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A Scalable Process for the Synthesis of the Bcl Inhibitor Obatoclax

Kenza Daïri,* Yuxing Yao,† Michael Faley,† Sasmita Tripathy, Elise Rioux, Xavier Billot, Daniel Rabouin, Gerson Gonzalez, Jean-François Lavallée, and Giorgio Attardo

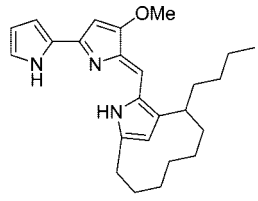
Department of Medicinal Chemistry, Gemin X Biotechnologies Inc., 3576 Avenue du Parc Suite 4310, Montréal, QC H2X 2H7, Canada

Abstract:

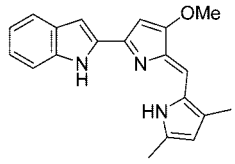
Recently we created the novel indolylprodigiosin derivative 2 (obatoclax) and demonstrated its ability to antagonize multiple members of the B-cell lymphoma (Bcl) family of antiapoptotic proteins. The compound has shown potent anticancer activity in several animal tumor models. Obatoclax is now in Phase 1b and 2 clinical trials directed against multiple hematologic and solid tumor malignancies. To support its clinical development, a new scalable synthesis was required. Obatoclax has been prepared using a three-step synthesis, starting from commercially available 4-methoxy-3-pyrrolin-2-one. The reaction sequence involves a haloformylation reaction followed by a Suzuki cross-coupling reaction with an indole-2-boronic acid. The synthesis is completed by an acid-mediated condensation with 2,4-dimethyl-1*H*-pyrrole.

Introduction

During the course of a screening campaign for small-molecule antagonists of the Bcl family of antiapoptotic proteins using natural product libraries, we identified an extract fraction that was able to inhibit the interaction between Bcl-2 and its counterpart, the proapoptotic Bax protein. Analysis of this fraction revealed that the active ingredient was Streptorubin B (**1**),[1] a prodigiosin derivative first isolated 30 years ago from *Streptomyces* species Y-42.[2] After an intensive structure–activity relationship (SAR) study on the interaction of various prodigiosin analogs with Bcl proteins, coupled with the investigation of their in vivo activity, compound **2** was selected as the lead candidate for clinical trials.[3]

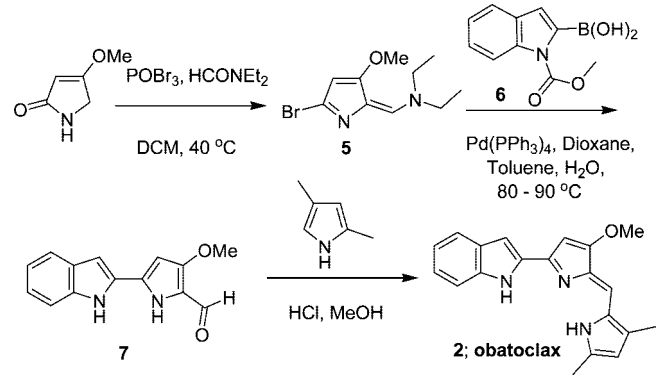


1: Streptorubin B

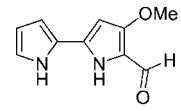


2: obatoclax

Scheme 1. **Improved three-step process of obatoclax (2)**



Early reported syntheses of these tripyrrole systems required the preparation of the 2,2′-bipyrrole aldehyde **3**,[4,5] until the publication in 1996 of a novel approach by d'Alessio and Rossi.[6,7] This new four-step process involved the formation of the pyrromethene moiety **4** which was treated under Suzuki coupling conditions with the desired pyrrole-2-boronic acid.



