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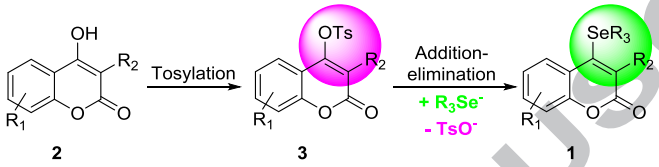

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Convenient Michael addition/β-elimination approach to the synthesis of 4-benzyl- and 4-aryl-selenyl coumarins using diselenides as selenium sources

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ABSTRACT

A concise and efficient, two-step approach toward 4-organoselenyl coumarin derivatives from the easily available 4-hydroxycoumarins, is reported. The synthesis was based on conventional tosylation followed by a tandem selena-Michael addition/β-elimination reaction of an aryl-/benzyl- selenolate anion on the corresponding 4-tosyloxycoumarins. The selenolate anions were conveniently generated *in situ* by exposure of the corresponding diselenides to $NaBH_4$. Selected compounds demonstrated to exhibit antioxidant properties in mice cortex and hippocampus.

The coumarin nucleus, which embodies an α,β-unsaturated lactone motif, is a biologically relevant and highly privileged structure, which is found in numerous natural products and bioactive compounds, including pharmaceuticals.[1] Despite substituted coumarins have shown to exhibit a wide array of biological activities, including anticoagulant,[2a] antibacterial,[2b] antiviral,[2c] and anti-inflammatory,[2d] they have recently emerged as scaffolds for antioxidant and anticancer compounds.

On the other hand, selenium is an important trace element found in glutathione reductase, thioredoxin reductase, glutathione peroxidase and other enzymatic systems, where it is known to play a key biological role as antioxidant; for example, by converting H_2O_2 into H_2O.[3a-c] In addition, selenium derivatives have numerous valuable properties, useful in organic synthesis. Among them, the selenolates are interesting because they are prone to engage in Michael additions to α,β-unsaturated carbonyls[3d,e] and other species, forming new C-Se bonds.

A small array of coumarin derivatives diversely decorated with selenium functionalities has been prepared and some of them have shown to exhibit valuable properties (Figure 1). Among the heterocycles designed for analytical purposes, a 3-arylselenium 3,4-dihydrocoumarin proved to be useful as a fluorescence probe to detect $HClO/ClO^-$,[4a,b] and a coumarin–Se_2N chelating conjugate has been synthesized and characterized as a fluorescent chemosensor for Ag^+, taking advantage of both, the high photostability of the coumarin fluorophore and the high selenophilicity of the silver cation.[4c] Further, two coumarin-labelled derivatives of ebselen were designed as fluorescence probes, suitable for biological and medicinal studies.[4d]

Other 3,4-dihydrocoumarins containing a C-3 associated selenium atom have been prepared as antitumor agents[5a] and as intermediates during the solid-phase synthesis of coumarins. In the latter case, the selenium moiety was part of the tether, strategically lost in the last stage, by selenoxide elimination.[5b,c] 7-Phenylselenyl coumarines have also been accessed by arylation of selenocysteine[5d] and solid-phase methodologies.[5e]

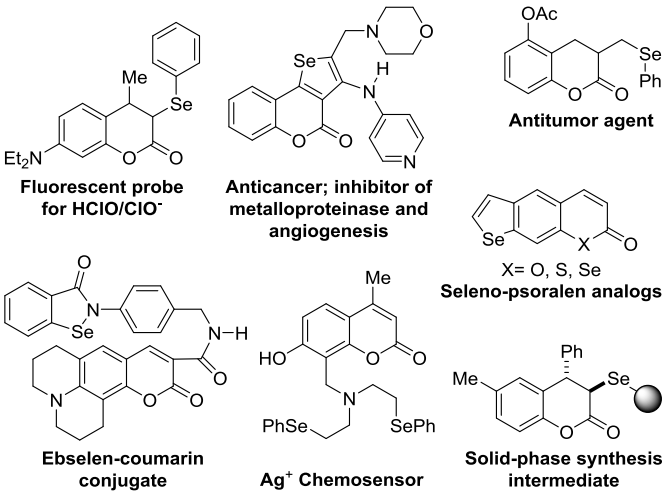

Figure 1. Examples of relevant selenium derivatives of coumarins.

