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Synthesis of SB 222618. A potential PDE IV inhibitor†

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Abstract

PDE IV inhibitor SB 222618 was prepared by regioselective S_N2' addition of **9** to bromoallene **6a** followed by a stereoselective borane reduction of **4** to afford **2** which by a palladium mediated coupling with **3**, delivered SB 222618 (**1**) in good yield.

SB 222618 (**1**) has been a target of synthetic chemists at SmithKline Beecham owing to its potential PDE IV[1] inhibitor activity against inflammatory diseases such as asthma. Apart from its biological activity, this cyclohexanol provided the opportunity to explore the non-obvious construction of the quaternary C_4 of **1** whose retrosynthesis is shown below (Scheme 1).

As depicted in Scheme 1, SB 222618 (**1**) could be obtained via the Sonogashira[2] coupling protocol between heterocycle **3** and alkyne **2**. The substituted cyclohexanol **2** could then be made from ketone **4** by selectively reducing the keto group delivering the desired stereochemistry at C_1. To prepare **4**, we envisioned the possibility of performing a S_N2' addition of cuprate **9** to bromoallene **6a** which would be obtained from the corresponding carbinol **7** coming from treating ketone **8** with lithium acetylide.

The most critical steps in the synthesis of SB 222618 are the preparation of intermediate **4** and further selective reduction of the keto group to deliver **2**. The preparation of bromoallenes is well precedented in the literature. Reagents such as HBr,[3] PBr_3,[4] $SOBr_2$[5] were extensively used to synthesize bromoallenes from propargylic alcohols. Other conditions such as addition of cuprates[6] to propargylic mesylates or tosylates are also known.

Propargylic alcohol **7** was prepared without incident from commercially available cyclohexanedione mono-ethyleneketal **8** by reaction with excess of lithium acetylide[7] (Scheme 2). For the preparation of bromoallene **6a**, we first decided to investigate the S_N2' addition of milder reagents such as $LiCuBr_2$[8] to the corresponding mesylate. This reaction afforded a mixture of regioisomers **6a** and **6b** (2:1).

This poor regioselectivity was later improved by using $SOBr_2$ in the presence of Et_3N as acid scavenger obtaining bromoallene **6a** as the sole product in 90% yield.

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† This work is dedicated to the memory of Dr. Lendon Pridgen

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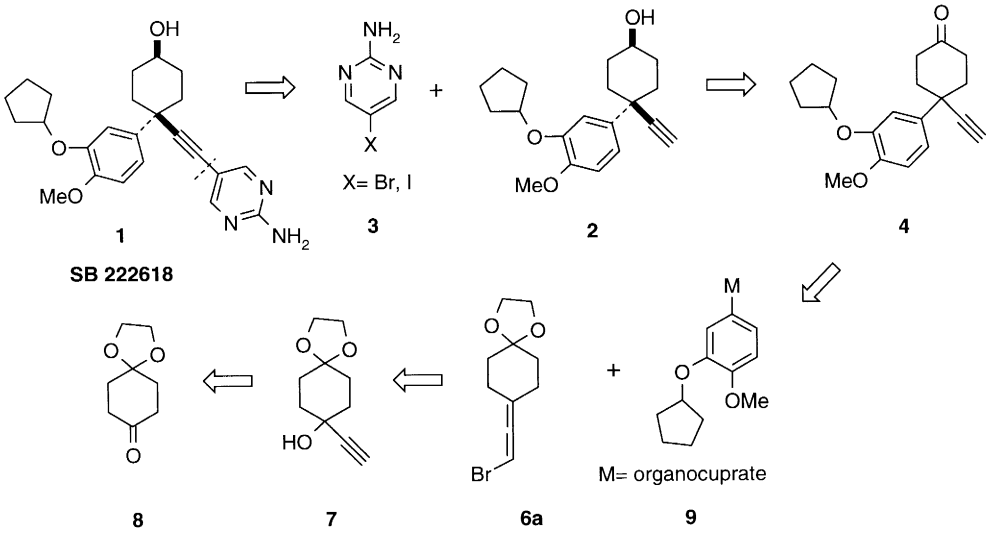
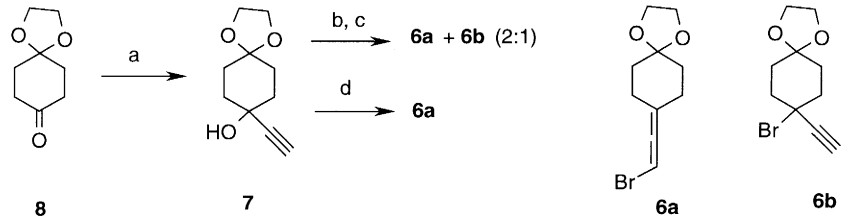
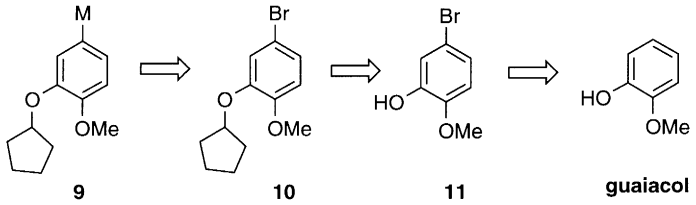


