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Development of a Multigram Synthesis of URB937, a Peripherally Restricted FAAH Inhibitor

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Supporting Information

ABSTRACT: A new synthetic approach to URB937 was developed starting from the inexpensive and widely available 4-benzyloxyphenol. A reproducible four-step procedure, requiring no chromatographic purifications, was optimized that allowed the preparation of 100 g of URB937 in 45% overall yield.

1. INTRODUCTION

Fatty-acid amide hydrolase (FAAH) is an intracellular membrane-bound serine hydrolase that catalyzes the hydrolysis of the endocannabinoid signaling molecule anandamide and of other noncannabinoid fatty-acid ethanolamides such as oleoylethanolamide and palmitoylethanolamide.[1,2] Natural FAAH substrates, such as anandamide, play important physiological roles and have been implicated in several disease conditions, which might be caused in part by deficits in their normal function.[3] Inhibition of FAAH activity may reduce such deficits and, therefore, is of considerable pharmaceutical interest. Among the different chemical classes of FAAH inhibitors disclosed so far,[4] the *O*-aryl carbamates[5] and the piperidine/piperazine ureas[6] have been shown to have favorable profiles with respect to both selectivity and pharmacological activity in vivo. The *O*-aryl carbamates comprise *N*-cyclohexylcarbamic acid *O*-aryl ester derivatives such as URB597 (**1**, Figure 1), which demonstrated in animals an interesting

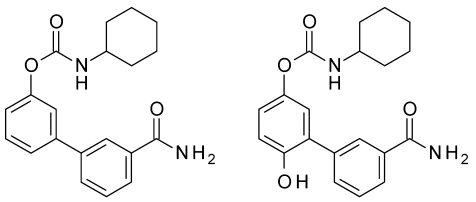
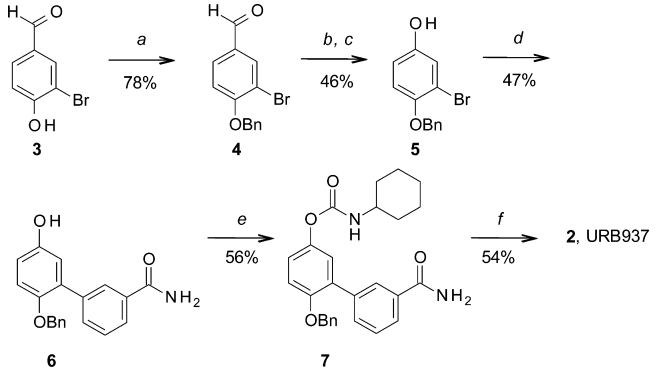


Figure 1. *O*-aryl carbamate FAAH inhibitors.

combination of anxiolytic, antidepressant, and analgesic properties.[7] URB937, [3-(3-carbamoylphenyl)-4-hydroxyphenyl]-*N*-cyclohexylcarbamate (**2**, Figure 1), a close analogue of URB597, is a potent inhibitor of FAAH (*rat* FAAH IC_{50}: 26.8 nM) and is unique among the *O*-arylcarbamate FAAH inhibitors because it is actively extruded from the central nervous system (CNS) thus increasing anandamide levels exclusively in peripheral tissues.[8] Recent studies have suggested that ABCG2 is the major transporter responsible for extrusion of URB937 from the CNS.[9] Despite its peripherally restricted distribution, URB937 exhibited marked analgesic properties in rodent models of nociceptive and inflammatory pain[8,10] and therefore represents the prototype of new analgesic agents devoid of central side effects. To investigate in detail the pharmacology of URB937, multigram amounts of compound are required.

The previously described synthesis of URB937[8,10] starting from the commercially available 3-bromo-4-hydroxybenzaldehyde **3** is depicted in Scheme 1.

Scheme 1. Medicinal Chemistry Route to URB937



(a) BnCl (1.1 equiv), Cs_2CO_3 (1.1 equiv), DMF, 23 °C, 3 h; (b) *m*-CPBA (3.0 equiv), CH_2Cl_2, 23 °C, 4 h; (c) 1 M NaOH, MeOH, 23 °C, 18 h; (d) 3-carbamoylphenylboronic acid (1.2 equiv), 5% $Pd(PPh_3)_4$, Na_2CO_3 (5 equiv), toluene/H_2O, reflux, 18 h; (e) *c*-hexNCO (1.2 equiv), Et_3N (0.15 equiv), EtOH/MeCN, reflux, 4 h; (f) H_2 (4 atm.) 10% Pd/C, EtOAc/EtOH, 50 °C, 4 h.

This versatile six-step procedure allowed a quick exploration of the structure−activity relationships of URB937 close analogues. In fact, different carbamate residues and distal phenyl rings can be introduced late in the synthesis, thus making possible a time-efficient preparation of an array of differently substituted derivatives for the investigation of the impact of structural modifications on the inhibition of FAAH

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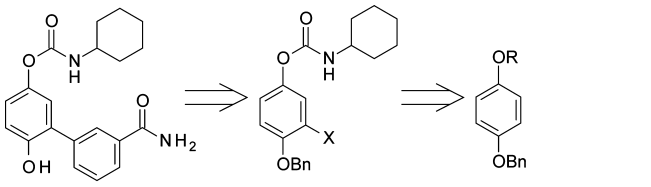
activity. However, this route suffers from suboptimal yield in several steps, and required chromatographic purifications in order to isolate the intermediates and the final compound in pure form. When this synthetic procedure was scaled up to prepare 1 g of URB937, a 5% overall yield was obtained, thus making this synthesis unsuitable for the preparation of large quantities of the compound.

Herein, we report the results of our studies which led to a more efficient, higher-yielding, and robust route for the preparation of URB937 in up to 100 g amount.

