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Highly convergent synthesis of a rebeccamycin analog with benzothioeno(2,3-*a*)pyrrolo(3,4-*c*)carbazole as the aglycone

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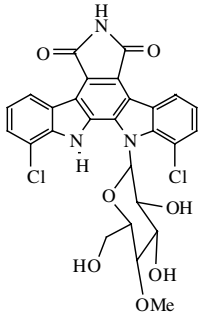
Abstract—A highly convergent, scalable synthesis of the rebeccamycin analog **2** was demonstrated in seven steps and 31% overall yield based on the *N*-protected building block dibromomaleimide **7**. The practical synthesis of other two building blocks, 5,6-difluoro-3-benzothiopheneboronic acid **6** and 5,6-difluoroindole **8**, is described.

1. Introduction

Rebeccamycin **1** and its family members are potent antitumor agents which act by inhibition of protein kinase C and have topoisomerase activity.[1–3] As part of a program for optimization of their biological activity by modification of both the aglycone and the sugar portions, we required a practical route to the rebeccamycin analog **2** with benzothioeno(2,3-*a*)pyrrolo(3,4-*c*)carbazole as the aglycone. In particular, we were interested in the practical synthesis of the *N*-protected aglycone benzothioeno(2,3-*a*)pyrrolo(3,4-*c*)carbazole **3**, which we needed in large quantities.

Our highly convergent synthetic strategy is shown in Scheme 1. We envisioned that the β-glycosidic bond in the target molecule **2** could be formed by Mitsunobu coupling of the aglycone **3** with the benzyl protected D-glucopyranose **4**. The key intermediate, *N*-protected benzothioeno(2,3-*a*)pyrrolo(3,4-*c*)carbazole **3**, could be assembled starting from the three building blocks **6**, **7**, and **8**. Consecutive displacement of two bromine atoms in *N*-protected dibromomaleimide **7** by condensation with the magnesium anion of 5,6-difluoroindole (**8**) followed by Suzuki coupling with 5,6-difluoro-3-benzothiopheneboronic acid (**6**) would afford intermediate **5**. Using our new methodology described previously,[4] the



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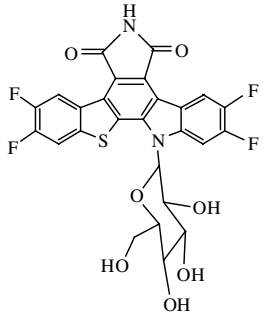

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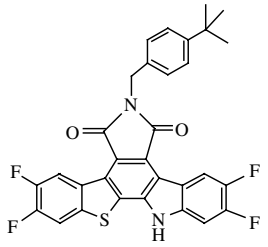

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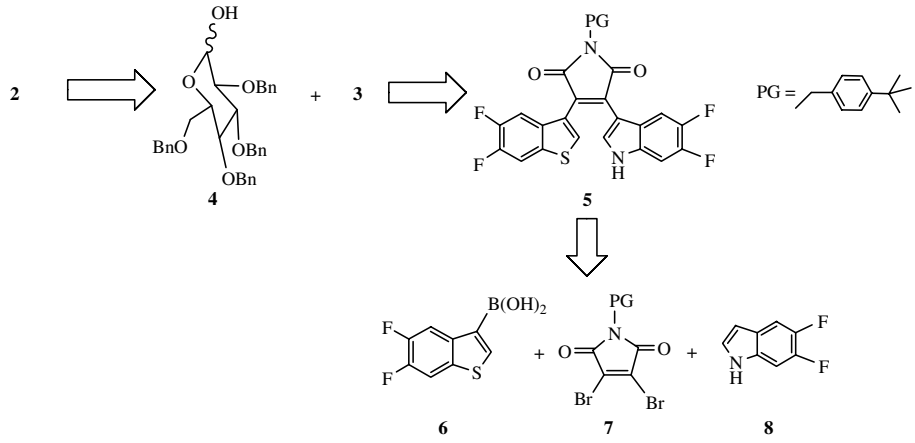


Scheme 1. Retrosynthesis of **2**.

oxidative cyclization of the above assembled intermediate **5** should afford the desired aglycone **3**.