3-Organoselenyl coumarines[6a,b] have been synthesized by Lewis acid-mediated cyclizations and the access to 4-hydroxy selenocoumarins has also been disclosed.[6c,d] In addition, selenopheno[2,3-*f*]coumarin have been prepared,[7a] whereas

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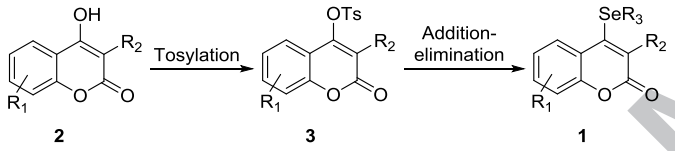
selenopheno[3,2-*g*]coumarins and selenopheno[3,2-*g*]thio- and seleno-coumarins have been synthesized as psoralen analogs, which exhibited high photoactivity toward DNA, being potentially useful for treatment of skin diseases.[7b,c]

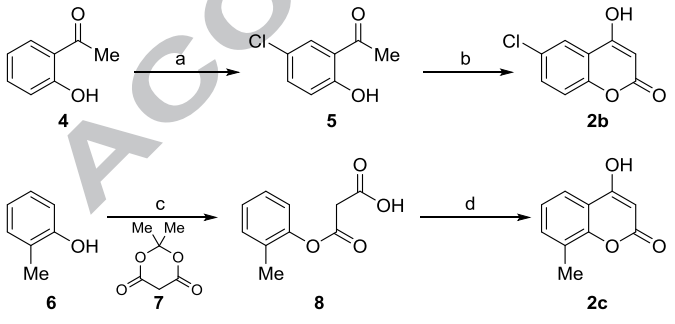
The synthesis of condensed selenophenes, including selenopheno[3,2-*c*]coumarins has been disclosed.[7d] In addition, 4-seleno-derivatives of 3-formylcoumarin were prepared as potential starting materials for the synthesis of condensed coumarins incorporating selenium-containing heterocyclic rings.[7e] The corresponding selenopheno[2,3-*c*]coumarins[7f] were more recently synthesized and proven to be cytotoxic, also acting as angiogenesis and matrix metalloproteinase (MMP-1–MMP-14) inhibitors, as well as antioxidant and pro-oxidant agents.

For many years, we have been engaged in the development of new synthetic methodologies involving selenium species[8] and in the selenofunctionalization of privileged structures,[9] including their applications to natural product synthesis.[10] In continuation of our research on the preparation of potentially useful selenium derivatives, herein we report a facile and convenient access to 4-selenocoumarin derivatives **1**, through the addition-elimination of organoselenolates with tosylates **3**, derived from 4-hydroxy coumarins (**2**), as shown in Scheme 1. Despite its potential utility in organic synthesis, precedents on this type of reaction involving selenium derivatives are extremely scarce.[11] The activity of selected heterocycles as antioxidants is also reported.



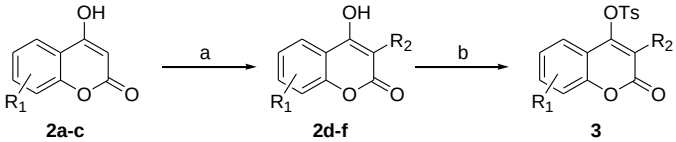
Scheme 1. Proposed reaction sequence toward the 4-selenocoumarins **1**.

Coumarin (**2a**) is commercial. The simplest starting 4-hydroxycoumarins (**2b,c**) were synthesized (Scheme 2) according to the literature. For example, 2-hydroxyacetophenone (**4**) was submitted to a highly *para*-regioselective TsOH-promoted chlorination with NCS,[12] and the resulting 4-chloroderivative **5**, obtained in 70% yield, was exposed to NaH and treated further with dimethyl carbonate, affording 82% of **2b**.[13] On the other hand, the reaction of *ortho*-cresol (**6**) with Meldrum's acid (**7**) gave quantitative yield of **8**,[14a] which was cyclized with Eaton's reagent (P_2O_5-$MeSO_3H$, 1:10, *w/w*) to furnish 72% of the coumarin **2c**.[14]



Scheme 2. *Reagents and conditions:* a) NCS, TsOH.H_2O, MeCN, r.t. 4h (70%); b) HNa, Me_2CO_3, PhMe, reflux, 4h (82%); c) Meldrum's acid, 3h, 110°C (100%); d) Eaton's reagent, 70°C, 4h (72%).

In order to increase substrate diversity and explore the scope and limitations of the proposed synthetic approach, the coumarins **2a-c** were next functionalized on C-3 (Scheme 3), introducing potentially labile groups. Thus, **2a-c** were brominated with NBS/NH_4AcO in MeCN,[15a,b] to furnish **2d-f** in 87-92% yield. In addition, they were submitted to a mild thioarylation with the PhSH/I_2 reagent system.[15c,d] This afforded 75-92% of the derivatives **2g-i** through an *in-situ* generation/ cleavage of diphenyldisulfide, followed by C-S bond formation.



