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# Efficient access to ATP mimics, potential FGF receptor tyrosine kinase inhibitors

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**Abstract**—Nucleophilic opening of bis-epoxide **1** derived from D-mannitol by organolithium species in the presence of boron trifluoride etherate allows the synthesis of enantiopure polyhydroxy tetrahydrofurane skeletons with aromatic moieties in the pseudo-anomeric position. *ortho*-Lithiation and transmetalation are the most appropriate conditions for the preparation of the organometallic derivatives where halogen–metal exchange is unfavorable. 

Fibroblast growth factor receptors (FGFRs) belong to a large family of transmembrane proteins with intrinsic tyrosine kinase activity. These receptors (FGFR1 through FGFR4) play key roles in the control of many cellular processes including cell proliferation and differentiation. Germinal missense mutations in FGFR3 which have been demonstrated to induce constitutive activation of the receptor have been associated with inherited human skeletal dwarfism.[1] Recently certain forms of cancer, in particular carcinomas (bladder and cervix) have been ascribed to somatic mutations of FGFR3 affecting the same amino acids as germinal mutations.[2]

To date, a number of tyrosine kinase inhibitors have been synthesized,[3] but none are reported to be efficient at counteracting the effects of activated FGFR3 in human disorders. Our goal was to design a new class of tyrosine kinase inhibitors able to mimic ATP and to specifically block the constitutive activation of FGFR3 in vitro and in vivo.

We report here preliminary results concerning the synthesis of enantiopure polyhydroxy tetrahydrofurane skeletons with an aromatic moiety in the pseudo-anomeric position in order to occupy the adenine site. In this context, the polyhydroxy tetrahydrofurane is equivalent to a scaffold able on one hand to mimic the D-ribose of ATP and on the other hand to position the aromatic group via a non-hydrolyzable bond. Furthermore, the primary alcohol function of the hydroxymethyl group in 5-position of the tetrahydrofurane skeleton could be subsequently used to introduce a carbon chain to bestow tissue specificity.

The retrosynthesis of the target compounds **2** is outlined in Fig. 1 and involves a one-pot tandem alkylation–cyclization of $C_2$-symmetrical L-*ido* bis-epoxide **1** derived from D-mannitol by action of nucleophiles.

We have previously reported, for the synthesis of glycosidase inhibitors, the nucleophilic opening of bis-epoxide **1** by amines leading to polyhydroxylated azepane or piperidine by *N*-heterocyclization.[4] In order to favor the 5-*exo*-*tet* *O*-cyclization **2** (*path a*), with regard to the 6-*endo*-*tet* *O*-cyclization **3** (*path b*) or eventually to the formation of the acyclic **4** compound, we investigated the opening of bis-epoxide **1** by hetero- and carbon nucleophiles in aprotic medium.

Obtention of the halogen-substituted derivative **2** (Nu = Br) is attractive since it is the precursor towards further transformations (Scheme 1). Dilithium tetrabromonickelate[5] reacted slowly on **1** at room temperature, yielding mainly the tetrahydropyrane **3a** ($[\alpha]_D^{20}$ +8 (*c* 1.0, $CH_2Cl_2$)), whereas lithium bromide afforded regiospecific ring cyclization promoted by a stoichiometric amount of $BF_3{\cdot}Et_2O$ leading to the desired tetrahydrofurane **2a** ($[\alpha]_D^{20}$ +62 (*c* 1.04, $CH_2Cl_2$)).

At the same time, we explored the possibility to introduce in one step an aromatic group at the pseudo-

*Keywords*: bis-epoxide; boron trifluoride etherate; lithiation; transmetalation; tyrosine kinase.

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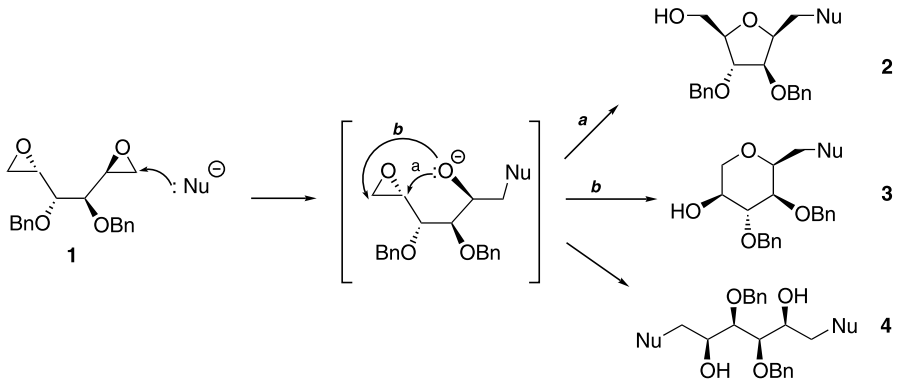
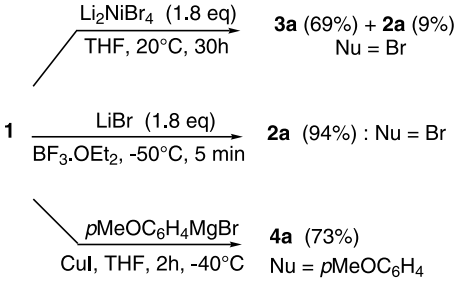