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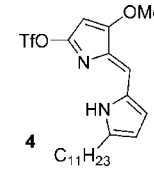

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To further improve this process, a novel three-step scalable route was designed to support the clinical development of obatoclax (**2**). This method incorporates the final biomimetic pyrrole condensation for producing prodigiosin analogues.[8,9]

Results and Discussion

In the first step of the process (Scheme 1) commercially available 4-methoxy-3-pyrrolin-2-one was treated with the

* To whom correspondence should be addressed. Tel: (514) 281-8989. Fax: (514) 281-1065. E-mail: kdairi@geminx.com.

† SAFC Madison, 645 Science Drive, Madison, WI 53711.

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Table 1. **Vilsmeier-Hack haloformylation of 4-methoxy-3-pyrrolin-2-one**

entry	$HCONEt_2$ (eq)	$POBr_3$ (eq)	reflux time (h)	crude yield (%)	purity (%) HPLC[a]	purity (%) weight assay	actual yield[b] (%)
1[c]	1.56	1.91	2	73.1	97.5	77.6	56.7
2[c]	1.56	1.91	3.5	70.2	93.8	71.7	50.4
3[d]	1.48	1.81	4	75.0	95.4	73.1	55.3
4[d]	1.64	2.01	4	82.2	95.6	73.0	60.0
5[d]	1.48	2.01	4	90.0	94.1	62.3	56.2
6[d]	1.64	1.81	3.5	93.0	92.9	64.2	59.7
7[e]	1.56	1.91	3.7	84.4	96.3	70.8	59.8

[a] HPLC method B, monitoring at 350 nm. [b] (crude yield) × (weight assay). [c] Desired amounts of reagents. [d] ±5% of the desired amounts of reagents. [e] Qualification run on 100 g scale.

Table 2. **Suzuki cross-coupling between bromo enamine 5 and indole-2-boronic acid 6**

entry	compd **5** purity (weight assay, %)	compd **7** yield (%)	compd **7** purity[a] (HPLC, %)	reaction conditions
1A	73.1	35	100	1.0 equiv of boronic acid, 10% water/dioxane, fast heating (5.5 °C/min)
1B	77.6	36.8	99.8	same as entry 1A, additional 0.1 equiv of boronic acid after 2.4 h reflux
2	71.7	32.8	99.8	0.9 equiv of boronic acid, 10% water/dioxane
3A	N/A	33	99.8	1.0 equiv of boronic acid, 10% water/dioxane, slow heating rate (0.28 °C/min)
3B	N/A	40.5	99.8	same as entry 3A, fast heating rate (5.5 °C/min)
4A	62.3	40.5	99.7	1.25 equiv of boronic acid, preheat Pd cat., 10% water/dioxane, product very dark color
4B	62.3	46.5	99.4	same as entry 4A, 40% water/dioxane, product very dark color
5A	73.0	38.4	100	1.25 equiv of boronic acid, mix all at room temp, 10% water/dioxane, normal heating rate (<1 °C/min)
5B	73.0	42.1	99.8	1.25 equiv of boronic acid, 30% water/dioxane, fast heating rate (6.5 °C/min)
6A	64.2	39.2	100	mix all at room temp, 1.0 equiv of boronic acid initially, additional 0.25 equiv after 0.5 h reflux, 30% water/dioxane, fast heating rate, no HCl quench
6B	64.2	38.4	100	same as entry 6A, HCl quench
7[b]	70.8	46	100	1.0 equiv of boronic acid initially, additional 0.4 equiv after 0.5 h reflux, 10% water/dioxane, slow heating rate (0.65 °C/min)
8[c]	N/A	48	100	1.3 equiv of boronic acid, 20% water /dioxane, mix all at room temp, heating rate 2.2 °C/min

[a] HPLC method B monitored by total wavelength absorbance (414 ± 370 nm). [b] Reaction performed on 200 g of crude compound **5**. [c] Reaction performed on 150 g of crude compound **5**.