2. RESULTS AND DISCUSSION

Our retrosynthetic plan (Scheme 2) envisaged the formation of the biphenyl system by a Suzuki coupling reaction on the aryl

Scheme 2. New Retrosynthetic Approach to URB937

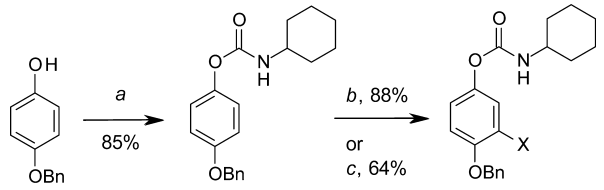


2, URB937 — **10a**, X = Br; **10b**, X = I — **9**, R = CONH-*c*-hexyl; **8**, R = H

halides **10a–b** obtained by regioselective halogenation of the *O*-aryl carbamate **9**, which in turn can be prepared by carbamoylation of the cheap and widely available 4-benzyloxyphenol **8**.

2.1. Synthesis of Aryl Halides 10a and 10b. The synthesis of the carbamate **9** was easily accomplished by reaction of **8** with *c*-hexylisocyanate in the presence of Et_3N (Scheme 3). The use of a 1:1 mixture of absolute EtOH and

Scheme 3. Synthesis of Intermediates 9, 10a, and 10b



8 — **9** — **10a**, X= Br; **10b**, X= I

(a) *c*-hexNCO (1.2 equiv), Et_3N (0.6 equiv), EtOH/MeCN, r.t., 16 h; (b) NBS (1.4 equiv), DMF, 75 °C, 16 h; (c) I_2 (1.25 equiv), HIO_3 (2 equiv), H_2SO_4 (1 equiv), DMF, 60 °C, 6 h.

MeCN as the solvent resulted in compound **9** crystallizing out from the reaction mixture. A simple filtration allowed the isolation of **9** in 85% yield. This step was repeated several times employing up to 50 g of **8**, and proved to be reproducible.

Different reaction conditions for the bromination and iodination of **9** were then studied: the results are summarized in Table 1.

Bromination reactions were conducted with Br_2 in AcOH, NaBr/Oxone, and *N*-bromosuccinimide (NBS), while iodination was performed with $I_2/HIO_3/H_2SO_4$ in AcOH or DMF. Br_2 in AcOH led to complete conversion of the starting material after 48 h at room temperature (entry 1). The use of NaBr/Oxone in MeOH has been reported as an efficient and

Table 1. Experimental Conditions and Conversion of Halogenation Reactions of Compound 9

entry	reagents	equiv	solvent	*T* (°C)	*t* (h)	conversion (%)[a]
1	Br_2/NaOAc	1.4/1.4	AcOH	22	48	100
2	NaBr/Oxone	1.1/1.1	MeOH	22	96	46[b]
3	NBS	1	DMF	22	96	83
4	NBS	1	AcOH	22	96	80
5	NBS	1.4	DMF	75	16	100[c]
6	$I_2/HIO_3/H_2SO_4$	1.25/2/1	AcOH	60	6	100
7	$I_2/HIO_3/H_2SO_4$	1.25/2/1	DMF	60	6	100[d]

[a]% conversion of compound **9** as measured by UPLC/MS analysis. [b]**9** was poorly soluble in the reaction mixture. [c]88% isolated yield. [d]64% isolated yield.

safe method for the bromination of electron-rich aromatic rings.[11] When this procedure was applied to our substrate, the reaction was exceedingly slow with only 46% conversion of compound **9** observed after 96 h (entry 2), most likely because of the limited solubility of **9** in MeOH.

The bromination reaction with NBS was run under various experimental conditions (entries 3–5). Incomplete conversion of the starting material after 96 h was observed when the reaction was conducted at room temperature with either DMF (entry 3) or AcOH (entry 4) as the solvent. Increasing the temperature to 75 °C (entry 5) led to complete conversion of **9** into **10a** after 18 h.

The iodo-derivative **10b** was prepared as an alternative reactant in the Suzuki coupling reaction (see Supporting Information). Iodination of compound **9** with the I_2/HIO_3 system[12] in the presence of H_2SO_4 in either AcOH (entry 6) or DMF (entry 7) provided compound **10b** in moderate yield (64% isolated yield, entry 7). The optimization of the synthesis of compound **10b** was not pursued, as in initial experiments the Suzuki coupling reaction of **10b** with 3-carbamoylphenyl boronic acid failed to produce the desired intermediate **7** (see section 2.2).

For our synthetic purposes, NBS was preferred to bromine due to its easier and safer handling. Bromination reactions of up to 53g of **9** were performed with 1.4 equivalents of NBS in DMF at 75 °C for 16 h. Bromination occurred at the *ortho* position to the benzyloxy group[13] with >99:1 selectivity, as determined by ^1H NMR analysis of the crude material.[14] Compound **10a** was easily isolated by precipitation with an aqueous sodium thiosulfate solution. After filtration and recrystallization from EtOH, **10a** was obtained in 88% yield as small white needles. This step was repeated several times and proved to have good reproducibility. The high yield of both the carbamoylation and the bromination reactions, coupled with their easy workup, allowed us to prepare more than 300 g of **10a** using common medicinal chemistry laboratory equipment and labware.

2.2. Synthesis of Intermediate 7. The Suzuki coupling reaction[15] on the *O*-arylcarbamates **10a** and **10b** was expected to be a challenging synthetic step due to the base-sensitivity of the carbamate functionality of both the starting material (**10a** or **10b**) and the product (**7**). In fact, under the basic conditions required for the reaction, compounds **10a**, **10b**, and **7** could hydrolyze to the corresponding phenols **5**, **12**, and **6**, respectively (Table 2).

