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Tetrahedron Letters 49 (2008) 2351–2354
Tetrahedron Letters

Synthesis of RHPS4 via an anionic ring closing cascade

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Received 2 January 2008; revised 28 January 2008; accepted 15 February 2008
Available online 19 February 2008

Abstract

A new and convergent synthesis of the potent telomerase inhibitor RHPS4 is presented. The key step is the construction of the pentacyclic framework via an anionic ring closing cascade in which two new rings are formed.

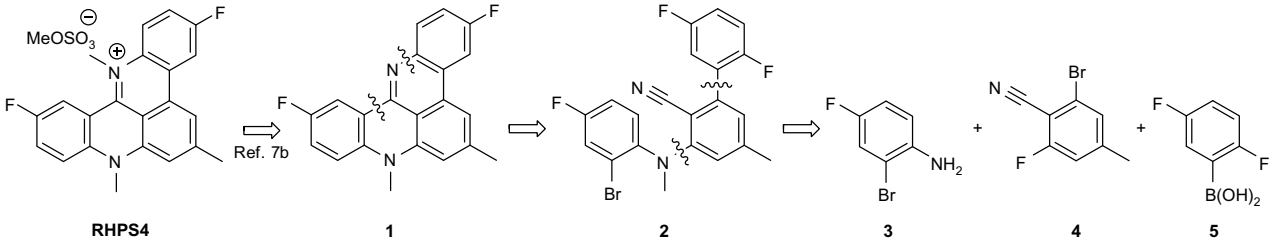
Keywords: Antitumour agents; Cyclizations; Fused-ring systems; Nucleophilic aromatic substitutions; Ring closure

1. Introduction

Telomerase inhibitors are an emerging class of compounds that show potential in the fight against cancer.[1] Their mode of action is based on the following principle: telomeres cap the terminal ends of chromosomes with a repetitive sequence of DNA base pairs (TTAGGG in mammals). During replication 50–200 base pairs are lost in each cycle, thereby shortening the chromosome, which eventually leads to cell death. Telomerase restores telomere length and is up-regulated in most human cancers, thereby allowing the tumour cells to proliferate uncontrolled. Thus, the inhibition of telomerase prevents the tumour cell from circumventing this growth-control mechanism.

RHPS4 (see Scheme 1) is a potent inhibitor of telomerase ($IC_{50} = 0.33\ \mu M$).[2] It is believed that it mediates its effect via intercalation and stabilization of G-quadruplex DNA in the telomere.[3] It shows acceptable pharmaceutical properties and is being evaluated as a candidate for clinical development.[4]

RHPS4 was first synthesized via a very intriguing dimerization of a quinaldinium salt.[2,5] Although this procedure gives access to gram quantities of material it lacks flexibility, that is, it is limited to RHPS4 and very similar analogues. Other synthetic efforts towards RHPS4 and substituted analogues thereof have focused on constructing the pentacyclic core of RHPS4 (**1** in Scheme 1). Subsequently, **1** can be converted to RHPS4 via methylation with



Scheme 1. Retrosynthetic analysis of RHPS4 using an anionic cascade ring closure as the key step.

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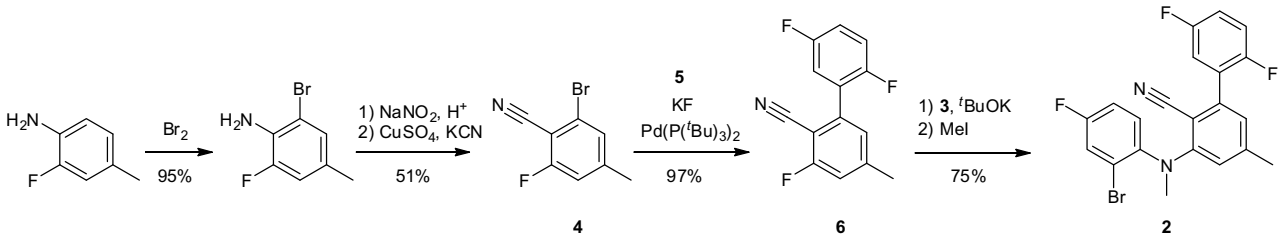
doi:10.1016/j.tetlet.2008.02.074



Scheme 2. Synthesis of key intermediate **2** in four steps from 2-fluoro-4-methylaniline.

dimethyl sulfate.[7b] Previous efforts towards **1** have relied primarily on two different approaches: thermal extrusion of nitrogen from triazolyl-substituted acridines at elevated temperatures[6] and palladium-mediated derivatization of 1-substituted acridin-9(10*H*)-ones followed by a condensation reaction to form the pentacyclic ring system.[7]