**Figure 1.**




**Scheme 1.**

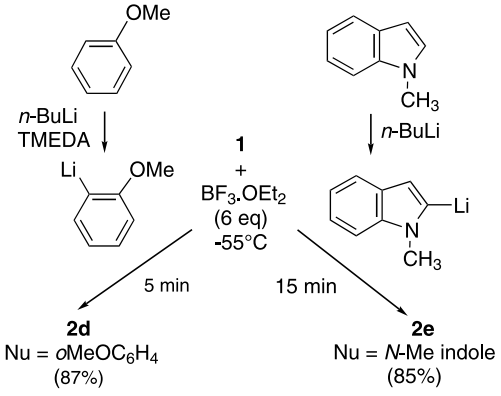
anomeric position. Only symmetrical substitution occurred with the *p*-methoxyphenyl organocuprous[6] leading to **4a**, when the reaction was carried out with either 1 or 2 equiv. of nucleophile with 45 and 73% yields, respectively.

In order to circumvent the bis-opening, we turned our attention towards organolithium species catalyzed by boron trifluoride etherate (1.5 equiv.)[7] which both increase steric hindrance around the epoxide and inhibit activation of a second addition. Thus, highly selective mono-opening was disclosed from $C_2$-symmetric bis-epoxide derived from pentane,[8] for which evolution by cyclization was unfavorable according to the Baldwin's rules.[9] These conditions seemed very attractive to us since $BF_3{\cdot}Et_2O$ did not prevent heterocyclization as shown before for **2a**. Indeed, from bis-epoxide **1**, heterocyclization always proceeds faster than a second addition of the nucleophile and bis-opening leading to the acyclic compound **4** has never been observed.

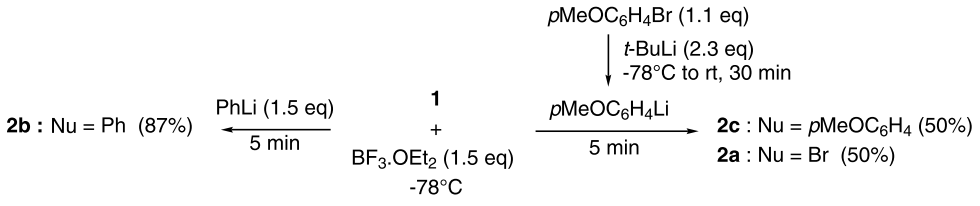
Commercial phenyl lithium reacted quickly with bis-epoxide **1** at −78°C yielding to tetrahydrofurane **2b** ($[\alpha]_D^{20}$ +67 (*c* 1.0, $CH_2Cl_2$)) (Scheme 2). When organolithium was prepared from *p*-bromoanisole by classical halogen–metal exchange with *t*-BuLi (2.3 equiv.),[10] tetrahydrofurane **2c** ($[\alpha]_D^{20}$ +63 (*c* 1.0, $CH_2Cl_2$)) was obtained along with bromo derivative **2a** in a 1:1 proportion.

Thus, the 5-*exo*-*tet* *O*-cyclization is always preferred with organolithium reagents in the presence of boron trifluoride etherate at low temperature, but the presence of bromide in the reaction mixture must be completely avoided. In our hands, different assays to eliminate halogens from reaction medium either by decantation or recrystallization of the organolithium failed.[11] Therefore to introduce various substituents at the pseudo-anomeric position, we studied *ortho*-lithiation and transmetalation from the corresponding organotin derivatives.