Scheme 3. *Reagents and conditions:* a) NBS, NH_4AcO, MeCN, r.t., 3h (R_2= Br) or PhSH, I_2, DMSO, 80°C, 3h (R_2= PhS), b) TsCl, Et_3N, CH_2Cl_2, r.t., overnight. For product yields, see Table 1.

In order to complete the sequence and to acquire the proposed heterocyclic acceptors, the whole set of coumarins was then subjected to a conventional tosylation, with TsCl in CH_2Cl_2, employing Et_3N as base. This afforded the required tosylates **3a-i** in 51-94% yield, as summarized in Table 1.[15e]

Table 1. Functionalization of the 4-hydroxycoumarins **2a-c** and synthesis of the tosylates **3a-i**.

Entry No	Starting Material	R_1	C-3 Product	R_2	Yield (%)[a]	Tosylate No	Yield (%)[a]
1	**2a**	H		H		**3a**	94
2	**2b**	6-Cl		H		**3b**	79
3	**2c**	8-Me		H		**3c**	68
4	**2a**	H	**2d**	Br	92	**3d**	91
5	**2b**	6-Cl	**2e**	Br	91	**3e**	57
6	**2c**	8-Me	**2f**	Br	87	**3f**	53
7	**2a**	H	**2g**	PhS	92	**3g**	79
8	**2b**	6-Cl	**2h**	PhS	75	**3h**	53
9	**2c**	8-Me	**2i**	PhS	88	**3i**	51

[a] Isolated yields after column chromatography.

In general, the tosylation of the substrates carrying the 3-phenylthio moiety proceeded in lower yield (entries 7-9), probably as a result of steric hindrance; it was also observed that, unexpectedly, the transformations of the 8-methylcoumarin derivatives were less efficient (entries 3, 6 and 9), being outperformed by their 6-chloro congeners (entries 2, 5 and 8).

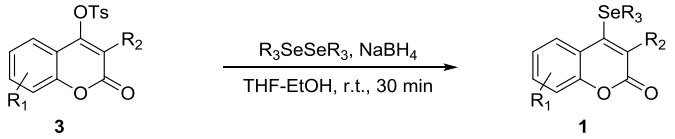
Next, the tosylates **3a-i** were submitted to the projected selenium addition-elimination reaction. Organoselenols are highly volatile and air-sensitive compounds; in addition, their unpleasant smell may result in a safety issue. Therefore, the reactions of the tosylates were performed with organoselenolate anions (R_3Se^-), generated *in situ* by reaction of the corresponding diselenides with $NaBH_4$.[16] The transformation (Table 2), which was carried out in THF-EtOH,[17] smoothly afforded the expected 4-aryl/benzyl selenocoumarins **1aa-1cl** in 30 min; these mild conditions ensured survival of the lactone moiety.[18]

It has been reported that Michael addition of benzeneselenol to α-bromo-α,β-unsaturated esters results in the formation of α-bromoselenides, presumably via intramolecular migration of the benzeneselenyl group in an initially-formed α-bromo-β-benzene selenylalkanoate through the intermediacy of a cyclic seleniranium ion.[19] No such transformation was observed during this study, possibly because of the presence of the tosyloxy moiety, which offered an alternative pathway to the reaction.

It was also observed that, in general, the reactions carried out with benzylselenolate (entries 4, 8, 12, 16, 20, 24, 28 and 36) gave lower performances that those with their less nucleophilic arylselenolate congeners, whereas unexpectedly the reactions of entries 17, 18 and 32 proceeded in low yields, furnishing complex mixtures. In addition, no clear tendencies were observed with regard to the product yields resulting from the reactions with the different arylselenolates. Interestingly, however, to the best of our knowledge, this approach toward 4-selenocoumarins has not been previously disclosed, the nearest analogy being the displacement of a vinylic chloride in 4-chlorocoumarins,

employing the less readily available PhSeZnCl as selenium source.[20]

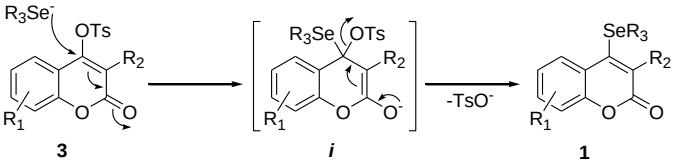
Table 2. Synthesis of the 4-arylselenocoumarins **1** by one-pot selena-Michael addition/β-elimination of tosylates **3** with organoselenolate anions R_3Se^- in THF-EtOH.[21]



