

SYNTHESIS OF TARGRETIN USING A CHEMOSELECTIVE METAL -
CATALYZED CROSS-COUPPLING REACTION OF 1-IODO-1-TRIBUTYLSTANNYL
ETHENE

Miguel J. Dabdoub, ^{*a} Gabriela R. Hurtado, ^a Vânia B. Dabdoub^b and Joseph P. Marino^{*b}

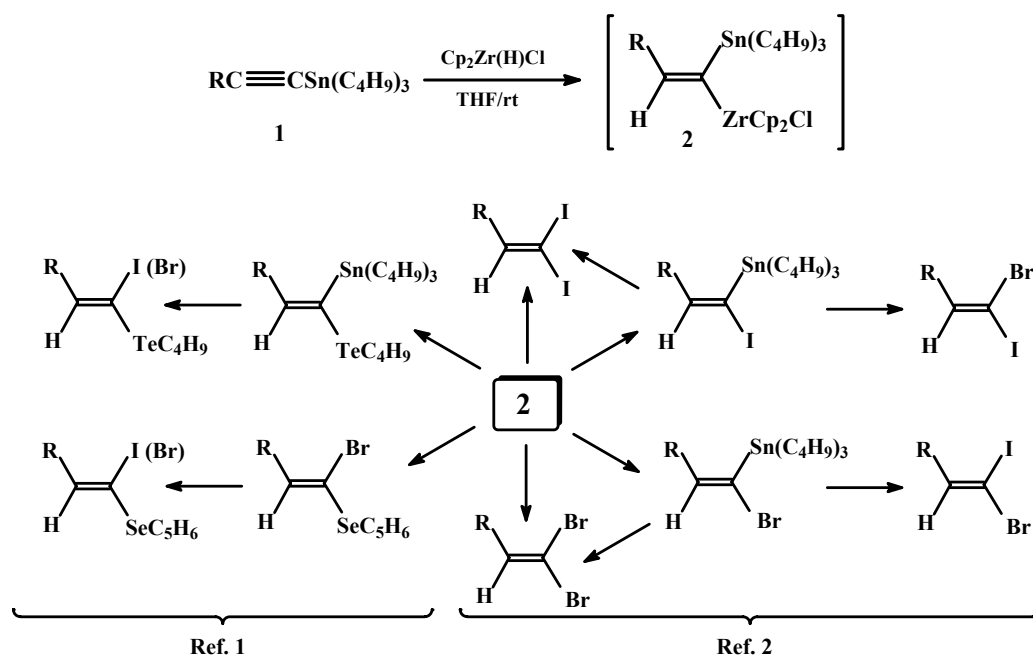
^a Laboratório de Síntese de Compostos Organocalcogênicos, Departamento de Química –
FFCLRP, Universidade de São Paulo, Av. Bandeirantes, 3900 – Ribeirão Preto, SP Brasil

^b Department of Chemistry, University of Michigan. Ann Arbor, Michigan

Targretin is a potent and highly selective ligand for the retinoid X receptors (RXRs). In this way, targretin has the potential to address a broad range of therapeutic indications, including oncologic and metabolic disease targets. This compound has recently been granted FDA approval for treatment of early and advanced-stage refractory cutaneous T-Cell Lymphoma (CTCL) and is in late-phase clinical trials for a variety of other indications, including breast cancer. Other preclinical studies suggest an important role for modulators of this receptor as insulin sensitizers. In this communication we describe the synthesis of this retinoid.

Recently,¹⁻³ we developed new methods for the synthesis of olefinic systems containing two different heteroatoms attached at the same double bond, with the aim to explore the selective reactivity of the carbon-heteroatom bonds. Some of these compounds are illustrated in Scheme 1.

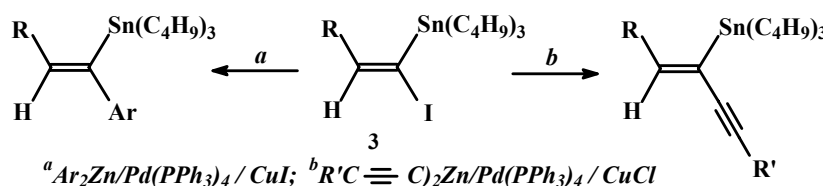
Scheme 1



Our interest on the metal-catalyzed cross-coupling reaction^{4,5} has prompted us to examine several reactions of vinyl iodides and vinyl tellurides with different organozinc reagents. At the present, our group is developing different methodologies employing diheteroatomic vinyl compounds to explore efficiently the ability to form carbon–carbon bonds rationally around a double bond, because the regio- and stereocontrol is a very important issue in organic synthesis.