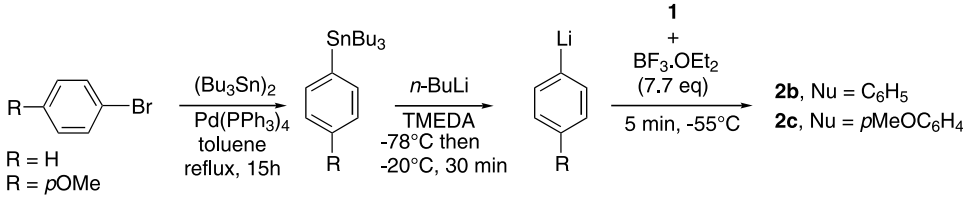
Anisole was easily converted to the corresponding *ortho*-lithiate by *n*-BuLi[10b] in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (Scheme 3).[12] In these conditions the reaction with **1** was carried out with an excess of $BF_3{\cdot}Et_2O$ to avoid total complexation




**Scheme 3.**




**Scheme 2.**



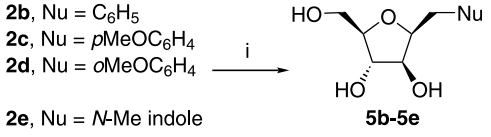

**Scheme 4.**

by TMEDA and led to **2d** ($[\alpha]_D^{20}$ +56 (*c* 1.0, $CH_2Cl_2$)) with good yield.[13] To our knowledge, this is the first example showing the compatibility of these two reagents.

After α-lithiation of *N*-methyl indole (3 equiv.) with *n*-BuLi,[14] addition to bis-epoxide **1** led to **2e** ($[\alpha]_D^{20}$ +79 (*c* 1.0, $CH_2Cl_2$)) with 50% yield which has been improved to 85% by a second addition of α-lithiate solution (2 equiv.).

Transmetalation of commercial tributylphenyltin by *n*-BuLi in the presence of TMEDA[15] followed by addition on **1** afforded **2b** in 79% yield (Scheme 4).[16] We thus applied this method to other organotin species which were obtained from the corresponding bromo aromatic derivatives[17] and easily purified by flash chromatography[18] preventing any contamination of by-product **2a** during the opening of bis-epoxide **1**.

Whereas total deprotection of hydroxyl groups (Scheme 5) was achieved for **2b**, **2c** and **2d** with hydrogen/Pd black in AcOH furnishing **5b–5d** with good yields (82–94%), deprotection of **2e** in these conditions failed. However, catalytic transfer hydrogenation with ammonium formate in the presence of Pd/C 10% in MeOH successfully furnished **5e** with 70% yield.[19]




**Scheme 5.** *Reagents and conditions*: (i) From **2b**–**2d**: $H_2$, Pd black, AcOH, 15 h; from **2e**: Pd/C 10%, $HCO_2NH_4$, MeOH, reflux, 5 h.

In conclusion, we have determined the optimal conditions to obtain enantiopure polyhydroxy tetrahydrofurane skeletons with aromatic moieties in the pseudo-anomeric position by nucleophilic opening of bis-epoxide **1** derived from D-mannitol by organolithium derivatives followed by hydrogenolysis with yields up to 50% for the two steps. We are currently applying the methodology to provide a flexible route to various aromatic and heteroaromatic substituents to obtain FGFR3 tyrosine kinase inhibitors.

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13. Typical experimental procedure for *ortho*-lithiation: To a solution of *n*-BuLi (360 μL, 1.7 M in pentane, 0.612 mmol) in ether (1 mL) and TMEDA (93.3 μL, 0.612 mmol) under argon was added anisole (33.6 μL, 0.306 mmol). After stirring for 30 min, the yellow reaction mixture was added via cannula to a solution of bis-epoxide (50 mg, 0.153 mmol) in THF (1 mL) and $BF_3{\cdot}Et_2O$ (120 μL, 0.947 mmol) at −55°C. After stirring for 5 min, the reaction was quenched with saturated $NaHCO_3$ and the solution was warmed to room temperature. The mixture was then extracted with EtOAc, dried ($Na_2SO_4$)

and concentrated under reduce pressure. Flash chromatography (cyclohexane/EtOAc, 75:25, $R_f$=0.2), afforded **2d** (58.2 mg, 87%) as a colorless oil: $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 2.38 (brs, 1H, OH), 3.0–3.2 (m, 2H, $H_1$), 3.6–3.9 (m containing s at 3.78, 6H, $CH_3$, $H_3$, $H_6$), 4.0–4.1 (m, 2H, $H_4$, $H_5$), 4.32 (dt, $J_{2,3}$=3.5 Hz, $J_{2,1}$=$J_{2,1'}$=7.0 Hz, 1H, $H_2$), 4.39, 4.58 (AB, $J_{AB}$=11.5 Hz, 2H, $CH_2$Ph), 4.48, 4.51 (A′B′, $J_{A'B'}$=11.7 Hz, 2H, $CH_2$Ph), 6.8–7.0 (m, 2H, $H_{arom}$), 7.2–7.4 (m, 12H, $H_{arom}$); CIMS ($NH_3$) $m/z$: 452 ($M$+18, 100%).