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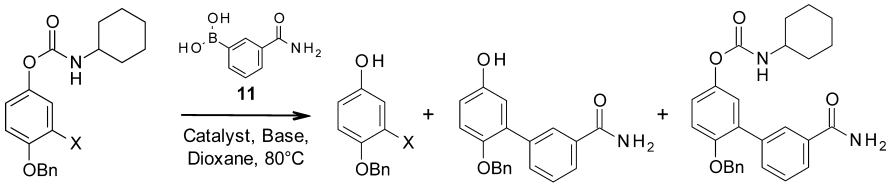
Table 2. Experimental Conditions and Outcome of Suzuki Coupling Reactions of Compounds 10a and 10b with 3-Carbamoyl Phenylboronic Acid 11[a]



10a, X = Br
10b, X = I

5, X = Br
12, X = I

6

7

entry	aryl halide	catalyst	base	**10** (%)[b]	**5** (or **12**) (%)[b]	**6** (%)[b]	**7** (%)[b]
1	**10a**	**A**	KOAc	88	2	0	10
2	**10a**	**A**	Na_2CO_3	90	1	0	9
3	**10a**	**A**	CsF	100	0	0	0
4[c]	**10a**	**A**	CsF	19	14	17	50
5[d]	**10a**	**A**	CsF	40	60	0	0
6[e]	**10a**	**A**	KOAc	85	2	1	12
7[c]	**10a**	**A**	KOAc	38	11	4	47
8	**10a**	**B**	CsOAc	31	5	7	57
9	**10b**	**B**	CsOAc	66	34	0	0
10[c]	**10b**	**A**	KOAc	72	28	0	0

[a]General conditions: 1.5 equiv of **11**, 2.5 equiv of base, 5% catalyst in anhydrous dioxane, 80 °C, 120 min; **A**: $Pd(PPh_3)_4$; **B**: $PdCl_2$dppf. [b]% of compound remaining (**10a** or **10b**) or formed (**5**, **12**, **6**, and **7**) as measured by UPLC/MS analysis after 120 min. [c]Addition of 50 equiv of H_2O. [d]Toluene/H_2O 1:1. [e]Addition of 10 equiv of H_2O.

This consideration prompted us to first investigate the stability of **10a** under different experimental conditions commonly used in Suzuki coupling reactions. Various combinations of solvents and bases were tried. As expected, a fast hydrolysis ($t_{1/2}$ < 20 min as measured by UPLC/MS analysis) occurred upon heating compound **10a** at 80 °C in polar solvents like DMF or MeCN, even employing weak bases such as KOAc or CsF. On the contrary, under the same conditions the stability of compound **10a** was acceptable[16] when the polar solvents were replaced with THF, dioxane, and toluene. With these data in hand, we started the optimization of the Suzuki coupling reaction: the results are summarized in Table 2.

The bromide **10a** was initially reacted with 3-carbamoyl phenylboronic acid **11** in dioxane at 80 °C using $Pd(PPh_3)_4$ as the catalyst and KOAc or Na_2CO_3 as the base. Under these reaction conditions, compound **10a** was stable, even on prolonged heating, but a maximum of 10% conversion was observed (entries 1 and 2).

In order to verify whether a different base could accelerate the reaction, compound **10a** was reacted in the presence of CsF, which was successfully used in Suzuki coupling reactions on labile systems, such as aryl trifluoroacetamides[17] and nitroaryl esters.[18] Under our experimental conditions, CsF was ineffective (entry 3): no formation of the desired product **7** was observed after 2 h. Interestingly, adding a small amount of water greatly improved the conversion of the starting material (entry 4), while a biphasic toluene/water system led exclusively to the formation of the hydrolysis product **5** (entry 5).

The observed increase in the amount of compound **7** when water was added to the reaction mixture led us to speculate that the low conversion of **10a** (entries 1, 2, and 3) could be due, at least in part, to the poor solubility of 3-carbamoyl phenylboronic acid **11** in dioxane. Unfortunately, the higher reaction rate in the presence of water was accompanied, as expected, by an increase in the formation of the hydrolysis products **5** and **6**, as observed also with KOAc as the base (entries 6 and 7). Several attempts were made to adjust the amount of water in order to obtain a more favorable ratio between the conversion of the starting material and the amount of desired product. Difficulties encountered in obtaining reproducible results led us to abandon this approach.

We then turned our attention to the $PdCl_2$dppf/CsOAc system, which has been recently employed with success in a Suzuki coupling reaction under anhydrous conditions on hydrolytically labile systems such as [3-(trifluoromethylsulfonyloxy)phenyl]acetate.[19] When $PdCl_2$dppf was used as the catalyst and CsOAc as the base (entry 8), the desired compound **7** was the major component (57%) of the reaction mixture, with the combined hydrolysis products **5** and **6** accounting for only 12%.

The aryl iodide **10b** did not lead to the desired compound **7** when reacted under the reaction conditions (entries 9 and 10) which gave the best results with the bromide **10a**. This is in sharp contrast with literature reports on Suzuki reactions on dialkoxyaryl iodides, where high yields were observed in several cases.[20]

Encouraged by the good result obtained by reacting **10a** with $PdCl_2$dppf and CsOAc in refluxing dioxane (entry 8), we directed our efforts to the identification of a suitable 3-carbamoyl phenylboronic acid derivative with higher solubility in our experimental conditions. We focused our attention on boronic acid esters **13**–**15** (Scheme 4). The pinacol ester **13** is commercially available, while esters **14** and **15** were synthesized in situ by heating **11** with the corresponding diol (see Supporting Information).