Vilsmeier reagent,[10] obtained by reacting phosphorus oxybromide and *N,N*-diethylformamide, in refluxing dichloromethane (Scheme 1). HPLC analysis of the isolated bromo enamine **5** revealed a purity of 93–97% based on peak area percentage, but weight assay analyses showed a purity of only 62–77%, likely due to non-UV-active impurities. The isolated yields after column chromatography were in the 50–60% range; attempts to increase the yield by modifying the reaction parameters did not lead to any significant improvement (Table 1).

The material was used directly in the next step after a simple methyl *tert*-butyl ether/heptane precipitation to remove solid impurities. A range findings study showed that the process was robust, as determined by carrying the crude material to the next step and consistently isolating compound **7** in high purity (Table 2).

The next step in the process consisted of two sequential chemical transformations: a palladium-catalyzed Suzuki coupling[6,7,11] between the bromo enamine **5** and 1-(*N*-methoxycarbonyl)indole-2-boronic acid (**6**)[12] to give a coupled intermediate, followed by hydrolysis of both the enamine and *N*-methoxycarbonyl groups to afford the indolylpyrrole aldehyde **7** (Scheme 1, Table 2). This transformation, whereby a methyl carbamate on indole was prepared, proved to be a cost-effective alternative to using the commercially available 1-[*N*-(*tert*-butoxycarbonyl)]indole-2-boronic acid.[9] To the best of our knowledge, methyl carbamate protection had never been reported for the preparation of indole-2-boronic acids, and we were pleased to discover that the coupling step using indole **6** not only led to higher isolated

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yields but also reduced the amount of impurities found in the final indolylpyrrole aldehyde **7**.

The Suzuki coupling reaction proceeded rapidly, typically under 1 h at reflux, while the hydrolysis of intermediates required an additional 3–5 h of heating. It became apparent that the coupling step and decomposition of the boronic acid **6** under heating (by loss of the boronic acid group) were competitive processes, but a rapid heating rate helped favor the coupling reaction (Table 2, entries 3A vs 3B and 5A vs 5B). An excess of boronic acid **6** (1.2–1.3 equiv, based on 60% yield for **5**) was usually required for the reaction to reach higher yields; this excess did not result in a reduction of the purity of product **7** nor did it complicate its purification. The use of 20–40% versus 10% water/dioxane increased the reaction yield, as it slowed down the decomposition of the indole-2-boronic acid **6** (Table 2, entries 4A vs 4B, 5A vs 5B, 6A vs 6B, and 8). Variation in the purity of the bromo enamine **5** did not noticeably affect the purity of the isolated indolylpyrrole aldehyde **7** (Table 2). The compound did, however, contain 0.5–2.7% palladium, as determined by an ICP test. That amount was reduced to less than 10 ppm upon treatment with Bu_3P.[13]

The final step of the process involved the acid-mediated condensation[5a] of the indolylpyrrole aldehyde **7** with 2,4-dimethyl-1*H*-pyrrole to provide the HCl salt of obatoclax (**2**). The reaction required a slight excess of both 2,4-dimethyl-1*H*-pyrrole and HCl to reach completion in under 1 h, in spite of the heterogeneous medium that was generated. The salt was isolated by filtration and then treated with ammonium hydroxide to give the free base of obatoclax (**2**). It was preferable to initially isolate the HCl salt of **2** for two reasons: (1) protonation of the pyrrole nitrogen greatly reduced the metal chelating properties of the compound, which decreased the levels of palladium that remained in the final material; and (2) it allowed further increasing the purity of the final material by methanol washes. Once the free base was formed, the material was subjected to a DMF-water precipitation in order to generate amorphous material. The precipitates were collected by filtration and dried under high vacuum at 40–80 °C to afford obatoclax (**2**) as a reddish brown powder that contained less than 10 ppm for both Pd and P as determined by ICP test.

