# Total synthesis of targretin via palladium catalyzed cross-coupling reaction of a vinyl organozinc intermediate

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*Keywords: targretin, anticancer, synthesis, paladdium-cross coupling reaction*

## INTRODUCTION

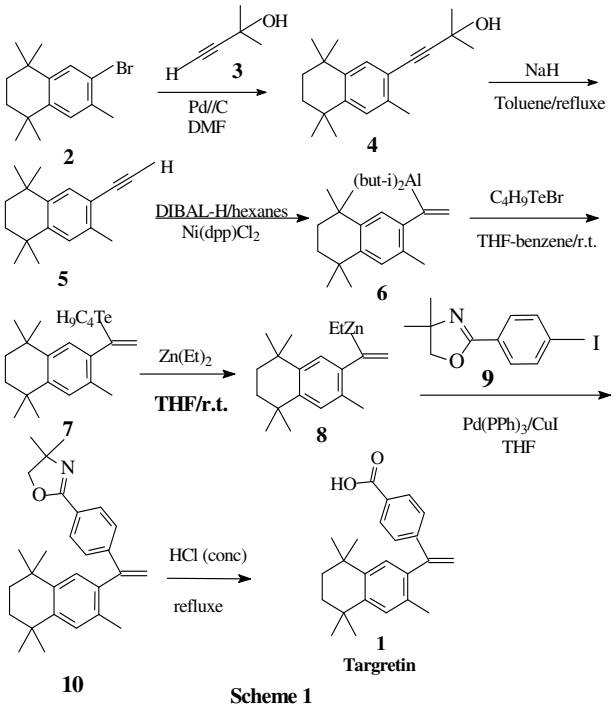
In the last two decades, retinoids as isotretinoin, etretinate and acitretin have been utilized in treatment of primary cutaneous T-cell lymphoma (CLTC) showing modest response in rats.[1] However, the bexarotene (targretin®) **1** emerged as a potent and highly selective ligand for the retinoid X receptors (RXRs) applied in human patients to combat the CLTC, which have become a serious public health problem.

## RESULTS AND DISCUSSION

The oral targretin was approved by the Food and Drug Administration (FDA) in 1999 and in 2002 in Europe. Actually it is widely used for treatment of breast cancer,[2] mycosis fungoides[1] and Sézary syndrome.[1]

Considering their pharmacological activities, we described a short and efficient total synthesis of targretin which was started using the cross coupling reaction involving the 7-bromo-1,2,3,4,-tetrahydro-1,1,4,4,6-pentamethyl naftalene (obtained following experimental procedure described in the literature)[3] **2** and 3-dimethyl-2-propyn-1-ol **3,** furnishing the disubstituted acetylene **4.** Next, the retro-Favorsky elimination of **4** resulted in the terminal acetylene **5** which was hydrometallated[4] with DIBAL-H/Ni(ddp)$Cl_2$, followed by Te/Al transmetallation affording the α-vinyl alana **6,** which was reacted with $C_4H_9TeBr$ leading to the 1,1,-disubstituted vinyl telluride **7.** The key step in the synthesis of targretin involved the $Pd(PPh_3)_4$/CuI cross coupling catalyzed reaction of aryl organozinc compound **8** (prepared in situ via Te/Zn transmetallation from **7**)[5] with the aryl iodide **9** to give the targretin-oxazoline **10**.

Finally, the desprotection of 1**0** under concentrated HCl furnished the free carboxylic acid targretin **1** in 23 % overall yield from disubstituted acetylene **4** (Scheme 1).




**Scheme 1**

## CONCLUSION

We described here a novel and efficient total synthesis of the anticancer targretin.

## ACKNOWLEDGEMENTS

CNPq, CAPES and Fundação Araucária

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