Pinacol-derived boronic esters are commonly used in Suzuki coupling reactions due to their exceptional stability while maintaining good reactivity, and many are commercially available, such as **13**. Catechol-derived boronic esters have not received as much attention as their pinacol counterparts due to their easy hydrolysis. For this reason, they have been

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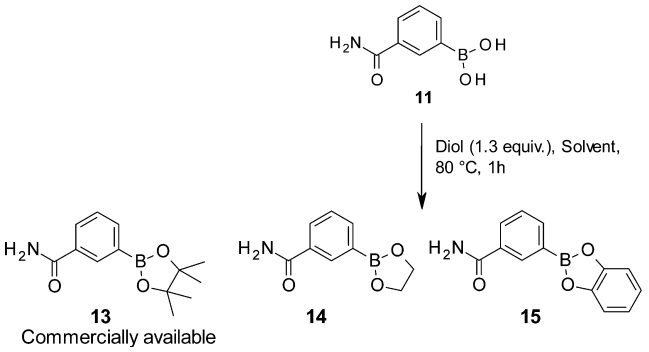
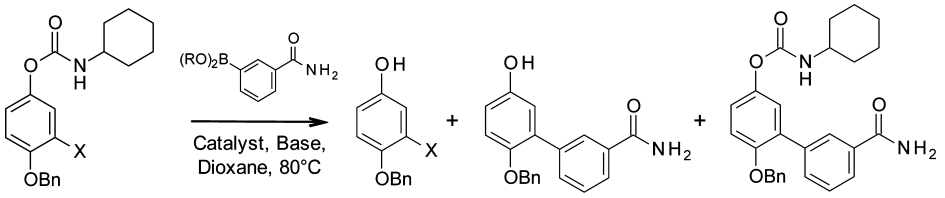
Scheme 4. Preparation of Boronic Acid Esters 14 and 15



used more as protective group of the boronic acid moiety[21] than as reagents for C−C bond formation.[22] Boronic esters derived from ethylene glycol have found more widespread use, particularly in the asymmetric synthesis of chirotropic biaryls, where the steric hindrance of the reagents can affect the enantiomeric excess of the final product.[23] The results obtained in the reaction of compound **10a** with boronic acid esters are reported in Table 3.

A first attempt of Suzuki coupling reaction was conducted with the pinacol ester **13**, 5% $PdCl_2$dppf, and CsOAc as the base in dioxane (entry 1). The reaction proceeded slowly, and significant amounts of the hydrolysis products **5** and **6** were observed. We then tested the ethylene glycol ester **14** (entry 2). Under the previous experimental conditions, the reaction was faster, with only 13% of unreacted starting material **10a** left after 120 min, and the combined hydrolysis products **5** and **6** accounting for only 8% of the reaction mixture.[24] The catechol-derived boronic ester **15** showed comparable reactivity with respect to **14**: almost complete consumption of **10a** was observed after 120 min at 80 °C (entry 3), but the combined hydrolysis products **5** and **6** accounted for 12% of the reaction mixture. Replacement of CsOAc with CsF, KOAc, or K_2CO_3 coupled with the boronic acid ethylene glycol ester **14** resulted in low conversion (entries 4, 5, and 6). Compound **10a** was instead quite reactive in the presence of K_3PO_4, even if hydrolysis to **6** still remained an issue, the latter compound accounting for 23% of the reaction mixture (entry 7). Interestingly, weak bases like K_2HPO_4 and $KHCO_3$ (entries 8 and 9) resulted in very low percentage of the hydrolysis products **5** and **6**, but ca. 40% of the starting material was still present after 120 min. Addition of base and/or catalyst did not

Table 3. Experimental Conditions and Outcome of Suzuki Coupling Reactions of 10a or 10b with Boronic Acid Esters 13, 14, and 15[a]



10a, X = Br
10b, X = I

5, X = Br
12, X = I

6

7

entry	ArX	$ArB(OR)_2$	catalyst	base	T (°C)	**10**[b] (%)	**5** or **12**[b] (%)	**6**[b] (%)	**7**[b] (%)
1	**10a**	**13**	**B**	CsOAc	80	25	18	19	38
2	**10a**	**14**	**B**	CsOAc	80	13	2	6	79
3	**10a**	**15**	**B**	CsOAc	80	7	6	6	81
4	**10a**	**14**	**B**	CsF	80	46	6	2	46
5	**10a**	**14**	**B**	KOAc	80	22	4	5	69
6	**10a**	**14**	**B**	K_2CO_3	80	52	3	3	42
7	**10a**	**14**	**B**	K_3PO_4	80	6	3	23	68
8	**10a**	**14**	**B**	K_2HPO_4	80	40	1	1	58
9	**10a**	**14**	**B**	$KHCO_3$	80	42	1	2	55
10	**10a**	**14**	**B**	Et_3N	80	67	2	2	29
11	**10a**	**14**	**B**	DBU	80	0	70	30	0
12	**10a**	**14**	**B**	CsOAc	60	30	10	3	57
13	**10a**	**14**	**B**	CsOAc	100	3	7	49	41
14	**10a**	**15**	**B**	CsOAc	60	42	6	6	46
15	**10a**	**14**	**A**	CsOAc	80	65	35	0	0
16	**10a**	**14**	**C**	CsOAc	80	9	4	25	62
17	**10a**	**14**	**D**	CsOAc	80	20	18	18	44
18	**10a**	**14**	**D**	K_2CO_3	80	47	2	4	47
19[c]	**10a**	**14**	**B**	CsOAc	80	30	5	7	58
20[d]	**10a**	**14**	**B**	CsOAc	80	19	7	10	64
21[e]	**10a**	**14**	**B**	CsOAc	80	21	18	15	46
22	**10b**	**14**	**B**	CsOAc	80	69	31	0	0

[a]General conditions: 1.5 equiv of pre-formed boronic ester, 2.5 equiv of base, 5% catalyst in anhydrous dioxane at the reported temperature, 120 min; **A**: $Pd(PPh_3)_4$; **B**: $PdCl_2$dppf; **C**: 10% SPhos/5% $Pd(OAc)_2$; **D**: PEPPSI-Ipr. [b]% of compound remaining (**10a** or **10b**) or formed (**5**, **12**, **6**, and **7**) as measured by UPLC/MS analysis after 120 min. [c]Toluene as solvent. [d]2Me-THF as solvent. [e]2.5% of $PdCl_2$dppf.

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improve the conversion of the starting material. Soluble organic bases[25] were also tried. While Et_3N resulted in low conversion (entry 10), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) led exclusively to the formation of hydrolysis products (entry 11).