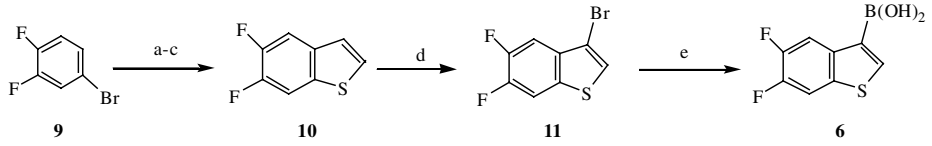
As for the three building blocks, the synthesis of *N*-protected dibromomaleimide **7** has been disclosed in our previous publication.[4] Herein, we disclose a practical synthesis of other two building blocks, 5,6-difluoro-3-benzothiopheneboronic acid (**6**) and 5,6-difluoroindole (**8**). The ultimate assembly of these building blocks into the aglycone, benzothioeno(2,3-*a*)pyrrolo(3,4-*c*)carbazole (**3**) followed by conversion to the final product **2** is described below.

2. Synthesis of 5,6-difluoro-3-benzothiopheneboronic acid 6 (Scheme 2)

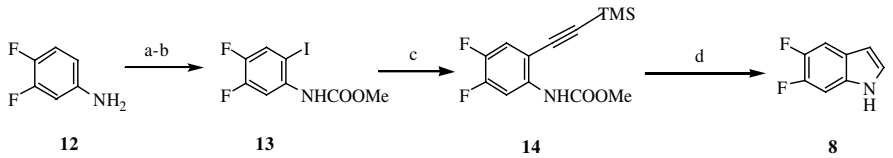
The Grignard reagent, derived from reaction of bromide **9** with magnesium, on quenching with sulfur gave a 76% yield of the thiophenol.[5,6] Treatment with 1-chloro-2,2-diethoxyethane afforded the acetal in 95% yield. Cyclization of the crude acetal with PPA in chlorobenzene gave 5,6-difluorobenzothiophene (**10**) in 67% yield. Bromination (Br_2)[7–9] of **10** gave the expected **11** in low yield (38%). The major impurity was identified as 2,3-dibromo-5,6-difluorobenzothiophene. With NBS as the brominating reagent, significantly less of the dibromide impurity was formed. Bromination of 5,6-difluorobenzothiophene (**10**) with 1.2 equiv of NBS in a mixture of solvents (acetic acid, 10% by v/v in α,α,α-trifluorotoluene) at 80 °C for 4 h afforded **11** in 71% yield. A solvent effect was observed during the preparation of boronic acid **6**; *tert*-butyl methyl ether in place of THF gave much better quality and yield of the product. Lithium–bromine exchange of bromide **11** with *n*-BuLi at −80 °C in *tert*-butyl methyl ether followed by quenching the resulting anion with trimethyl borate, then hydrolysis of the crude borate with 3 N HCl, completed the synthesis of 5,6-difluoro-3-benzothiopheneboronic acid **6**, obtained as a white solid in five steps and 25% overall yield from **9**.

3. Synthesis of 5,6-difluoroindole 8 (Scheme 3)

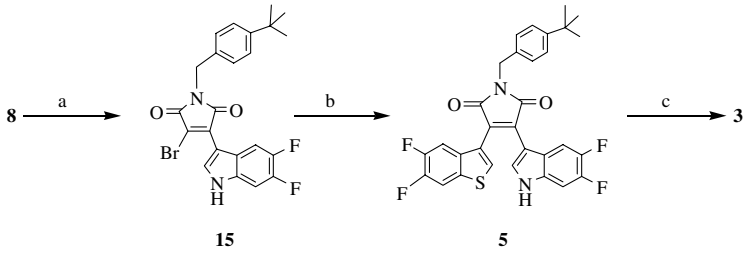
Iodination of 3,4-difluoroaniline (**12**) with ICl in acetic acid gave 2-iodo-4,5-difluoroaniline in 96% yield.[10,11] Without further purification, protection of the amino group by reaction with chloromethylformate afforded carbamate **13** in 89% yield. Heck coupling of carbamate **13** with trimethylsilylacetylene mediated by $Pd(OAc)_2$ (1.5% mol) and tris-*o*-tolylphosphine (2.0% mol) in Et_3N afforded acetylenide **14** in 94% yield. Treatment



