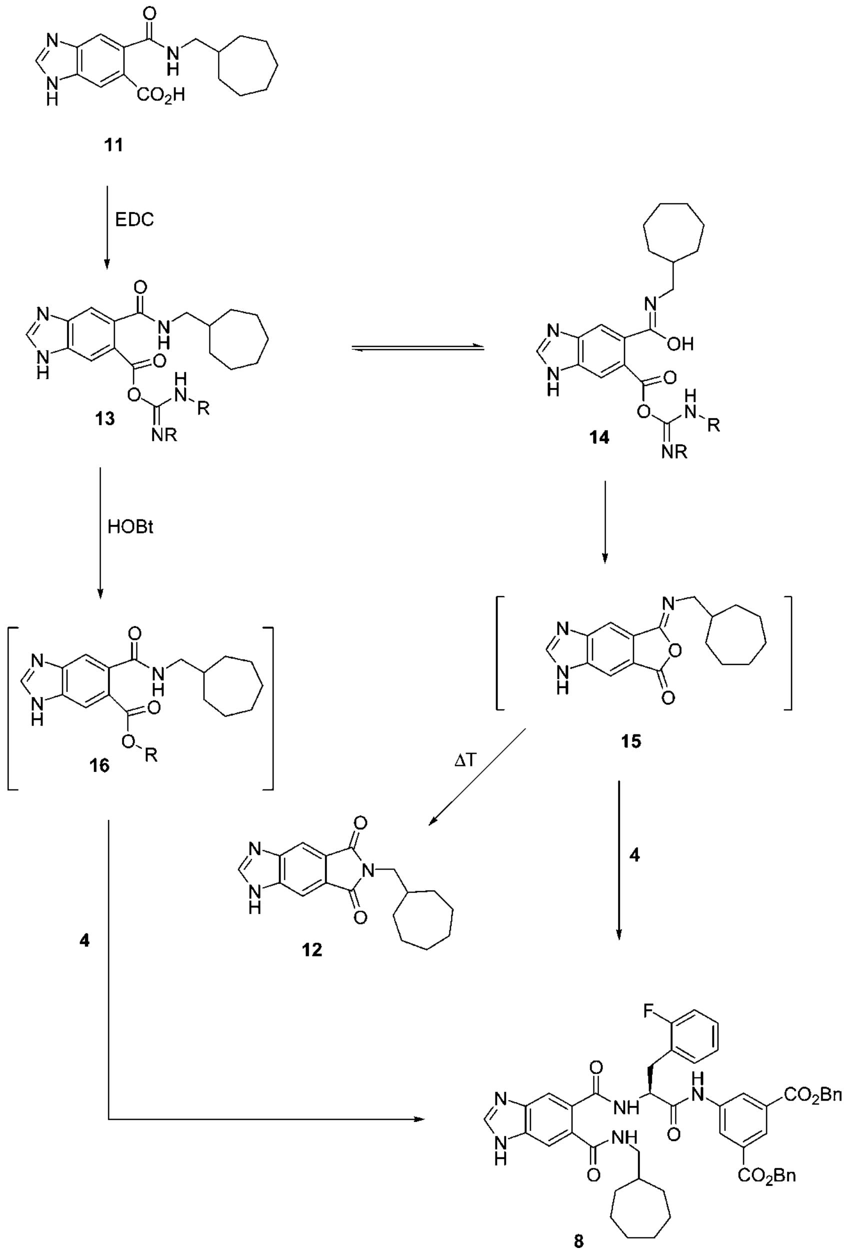
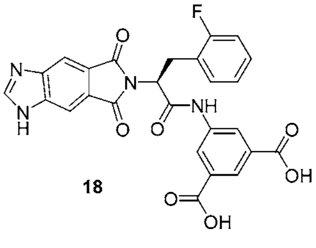
(7) (a) Roderick, W. R.; Parshotam, L. B. *J. Org. Chem.* **1963**, *28*, 2018. (b) Díaz de Toranzo, E. G.; Brieux, J., A. *J. Med. Chem.* **1967**, *10*, 982. (c) Guirado, A.; Zapata, A.; Fenor, M. *Tetrahedron Lett.* **1991**, *32*, 2633. (d) Guirado, A.; Zapata, A.; Ramírez de Arellano, M. C. *Tetrahedron* **1997**, *53*, 5305.