Conclusion

A scalable[14] process of over 90 g of the free base obatoclax (**2**) was developed in three steps with an overall yield of 36–41%. The isolated product showed a low level of Pd (<10 ppm) and high chemical purity (>99.5% by HPLC). The use of the newly reported 1-(*N*-methoxycarbonyl)indole-2-boronic acid (**6**) as opposed to its 1-*N*-(*tert*-butoxycarbonyl) version not only led to a dramatic decrease in the impurity profile of the Suzuki coupling step but also to a reduction in the cost of the overall production of obatoclax. This three-step process was recently applied to the production of 1.5 kg of obatoclax to support clinical studies, for which 1-(*N*-methoxycarbonyl)indole-2-boronic acid (**6**) was obtained commercially.

Experimental Section

General Procedures. Commercially available materials were used as received unless otherwise noted. ^{1}H NMR and ^{13}C spectra were recorded on a Varian 300 MHz Mercury Plus instrument. HPLC chromatography was run on an Agilent 1100 HPLC instrument with a DAD detector. Mobile phases were as follows: method 1, (A) 0.05% TFA in 10% THF/H_2O and (B) 0.05% TFA in 10% THF/CH_3CN with monitoring at 538 nm; method 2, (A) 20 mM ammonium formate/H_2O adjusted to pH 9 with NaOH and (B) CH_3CN with monitoring at 254, 325, and 538 nm. The column used was a YMC J′-sphere ODS-H80 0.4.6 × 150 mm column with 4 μm particles.

[(5-Bromo-3-methoxypyrrol-2-ylidene)methyl]diethylamine (5). A 5 L flask containing dichloromethane (1.15 L) and *N*,*N*-diethylformamide (154 mL, 1.38 mol) was cooled to 0–5 °C in an ice bath. Phosphorus oxybromide (484 g, 1.69 mol) was dissolved in dichloromethane (300 mL) at room temperature (endothermic) and added slowly via addition funnel at a rate which maintained the inner temperature within a range of 0–15 °C (addition time: 11 min). After addition, the reaction mixture was stirred for an additional 10–20 min. 4-Methoxy-3-pyrrolin-2-one (100 g, 0.88 mol) was added (in two portions, over 5 min) at a rate which maintained the inner temperature between 0 and 25 °C. The reaction mixture was stirred for 20 min and then heated to reflux (40 °C) for 3.5 h. The reaction was cooled to 0–5 °C in an ice–methanol bath. Water (170 mL) was added dropwise over 10 min, while maintaining the inner temperature between 0 and 25 °C, followed by 15 wt % aqueous NaOH (11.6 L) over 40 min, while maintaining the inner temperature between 0 and 25 °C. The reaction mixture was stirred at 0–5 °C for 10–20 min. The two layers were separated, and the aqueous layer (pH 7–8) was extracted with dichloromethane (300 mL). The combined organic layers were washed with water (300 mL); this caused the formation of a large amount of solid that remained in suspension above the dichloromethane layer and was easily removed during phase separation. The organic layer was isolated and concentrated in vacuo. 1,4-Dioxane was added to the residue, and the solution was concentrated in vacuo. Methyl *tert*-butyl ether (200 mL) was added with stirring, followed by heptane (100 mL), and the mixture was stirred for 30 min. The supernatant was filtered through a C class funnel and washed with methyl *tert*-butyl ether/heptane (30/15 mL). The filtrate was concentrated to dryness to give **1** as a brown oil, which was used in the next step without purification (180.3 g, assumed yield of 60%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.24–1.37 (6H, m), 3.31–3.46 (2H, q, J = 7.1), 3.76 (3H, s), 4.03–4.18 (2H, q, J = 7.1), 5.58 (1H, s), 6.98 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.6, 14.8, 44.6, 51.2, 58.0, 96.3, 120.6, 133.4, 138.5, 165.1.