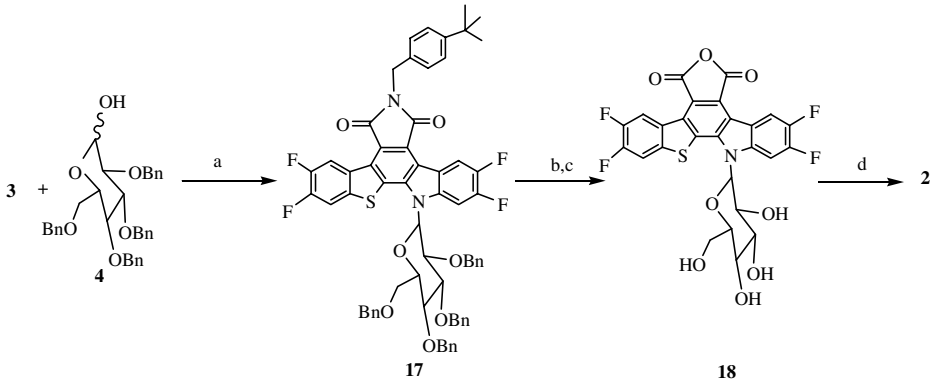
Scheme 2. Reagents and conditions: (a) 1. Mg, 2. Sulphur, 76%; (b) $ClCH_2CH(OEt)_2$, EtONa, reflux 36 h, 95%; (c) PPA, PhCl, reflux, 3 h, 67%; (d) NBS, 1.2 equiv, AcOH, 80 °C, 4 h, 71%; (e) 1. *n*-BuLi, 1.08 equiv, −80 °C, 30 min, 2. $B(OMe)_3$, 2.4 equiv, −80 °C, 1 h, 3. HCl, 3 N, rt, 1.5 h, 72%.



Scheme 3. Reagents and conditions: (a) ICl, HOAc, rt, 0.5 h, 96%; (b) ClCOOMe, pyridine, 0 °C, 2 h, 89%; (c) $Pd(OAc)_2$, 1.5 mol%, $(o\text{-tolyl})_3P$, 2.0 mol%, EtN_3, TMSacetylene, rt, 16 h, 94%; (d) EtONa, EtOH, 70 °C, 14 h, 82%.



Scheme 4. Reagents and conditions: (a) 1. EtMgBr, 2. **7**, rt, 3 h, then 50 °C, 2 h, 91%; (b) **6**, $PdCl_2(PPh_3)_2$, 20 mol%, Na_2CO_3, DME/EtOH, 5:1, reflux 2 h, 82%; (c) air, $Pd(OAc)_2$, 5 mol%, $CuCl_2$, 100 mol%, 90 °C, 6 h, 70%.



Scheme 5. Reagents and conditions: (a) PPh_3, 1.5 equiv, DIAD, 1.5 equiv, THF, rt, 20 h, 95%; (b) $Pd(OH)_2/C$, cyclohexene, EtOH, reflux 7 h; (c) KOH, 4.45 equiv, EtOH, 30 °C 16 h; then conc. HCl, pH < 1.5, 80%; (d) $HN(TMS)_2$, 10 equiv, MeOH, rt, 6 h, 78%.

of **14** with EtONa (70 °C, 14 h) in EtOH[12,13] completed the synthesis of another building block, 5,6-difluoroindole (**7**) in four steps and 66% yield.