(8) Greene, T. W.; Wuts, P. G. M., *Protective Groups in Organic Synthesis*, 3rd ed., John Wiley & Sons Inc.: New York, 1999.

Scheme 5. **Proposed coupling pathways of 4 and 11 using EDC in the presence and absence of HOBt**



imide **18**. Performing the reaction in THF alone gave a very slow reaction as after one of the benzyl groups had been removed, the mono-acid compound crystallized which required a large volume of solvent to redissolve and hence allow further reaction. The most efficient solvent was found to be DMA, Table 2. This allowed the reaction to be carried out in a small volume of solvent (1.5 L/mol) at room temperature, and the quantity of catalyst could be reduced to 1 mol %. After filtration of the catalyst, the product was isolated by pouring the filtrate into 2-butanone, a solvent in which **10** has very low solubility, and after approximately 20 min stirring at room temperature **10** precipitates from the solution. Unfortunately the isolated solid contained approximately 14% (by weight) of DMA, a quantity which remained virtually unchanged even after prolonged drying at 70 °C under vacuum. The DMA was successfully removed in the following synthetic step.



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The final step in the synthesis is the sodium salt formation. Whereas this was originally carried out in water and the product isolated by freeze-drying, on larger scale this was performed in methanol using a 3.6 M aqueous solution of sodium carbonate as base. **JB95008** was then precipitated by adding the reaction mixture to acetone. After filtration and drying, the final product was isolated in good yield in high chemical and optical purity. It should here be noted that attempts to form **JB95008** via direct hydrolysis of **8**

