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Facile TMSOI catalysed stereoselective synthesis of 2-Methylene selanyl-4-chromanols and *anti*-cancer activity

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ABSTRACT

In the present study, a catalytic synthesis of 2-methylene selanyl-4-chromanols has been described. The manuscript highlights a facile Trimethylsulphoxonium iodide (TMSOI) catalysed intramolecular *6-exo-trig* coupling reaction in metal-free environment. The reaction exhibits satisfactory yields in presence of multiple free -hydroxyl groups. A stereoselective generation of *syn*-3-hex-yne-1,5diols has been explored. The relative stereochemistry has been confirmed by single-crystal X-ray of crystalline-selanyl-chromanols. To determine the anticancer efficacy of the synthesized compounds, cell viability assay using MTT was performed against MCF-7 breast cancer cell line. Notably, Compound **9j** (IC_{50} = 3.157 μmol) was found to exhibit potent cytotoxic activity. Compounds **9a** and **9e** also showed activity with IC_{50} values of 31.60 ± 4.012 and 36.797 ± 2.72 μmol respectively highlighting the potential of the synthesized compounds as novel lead molecules for future development of potent *anti*-cancer therapeutics.

1. Introduction

Selenium has been element of prime importance for human health to Organic Synthesis. Interestingly, appropriately designed modern organoselenium molecules have shown impressive responses in apoptosis and cell cycle analysis studies and thus have been already identified as important *anti*-cancer agents.[1] Thus an urge to find newer organoselenium derivatives along with creation of innovative methodologies certainly demand for attention.[2] Recent studies on selenium compounds have shown to possess *anti*-cancer activity with selective reactivity towards specific tumor cells. Trials for biomimetic designing of such peptides have been limited.[3] The latest developments of Pincer selenium ligands has also been very inspiring which opens up a new direction of selenium research.[4] Ring annulations encapsulating an organoselenium backbone at metal free conditions have not been explored to satisfactory levels.[5] The interesting point lies with the fact that such organoseleniums can easily be removed employing oxidative elimination[6] or even can be replaced with facile nucleophilic protocols.[7] Surprisingly, only few catalytic approaches have been designed to develop functionalized organoselenium compounds.[8] Thus, metal free catalytic approaches towards development of these crucial organoselenium compounds requires immediate attention.

Concurrently, flavonoids and chromanoids constitute a huge class of biologically active natural benzopyrans and they have high commercial demand today.[9] Amongst this huge group, 2H-chromene derivatives and 2-methylene chromanols categorically embrace an important member of this set, not only because of their pronounced biological and pharmaceutical activity but also of interesting structural outlay (Fig. 1).[10–14]

The 2H- chromenes thus act as vital building blocks in natural product synthesis.[17–19] It was anticipated that selenium tagged with such chromanoid moieties may prove important molecules of medical interest (see Scheme 1).

The celebrated ylide Trimethylsulfoxonium Iodide (TMSOI) also known for the Corey - Chaykovsky reaction,[20] has been known as a methylene transfer and cyclopropanating reagent, albeit to the best of our knowledge, there is no report which recognizes TMSOI as an effective reagent for ring annulation. Herein, we report a facile

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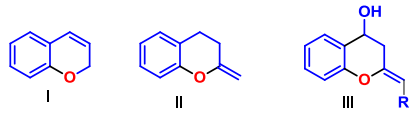
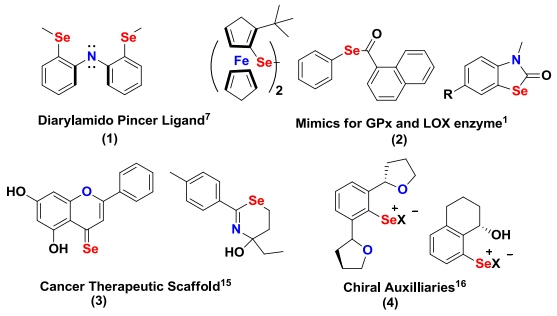


Fig. 1. 2H- chromene(I), 2-methylenechroman (II), 2-methylenechroman-4-ol (III).