1-(*N*-Methoxycarbonyl)indole-2-boronic Acid (6). NaH (49.8 g, 1.30 mol, 60% oil dispersion) was placed in a 5 L flask, washed with pentane (2 × 100 mL), dried under nitrogen, and then suspended in DMF (1.8 L). The suspension was cooled to 0 °C, and a solution of 1*H*-indole (117 g, 1.0 mol) in DMF (200 mL) was added dropwise via an addition funnel over 30 min. Once the addition was complete, the mixture was warmed

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(14) The process no longer requires the use of NaH, diethyl ether, or pentane as described in the Experimental Section. 1-(*N*-Methoxycarbonyl)indole-2-boronic acid is now commercially available from SAFC.

to room temperature and stirred for 2 h. The flask was placed in an ice bath, and the solution was treated dropwise with methyl chloroformate (116 mL, 1.5 mol) via an addition funnel over 40 min. The flask was removed from the ice bath, and the mixture was stirred at room temperature for 18 h. The mixture was poured onto ice and diluted with diethyl ether (2 L). The layers were separated; the aqueous layer was saturated with NaCl and extracted twice with diethyl ether (1 L). The organic layers were combined, washed with brine, dried over anhydrous magnesium sulfate, filtered through a C class funnel, and concentrated in vacuo to provide indole-1-carboxylic acid methyl ester[12] as a colorless oil that was used in the next step without purification.

A solution of indole-1-carboxylic acid methyl ester[12] (1.0 mol) and triisopropyl borate (369 mL, 1.6 mol) in THF (1.7 L) was cooled to –10 °C (internal temperature, salt/ice bath). A solution of lithium diisopropylamide (833 mL, 1.5 mol, 1.8 M in hexanes) was added over 1 h to the mixture via an addition funnel at a rate which maintained the inner temperature within a range of –10 to –5 °C. The reaction was stirred for 3.5 h at –10 °C, after which an aqueous solution of HCl (2 N, 850 mL) was poured into the reaction mixture. The pH of the solution was lowered to 8 by adding aqueous 1 N HCl, and the mixture was diluted with diethyl ether (2 L) and brine (1 L). The layers were separated, and the aqueous phase was extracted with diethyl ether (2 × 1 L). The organic layers were combined, washed with brine, dried over anhydrous magnesium sulfate, filtered through a C class funnel, and concentrated in vacuo to give the crude compound as a beige oil. The compound was then purified by precipitation from ethyl acetate/hexanes, collected by filtration, and washed with pentane to give the pure boronic acid **6** as a white solid (150 g, 70% over 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.17 (s, 3H), 7.09 (s, 1H), 7.27 (td, 1H, J = 7.9, 1.2 Hz), 7.37 (td, 1H, J = 8.5, 1.5 Hz), 7.52 (s, 1H), 7.61 (d, 1H, J = 7.6 Hz), 8.00 (d, 1H, J = 8.5 Hz). ^{13}C NMR (75 MHz, DMSO-d_6) δ 53.8, 113.7, 114.4, 120.7, 122.6, 124.1, 130.4, 136.0, 151.7.

5-(1*H*-Indol-2-yl)-3-methoxy-1*H*-pyrrole-2-carbaldehyde (7). All reaction solvents used at this step were degassed with nitrogen prior to use.