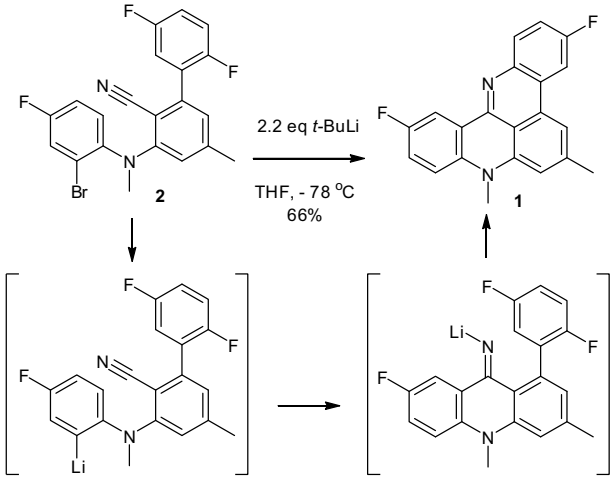
Herein a radically different and flexible synthesis of the pentacyclic core (**1**) of RHPS4 is presented. It is based on an anionic ring closing cascade reaction, previously reported for the synthesis of the parent quinoline-acridine ring system of RHPS4.[8]

Making the two disconnections in **1**, as indicated in Scheme 1, leads to **2** as the key intermediate for the anionic ring closure. Two further disconnections generate the three building blocks needed for the assembly of **2**: 2-bromo-4-fluoroaniline (**3**), 2-bromo-6-fluoro-4-methylbenzonitrile (**4**) and 2,5-difluorophenylboronic acid (**5**). It was envisaged that **4** and **5** initially could be joined in a Suzuki–Miyaura coupling.[9] Selective nucleophilic aromatic substitution of **3**, using the conditions developed by Gorvin,[10] followed by methylation should then lead to **2**. Two of the required building blocks (**3** and **5**) are commercially available, whereas **4** can be prepared in two steps. The entire sequence leading to **2** is outlined in Scheme 2.

Commercially available 2-fluoro-4-methylaniline was brominated, giving 2-bromo-6-fluoro-4-methylaniline[11] in 95% yield. Subsequent diazotization/cyanation gave the corresponding benzonitrile **4** in a modest 51% yield. Suzuki–Miyaura coupling of **4** with **5** proceeded very efficiently to give biaryl **6** in 97% yield, using conditions described earlier for a similar coupling.[12] Selective nucleophilic aromatic substitution of the most reactive fluorine situated *ortho* to the cyano group in **6** by the potassium salt of **3** followed by in situ quenching of the resulting diarylamine anion with methyl iodide gave **2** in 75% yield.

The stage was now set for the ring closure, see Scheme 3. Bromine–lithium exchange should generate an aryl lithium species which would attack the cyano group in a Parham-type cyclization.[13] Subsequent intramolecular nucleophilic aromatic substitution generates the second ring in the sequence.

Gratifyingly, the treatment of **2** with 2.2 equiv of *tert*-butyllithium at −78 °C produced the pentacyclic core of RHSP4 (**1**) in 66% yield after the recrystallization of the crude product.[14] Pentacycle **1** could subsequently be converted to RHPS4 as described by Stevens,[7b] thus completing the synthesis in six steps from 2-fluoro-4-methylaniline.



Scheme 3. Construction of the pentacyclic core of RHPS4 via an anionic cascade ring closure.

It is worth noting that no protecting groups are used at any point in the synthesis and no oxidation/reduction steps are required. With the right building blocks in hand the pentacyclic core is assembled in just three steps. This modular feature makes this synthetic approach to analogues of RHPS4 very attractive. Substituents on different rings can be brought into the sequence at a very late stage, and a large number of analogues of the starting building blocks **3**, **4** and **5** with the required functionality to eventually form the pentacyclic framework are either commercially available or can be accessed in very few steps. Combining **3**, **4**, **5** and substituted derivatives thereof in the desired way gives full control over the substitution pattern of the resulting pentacyclic core.

In conclusion, a new, flexible and highly convergent synthesis of RHPS4 has been developed.