4. Assembly of 6, 7, and 8 into the key intermediate 3 (Scheme 4)

With the three building blocks **6**, **7**, **8** in hand, we embarked on their assembly and conversion to the key intermediate **3**. Reaction of 5,6-difluoroindole **8** with *N*-protected dibromomaleimide **7** mediated by EtMgBr at 40 °C for 8 h afforded the bromide **15** in 91% yield. Protection of the indole nitrogen was not necessary for the subsequent Suzuki coupling reaction. The cross-coupling of **15** with boronic acid **6** catalyzed by $PdCl_2(PPh_3)_2$ and Na_2CO_3 as the base gave the coupled product **5** in 82% yield. Oxidative cyclization of **5** using DDQ[14,15] gave the expected product **3**, but in low isolated yield (<50%) due to the poor solubility of **3** and the resultant difficulties in removing reduced DDQ. As an alternative, using atmospheric O_2 as the stoichiometric oxidant and $Pd(OAc)_2$ (5 mol%)/$CuCl_2$ (100 mol%) as the catalysts,[4] afforded the key intermediate **3** in three steps and 52% overall yield from the building block **8**.

5. Synthesis of the target molecule 2 (Scheme 5)

As expected,[16,17] Mitsunobu coupling of the aglycone **3** with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **4** gave almost exclusively the β-anomer **17** in 95% yield. The four benzyl protecting groups in **17** were removed by hydrogenation on $Pd(OH)_2/C$ in the presence of cyclohexene. Without further purification, treatment with 4.45 equiv of KOH in EtOH for 16 h at 30 °C followed by HCl acidification (pH < 1.5) afforded anhydride **18** in 80% yield. Reaction of **18** with 10 equiv of $HN(TMS)_2$ in MeOH at rt for 6 h accomplished our synthesis of target molecule **2**[18] in four steps and 59% yield from the key intermediate **3**.

In summary, we have developed a convergent, scalable synthesis of **2** in seven steps and 31% overall yield based on the *N*-protected building block dibromomaleimide **7**. We also demonstrated the practical synthesis of the two building blocks 5,6-difluoro-3-benzothiophenebronic acid (**6**) and 5,6-difluoroindole (**8**).

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18. Selected MS and ^{1}H NMR data: Building block boronic acid **6**: MS: $(M+H)^+$ 215; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.3 (s, 2H), 8.35 (dd, J = 8.2, 12.9, 1H), 8.33 (s, 1H), 8.21 (dd, J = 8.5, 11.4, 1H) ppm. Building block 5,6-difluoroindole **8**: MS: $(M+H)^+$ 154; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (s, 1H, N–H), 7.49 (dd, J = 7.7, 10.3, 1H), 7.25 (d, J = 2.9, 1H), 7.40 (dd, J = 7.0, 11.3, 1H), 6.51 (d, J = 2.9, 1H) ppm. Compound **3**: $(M+H)^+$ 561; ^{1}H NMR (500 MHz, THF-d_8) δ 11.63 (s, 1H), 9.74 (dd, J = 12.4, 8.1 Hz, 1H), 8.92 (dd, J = 10.8, 8.4 Hz, 1H), 7.88–7.85 (m, 1H), 7.45 (d, J = 8.1 Hz, 2H), 7.40–7.35 (m, 3H), 4.88 (s, 2H), 1.3 (s, 9H) ppm. Final product **2**: MS: yellow solid; $(M+H)^+$ 577; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.52, 11.48 (s, 1H), 9.74, 9.48 (dd, J = 12.7, 8.1 Hz, 1H), 8.95, 8.91 (dd, J = 11.2, 8.5 Hz, 1H), 8.31, 8.00 (dd, J = 10.3, 7.7 Hz, 1H), 8.22, 7.90 (dd, J = 12.2, 6.9 Hz, 1H), 6.14, 6.05 (d, J = 8.9 Hz, 1H), 5.30–4.78 (br s, 2H), 4.08–3.28 (m, 8H) ppm.