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Towards the synthesis of osteoclast inhibitor SB-242784

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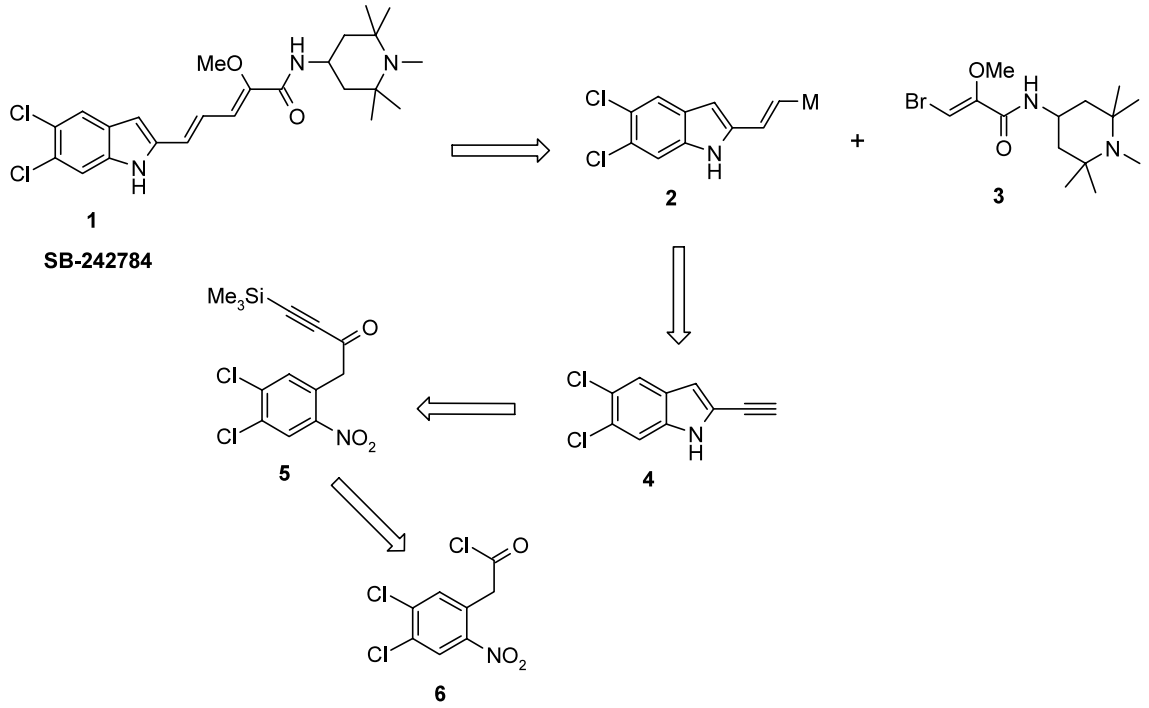
Abstract—Osteoclast inhibitor SB-242784 (**1**) was prepared from pivotal indol intermediate **4**. A 'Stille' cross coupling of organotin **2c** with bromo acrylate **11** afforded diene **12** which was also obtained via a reduction–isomerization process of enyne **16**. Bromoamide **3** was prepared from the corresponding acid **7** which was readily obtained from bromopyruvic acid.

SB-242784 (Scheme 1) has been reported to be a potential osteoclast inhibitor of the vacuolar H^+-ATPase for the treatment of osteoporosis. Although an alternative approach was demonstrated in our labs featuring a 'three-component' palladium-catalyzed process, it was neither cost effective nor suitable for large scale preparation.[1]

We needed a low cost and reliable synthesis by which SB-242784 could be prepared on large scale. Herein we report a highly efficient process for the preparation of this novel osteoclast inhibitor. For the synthesis of **1** we envisioned the assembling of **2** and **3** via a cross-coupling process (Scheme 1), where **2** would come from alkyne **4** which in turn could be prepared from the nitro



Scheme 1.

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compound **5** as a result of a reductive cyclization. Alkylation of **6** with the corresponding alkyne would afford **5**. On the other hand, amide **3** (Scheme 2) could potentially come from **7** which can be obtained from bromopyruvic acid (**9**).

Thus commercially available dichlorophenyl acetic acid (Scheme 3), was nitrated under standard conditions[2] and then converted into the corresponding acid chloride.[3] The reaction of this acid chloride with *bis*-trimethylsilylacetylene[4] in the presence of a stoichiometric amount of $AlCl_3$ afforded **5** which was used as crude in the next step.

