Substrate Directable Heck-Matsuda Reactions: A Short and Stereoselective Total Synthesis of $S1P_1$ Agonist

Caio C. Oliveira, Emerson Andrade Ferreira dos Santos, Carlos Roque Duarte Correia*

State University of Campinas, Chemistry Institute. –Campinas, São Paulo, Brazil.

**e-mail roque@iqm.unicamp.br*:

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INTRODUCTION

Selective agonists for the sphingosine-1-phosphate receptor subtype 1 ($S1P_1$) constitutes an important class of drugs for the treatment of multiple sclerosis.[1] In 2007, the aminoalcohols **1a-b** were rationally designed to act as $S1P_1$ orally active agonists. The two isomers show good activity *in vitro*, but compound **1b** was more active in *in vivo* tests.[2]

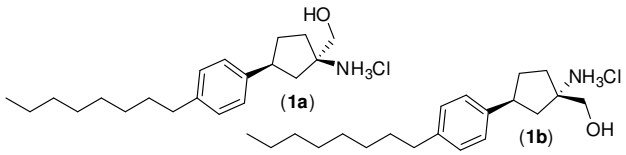
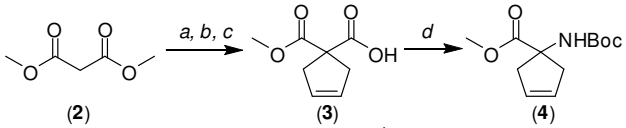


Figure 1. Orally active $S1P_1$ agonists.

In order to obtain these molecules and new analogs we decided to employ the practical and effective Heck-Matsuda reaction as a key step in their synthesis.

RESULTS AND DISCUSSION

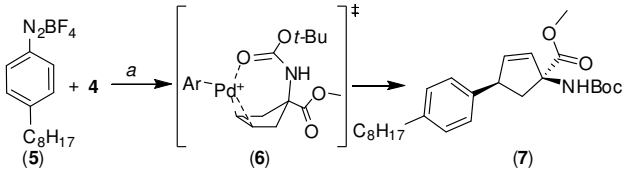
Our approach began with the preparation of multigram quantities of **4** from dimethyl malonate (**2**) in four steps: diallylation of **2** with allyl bromide (98% yield), ring-closing metathesis (98% yield), followed by monohydrolysis to provide the half-ester **3** (95% yield). The last step consisted in the Curtius rearrangement, and was carried out according to the *one-pot* methodology developed by Label (42% yield).[3]



a) NaH, Ally bromide, THF. *b*) Grubbs 2nd, DCM. *c*) KOH, H_2O/THF
d) NaN_3, Bu_4NBr, $(Boc)_2O$, $Zn(OTf)_2$, THF, 50ºC, (38% from **2**)

Scheme 1. Synthesis of N-Boc-ester **4**.

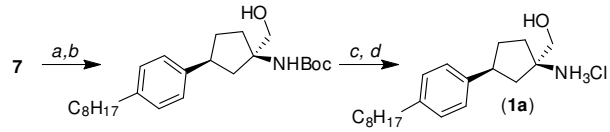
The key step of our synthesis was the stereoselective arylation of **4** with arenodiazonium salt **5**. We rationalized that anchimeric assistance of the carbonyl group from carbamate would direct arylation to the same face on the ciclopentene (**6**). We believe that this approach is favored because carbamates are better electron donating groups than esters and, in this case it would provide a less strained cyclic intermediate. In fact, the Heck-Matsuda reaction furnished the desired product **7** in 60% yield with high stereoselectivity (94:6).



a) Pd_2dba_3.dba (4 mol%), NaOAc, PhCN, (60%)

Scheme 2. Substrate directable Heck-Matsuda.

The synthesis was completed by: i) reduction of **7** to alcohol **8** using $NaBH_4$ in the presence of $CaCl_2$ (78% yield), ii) hydrogenation of olefin (77% yield), *iii*) deprotection of Boc group and, *iv*) precipitation of the aminoalcohol by addition of HCl (43% yield for the last two steps). All reactions in this synthesis are not optimized.



a) $NaBH_4$, $CaCl_2$, EtOH (78%). *b*) H_2, Pd/C, EtOAc (77%).
c) TFA/DCM (1:3). *d*) HCl $_{(37\%)}$ (42% for the two steps).

Scheme 3. Synthesis of aminoalcohol **1a**.

CONCLUSION

We have developed a practical and highly stereoselective synthesis of the $S1P_1$ agonist **1a**. Studies concerning the enantioselective approach to the Heck-Matsuda step and synthesis of **1b** are currently in course on our group.

ACKNOWLEDGEMENTS

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