Scheme 1.



Scheme 2. Reaction conditions. (a) lithium acetylide·EDA/dioxane/rt/80%; (b) *n*BuLi/MsCl/THF −60°C; (c) $LiCuBr_2$/−60°C to rt (33% of **6a**); (d) $SOBr_2/Et_3N$/TBME/0°C/90%

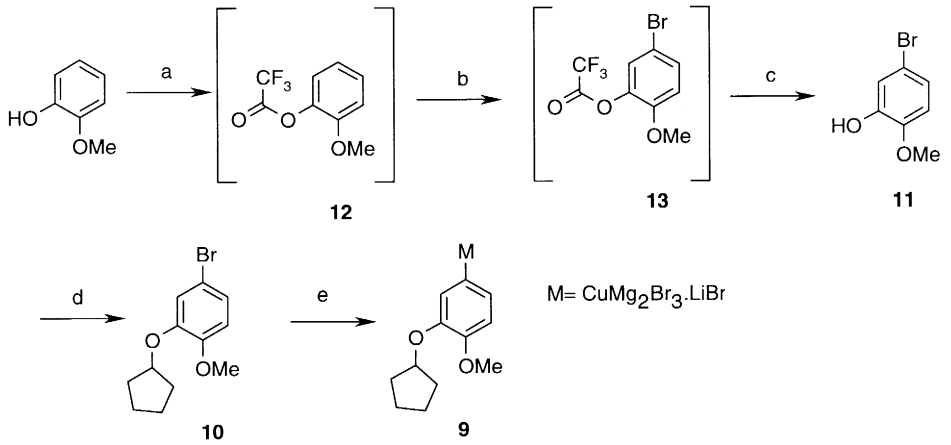
The preparation of cuprate **9** (Scheme 3) would require having bromophenol **11** in place which then would be alkylated to afford **10.** Starting with readily available guaiacol, preliminary attempts to regioselectively brominate the 5 position were unsuccessful and gave, instead, mixtures of 4-bromo-2-methoxyphenol (major), some desired product (**11**) and dibrominated by-products.



Scheme 3.

To overcome this problem we masked the hydroxy group in situ as its trifluoroacetate intermediate **12** (Scheme 4) which without isolation cleanly afforded bromide **13** upon reaction with NBS. Further conversion into **11** after aqueous work-up followed by alkylation with cyclopentyl bromide gave **10** in excellent yield.