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16. Typical experimental procedure for transmetalation: To a solution of *n*-BuLi (360 μL, 1.7 M in pentane, 0.306 mmol) in THF (1 mL) and TMEDA (47 μL, 0.31 mmol) under argon was added tributylphenyltin (155 μL, 0.46 mmol) at −78°C. After stirring for 30 min at −20°C, the reaction mixture was added via cannula to a solution of bis-epoxide (50 mg, 0.153 mmol) in THF (2 mL) and $BF_3{\cdot}Et_2O$ (150 μL, 1.184 mmol) at 55°C. After stirring for 5 min, the reaction was quenched with saturated $NaHCO_3$ and the solution was warmed to room temperature. The mixture was then extracted with EtOAc, dried ($Na_2SO_4$) and concentrated under reduce pressure. Flash chromatography (toluene/EtOAc, from 1:0 to 4:1, $R_f$= 0.3), afforded **2b** (49 mg, 79%) as a colorless oil: $^1$H NMR (250 MHz, $CDCl_3$+$D_2O$) $\delta$ 3.06 (d, $J_{1',2}$=7.0 Hz, 2H, $H_1$), 3.67 (dd, $J_{6,6'}$=11.6 Hz, $J_{6,5}$=3.8 Hz, 1H, $H_6$), 3.74 (d, $J_{3,2}$=3.2 Hz, 1H, $H_3$), 3.81 (dd, $J_{6',6}$=11.6 Hz, $J_{6',5}$=3.0 Hz, 1H, $H_{6'}$), 4.0–4.1 (m, 2H, $H_4$, $H_5$), 4.27 (dt, $J_{2,3}$=3.2 Hz, $J_{2,1}$=7.1 Hz, 1H, $H_2$), 4.38, 4.58 (AB, $J_{AB}$=11.5 Hz, 2H, $CH_2$Ph), 4.51 (s, 2H, $CH_2$Ph), 7.2–7.4 (m, 15H, $H_{arom}$); $^{13}$C NMR (63 MHz, $CDCl_3$) $\delta$ 34.6 ($C_1$), 63.2 ($C_6$), 71.3, 71.8 ($CH_2$Ph) 82.2, 82.5, 82.7, 84.7 ($C_2$, $C_3$, $C_4$, $C_5$), 126.2, 127.5, 127.9, 128.3, 128.5, 129.1 ($CH_{arom}$), 137.3, 137.5, 138.4 ($Cq_{arom}$); CIMS ($NH_3$) $m/z$: 422 ($M$+18, 100%).
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18. Purification of organotin species by flash chromatography using cyclohexane/EtOAc as solvent required the presence of 2% $Et_3N$.
19. Physical data of final compounds: **5b** ($[\alpha]_D^{20}$ +24 (*c* 1.0, MeOH); $^1$H NMR (250 MHz, MeOD) $\delta$ 2.89 (dd, $J_{1,1'}$= 13.6 Hz, $J_{1,2}$=7.0 Hz, 1H, $H_1$), 3.00 (dd, $J_{1',1}$=13.6 Hz, $J_{1',2}$=7.0 Hz, 1H, $H_{1'}$), 3.6–3.8 (m, 4H, $H_3$, $H_5$, $H_6$), 3.99 (brs, 1H, $H_4$), 4.15 (dt, $J_{2,3}$=3.0 Hz, $J_{2,1}$=$J_{2,1'}$=7.0 Hz, 1H, $H_2$) 7.1–7.4 (m, 5H, $H_{arom}$); $^{13}$C NMR (63 MHz, MeOD) $\delta$ 37.8 ($C_1$), 63.6 ($C_6$), 78.3, 80.4, 84.1, 87.7 ($C_2$, $C_3$, $C_4$, $C_5$), 