2. Experimental

2.1. 2-Bromo-6-fluoro-4-methylaniline

Bromine (2.26 mL, 44 mmol) in 16 mL of AcOH was added dropwise to a solution of 2-fluoro-4-methylaniline (5.00 g, 40.0 mmol) in 6 mL of MeOH and 6 mL of AcOH

at 0 °C. The reaction mixture was stirred for 1 h, before 1 N NaOH (100 mL) and $Na_2S_2O_3$ (10 g) were added. The mixture was extracted with CH_2Cl_2 (1 × 100 mL + 2 × 50 mL) and the combined organic phases were dried over $MgSO_4$ and concentrated it in vacuo yielding 7.74 g (95%) of 2-bromo-6-fluoro-4-methylaniline[11] as a dark solid. ^{1}H NMR ($CDCl_3$, 300 MHz): 2.21 (s, 3H), 3.94 (br s, 2H, NH_2), 6.72–6.78 (m, 1H), 6.98–7.01 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): 20.2 (d, $J_{C-F} = 2$ Hz), 109.3 (d, $J_{C-F} = 5$ Hz), 114.8 (d, $J_{C-F} = 19$ Hz), 127.6 (d, $J_{C-F} = 2$ Hz), 128.2 (d, $J_{C-F} = 8$ Hz), 130.7 (d, $J_{C-F} = 15$ Hz), 150.8 (d, $J_{C-F} = 240$ Hz). The crude material (>99% pure as judged from TLC, GC–MS and ^{1}H NMR) was used in the following step without further purification.

2.2. 2-Bromo-6-fluoro-4-methylbenzonitrile (4)

The following procedure is a slight modification of that reported earlier by Paek et al.[15] 2-Bromo-6-fluoro-4-methylaniline (4.08 g, 20.0 mmol) was suspended in a mixture of H_2O (8.5 mL) and glacial AcOH (14 mL), and concd H_2SO_4 (3 mL) was added slowly. The mixture was cooled to 0 °C before $NaNO_2$ (1.63 g, 23.6 mmol) dissolved in H_2O (3 mL) was added dropwise with vigorous stirring. In another 500 mL round-bottomed flask, $CuSO_4$ hydrate (4.06 g, 25 mmol) was dissolved in H_2O (16 mL), and KCN (6.9 g, 0.1 mol) dissolved in H_2O (16 mL) was added slowly. $NaHCO_3$ (14 g) and toluene (20 mL) were added before the flask was lowered into an oil bath preheated to 55 °C. To this flask, the above prepared solution of the diazonium salt was added dropwise with vigorous stirring over 10 min. Subsequently, the mixture was stirred for 15 min before being cooled to rt. CH_2Cl_2 (50 mL) was added and the mixture was filtered through Celite into a separating funnel. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with brine (100 mL) and then dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (heptane/EtOAc 9:1) yielded 2.17 g (51%) of **4** as a yellow powder, which could be recrystallized from EtOAc/heptane to give **4** as a white powder, mp 76 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): 2.44 (s, 3H), 7.01 (d, 1H, $J = 9$ Hz), 7.33 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): 21.8 (d, $J_{C-F} = 2$ Hz), 102.3 (d, $J_{C-F} = 18$ Hz), 112.5, 115.6 (d, $J_{C-F} = 20$ Hz), 125.2 (d, $J_{C-F} = 2$ Hz), 139.4 (d, $J_{C-F} = 3$ Hz), 147.1 (d, $J_{C-F} = 9$ Hz), 163.4 (d, $J_{C-F} = 260$ Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): −103.6. Anal. Calcd for C_8H_5BrFN: C, 44.89; H, 2.35; N, 6.54. Found: C, 44.51; H, 2.39; N, 6.41.

2.3. 2′,3,5′-Trifluoro-5-methylbiphenyl-2-carbonitrile (6)

Benzonitrile **4** (960 mg, 4.49 mmol), 2,5-difluorophenylboronic acid **5** (850 mg, 5.38 mmol) and KF (860 mg, 14.8 mmol) were dissolved in dry THF (15 mL). Nitrogen was bubbled through the solution for 10 min before bis(tri-*tert*-butylphosphine)palladium(0) (46 mg, 0.09 mmol) was added. The flask was sealed and lowered into an oil bath preheated to 50 °C, and the reaction mixture was stirred for 1 h. Afterwards, the mixture was partitioned between brine (25 mL) and CH_2Cl_2 (25 mL), and the aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed in vacuo. Flash chromatography (heptane/EtOAc 9:1) yielded 1.075 g (97%) of **6** as an off-white powder, mp 109 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): 2.45 (s, 3H), 7.01–7.21 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): 21.9 (d, $J_{C-F} = 2$ Hz), 99.0 (d, $J_{C-F} = 16$ Hz), 112.8, 116.3 (d, $J_{C-F} = 20$ Hz), 117.2 (dd, $J_{C-F} = 25$, 8 Hz), 117.3 (dd, $J_{C-F} = 25$, 4 Hz), 117.4 (dd, $J_{C-F} = 23$, 8 Hz), 125.8 (ddd, $J_{C-F} = 18$, 6, 8 Hz), 127.1 (dd, $J_{C-F} = 3$, 1.5 Hz), 139.4, 146.1 (d, $J_{C-F} = 7$ Hz), 155.1 (dd, $J_{C-F} = 243$, 3 Hz), 158.1 (dd, $J_{C-F} = 242$, 3 Hz), 163.4 (d, $J_{C-F} = 257$ Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): −122.6, −119.9, −108.1. Anal. Calcd for $C_{14}H_8F_3N$: C, 68.02; H, 3.26; N, 5.67. Found: C, 67.89; H, 3.64; N, 5.40.