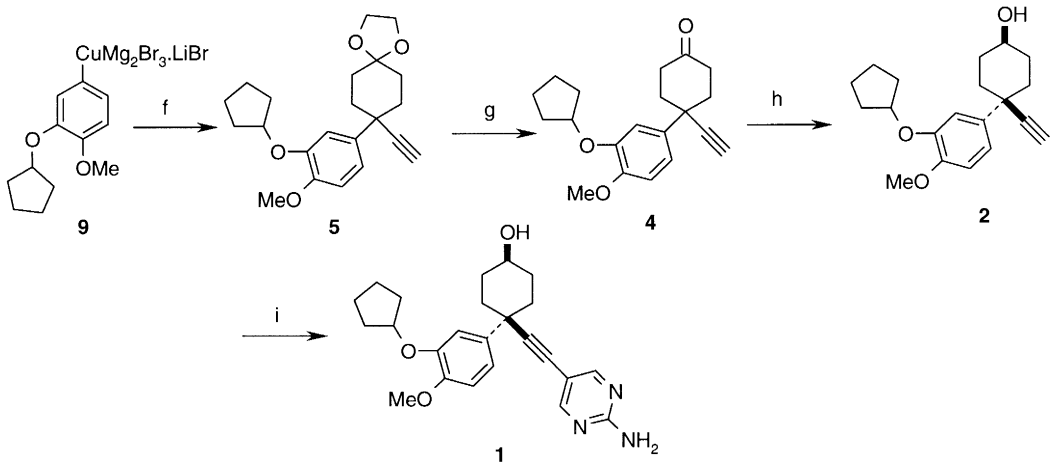
With **10** in hand, we prepared and evaluated the addition of several organocuprates (M=CuLi and M=CuCN) to bromoallene **6a**. The majority of these reagents produced mixtures of regioisomers among other impurities. We then found a report[9] in the literature regarding the fact that Vermeer-type[10]



Scheme 4. Reaction conditions. (a) $(CF_3CO)_2O$/cat. KtOBu/CH_3CN/30 min; (b) NBS/rt/36 h; (c) NaOH (3N) then HCl (3N)/85%; (d) cyclopentyl bromide/K_2CO_3/DMF/100°C/90%; (e) Mg/THF/rt/$CuLiBr_2$/−70°C to rt/80%

organocopper species of formula $RCuMg_2Br_3 \cdot LiBr$ were far more regioselective by adding preferentially in a S_N2' fashion instead of direct bromide displacement.

Hence, **9** (M=$CuMg_2Br_3$.LiBr) was prepared (Scheme 4) and reacted with **6a** to yield the desired product (**5**) which was then hydrolyzed to give ketone **4** (Scheme 5) that was submitted to a variety of reducing agents such as DIBALH, $NaBH_4$, $LiBH_4$ and $BH_3 \cdot THF$ under various conditions. The addition of less hindered hydride donors to cyclohexanones tends to give predominantly the equatorial alcohol. One explanation of the preference for formation of the equatorial isomer involves the torsional strain that develops in formation of the axial alcohol.[11] We found that selectivity decreased in the order: $BH_3 \cdot THF$ (96% d.e.)>$LiBH_4$ (93% d.e.)>$NaBH_4$ (85% d.e.)»>DIBALH. Hence carbonyl reduction with BH_3 at −40°C afforded alcohol **2**[12] in 80% yield. SB 222618 (**1**) was finally obtained by Pd(0)/Cu(I) catalyzed coupling with aminopyrimidine **3**.



Scheme 5. Reaction conditions. (f) **6a**/THF/−70°C to rt/60%; (g) AcOH (50%)/90°C/90%; (h) $BH_3 \cdot THF$/−40°C/80%; (i) **3**/$Pd(PPh_3)_4$/CuI/Et_2NH/DMSO/80%

In summary, we report herein a very efficient synthesis of PDE IV inhibitor SB 222618 (**1**) by using as key step the S_N2' addition of organocuprate **9** to bromoallene **6a** followed by BH_3 reduction of **4** to give

2 in 96% d.e. We also developed a one-pot regioselective method of bromination of 2-methoxyphenol to afford **11**. Application of this methodology to different substituted phenols is currently in progress.

Acknowledgements

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