Entry No	Starting Tosylate No	R_1	R_2	R_3	Product No	Yield (%)[a]
1	**3a**	H	H	Ph	**1aa**	81
2	**3a**	H	H	4Cl-C_6H_4	**1ab**	77
3	**3a**	H	H	4Me-C_6H_4	**1ac**	73
4	**3a**	H	H	Bn	**1ad**	72
5	**3b**	Cl	H	Ph	**1ae**	84
6	**3b**	Cl	H	4Cl-C_6H_4	**1af**	64
7	**3b**	Cl	H	4Me-C_6H_4	**1ag**	70
8	**3b**	Cl	H	Bn	**1ah**	22
9	**3c**	Me	H	Ph	**1ai**	74
10	**3c**	Me	H	4Cl-C_6H_4	**1aj**	80
11	**3c**	Me	H	4Me-C_6H_4	**1ak**	64
12	**3c**	Me	H	Bn	**1al**	56
13	**3d**	H	Br	Ph	**1ba**	85
14	**3d**	H	Br	4Cl-C_6H_4	**1bb**	74
15	**3d**	H	Br	4Me-C_6H_4	**1bc**	78
16	**3d**	H	Br	Bn	**1bd**	48
17	**3e**	Cl	Br	Ph	**1be**	-[b]
18	**3e**	Cl	Br	4Cl-C_6H_4	**1bf**	-[b]
19	**3e**	Cl	Br	4Me-C_6H_4	**1bg**	74
20	**3e**	Cl	Br	Bn	**1bh**	42
21	**3f**	Me	Br	Ph	**1bi**	77
22	**3f**	Me	Br	4Cl-C_6H_4	**1bj**	70
23	**3f**	Me	Br	4Me-C_6H_4	**1bk**	72
24	**3f**	Me	Br	Bn	**1bl**	53
25	**3g**	H	SPh	Ph	**1ca**	80
26	**3g**	H	SPh	4Cl-C_6H_4	**1cb**	74
27	**3g**	H	SPh	4Me-C_6H_4	**1cc**	66
28	**3g**	H	SPh	Bn	**1cd**	42
29	**3h**	Cl	SPh	Ph	**1ce**	79
30	**3h**	Cl	SPh	4Cl-C_6H_4	**1cf**	74
31	**3h**	Cl	SPh	4Me-C_6H_4	**1cg**	80
32	**3h**	Cl	SPh	Bn	**1ch**	-[b]
33	**3i**	Me	SPh	Ph	**1ci**	68
34	**3i**	Me	SPh	4Cl-C_6H_4	**1cj**	66
35	**3i**	Me	SPh	4Me-C_6H_4	**1ck**	56
36	**3i**	Me	SPh	Bn	**1cl**	42

[a] Isolated yields after column chromatography. [b] Complex mixture.

The exact details of the reaction mechanism are still unclear. Alkenes bearing electron withdrawing groups can react with nucleophiles in a conjugate fashion, generating a stabilized anion. If the β-carbon carries a suitable leaving group, its displacement can further stabilize the system by regenerating the conjugated system. On the other side, direct substitution of phenolic tosylates with phenylselenols has some recent precedents;[22] however, it can be proposed instead that the transformation takes place as shown in Scheme 4, through a sequential selena-Michael addition/β-elimination process.



Scheme 4. Proposed reaction mechanism.

In this case, the *in situ* generated highly nucleophilic selenium anion should attack the conjugated double bond system of the heterocycle **3** to afford the anion of a ketene acetal type intermediate (***i***), which could rapidly regenerate the ene-lactone motif with concomitant release of tosylate anion, furnishing **1**.[23]

The group of Rappoport examined the nucleophilic substitution of vinylic halides, finding that the electrophilicity of the β-carbon atom determines the reaction rate. The latter increases with the electronegativity of the β-substituent, because it renders the β-carbon more electrophilic. Interestingly, its leaving group ability increases in the reverse order.[24]

Sulfonates are ideal partners for this transformation. Conjugated enol tosylates have been used as reactants in Michael addition-elimination sequences.[25a] including in the synthesis of other vinylic chalcogenides.[25b] In principle, the addition is a reversible process, and hetero-Michael reactions have been shown to be useful means for functionality transfer between other heteroatom-supported functionalities.[26] Further, this kind of transformation is at the heart of many biochemical and toxicological mechanisms[27] and has been employed as a chemical mechanism for the detection of biothiols.[20b]

However, the leaving group ability of the tosylate which should also favor the reaction, may turn the selena-Michael addition irreversible because despite being a less favored leaving group, once it undergoes elimination, it is unable to compete with the selenolate anion, in attacking the heterocycle **1** and regenerate the starting tosylate.