Scheme 6. **Reaction of isoimide 17 with cycloheptylmethylamine 7**

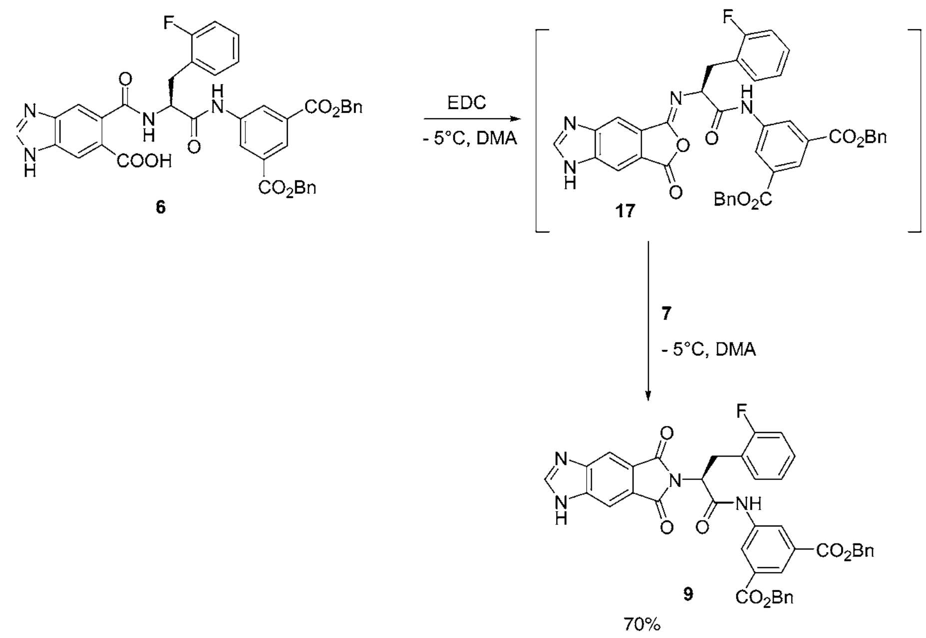


Table 2. **Composition of products obtained from debenzylation of 8**

	solvent	temp (°C)	purification solvent	physical yield (%)	L C profile		
					chemical purity **10** (area %)	**18** (area %)	optical purity (%)
1	THF/MeOH	24	acetone	72	100	n.d[d]	/
2	THF/MeOH	24	*i*PrOH	70	94	n.d	/
3	*i*PrOH/THF	50	*i*PrOH	74	94	3	/
4	*i*PrOH[a]	50	/		93	1.4	100
5	THF	50	*i*PrOH	58	92.5	0.1	99.2
6	PGMME[b]	24	/	/	/	/	/
7	monoglyme[a]	24	/	/	73	8.5	/
8	DMA	24	*i*PrOH	93	99	n.d	100
9	DMA	22	2-butanone	105[c]	99	n.d	99.6

[a] Product not isolated. [b] No reaction, starting material recovered. [c] Physical yield is greater than 100% because the isolated solid contains DMA. [d] n.d = not detected.

always resulted in the formation of a number of impurities along with some racemization.

Conclusion

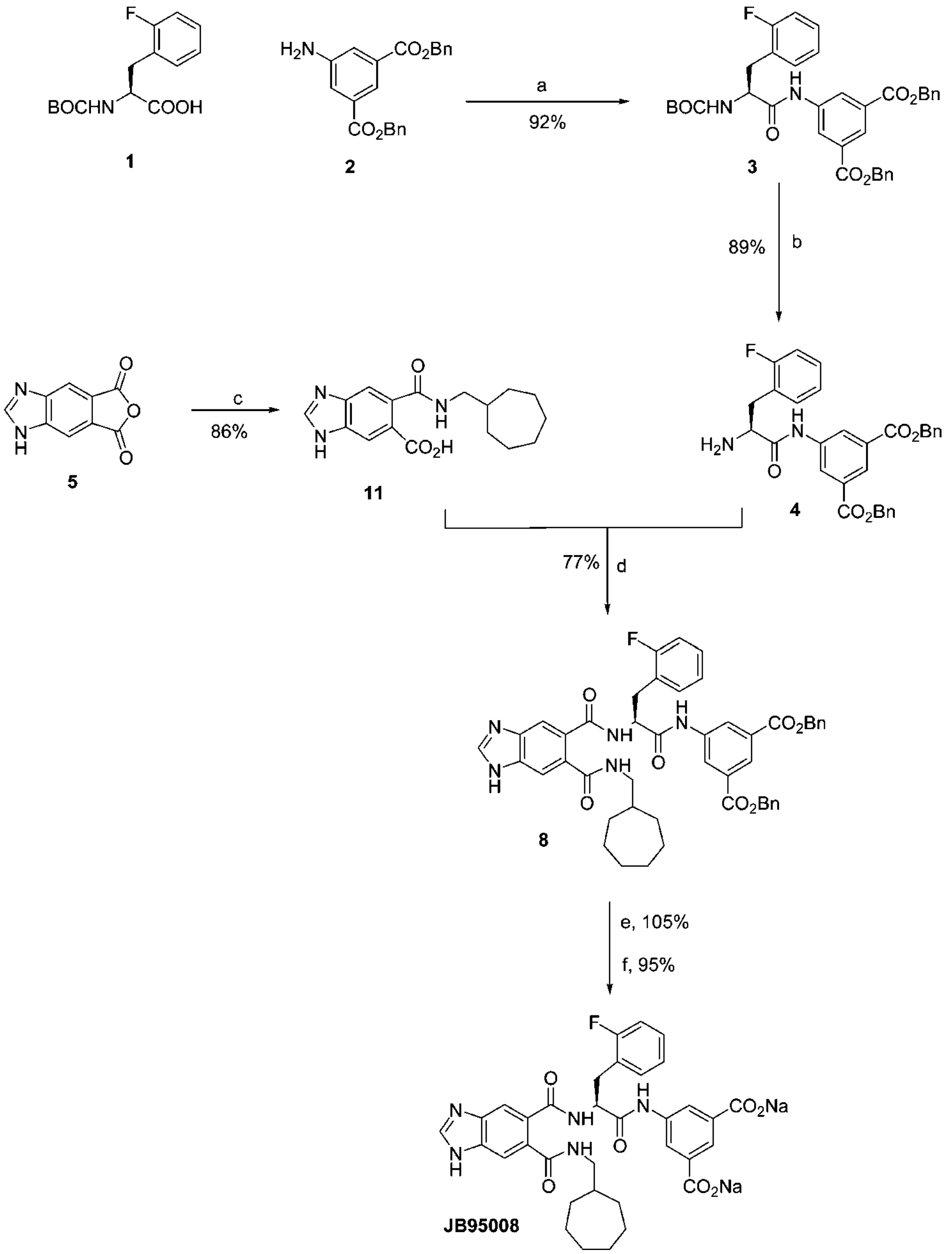
In conclusion we have developed a process that has been used on pilot-plant scale to synthesize two 10-kg batches of **JB95008**, Scheme 7. The route now avoids purification by column chromatography and the need to evaporate solutions containing product to dryness. Furthermore, we have increased the efficiency of the second amine coupling to **8** and found evidence that this reaction is probably proceeding via an isoimide intermediate. The use of some expensive and/or toxic reagents and solvents has also been circumvented.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were measured on a Bruker AV600 spectometer in DMSO-d_6. The chemical purities were determined by quantitative and qualitative methods on a HP 1090 series II HPLC instrument using a Hypersil BDS-C18 column, 3 μm particle size (4.0 mm × 100 mm), and UV detection. Enantiomeric purities of compounds **3**, **4**, and **8** were determined by chiral HPLC on a HP 1090 series using an Astec chirobiotic T column and UV detection. Enantiomeric purity of **JB95008** was determined by capillary electrophoresis on a Beckman P/ACE 5500 series instrument. Boc- 2-(L)-fluorophenylalanine **1** was purchased from Chirotech Technology Ltd. and used with no further purification. 3,5-Dibenzyloxycarbonylaniline **2**, benzimidazole anhydride **5**, and cycloheptylmethylamine **7** were purchased from Palmer Research Laboratories and used with no further purification. 2-Ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) was purchased from Van Overbeek Chemie and Mitsui & Co Benelux and was used with no further purification.