A 3 L three-neck round-bottom flask was purged with nitrogen and loaded with a solution of bromo enamine **5** (144.1 g, 0.424 mol) in 1,4-dioxane (504 mL), followed by toluene (144 mL), palladium acetate (2.8 g, 13 mmol), and triphenylphosphine (13.4 g, 50.9 mmol). The reaction mixture was stirred for 10–20 min, and then 1-(*N*-methoxycarbonyl)indole-2-boronic acid (**6**; 121 g, 551 mmol) was added, followed by water (100 mL) and sodium carbonate (112 g, 1.06 mol). The mixture was heated to reflux (85 °C) for 5.5 h, after which tributylphosphine was added and the stirring continued for an additional 5–10 min. Ethyl acetate (432 mL) and water (432 mL) were added; the reaction mixture was cooled to room temperature and treated with 3 N aqueous HCl (420 mL, over 3 min). The mixture was stirred for 10–20 min. The slurry was filtered through a C class funnel, and the resulting solid was washed with water (3 × 220 mL) and ethyl acetate (3 × 145 mL). The solid was dried under vacuum to give 5-indolyl-3-methoxypyrrole-2-carboxaldehyde (**6**; 81.8 g, 48.1% over two steps). ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.89 (s, 3H), 6.55 (s, 1H), 6.99 (t, 1H, J = 7.1 Hz), 7.09 (s, 1H), 7.11 (t, 1H, J = 7.1 Hz), 7.37 (d, 1H, J = 7.6 Hz), 7.51 (d, 1H, J = 7.6 Hz), 9.39 (s, 1H), 11.28–11.52 (bs, 1H), 11.66–11.96 (bs, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 57.9, 93.2, 100.7, 111.21, 118.6, 119.7, 120.3, 122.3, 128.1, 129.4, 131.7, 136.7, 157.9, 172.98.

2-{2-[(3,5-Dimethyl-1*H*-pyrrol-2-yl)methylene]-3-methoxy-2*H*-pyrrol-5-yl}-1*H*-indole (2, Obatoclax). The indolylpyrrole aldehyde **6** (74.8 g, 311 mmol) was suspended in methanol (1.5 L) and cooled with a tap water bath (16 °C). 2,4-Dimethyl-1*H*-pyrrole (35.5 g, 374 mmol) was added, followed by a solution of 0.8700 M hydrogen chloride in methanol (465 mL, freshly titrated prior to use) in one portion, while maintaining the inner temperature at 18–20 °C. The slurry was stirred for 30 min, and methanol (150 mL) was added to rinse the wall of the flask. The reaction was shown to be complete by HPLC chromatography (method A) after 5 min. The mixture was filtered through a class D frit funnel (total reaction time 1 h 20 min) and washed with methanol (2 × 240 mL). The black salt was transferred into a 2 L three-neck round-bottom flask, methanol was added (1 L), and the mixture was stirred. A concentrated solution of ammonium hydroxide (120 mL) was poured in one portion, and the mixture was stirred for 20 min. Methanol (150 mL) was added to rinse the walls of the flask. After an additional 10 min of stirring, the mixture was filtered through a class D frit funnel. The solid was washed with methanol (2 × 240 mL) and dried under high vacuum at 70 °C for 4 h to give 95 g of crude **3** (yield 95%, HPLC purity 99.8%, method A).

The solid (95 g) was dissolved in DMF (511 mL) and stirred for 20 min. The solution was filtered through a 0.5 μm filter and rinsed with DMF (46 mL). The solution was then slowly added into cold water (2 °C, 1.86 L), and the mixture was stirred for 10 min and then filtered through a class D frit funnel. The solid was washed with water (400 and 800 mL) and dried under vacuum at 40–80 °C to give 2-{2-[(3,5-dimethyl-1*H*-pyrrol-2-yl)methylene]-3-methoxy-2*H*-pyrrol-5-yl}-1*H*-indole (**2**; 93.5 g, 98% recovery, HPLC purity 99.6% (method A), Pd 3 ppm, P <10 ppm). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.78 (s, 3H), 2.23 (s, 3H), 4.08 (s, 3H), 5.66 (s, 1H), 6.32 (s, 1H), 6.72–6.81 (d, 1H, J = 8 Hz), 6.85–7.06 (m, 4H), 7.08–7.12 (s, 1H), 7.43–7.53 (d, 1H, J = 8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.7, 12.3, 58.7, 96.2, 104.8, 111.6, 112.7, 115.8, 119.6, 120.8, 123.4, 126.7, 128.4, 133.8, 134.0, 136.1, 137.9, 141.2, 144.1, 158.7, 168.9.

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