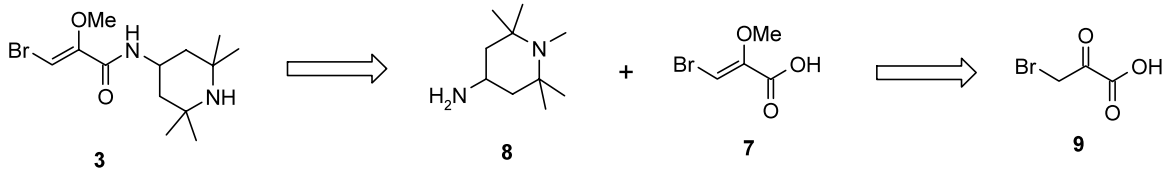
Reduction of the nitro group of **5**[5] followed by basic work-up gave pivotal intermediate **4** in >55% overall yield from **6**. We then thought of using intermediate **2** where M = AlLn or BLn capable to undergo cross-coupling processes with halide **3**. The synthesis of **2** presented more problems than expected since several attempts to prepare various organoboron derivatives[7] **2a** or organoalanes **2b** failed. We then decided to prepare the corresponding organotin, as the plan was to perform a 'Stille'[8] cross-coupling reaction with bromide **3**. Different conditions reported in the literature[9] for the synthesis of tributyltin species were evalutated. In our case the best conditions to prepare **2c**, was exposing alkyne **4** to $(Bu_3Sn)BuCuCNLi_2$[10] which afforded **2c** in 90% yield (Scheme 3).

On the other hand halide **3** was obtained via a ketalization–dehydration process in acidic media (Scheme 4) in 60% overall yield. Subsequent hydrolysis of **11** followed by reaction with amine **8**[6] via the mixed anhydride intermediate afforded **3**.

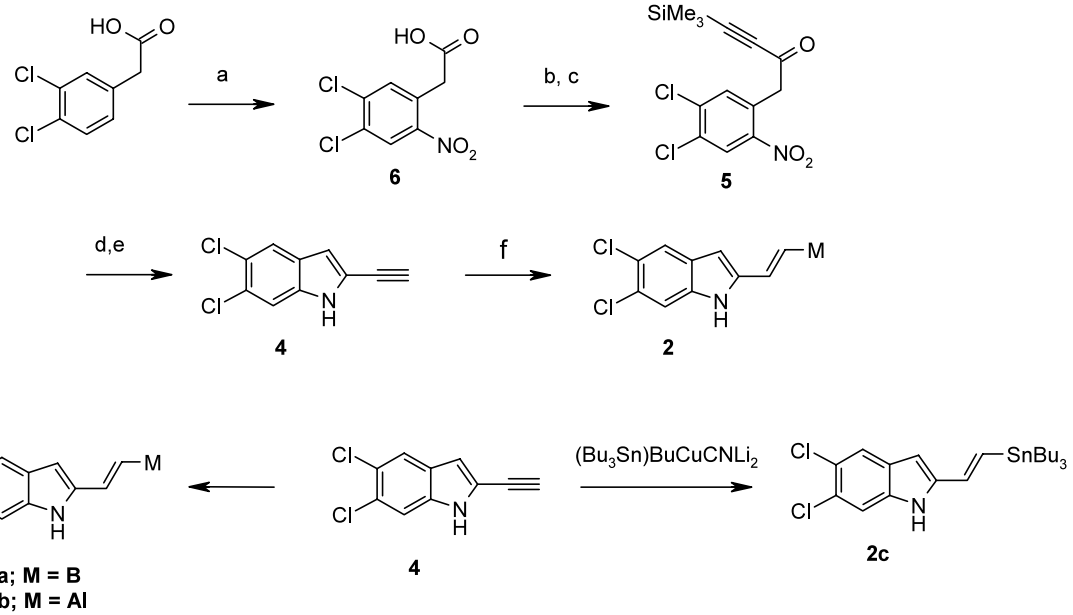
Subsequent reaction of **2c** with ester **11** under the conditions shown in Scheme 5, yielded the desired diene **12** in 80%. When amide **3** was used instead, SB-242784 was obtained in poorer yield (40%).