127.1, 129.3, 130.2 ($CH_{arom}$), 140.1 ($Cq_{arom}$); HRMS calcd for $C_{12}H_{17}O_4$ ($M$H$^+$) 225.1127, found 225.1124. **5c** ($[\alpha]_D^{20}$ +26.5 (*c* 1.13, MeOH); $^1$H NMR (250 MHz, MeOD) $\delta$ 2.83 (dd, $J_{1',1}$=13.7 Hz, $J_{1,2}$=6.8 Hz, 1H, $H_1$), 2.94 (dd, $J_{1,1'}$=13.7 Hz, $J_{1',2}$=7.3 Hz, 1H, $H_{1'}$), 3.6–3.8 (m containing s at 3.74, 7H, $CH_3$, $H_3$, $H_5$, $H_6$), 3.98 (brs, 1H, $H_4$), 4.10 (dt, $J_{2,3}$=3.0 Hz, $J_{2,1}$=$J_{2,1'}$=7.1 Hz, 1H, $H_2$), 6.81, 7.20 (2d, $^3J$=8.5 Hz, 4H, $H_{arom}$); $^{13}$C NMR (63 MHz, MeOD) $\delta$ 34.4 ($C_1$), 55.3 ($CH_2$), 63.2 ($C_6$), 77.8, 80.1, 83.9, 87.3 ($C_2$, $C_3$, $C_4$, $C_5$), 114.4, 130.9 ($CH_{arom}$), 131.7, 159.2 ($Cq_{arom}$); HRMS calcd for $C_{13}H_{19}O_5$ ($M$H$^+$) 255.1232, found 255.1231. **5d** ($[\alpha]_D^{20}$ +37.5 (*c* 0.32, MeOH); $^1$H NMR (250 MHz, MeOD) $\delta$ 2.94 (dd, $J_{1,1'}$=13.4 Hz, $J_{1,2}$=6.7 Hz, 1H, $H_1$), 2.98 (dd, $J_{1',1}$=13.4 Hz, $J_{1',2}$=7.0 Hz, 1H, $H_{1'}$), 3.6–3.9 (m containing s at 3.81, 7H, $CH_3$, $H_3$, $H_5$, $H_6$), 3.98 (brs, 1H, $H_4$), 4.20 (dt, $J_{2,3}$=2.9 Hz, $J_{2,1}$=$J_{2,1'}$=6.8 Hz, 1H, $H_2$), 6.8–7.0 (m, 2H, $H_{arom}$), 7.1–7.3 (m, 2H, $H_{arom}$); $^{13}$C NMR (63 MHz, MeOH) $\delta$ 29.8 ($C_1$), 55.5 ($CH_3$), 63.3 ($C_6$), 78.1, 80.1, 82.1, 87.3 ($C_2$, $C_3$, $C_4$, $C_5$), 111.1, 121.2, 128.4, 131.8 ($CH_{arom}$), 127.7, 158.7 ($Cq_{arom}$); HRMS calcd for $C_{13}H_{19}O_5$ ($M$H$^+$) 255.1232, found 255.1237. **5e** ($[\alpha]_D^{20}$ +32 (*c* 1.0, MeOH); $^1$H NMR (250 MHz, MeOD) $\delta$ 3.05 (dd, $J_{1,1'}$=15.4 Hz, $J_{1,2}$=7.0 Hz, 1H, $H_1$), 3.11 (dd, $J_{1',1}$=13.6 Hz, $J_{1',2}$=7.0 Hz, 1H, $H_1$), 3.64–3.74 (m, 2H, $H_6$), 3.68 (s, 3H, $CH_3$), 3.79–3.83 (m, 1H, $H_5$), 3.87 (d, $J_{3,2}$=2.4 Hz, 1H, $H_3$), 4.02 (brs, 1H, $H_4$), 4.51 (ddd, $J_{2,3}$=2.4 Hz, $J_{2,1}$=7.0 Hz, $J_{2,1'}$=6.7 Hz, 1H, $H_2$), 6.8 (s, 1H, $H_{arom}$), 7.2–7.4 (m, 4H, $H_{arom}$); $^{13}$C NMR (63 MHz, MeOD) $\delta$ 26.9 ($C_1$), 29.8 ($CH_3$), 63.6 ($C_6$), 78.5, ($C_3$), 80.4 ($C_4$), 82.3 ($C_2$), 87.7 ($C_5$), 109.8, 120.0, 120.5, 121.5 ($CH_{arom}$), 129.4, 138.8, 139.4 ($Cq_{arom}$); HRMS calcd for $C_{15}H_{20}NO_4$ ($M$H$^+$) 278.1392, found 278.1397.