The effect of the temperature was also investigated. When the reaction of **10a** with **14** was run using $PdCl_2$dppf as the catalyst and CsOAc as the base, the best results were observed at 80 °C (entry 2). At 60 °C the reaction proceeded much more slowly (entry 12), while raising the temperature to 100 °C led to an increase in the reaction rate, along with an extensive hydrolysis of compound **7** to **6** (entry 13). A decrease in the conversion of compound **10a** with a decrease in the reaction temperature was also observed with the boronic ester **15** (entry 14).

To ascertain how the catalyst could affect the reaction outcome, we first reacted compound **10a** with **14** in the presence of $Pd(PPh_3)_4$ and CsOAc (entry 15); under these conditions, only the hydrolysis product **5** was observed. The Buchwald's catalyst Sphos/$Pd(OAc)_2$[26] (entry 16) showed a comparable reactivity to $PdCl_2$dppf (entry 2). Finally, we tested the PEPPSI-Ipr catalyst, which was reported to be a general and effective system for various palladium catalyzed reactions.[27] However, in our hands this catalyst did not perform as well as $PdCl_2$dppf (entry 2), and a high percentage of the hydrolysis compounds **5** and **6** was observed (entry 17). When the reaction was run with K_2CO_3 as the base (entry 18), the conversion of the starting material was comparable to that observed with $PdCl_2$dppf as the catalyst (entry 6) but lower than the one observed with the $PdCl_2$dppf/CsOAc system (entry 2).

The influence of the solvent was briefly investigated by reacting compound **10a** under the reaction conditions of entry 2. Replacement of dioxane with toluene resulted in a lower conversion (entry 19), probably due to the low solubility of CsOAc in this solvent. 2-Methyl-THF was tested as a greener alternative to dioxane; the conversion was higher than in toluene (entry 20), but lower than in dioxane (entry 2).

Finally, an attempt was made to reduce the amount of palladium catalyst to 2.5% (entry 21). Unfortunately, this resulted in a decrease in the conversion of **10a** and the formation of much higher percentage of the hydrolysis products **5** and **6**.

A further attempt was made to replace the aryl bromide **10a** with the iodide **10b** as the substrate in the Suzuki coupling reaction. When **10b** was reacted with the boronic ester **14** in the presence of $PdCl_2$dppf and CsOAc in dioxane (entry 22), the hydrolysis compound **12** was the only product observed after 120 min at 80 °C, in keeping with the result obtained in the reaction with 3-carbamoylphenyl boronic acid.

From the previous work, the best results in the Suzuki coupling reaction were obtained using Wang-Sun's conditions (5% $PdCl_2$dppf, CsOAc in dioxane at 80 °C) with the boronic acid esters **14** and **15**. As the boronic acid ester **15** leads to the formation of catechol, which was difficult to separate from the final product, the ester **14** was selected for further scale-up of the reaction. Starting from these experimental conditions, a final optimization effort was undertaken to identify the reaction time that simultaneously maximized the conversion of bromide **10a** into compound **7** and reduced the formation of the hydrolysis products **5** and **6**. We found that after 100 min compound **7** and the combined hydrolysis products **5** and **6** accounted for 80% and 7%, respectively, of the reaction mixture (see Supporting Information, Table 1). Therefore, a reaction time of 100 min was selected for the reaction's scale-up.

In conclusion, the scale-up of the Suzuki coupling reaction of **10a** with the boronic acid esters **14** was conducted in dioxane at 80 °C, for 100 min, using 5% $PdCl_2$dppf as the catalyst and CsOAc as the base. Compound **7** was isolated in 66% yield after aqueous workup, extraction with EtOAc, evaporation of the solvent to small volume, precipitation with MeCN, and recrystallization from the same solvent. This step was repeated several times starting from up to 33 g of **10a**, and showed good reproducibility.

2.3. Debenzylation of 7 to 2 (URB937). The final step of the synthesis consisted of the removal of the *O*-benzyl group from intermediate **7**. This reaction was previously performed on a 2 g scale by catalytic hydrogenation with H_2 (4 atm), 10% Pd/C in a mixture of EtOAc and MeOH as solvent. As the high pressure apparatus required for scaling up this reaction was not available in our laboratories, we decided to run a transfer hydrogenation reaction.

The different solubility of the starting material **7** and of **2** in the solvents commonly used in hydrogenation reactions, prompted us to carefully verify the compounds' solubility in order to avoid the formation of precipitate during the reaction. Alcohols like MeOH, EtOH, or *i*PrOH solubilize **2** well, while the starting material **7** is sparingly soluble in these solvents. Ethereal solvents like THF or dioxane solubilize both **7** and **2**. Dioxane was selected for its higher boiling point that allows for a safer and faster reaction.

Many common reducing agents[28] were tested and the results are summarized in Table 4. Cyclohexene[29] gave a fast and efficient conversion of the starting material only when used as cosolvent (Table 4, entries 1−3). The more reactive γ-terpinene allowed reducing the amount of reducing agent to 10 equiv (entry 4). Surprisingly, its conjugated diene isomer, α-phellandrene, performed poorly, with only 23% conversion of the starting material observed under the same reaction conditions (entry 5). Transfer hydrogenation reaction with poly(methylhydroxysiloxane) (PMHS)[30] in dioxane ran to

Table 4. Experimental Conditions and Conversion of Transfer Hydrogenation Reactions of Intermediate 7

7 URB937, **2**

entry	reducing agent	solvent	equiv	*T* (°C)	*t* (min)	conversion[a] (%)
1	cyclohexene	dioxane	10	80	180	/
2	cyclohexene[b]	dioxane	–	80	60	100
3	cyclohexene[b]	THF	–	65	150	100
4	γ-terpinene	dioxane	10	80	60	100
5	α-phellandrene	dioxane	10	80	60	23
6	PMHS	dioxane	10	80	60	100
7	HCO_2H/Et_3N[c]	–	–	80	300	74

[a]% conversion of compound **7** as measured by UPLC/MS analysis. [b]Cyclohexene/solvent 1:3 (v/v). [c]Used as solvent.