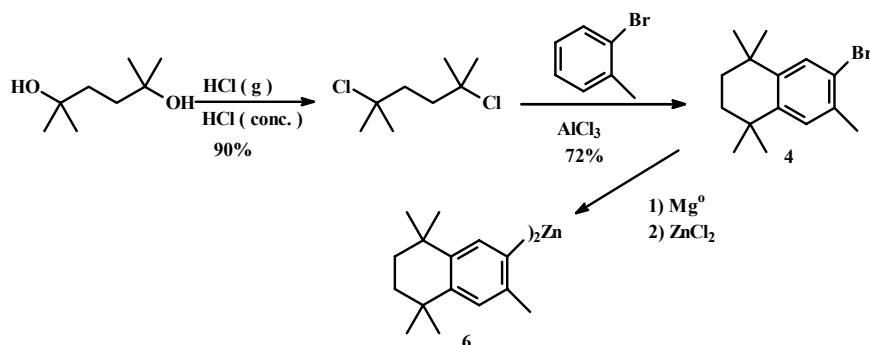
In particular, we describe here one of our new contributions to this area that involves the sequential palladium-catalyzed cross-coupling reactions of 1-iodo-1-tributylstannyl alkenes of type 3 with diaryl or dialkynyl zinc compounds employing the Pd(PPh₃)₄ / CuI / THF / DMF system (Scheme 2), followed by the Stille type cross-coupling reaction, under conditions [Pd(PPh₃)₄ / CuCl] recently described by Corey et al.⁶

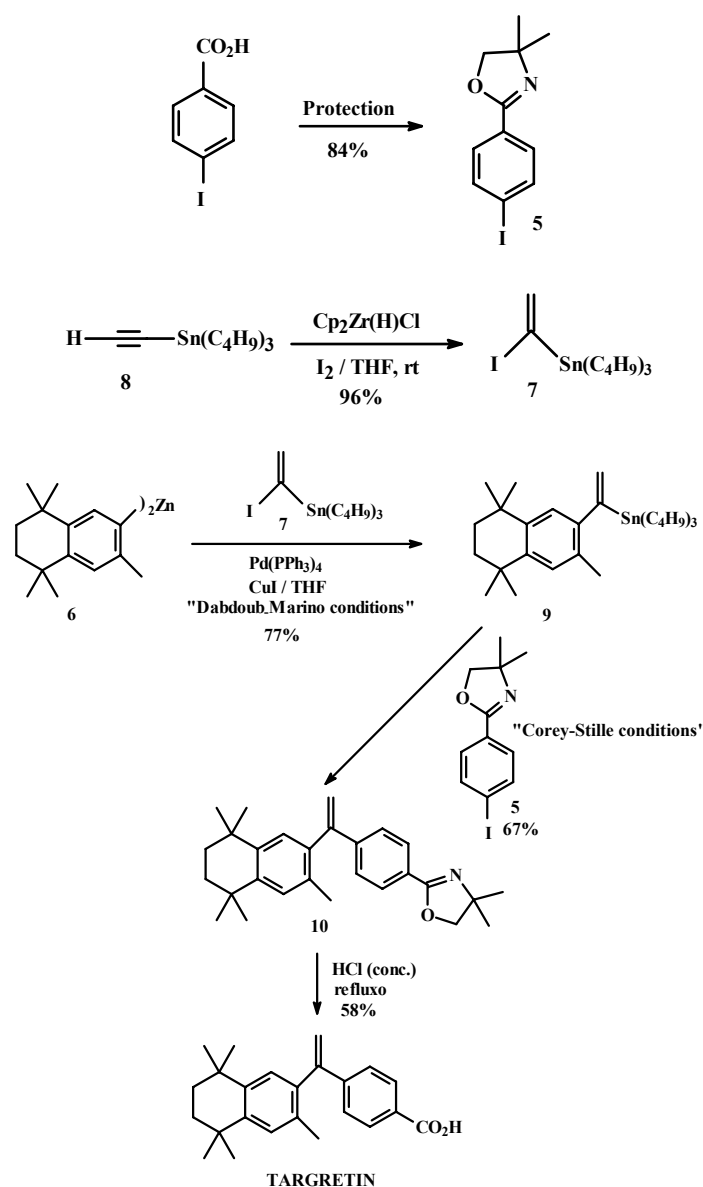
Scheme 2



The use of these reactions for the total, short and efficient synthesis of targretin as depicted in Scheme 4 was performed. Reagents like the aryl bromide 4 (Scheme 3) and the aryl iodide 5 were obtained following experimental procedures previously described. The key step involve the $Pd(PPh_3)_4/CuI$ catalyzed reaction of the diarylzinc compound 6 (prepared in situ from 4) with the 1-iodo-1-tributylstannyl ethene 7 which was obtained from 8 in 96% isolated yield. The reaction was performed in THF/DMF at room temperature affording in 77% yield the corresponding vinyl stannane 9, which followed by the cross-coupling with the aryl iodide 5 under “Corey-Stille” conditions⁶ $(PdPPh_3)_4/CuCl$ afforded 10 in 67% yield. In the last step, the free carboxylic acid was obtained in 58% by treatment of 10 under acid conditions (concentrated HCl/reflux). Targretin was obtained in 29% overall yield from the tributylstannylacetylene 8.

Scheme 3





References:

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