Next, we turned our attention to the antioxidant activity of these heterocycles, selecting compounds **1bj**, **1aj**, **1cb** and **1bc** as models. Antioxidants protect biological targets against oxidative damage caused by reactive species (RS). The oxidative stress phenomenon is found in several psychiatric disorders, such as major depression, schizophrenia and anxiety,[28a] also being at the root of many other diseases; hence, antioxidants are widely used as prevention agents against oxidative damage. NaN_3 is capable to induce RS such as H_2O_2 and OH. These species can be determined intracellularly using dichlorodihydrofluorescein-2,7-diacetate (DCFH-DA),[28b] a non-fluorescent reagent that diffuses readily through the cell membranes, being cleaved by esterases to DCF. In the presence of RS, mainly H_2O_2, DCF is oxidized to its fluorescent form, which can be measured by spectrofluorimetry.

When the levels of RS formed in cortex and hippocampus of mice were determined with DCHF-DA,[29] it was observed (Table 3) that in the cortex compounds **1bj** and **1aj** significantly decreased the levels of RS formation at 0.1 μM, while compound **1bc** did the same at 1 μM and compound **1cb** acted similarly at 5 μM. Interestingly, the effectivity of the protection against formation of RS was different in the hippocampus, where **1bj**, **1aj** and **1cb** significantly decreased the levels of RS at 5 μM, while compound **1bc** produced meaningful results at 1 μM.

Furthermore, among the tested compounds, **1bc** proved to be the most potent, exhibiting the lowest IC_{50} values in cortex (1.0 ± 0.2 μM) and hippocampus (2.7 ± 2.0 μM). In addition, it also demonstrated to be the most efficient, with the highest I_{max} values for the cortex (93.1 ± 0.3 μM) and hippocampus (81.4 ± 1.1 μM).

Lipid peroxidation entails an oxidative deterioration of lipids containing carbon–carbon double bonds. In biological systems, this process can lead to various pathological consequences.[30] The brain is more susceptible to oxidative stress than other organs due to its important oxygen consumption and high iron content in some areas, combined with the presence of large amounts of unsaturated fatty acids.

Increased neuronal oxidative stress levels cause deleterious effects on signal transduction and structural plasticity, mostly by inducing lipid peroxidation in membranes, proteins and genes.[31]

Table 3. Antioxidant activity of compounds **1bj**, **1aj**, **1cb** and **1bc** in the assay of inhibition of RS in cortex and hippocampus of mice.

Comp. No	Place	Compound concentration (μM) 0.01	0.1	1	5	10	50	IC_{50} (μM)	I_{max} (%)
1bj	Cortex	101.9 ± 3.2	81.5 ± 8.0**	72.1 ± 12.5***	44.3 ± 6.7***	37.4 ± 8.3***	29.6 ± 11.4***	4.4 ± 1.2	67.8 ± 11.4
1aj	Cortex	109.6 ± 10.2	72.0 ± 11.2**	55.1 ± 13.8***	53.2 ± 4.6***	24.5 ± 11.2***	18.3 ± 6.6***	6.8 ± 1.1	72.7 ± 9.9
1cb	Cortex	-	-	92.5 ± 9.6	53.5 ± 3.0**	48.0 ± 7.9**	20.9 ± 10.3***	19.0 ± 19.5	63.3 ± 10.3
1bc	Cortex	-	95.6 ± 6.3	54.5 ± 3.9***	39.6 ± 3.8***	28.6 ± 4.8***	29.4 ± 5.0***	1.0 ± 0.2	93.1 ± 0.3
1bj	Hippocampus	-	-	76.3 ± 7.7	54.2 ± 16.1**	44.0 ± 18.7**	39.9 ± 18.0**	21.6 ± 26.4	47.3 ± 9.2
1aj	Hippocampus	-	-	86.0 ± 1.7	77.9 ± 9.0*	75.5 ± 5.3**	18.4 ± 15.2***	39.3 ± 1.0	46.2 ± 11.2
1cb	Hippocampus	-	-	94.0 ± 0.7	71.5 ± 3.7**	71.9 ± 2.9**	53.3 ± 7.7***	-	35.6 ± 8.4
1bc	Hippocampus	-	118.3 ± 10.6	43.4 ± 9.3***	32.6 ± 9.8***	47.2 ± 10.9***	21.3 ± 2.2***	2.7 ± 2.0	81.4 ± 1.1

Data are expressed as mean ± SD (n = 4) of % reactive species production; IC_{50} = concentration (μM) to decrease 50% RS formation; I_{max} = % maximal inhibition; asterisks denote $p< 0.05$ (*); $p< 0.01$ (**) and $p< 0.001$ (***), when compared to the NaN_3-induced oxidation, by the Student-Newman-Keuls test.