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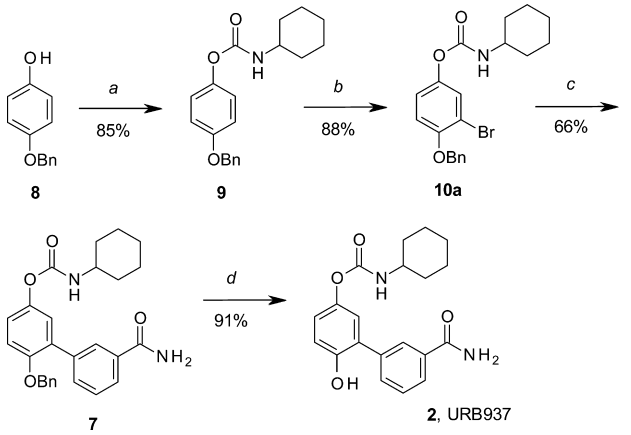
completion in 60 min (entry 6), but the removal of excess polymeric reagent made the work-up difficult. The use of HCOOH as reducing agent in Et_3N as the solvent[31] led to incomplete conversion of the starting material even after 300 min (entry 7). On the basis of these results, cyclohexene was selected due to its low boiling point, that allows easy removal, and low cost. This reaction was repeated several times starting from up to 32 g of **7**.

After debenzylation, compound **2** was obtained as white foam after filtration of the catalyst and removal of the solvents. Treatment with MeCN led to the formation of a white powder consisting of a 1:1 mixture of compound **2** and MeCN, as determined by NMR analysis. Several prolonged drying procedures failed to remove MeCN, thus suggesting that a solvate was likely formed. According to the ICH Q3C guidelines,[32] MeCN is a class 2 solvent, and therefore its content in pharmaceutical products should be limited because of inherent toxicity. To remove MeCN, the solid was dissolved in absolute EtOH and then precipitated with H_2O as a free-flowing white powder in 91% yield. The compound showed >99% purity by UPLC/MS analysis, >98% purity by quantitative NMR (1.5% EtOH was the only impurity observed in the spectrum). The high percentage of the metal catalyst in the Suzuki coupling reaction raised the concern for the palladium content in the final product. Therefore, compound **2** was subjected to inductively coupled plasma−mass spectrometry (ICP-MS) analysis: gratifyingly, the palladium content[33] was found to be $\leq$0.1 ppm, well below the 10 ppm limit set for drug substances.[34]

In conclusion, a total of 100 g of URB937 was prepared in 45% overall yield via a four-step synthesis. The optimized synthesis is summarized in Scheme 5.

Scheme 5. Optimized Synthesis of URB937



(a) *c*-hexNCO (1.2 equiv), Et_3N (0.6 equiv), EtOH/MeCN, 22 °C, 16 h; (b) NBS (1.4 equiv), DMF, 75 °C, 16 h; (c) **15** (1.5 equiv), 5% $PdCl_2$dppf, CsOAc (2.5 equiv), dioxane, 80 °C, 100 min; (d) 10% Pd/C, cyclohexene/dioxane 3:10, 80 °C, 120 min.

3. CONCLUSIONS

We developed a new synthetic route to the *O*-arylcarbamate URB937 that allowed the preparation of this compound on a multigram scale. The key step of the synthesis is the construction of the biphenyl core of URB937 by a Suzuki coupling reaction. We optimized the reaction conditions by investigating the influence of solvent, base, catalyst, aryl boronic species, and reaction time. Although a relatively high catalyst loading was required for optimal yield, the palladium content in the final product was in the sub-ppm range. This four-step procedure proved to be robust and reproducible, required no chromatographic purifications, and provided URB937 in 45% overall yield.

4. EXPERIMENTAL SECTION

Solvents and reagents were obtained from commercial suppliers and were used without further purification. Anhydrous dioxane was purchased from Sigma Aldrich. For simplicity, solvents and reagents were indicated as follows: acetic acid (AcOH), acetonitrile (MeCN), Celite (diatomaceous earth), cesium acetate (CsOAc), dimethylsulfoxide (DMSO), ethanol (EtOH), ethylacetate (EtOAc), *N*-bromosuccinimmide (NBS), nitrogen (N_2), *N*,*N*-dimethylformamide (DMF), palladium on carbon (Pd/C), triethylamine (Et_3N), and water (H_2O). Melting points are uncorrected. NMR experiments were run on a Bruker Avance III 400 system (400.13 MHz for ^1H, and 100.62 MHz for ^{13}C), equipped with a BBI probe and *Z*-gradients. Spectra were acquired at 300 K, using deuterated dimethylsulfoxide (DMSO-d_6) or deuterated chloroform ($CDCl_3$) as solvents. Chemical shifts for ^1H and ^{13}C spectra were recorded in parts per million using the residual nondeuterated solvent as the internal standard (for $CDCl_3$: 7.26 ppm, ^1H; 77.16 ppm, ^{13}C; for DMSO-d_6: 2.50 ppm, ^1H; 39.52 ppm, ^{13}C). All compounds except **15** were characterized by ^1H NMR, ^{13}C NMR, $^1H-^1H$-MQF-COSY, and $^1H-^{13}C$-HSQC. Structure of compounds **10a** and **10b** was determined by ^1H-NOESY experiments. UPLC/MS analyses were run on a Waters ACQUITY UPLC/MS system consisting of a SQD (single quadropole detector) Mass Spectrometer (MS) equipped with an electrospray ionization (ESI) interface and a photodiode array detector. PDA range was 210−400 nm. Chromatographic analyses were performed on an ACQUITY UPLC HSS T3 C_{18} column (50 × 2.1 mmID, particle size 1.8 μm) with a VanGuard HSS T3 C_{18} precolumn (5 × 2.1 mmID, particle size 1.8 μm). The mobile phase was: (A) 10 mM NH_4OAc in H_2O, pH 5, and (B) 10 mM NH_4OAc in MeCN/H_2O (95:5) pH 5, gradient 5% to 95% B over 3 min, flow rate 0.5 mL/min, temperature 40 °C. Accurate mass measurement was performed on a Synapt G2 Quadrupole-Tof Instrument (Waters, USA), equipped with an ESI ion source; compounds were diluted to 10 μM in H_2O/MeCN and analyzed. Leucine Enkephalin (2 ng/mL) was used as lock mass reference compound for spectra calibration.