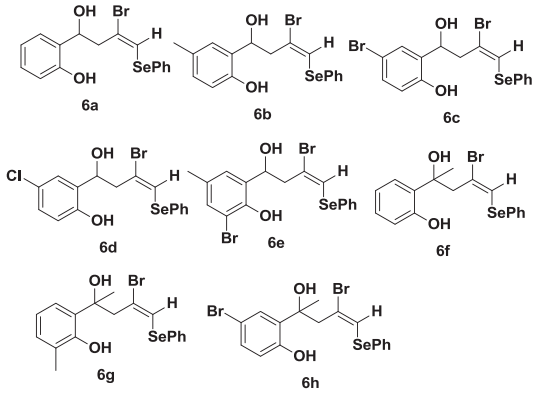


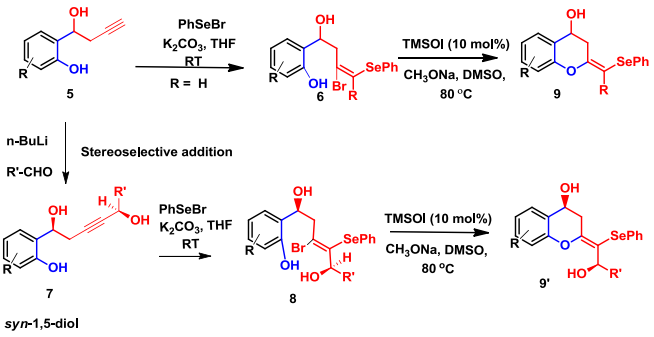
Scheme 1. Potent organoselenium molecules.[15,16]

metal free TMSOI catalysed protection group free synthesis of 2-Methylene selanyl 4-chromanols via an interesting 6-*exo*-*trig* ring annulation employing a seleno functionalization of alkynes. A stereoselective synthesis of *syn*-1,5 diols has been encountered and explored (Scheme 2). In the latter part, the study also reveals notable *anti*-cancer properties against MCF-7 breast cancer cell line by these molecules.

Retro-synthetically it was envisaged that a two way approach would be a preferred trajectory towards developing such moieties. The first one being a facile catalytic halogen exchange of the vinyl selenium bromide followed by a concomitant phenoxide induced ring closure (Path A) or a metal assisted intramolecular6-*exo*-*trig* annulation to an activated vinyl-selenium bromides towards the access of these selanyl chromanols (Path-B) (Fig. 2), Path-A would be the preferred 6-*exo*-*trig* coupling (see Fig. 3).

At the outset, 2-(1-hydroxybut-3-yn-1-yl) phenol (**5**) was chosen as model substrate to check our hypothesis (Scheme 2). The 2-(1-hydroxybut-3-yn-1-yl) phenol (**5**) was transformed into the corresponding organoselenium bromide, (*E*)-2-(3-bromo-1-hydroxy-4-(phenylselanyl)but-3-en-1-yl) phenol **(6)** in a simple reaction using phenylseleniumbromide and potassium carbonate as a base. The selenylated phenol (Scheme 3) was screened through a various catalytic systems in different experimental conditions as stated in Table 1.





Scheme 2. Synthesis of 2-methylene-selanyl-4-chromanols.

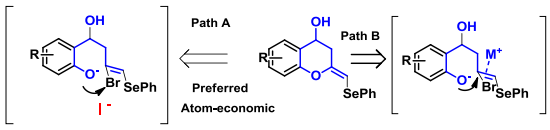


Fig. 2. Retrosynthetic perspective.

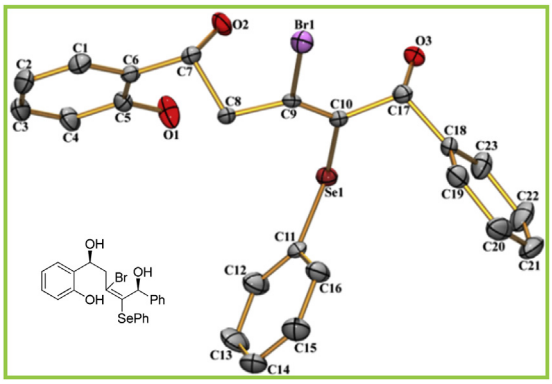
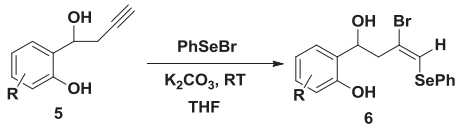


Fig. 3. ORTEP view and atom numbering scheme of complex (**1**) ((1*S*,5*S*)/(1*R*/5*R*), *E*)-3-bromo-5-(2-hydroxyphenyl)-1-phenyl-2-(phenylselanyl)pent-2-ene-1,5-diol**(8b)**. The displacement thermal ellipsoids are drawn at 30% probability level. (**CCDC No. 1517795**).



Scheme 3. Seleno functionalization of 2-(1-hydroxybut-3-yn-1-yl) phenol.

To our delight, a combination of trimethylsulphoxonium iodide (TMSOI, 10 mol%) and (*E*)-2-(3-bromo-1-hydroxy-4-(phenylselanyl) but-3-en-1-yl)phenols **(6)** delivered the cyclized (*E*)-2-((phenylselanyl)methylene)chroman-4-ols (**9**) in excellent yields at room temperature in shorter time span.

Screening of various bases, iodides and solvents puts up an impression that, CH_3ONa and DMSO to be the best combination for the reaction. No protection of the benzylic alcohol is necessary for this transformation. TMSOI as catalyst is concluded to deliver the best yields.

Encouraged by these results, the scope was then explored with a variety of Phenylselanyl-but-3-en-1-yl phenols as shown in Table 3. As expected tertiary-alcohols (**9g**, **9h**, **9k**) exhibited moderate