2.4. 3-((2-Bromo-4-fluorophenyl)(methyl)amino)-2′,5′-difluoro-5-methylbiphenyl-2-carbonitrile (2)

Potassium *tert*-butoxide (320 mg, 2.85 mmol) was dissolved in dry DMSO (4 mL) at rt. 2-Bromo-4-fluoroaniline **3** (193 μL, 1.69 mmol) was added neat via syringe giving a dark yellow-brown solution. After 10 min at rt the flask was cooled to ~10 °C before **6** (348 mg, 1.41 mmol) dissolved in DMSO (1 mL) was added dropwise, and the mixture was subsequently stirred for 1 h at rt prior to the addition of MeI (600 μL, 9.63 mmol). After 30 min, the mixture was quenched with satd aqueous NH_4Cl (50 mL) and extracted with Et_2O (4 × 50 mL). The combined organic phase was washed with brine (20 mL), dried (Na_2SO_4) and concentrated. Flash chromatography (heptane/EtOAc 9:1) yielded 458 mg (75%) of **2** as a white powder, mp 121 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): 2.40 (s, 3H), 3.36 (s, 3H), 6.76 (d, 2H, $J = 7.8$ Hz), 6.99–7.21 (m, 4H), 7.26 (s, 1H) 7.40 (dd, 1H, $J = 8.1$, 2.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): 22.1, 41.8 (d, $J_{C-F} = 2$ Hz), 100.0 (d, $J_{C-F} = 1$ Hz), 115.6 (d, $J_{C-F} = 23$ Hz), 116.0, 116.5 (dd, $J_{C-F} = 23$, 8 Hz), 116.8 (dd, $J_{C-F} = 25$, 9 Hz), 117.4 (dd, $J_{C-F} = 25$, 3 Hz), 118.1, 121.1 (d, $J_{C-F} = 25$ Hz), 123.1 (d, $J_{C-F} = 2$ Hz), 123.4 (d, $J_{C-F} = 10$ Hz), 127.7 (dd, $J_{C-F} = 18$, 8 Hz), 128.7 (d, $J_{C-F} = 9$ Hz), 140.6, 143.3 (d, $J_{C-F} = 4$ Hz), 143.8, 152.5, 155.2 (dd, $J_{C-F} = 242$, 2 Hz), 158.0 (dd, $J_{C-F} = 242$, 3 Hz), 160.0 (d, $J_{C-F} = 249$ Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): −122.8, −120.8, −115.2. Anal. Calcd for $C_{21}H_{14}BrF_3N_2$: C, 58.49; H, 3.27; N, 6.50. Found: C, 58.60; H, 3.40; N, 6.32.

2.5. 3,11-Difluoro-6,8-dimethyl-8H-quinolino[4,3,2-kl]acridine (1)

tert-Butyllithium, 1.7 M in pentane (720 μL, 1.22 mmol), was added to THF (3 mL) at −78 °C. After 5 min, **2** (240 mg, 0.56 mmol) dissolved in THF (1 mL)

was added dropwise, causing an instant colouring of the solution (brown). After the addition, stirring was continued at −78 °C for 5 min before glacial AcOH (1 mL) was added, causing an instant change of colour to orange. The mixture was warmed to rt and satd aqueous $NaHCO_3$ (25 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were dried (Na_2SO_4) and the evaporation of the solvent gave a crude product as a dark orange powder (220 mg). Recrystallization from EtOAc/heptane yielded 123 mg (66%) of **1** as a yellow-orange powder, mp 279 °C (reported:[7b] 256–258 °C). ^{1}H NMR (DMSO-d_6, 500 MHz): 2.60 (s, 3H), 3.67 (s, 3H), 7.24 (s, 1H), 7.48 (ddd, 1H, $J = 9.4$, 7.6, 3.3 Hz), 7.53 (td, 1H, $J = 8.5$, 2.8 Hz), 7.60 (dd, 1H, 9.2, 4.4 Hz), 7.92 (dd, 1H, $J = 9$, 5.8 Hz), 7.96 (s, 1H), 8.31 (dd, 1H, $J = 10.6$, 2.6 Hz), 8.36 (dd, 1H, $J = 9.4$, 3.3 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): −124.3, −116.1.

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