Although this process was scaled up and proven to be reliable, we had to somehow eliminate the Bu_3SnBr produced in the reaction. Despite our efforts to remove organotin in final drug substance, the levels remained unacceptable. An alternative (Scheme 6) solution to this problem, was the attempted coupling of **14** under Heck conditions[11] with the corresponding acrylates **15a**[12] or **15b**.[13] Unfortunately, none of the desired products were obtained.

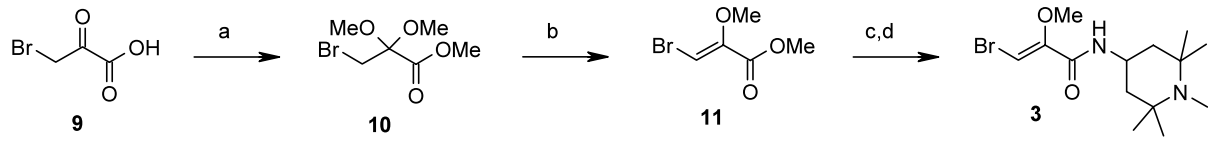
Based on these results, we abandoned this strategy, however we still wanted to utilize **4** as it is stable and easy to prepare. Assessing other possibilities, we real-



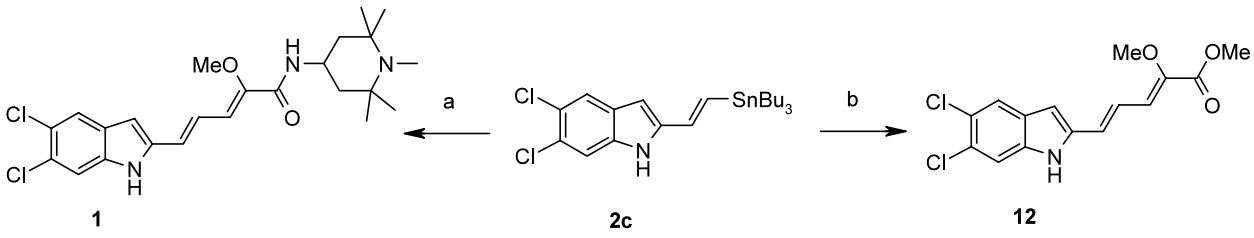
Scheme 2.



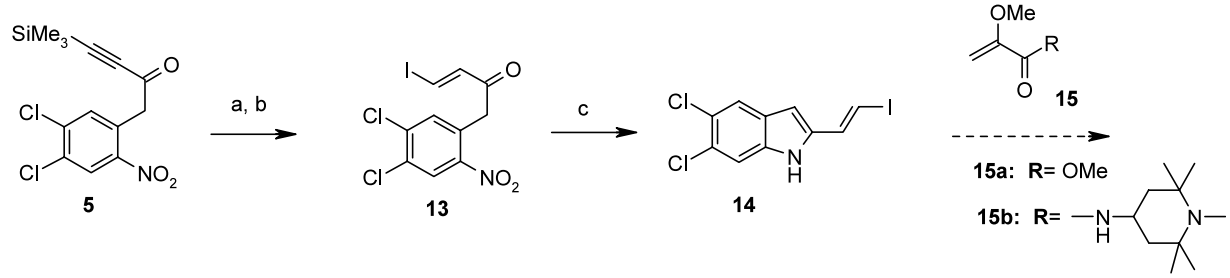
Scheme 3. *Reagents and conditions*: (a) HNO_3, H_2SO_4, 0°C to r.t., 70%; (b) $SOCl_2$, reflux, 2 h; (c) bis-TMS-acetylene, $AlCl_3$, CH_2Cl_2, 0°C; (d) Fe, AcOH, 95°C; (e) NaOH (1N), MeOH, 55% yield from **6**; (f) DIBALH or BLn.



Scheme 4. *Reagents and conditions*: (a) $HC(OMe)_3$, H_2SO_4, MeOH, 82%; (b) *p*TsOH, 200°C, 86%; (c) LiOH, MeOH, 77.5%; (d) $ClCO_2Et$, **8**, Et_3N, CH_2Cl_2, 5°C to r.t., 71%.