Therefore, to further determine the antioxidant profile of the compounds, their inhibitory effect on the sodium nitroprusside (SNP)-induced lipid peroxidation was also determined in mice brain tissue (cortex and hippocampus) through the formation of thiobarbituric acid reactive substances (TBARS).[32] It was observed that compounds **1bj**, **1aj** and **1cb** were not effective even at 50 μM, whereas **1bc** significantly decreased the levels of lipid peroxidation at a 5 μM concentration. It also exhibited good IC_{50} values for the assays in both, cortex (8.0 ± 1.0 μM) and hippocampus (7.3 ± 1.5 μM), and displayed high I_{max} values (93.1 ± 0.3 μM for cortex and 81.4 ± 1.1 μM for hippocampus), as depicted in Table 4. These results suggest that incorporation of selenium functionalities into certain coumarin structures can increase their potential as antioxidant agents.

Table 4. Antioxidant activity of compound **1bc** in the TBARS assay, in mice brain tissues (cortex and hippocampus).

Tissue	Compound concentration (μM) 1	5	10	50	IC_{50} (μM)	I_{max} (%)
Cortex	118.9 ± 11.9	92.3 ± 13.5*	14.6 ± 4.2***	18.3 ± 2.6***	8.0 ± 1.0	80.4 ± 2.7
Hippocampus	111.2 ± 9.9	72.6 ± 3.6**	51.5 ± 17.6***	19.0 ± 3.5***	7.3 ± 1.5	85.3 ± 3.4

Data are expressed as mean ± SD (n = 4) of % lipid peroxidation; IC50 = concentration (μM) to decrease 50% of lipid peroxidation; I_{max} = % maximal inhibition; asterisks denote $p< 0.05$ (*); $p< 0.01$ (**) and $p< 0.001$ (***), when compared to the SNP-induced oxidation, by the Student-Newman-Keuls test.

In conclusion, we have developed a facile and convenient approach toward 4-organoselenyl coumarins from 4-hydroxy coumarin tosylates, using the corresponding diorgano diselenides as selenium sources. The transformation seems to proceed through a one-pot sequential selena-Michael addition/β-elimination mechanism, with tosylate as the leaving group.

The reaction is carried out at room temperature, where it is tolerant to different substituents on the coumarin ring, including sensitive halides and the phenylthio moiety, and delivers the expected products, that may otherwise be more difficult to obtain in a single step. The easy availability of the starting materials and the mild reaction conditions turn the proposed procedure amenable to use in synthetic organic chemistry. In addition, the observed results of the biological tests on mice brain tissue of cortex and hippocampus indicate that the 4-selenocoumarin derivatives have antioxidant properties.

Acknowledgments

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References and notes

1 a) Kontogiorgis, C.; Detsi, A.; Hadjipavlou-Litina, D. *Expert Opin. Ther. Pat.* **2012**, *22*, 437-454; b) Thakur, A.; Singla, R.; Jaitak, V. *Eur. J. Med. Chem.* **2015**, *101*, 476-495; c) Venugopala, K. N.; Rashmi, V.; Odhav, B. *BioMed Res. Int.* **2013**, Art. ID 963248; d) Musa, M. A.; Cooperwood, J. S.; Khan, M. O. F. *Curr. Med Chem.* **2008**, *15*, 2664–2679.

2 a) Kidane, A. G.; Salacinski, H.; Tiwari, A.; Bruckdorfer, K. R.; Seifalian, A. M. *Biomacromolecules* **2004**, *5*, 798–813; b) Appendino, G.; Mercalli, E.; Fuzzati, N.; Arnoldi, L.; Stavri, M.; Gibbons, S.; Ballero Maxia, A. *J. Nat. Prod.* **2004**, *67*, 2108–2110; c) Ma, T.; Liu, L.; Xue, H.; Li, L.; Han, C.; Wang, L.; Chen, Z.; Liu, G. *J. Med. Chem.* **2008**, *51*, 1432–1446; d) Fylaktakidou, K. C.; Hadjipavlou-Latina, D. J.; Litinas, K. E.; Nicolaides, D. N. *Curr. Pharm. Des.* **2004**, *10*, 3813–3833.

3 a) Manjare, S. T.; Kim, Y.; Churchill, D. G. *Acc. Chem. Res.* **2014**, *47*, 2985−2998; b) Mukherjee, A. J.; Zade, S. S.; Singh, H. B.; Sunoj, R. B. *Chem. Rev.* **2010**, *110*, 4357−4416; c) Mugesh, G.; du Mont, W.-W.; Sies, H. *Chem. Rev.* **2001**, *101*, 2125−2179; d) Miyashita, M.; Yoshikoshi, A. *Synthesis* **1980**, 664-666; e) Suzuki, M.; Kawagishi, T.; Noyori, R. *Tetrahedron Lett.* **1981**, *22*, 1809–1812.