Bis(phenylmethyl) (*S*)-5-[[2-[[(1,1-Dimethylethoxy)carbonyl]amino]-3-(2-fluorophenyl)-1-oxopropyl]amino]-1,3-benzenedicarboxylate (3). Dichloromethane (212.2 L) was added to a reaction vessel under an atmosphere of nitrogen charged with Boc-2-(L)-fluorophenylalanine **1** (10.74 kg, 37.9

Scheme 7. **Development synthesis of JB95008[a]**



[a] Reagents and conditions: a) EEDQ, CH_2Cl_2, 20 °C. b) Toluene, HCl/iPrOH, $NaHCO_3$, H_2O, 40 °C. c) Cycloheptylmethylamine, MeOH, 0−5 °C. d) EDC, DMA, 0−5 °C, $NaHCO_3$, H_2O, 4-methyl-2-pentanone. e) DMA, Pd/C, H_2, 2-butanone, 22 °C. f) MeOH, Na_2CO_3, H_2O, acetone, 22 °C.

mol), aniline **2** (13.71 kg, 37.9 mol) and 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (9.4 kg, 37.9 mol). The resulting homogeneous solution was stirred at 20 °C for 22 h. Dichloromethane (136 L) was distilled off under atmospheric pressure and propylene glycol monomethyl ether (190 L) was added. The distillation was continued until the internal temperature reached 115 °C. The mixture was then allowed to cool to 22 °C over 15 h. The solids were then filtered and washed with propylene glycol monomethyl ether. Drying under vacuum at 50 °C gave the title compound as a white solid (wt = 21.87 kg, 92%). HPLC: 99.6% w/w; Chiral HPLC: 99.0% *(S)*. MS (CI) *m*/*z* 627 (MH^+). ^1H NMR (600 MHz, DMSO-d_6) δ 1.33 (s, 9H), 2.94 (dd, $J = 13.6, 9.1$ Hz, 1H), 3.10 (dd, $J = 13.6, 5.9$ Hz, 1H), 4.32−4.51 (m, 1H), 5.40 (s, 4H), 7.04−7.15 (m, 2H), 7.19 (d, $J = 8.3$ Hz, 1H), 7.29−7.29 (br s, 1H), 7.32 (t, $J = 7.4$ Hz, 1H), 7.40 (d, $J = 7.2$ Hz, 2H) 7.43 (t, $J = 7.2$ Hz, 4H), 7.49 (d, $J = 7.2$ Hz, 4H), 8.24 (s, 1H), 8.52 (s, 2H), 10.47 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 28.05, 30.78, 55.01, 66.70, 78.28, 115.00 (d, $J = 21.9$ Hz), 124.03, 124.17, 124.38, 128.17, 128.26, 128.55, 130.63, 131.58, 135.77, 139.75, 155.17, 159.95 (d, $J = 244.8$ Hz), 164.6, 170.89.

1S−(3,5-Dibenzyloxycarbonylphenylaminocarbonyl)-2-(2-fluorophenyl)ethylamine (4). Hydrochloric acid (6N solution in 2-propanol, 16 L) was added to a suspension of **3** (20.1 kg, 32.07 mol) in toluene (200 L). The resulting mixture was heated to 40 °C and stirred for 6.5 h. The reaction mixture was cooled to 22 °C. A solution of $NaHCO_3$ (10.8 kg, 128.3 mol) in water (91.4 L) was added dropwise with vigorous stirring. The biphasic mixture was warmed to

40 °C and stirred for 40 min. The two layers were separated at 40 °C. The organic layer was cooled to 0 − 5 °C and stirred at this temperature for 15 h. The solids were filtered and washed with toluene (3.2 L). Drying under vacuum at 50 °C gave the title compound as a white solid (wt = 15.03 kg, 89%). HPLC: 99.9% w/w; Chiral HPLC: 99.7% *(S)*. MS (CI) *m/z* 527 (MH$^+$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.58 (br s, 2H), 2.90 (dd, J = 14.1, 9.3 Hz, 1H), 3.43 (dd, J = 14.1, 4.0 Hz, 1H), 3.77 (dd, J = 9.3, 4.0 Hz, 1H), 5.38 (s, 4H), 7.02−7.11 (m, 2H), 7.18−7.28 (m, 2H), 7.31−7.42 (m, 6H), 7.42−7.48 (m, 4H), 8.46 (s, 2H), 8.48 (s, 1H), 9.71 (br s, 1H).

6-[(cycloheptanemethyl)amino]carbonyl-1H-benzimidazole-5-carboxylic acid (11). Benzimidazole-5,6-dicarboxylic acid anhydride **5** (6.5 kg, 34.6 mol) was added to methanol (54 L) cooled to between 0 and 5 °C. To this suspension was added dropwise a solution of cycloheptylmethylamine (4.40 kg, 34.6 mol) dissolved in methanol (15 L). The resulting mixture was stirred at 0−5 °C for 15 h. The reaction mixture was filtered over dicalite and the filter cake washed with methanol (3.7 L). The filtrate was added to water (145 L) and stirred for 1 h. The precipitate was filtered and washed with water (10 L). Drying under vacuum at 50 °C gave the title compound as a yellow solid (wt = 9.4 kg, 86%). HPLC: 95.5% w/w. MS (CI) *m/z* 316 (MH$^+$). ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.11−1.25 (m, 2H), 1.35−1.51 (m, 4H) 1.51−1.60 (m, 2H), 1.60−1.70 (m, 2H), 1.70−1.89 (m, 3H), 3.05 (t, J = 6.0 Hz, 2H), 7.57 (s, 1H), 7.97 (s, 1H), 8.31 (s, 1H), 8.40 (s, 1H), 12.75 (br s, 1H).