(4-Benzyloxyphenyl)-*N*-cyclohexylcarbamate (9). To a suspension of 4-benzyloxyphenol **8** (50 g, 0.250 mol, 1 equiv) in absolute EtOH (220 mL) in a three-necked 1 L round-bottomed flask, equipped with a 50 mm magnetic stirrer bar, a thermometer, and a 100 mL dropping funnel, was added MeCN (220 mL) under stirring to give a clear brown solution. The addition of MeCN was endothermic and the temperature dropped to +6 °C. Et_3N (20.77 mL, 0.150 mol, 0.6 equiv) was then added in one portion with no observable changes. To this mixture, cyclohexylisocyanate (38.3 mL, 0.300 mol, 1.2 equiv) was added dropwise under stirring over a period of 30 min. The reaction mixture was slowly allowed to reach +22 °C. After 15 min, a precipitate began to form and its quantity increased rapidly. The mixture was stirred at room temperature for 16 h. Absolute EtOH (120 mL) was added and the mixture was cooled to +4 °C with an ice−water bath for 1.5 h, then filtered on a Buchner funnel and washed with cold absolute EtOH (130

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mL). The filter cake was dried in vacuo at 45 °C until stable weight. Light pink solid; 69 g, 85% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61 (d, J = 11.2 Hz, 1H), 7.48−7.29 (m, 5H), 6.99 (m, 2H), 5.09 (s, 2H), 3.29 (m, 1H), 1.95−1.47 (m, 5H), 1.40−1.00 (m, 5H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 155.7, 154.3, 145.2, 137.6, 128.9, 128.3, 128.1, 123.1, 115.6, 70.0, 50.2, 33.0, 25.6, 25.0. UPLC/MS analysis: Rt 3.01 min. MS (ESI): 326 $(M+H)^+$; 324 $(M-H)^-$. HRMS $C_{20}H_{23}NO_3$ $[M+H]^+$: calculated 326.1756, measured 326.1763; Δppm 2.1. Mp: 144−146 °C.

(4-Benzyloxy-3-bromophenyl)-*N*-cyclohexylcarbamate (10a). To a solution of (4-benzyloxyphenyl) *N*-cyclohexylcarbamate **9** (53 g, 0.163 mol, 1 equiv) in DMF (580 mL) in a 2 L three-necked round-bottomed flask, NBS (40.64 g, 0.228 mol, 1.4 equiv) was rapidly added under vigorous stirring and the resulting clear orange solution was heated at 75 °C for 16 h. The reaction mixture was then cooled to +22 °C, transferred in 3 L bottle and cooled to +4 °C with an ice−water bath. Under vigorous stirring, an aqueous solution of sodium thiosulfate pentahydrate (0.3 M, 200 mL) was added over a period of 75 min. A precipitate formed and the mixture was stirred for additional 2 h. The yellow solid was filtered through a Buchner funnel and washed with H_2O (500 mL). The yellow cake was dried in vacuo at 45 °C until stable weight and then transferred in a 2 L one-neck round-bottomed flask and suspended in absolute EtOH (600 mL). The suspension was heated at reflux until a clear yellow solution was obtained. The mixture was maintained at the same temperature for additional 10 min and then allowed to reach +22 °C in about 1 h. A white solid rapidly crystallized out. The flask was cooled at +5 °C for 16 h; the solid was filtered through a Buchner funnel and dried in vacuo at 45 °C until stable weight. Small white needles; 57.6 g, 88% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61 (d, J = 11.2 Hz, 1H), 7.51−7.46 (m, 2H), 7.46−7.29 (m, 4H), 7.18 (d, J = 9.0 Hz, 1H), 7.08 (dd, J = 9.0, 2.7 Hz, 1H), 5.20 (s, 2H), 3.29 (m, 1H), 2.0−1.46 (m, 5H), 1.41−1.00 (m, 5H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 153.9, 152.2, 145.3, 137.1, 128.9, 128.4, 127.8, 126.9, 122.4, 114.6, 111.1, 70.9, 50.3, 32.9, 25.6, 25.0. UPLC/MS analysis: Rt 3.20 min. MS (ESI): 404 $(M+H)^+$, 406 $(M+H)^+$; 402 $(M-H)^-$, 404 $(M-H)^-$. HRMS: $C_{20}H_{22}NO_3Br$ $[M+H]^+$: calculated 404.0861, measured 404.0862; Δppm 0.2. Mp: 136−138 °C.