4 a) Fernández-Lodeiro, J.; Pinatto-Botelho, M. F.; Soares-Paulino, A. A.; Gonçalves, A. C.; Sousa, B. A.; Princival, C.; Dos Santos, A. A. *Dyes Pigm.* **2014**, *110*, 28–48; b) Li, G.; Zhu, D.; Liu, Q.; Xue, L.; Jiang, H. *Org. Lett.* **2013**, *15*, 2002–2005; c) Huang, S.; He, S.; Lu, Y.; Wei, F.; Zeng, X.; Zhao, L. *Chem. Commun.* **2011**, *47*, 2408–2410; d) Küppers, J.; Schulz-Fincke, A. C.; Palus, J.; Giurg, M.; Skarzewski, J.; Gütschow, M. *Pharmaceuticals* **2016**, *9*, 43.

5 a) Groutas, W. C.; Theodorakis, M. C.; Tomkins, W. A. F.; Herro, G.; Gaynor, T. *J. Med. Chem.* **1984**, *27*, 548–550; b) Tang, E.; Li, W.; Gao, Z. Y.; Gu, X. *Chin. Chem. Lett.* **2012**, *23*, 631–634; c) Tang, E.; Li, W.; Gao, Z. Y. *Synlett* **2012**, *23*, 907–912; d) Cohen, D. T.; Zhang, C.; Pentelute, B. L.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 9784−9787; e) Song, A.; Zhang, J.; Lam, K. S. *J. Comb. Chem.* **2004**, *6*, 112–120.

6 a) Mantovani, A. C.; Goulart, T. A. C.; Back, D. F.; Menezes, P. H.; Zeni, G. *J. Org. Chem.* **2014**, *79*, 10526–10536; b) Wadsworth, D. H.; Detty, M. R. *J. Org. Chem.* **1980**, *45*, 4611–4615; c) Weber, R.; Christiaens, L.; Thibaut, P.; Renson, M. *Tetrahedron* **1974**, *30*, 3865–3871; d) Ruwet, A.; Renson, M. *Bull. Soc. Chim. Belg.* **1969**, *78*, 449–457

7 a) Arsenyan, P.; Vasiljeva, J.; Belyakov, S. *Chem. Heterocyclic Comp.* **2011**, *47*, 237–241; b) Jakobs, A.; Piette, J. *J. Photochem. Photobiol. B* **1994**, *22*, 9–15; c) Tatchen, J.; Kleinschmidt, M.; Marian, C. M. *J. Photochem. Photobiol. A* **2004**, *167*, 201–212; d) Arsenyan, P.; Vasiljeva, J.; Shestakova, I.; Domracheva, I.; Jaschenko, E.; Romanchikova, N.; Leonchiks, A.; Rudevica, Z.; Belyakov, S. *Compt. Rend. Chim.* **2015**, *18*, 399–409; e) Nivorozhkin, A. L.; Toftlund, H.; Stein, P. C.; Jensen, F. *J. Chem. Soc., Perkin Trans 2* **1993**, 2423–2428; f) Abdel-Hafez, S. H.; Elkhateeb, A.; Gobouri, A. A.; El Azab, I. H.; Kirsche, G. *Heterocycles* **2016**, *92*, 1054–1062.

8 a) Silveira, C. C.; Rinaldi, F.; Guadagnin, R. C. *Eur. J. Org. Chem.* **2007**, 4935–4939; b) Silveira, C. C.; Rinaldi, F.; Guadagnin, R. C.; Braga, A. L. *Synthesis* **2009**, 469–473; c) Silveira, C. C.; Mendes, S. R.; Wolf, L. *J. Braz. Chem. Soc.* **2010**, *21*, 2138–2145; d) Silveira, C. C.; Mendes, S. R.; Rosa, D. D.; Zeni, G. *Synthesis* **2009**, *23*, 4015–4021.

9 a) Silveira, C. C.; Mendes, S. R.; Wolf, L.; Martins, G. M.; Von Mühlen, L. *Tetrahedron* **2012**, *68*, 10464–10469; b) Azeredo, J. B.; Godoi, M.; Martins, G. M.; Silveira, C. C.; Braga, A. L. *J. Org. Chem.* **2014**, *79*, 4125–4130.

10 a) Dabdoub, M. J.; Silveira, C. C.; Lenardão, E. J.; Guerrero Jr., P. G.; Viana, L. H.; Kawasoko, C. Y.; Baroni, A. C. M. *Tetrahedron Lett.* **2009**, *50*, 5569−5571; b) Silveira, C. C.; Felix, L. A.; Braga, A. L.; Kaufman, T. S. *Org. Lett.* **2005**, *7*, 3701−3704; c) Silveira, C. C.; Machado, A.; Braga, A. L.; Lenardão, E. J. *Tetrahedron Lett.* **2004**, *45*, 4077−4080.