5-(1S−(3,5-Dibenzyloxycarbonylphenylaminocarbonyl)-2-(2-fluorophenyl)ethylaminocarbonyl)-6-(cycloheptanemethylaminocarbonyl)benzimidazole (8). 6-[(Cycloheptanemethyl)amino]carbonyl-1H-benzimidazole-5-carboxylic acid (11) (6.64 kg, 21.06 mol) and 1S−(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-(2-fluorophenyl)ethylamine **(4)** (11.09 kg, 21.06 mol) were added to *N*,*N*-dimethylacetamide cooled to between 0 and 5 °C and under a nitrogen atmosphere. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide (5.25 kg, 27.4 mol) was added and the resulting mixture stirred at 0−5 °C for 15 h. The reaction mixture was added dropwise over a period of an hour to a solution of NaHCO$_3$ (5.30 kg, 63.18 mol) dissolved in 316 L water and stirred for a further hour. The solids were filtered, washed with water and dried under vacuum at 50 °C. The dry solid and 4-methyl-2-pentanone (86.7 L) were added to a reaction vessel and the mixture heated and stirred at 60 °C until all solids dissolved. The mixture was allowed to cool to room temperature and stirred for 10 h. The solids were filtered and washed with 4-methyl-2-pentanone (10.5 L). Drying under vacuum at 50 °C gave the title compound as a white solid (wt = 13.36 kg, 77%). HPLC: 96.5% w/w; Chiral HPLC: 99.7% *(S)*. ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.96−1.12 (m, 2H), 1.12−1.34 (m, 4H), 1.34−1.52 (m, 4H), 1.99−2.10 (m, 3H), 2.91−3.17 (m, 3H), 3.58 (m, 1H), 4.85 (m, 1H), 5.41 (s, 4H), 7.20−7.28 (m, 3H), 7.35−7.60 (m, 12H), 8.29 (s, 1H), 8.43 (s, 1H), 8.72 (s, 1H), 8.89 (s, 1H), 8.94 (d, J = 8.3 Hz, 1H), 10.38 (br s, 1H), 12.85 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 25.63, 27.93, 31.26, 31.39, 38.71, 45.77, 53.46, 66.59, 115.10 (d, J = 21.9 Hz), 124.11, 124.53, 124.77, 125.15, 125.25, 127.98, 128.20, 128.51, 130.64, 131.76, 135.84, 139.85, 160.83 (d, J = 244 Hz), 164.65, 168.67, 169.79, 170.41.