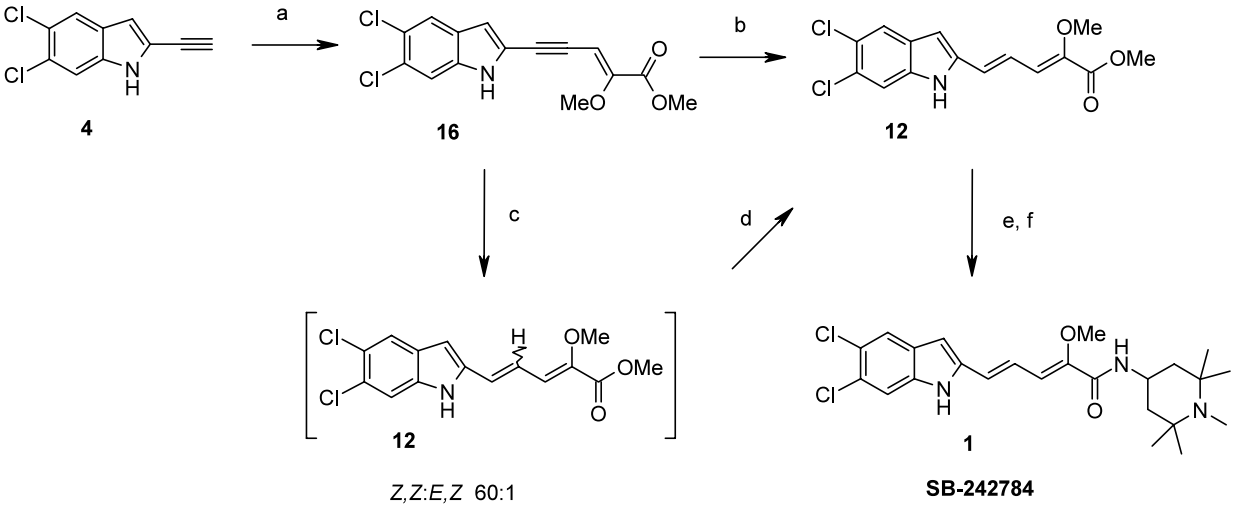


Scheme 5. *Reagents and conditions*: (a) **3**, $Pd(PPh_3)_4$, THF, 60°C, 40%; (b) **11**, $Pd(PPh_3)_4$, THF, 60°C, 80%.



Scheme 6. *Reagents and conditions*: (a) NaOH (1N), MeOH, r.t., 60%; (b) NaI, TFA, CH_2Cl_2, r.t., 68%; (c) Fe, AcOH, 60°C, 70%.

ized that we could prepare enyne **16** by the Sonogashira reaction between bromoester **11** and **4** (Scheme 7) and then selectively reduce the triple bond to afford diene **12** with the desired *E*,*Z* configuration.[14] Accordingly **4** was treated with bromoester **11** in the presence of Pd(0) to afford **16**[15] in good yield. **16** was exposed to $CrSO_4$[16] which unfortunately afforded **12** in only 20% yield after 6 days. We then pursued another alternative hoping to obtain **12** via an isomerization process of the unwanted *Z*,*Z* isomer. For that, enyne **16** (Scheme 7) was reduced via a Lindlar catalyzed hydrogenation obtaining as expected a *Z*,*Z*:*E*,*Z* mixture (60:1).[17] The catalyst was removed by filtration and the filtrate directly treated with catalytic amount of iodine in refluxing toluene which gave **12** as the sole compound in 66% overall yield from **16**. Subsequent hydrolysis of the ester group



Scheme 7. *Reagents and conditions*: (a) $Pd(PPh_3)_4$, CuI, Et_3N, DMF, 75%; (b) $CrSO_4$, DMF, 6 days, 20%; (c) H_2, Lindlar, 60 psi; (d) I_2, toluene, reflux, 16 h, 66% from **16**; (e) LiOH, MeOH; (f) **8**, EDCI, HOBt, CH_2Cl_2, 60% from **12**.

followed by coupling with amine **8**, afforded SB-242784 (**1**) in 60% yield (2-steps).

In conclusion we have described a covergent synthesis of osteoclast inhibitor SB 242784 by using pivotal intermediate **4** as template. From **4** it was possible to obtain diene **12** by a cross-coupling process as well as by the reduction–isomerization of the *Z*,*Z*:*E*,*Z* mixture.

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13. For the synthesis of **15b** see also Scheme 4.
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15. ^{1}H NMR (300 MHz, DMSO, TMS/ppm) δ 7.81 (s, 1H), 7.55 (s, 1H), 6.80 (s, 1H), 6.29 (s, 1H), 4.05 (s, 3H), 3.75 (s, 3H).
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