[4-Benzyloxy-3-(3-carbamoylphenyl)phenyl]-*N*-cyclohexylcarbamate (7). To a solution of 3-carbamoylbenzeneboronic acid **11** (32.7 g, 0.198 mol, 1.5 equiv) in anhydrous dioxane (700 mL) in a three-necked 2 L round-bottomed flask, equipped with a mechanical stirrer and a reflux condenser, ethylene glycol (14.9 mL, 0.264 mol, 2 equiv) was added in one portion under stirring and under a static N_2 atmosphere, and the funnel washed with anhydrous dioxane (100 mL). The reaction mixture was heated at 80 °C to give a slightly turbid solution. The conversion of **11** to **14** was monitored by ^{1}H NMR analysis. (4-Benzyloxy-3-bromophenyl)-*N*-cyclohexylcarbamate **10a** (53.4 g, 0.132 mol, 1 equiv) was then added portionwise, washing the funnel with anhydrous dioxane (200 mL), followed by the addition of CsOAc (63.5 g, 0.330 mol, 2.5 equiv) in one portion and, after 5 min, $PdCl_2$diphenylphosphinoferrocene (4.8 g, 6.61 mmol, 0.05 equiv). The mixture turned rapidly from red to a dark brown color. Heating was continued for 100 min at 80 °C, then the mixture was allowed to cool to +22 °C and EtOAc (800 mL) was added. The reaction mixture was transferred through a cannula into a mixture of a 3% aqueous solution of citric acid (2 L) and EtOAc (500 mL), in a 5 L bottle, kept under vigorous stirring. The resulting mixture was stirred for 2 h, the content was transferred into a 3 L separatory funnel, and the two phases separated. The organic phase was concentrated to yield a brown oil which upon treatment with MeCN (700 mL) led to the formation of a precipitate. The suspension was stirred at room temperature for 16 h and then filtered through a Buchner funnel and washed with MeCN (100 mL). In a 2 L one-neck round-bottomed flask, the crude was suspended in MeCN (1.6 L) and the mixture was heated at reflux to obtain a clear solution, which was maintained at the same temperature for 15 min. The solution was then allowed to cool to room temperature in about 60 min and the compound rapidly crystallized out. The solid was filtered through a Buchner funnel and dried in vacuo at 45 °C until stable weight. Light grey solid; 32.3 g, 55% yield. Concentration of the mother liquor (150 mL) allowed the production of a second crop of product. Total amount: 38.7 g, 66% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (m, 1H), 8.01 (bs, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.48 (t, J = 7.7 Hz, 1H), 7.43−7.25 (m, 5H), 7.18 (d, J = 8.9 Hz, 1H), 7.09 (m, 2H), 5.13 (s, 2H), 3.29 (m, 1H), 1.46−2.0 (m, 5H), 1.41−1.00 (m, 5H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.3, 154.2, 152.6, 145.3, 137.7, 137.5, 134.8, 132.5, 130.5, 128.8, 128.3, 128.1, 127.7, 126.8, 124.2, 122.4, 114.3, 70.6, 50.2, 33.0, 25.6, 25.0. UPLC/MS analysis: Rt 2.76 min. MS (ESI): 445 $(M+H)^+$. HRMS: $C_{27}H_{28}N_2O_4$ $[M+H]^+$: calculated 445.2127, measured 445.2136; Δppm 2.0. Mp: 187−189 °C.

[3-(3-Carbamoylphenyl)-4-hydroxyphenyl]-*N*-cyclohexylcarbamate (2, URB937). To a suspension of [4-benzyloxy-3-(3-carbamoylphenyl)phenyl] *N*-cyclohexylcarbamate **7** (32.3 g, 0.073 mol, 1.0 equiv) in dioxane (1L) in a 2 L three-necked round-bottomed flask, equipped with a magnetic stirrer bar, cyclohexene (300 mL) was added under a static N_2 atmosphere. The suspension was heated at 50 °C for 15 min in order to ensure complete dissolution. The mixture was allowed to cool to +22 °C and then 10% wet Pd/C (10g) was carefully added and the reaction mixture was heated at 80 °C for 120 min. Activated charcoal (7 g) was added and the mixture was allowed to cool to +22 °C. The mixture was filtered through a small pad of Celite and washed with dioxane (200 mL). The clear, colorless solution was concentrated to dryness to afford a white foam, which was treated with MeCN (200 mL) in one portion and under stirring leading to the formation of a white solid. The mixture was stored at +5 °C for 16 h, and then filtered on a Buchner funnel. The white solid was washed with cold MeCN (100 mL) and then dried under vacuum at 45 °C until stable weight. The solid was suspended in absolute EtOH (450 mL) in a 2 L round-bottomed flask, and the suspension heated at 80 °C until a clear colorless solution was obtained (10 min). After cooling to +22 °C, H_2O (1.2 L) was added dropwise over 30 min. A white precipitate rapidly formed. The stirring was maintained for 60 min, then the solid was filtered through a Buchner funnel, using Whatman grade 6 filtering paper, washed with H_2O (200 mL), and dried in vacuo at 30 °C until stable weight. White powder; 23.44 g, 91% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 (m, 2H), 7.80 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.48 (t, J = 7.7 Hz, 1H), 7.35 (bs, 1H), 7.04 (m, 1H), 6.92 (m, 2H), 3.32 (m, 1H), 1.48−2.0 (m, 5H), 1.00−1.41 (m, 5H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.5, 154.5, 151.8, 144.1, 138.3, 134.7, 132.4, 128.5, 128.3, 127.7, 126.4, 123.8, 122.4, 116.7, 50.2, 33.1, 25.6, 25.1. UPLC/MS analysis: Rt 2.14 min.

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MS (ESI): 355 $(M+H)^+$; 353 $(M-H)^-$. HRMS: $C_{20}H_{22}N_2O_4$ $[M+H]^+$: calculated 355.1658, measured 355.1669; Δppm 3.1. Mp: 193−195 °C.

■ ASSOCIATED CONTENT

Supporting Information

Procedures for the preparation of compounds **10b**, **14**, and **15**, copies of NMR spectra of compounds **2**, **7**, **9**, **10a-b**, **14**, and **15**, and reaction time course of the Suzuki coupling reaction of compound **14** with **10a**. This material is available free of charge via Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(24) Under the same experimental conditions, increasing the amount of catalyst to 10% resulted in a faster and slightly cleaner reaction, with 84% of compound **7** formed after 60 min, 10% of starting material **10a** remaining unreacted, and the combined hydrolysis products **5** and **6** accounting for 6% of the reaction mixture. . The high percentage of catalyst, however, raised the concern for possible contamination of the final product with palladium and/or phosphine ligand. Therefore, the optimization of the reaction conditions was performed using 5% catalyst.

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■ NOTE ADDED AFTER ASAP PUBLICATION

This article was published ASAP on February 27, 2013. Changes have been made to the footnotes of Schemes 1 and 5. The corrected version was reposted on March 1, 2013.