5-(1S−(3,5-Dicarboxyphenylaminocarbonyl)-2-(2-fluorophenyl)ethylaminocarbonyl)-6-(cycloheptanemethylaminocarbonyl)benzimidazole (10). To a solution of 5-(1S−(3,5-dibenzyloxycarbonylphenylaminocarbonyl)-2-(2-fluorophenyl)ethylaminocarbonyl)-6-(cycloheptanemethylaminocarbonyl)benzimidazole **(8)** (13.21 kg, 16.04 mol) in *N*,*N*-dimethylacetamide (24L) under a nitrogen atmosphere was added palladium, 5% (dry basis) on charcoal (wet, ±50% water, 640 g). The nitrogen was exchanged for a hydrogen atmosphere and the reaction mixture stirred at 22 °C until the uptake of hydrogen ceased. The reaction mixture was filtered under nitrogen over dicalite and the filter cake washed with ethanol (8 L). The filtrate was added dropwise to 2-butanone (80 L) and stirred at room temperature for 15 h. The precipitate was filtered and washed with 2-butanone (6.5 L). Drying under vacuum at 50 °C gave the title compound as a light gray solid (wt = 10.85 kg, 105%). HPLC: 87% w/w. MS (CI) *m/z* 644 (MH$^+$). ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.08−1.20 (m, 2H), 1.22−1.35 (m, 2H), 1.35−1.42 (m, 2H), 1.42−1.50 (m, 2H), 1.51−1.60 (m, 2H), 1.61−1.80 (m, 3H), 2.07 (DMA), 3.03 (t, J = 13.2 Hz, 1H), 3.10−3.20 (m, 3H), 3.25 (DMA), 3.65 (d, J = 13.6 Hz, 1H), 4.89 (m, 1H), 7.17 (s, 1H), 7.26 (m, 2H), 7.38 (m, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.95 (s, 1H), 8.28 (s, 1H), 8.45 (s, 1H), 8.76 (s, 1H), 8.82 (s, 2H), 8.96 (d, J = 8.3 Hz, 1H), 10.31 (s, 1H), 13−13.5 (br, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 20.15 (DMA), 25.73, 27.94, 31.31, 31.48, 35.82 (DMA) 38.80, 45.58, 53.39, 115.2 (d, J = 22 Hz), 124.19, 124.69, 125.18, 128.77, 131.91, 139.48, 161.0 (d, J = 244 Hz), 166.73, 168.72, 170.01, 170.37.

5-(1*S*-(3,5-Dicarbonylphenylaminocarbonyl)-2-(2-fluorophenyl)ethylaminocarbonyl)-6-(cycloheptanemethylaminocarbonyl)benzimidazole Disodium Salt (JB95008). To a solution of 5-(1*S*-(3,5-dicarboxylphenylaminocarbonyl)-2-(2-fluorophenyl)ethylaminocarbonyl)-6-(cycloheptanemethylaminocarbonyl)benzimidazole **(10)** (10.85 kg, 14.9 mol) in methanol (36.4 L) was added under pH control a solution of Na$_2$CO$_3$ (1.6 kg, 14.9 mol) in water (4.2 L). The pH during the addition was controlled so that it did not exceed 7.5. The mixture was stirred at 22 °C for 1 h before acetone (30 L) was added dropwise over a period of 30 min. The reaction mixture was filtered over dicalite and the filtrate returned to a reaction vessel. Acetone (149 L) was added dropwise over 2 h and the resulting mixture stirred at 22 °C for 16 h. The precipitate was filtered and washed with acetone. Drying under vacuum at 60 °C gave the title compound as a white solid (wt = 9.7 kg, 95%). HPLC: 99.5% w/w; CE: 99.9% *(S)*. ^{1}H NMR (600 MHz, DMSO-d_6) δ 0.92−1.15 (m, 2H), 1.22−1.35 (m, 2H), 1.35−1.42 (m, 2H), 1.42−1.50 (m, 2H), 1.51−1.60 (m, 2H), 1.61−1.80 (m, 3H), 2.97−

3.25 (m, 3H), 3.50 (br s, 2H), 4.81 (br s, 1H), 7.16−7.25 (m, 2H), 7.30 (m, 1H), 7.41 (br s, 1H), 7.52 (br s, 1H), 7.78 (br s, 1H), 8.28 (s, 1H), 8.36 (s, 1H), 8.42 (s, 2H), 8.47 (br, 1H), 10.25 (br, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 25.73, 27.92, 31.44, 31.50, 38.82, 45.81, 54.03, 115.0 (d, $J = 22$ Hz) 122.51, 124.09, 125.34, 125.68, 128.54, 131.08, 132.02, 137.34, 160.8 (d, $J = 245$ Hz), 168.57, 169.61, 170.42.

Received for review April 26, 2005.

OP0500638