11 a) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697–2699; b) Kissane, M.; Murphy, M.; O'Brien, E.; Chopra, J.; Murphy, L.; Collins, S. G.; Lawrence, S. E.; Maguire, A. R. *Org. Biomol. Chem.* **2011**, *9*, 2452–2472.

12 a) Bovonsombat, P.; Ali, R.; Khan, C.; Leykajarakul, J.; Pla-on, K.; Aphimanchindakul, S.; Pungcharoenpong, N.; Timsuea, N.; Arunrat, A.; Punpongjareorn, N. *Tetrahedron* **2010**, *66*, 6928–6935; b) Singh, P. P.; Thatikonda, T.; Kumar, K. A. A.; Sawant, S. D.; Singh, B.; Sharma, A. K.; Sharma; Singh, D.; Vishwakarma, R. A. *J. Org. Chem.* **2012**, *77*, 5823–5828.

13 a) Kym, P. R.; Iyengar, R.; Souers, A. J.; Lynch, J. K.; Judd, A. S.; Gao, J.; Freeman, J.; Mulhern, M.; Zhao, G.; Vasudevan, A.; Wodka, D.; Blackburn, C.; Brown, J.; Che, J. L.; Cullis, C.; Lai, S. J.; LaMarche, M. J.; Marsilje, T.; Roses, J.; Sells, T.; Geddes, B.; Govek, E.; Patane, M.; Fry, D.; Dayton, B. D.; Brodjian, B.; Falls, D.; Brune, M.; Bush, E.; Shapiro, R.; Knourek-Segel, V.; Fey, T.; McDowell, C.; Reinhart, G. A.; Preusser, L. C.; Marsh, K.; Hernández, L.; Sham, H. L.; Collins, C. A. *J. Med. Chem*. **2005**, *48*, 5888–5891; b) Zhao, P.-L.; Wang, L.; Zhu, X.-L.; Huang, X.; Zhan, C.-G.; Wu, J.-W.; Yang, G.-F. *J. Am. Chem. Soc*. **2010**, *132*, 185–194.

14 a) Ren, J.-L.; Zhang, X.-Y.; Yu, B.; Wang, X.-X.; Shao, K.-P.; Zhu, X.-G.; Liu, H.-M. *Eur. J. Med. Chem*. **2015**, *93*, 321–329; b) Bartlett, M. J.; Turner, C. A.; Harvey, J. E. *Org. Lett.* **2013**, *15*, 2430–2433; c) Gao, W.-T.; Hou, W.-D.; Zheng, M.-R.; Tang, L.-J. *Synth. Commun*. **2010**, *40*, 732–738.

15 a) Rao, M. L. N.; Kumar, A. *Tetrahedron* **2015**, *71*, 5137–5147; b) Kotharkar, S. A.; Shinde, D. B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6181–6184; c) Reddy Parumala, S. K.; Krishna Peddinti, R. *Green Chem*. **2015**, *17*, 4068-4072; d) Malik, S.; Equbal, D.; Lavekar, A. G.; Sinha, A. K. *Org. Biomol. Chem.* **2016**, *14*, 6111–6118; e) Zhang, L.; Meng, T.; Fan, R.; Wu, J. *J. Org. Chem.* **2007**, *72*, 7279–7286.

16 Denmark, S. E.; Montgomery, J. I. *J. Org. Chem.* **2006**, *71*, 6211–6220.

17 **Typical procedure:** $NaBH_4$ (19 mg, 0.5 mmol) was added to the diselenide (0.275 mmol) dissolved in EtOH-THF (4:1 *v/v*, 2.5 mL) and the reaction was stirred under argon until it became colorless (diselenide cleavage). Then, a THF solution of the tosylate (0.5 mmol, 2 mL) was added and the reaction was stirred at r.t. for 30 min. H_2O was added and the products were extracted with EtOAc (3 × 10 mL). The extract was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography.

18 Harrison, P. A.; Murtagh, L.; Willis, C. L. *J. Chem. Soc. Perkin Trans. 1* **1993**, 3047–3050.

19 Grayson, D. H.; Lyons, R. G.; Rasool, S. *Proceed. Royal Irish Acad. B* **1989**, *89B*, 167**–**172.

20 a) Santoro, S.; Battistelli, B.; Testaferri, L.; Tiecco, M.; Santi, C. *Eur. J. Org. Chem.* **2009**, 4921–4925; b) Kim, Y.; Mulay, S. V.; Choi, M.; Yu, S. B.; Jon, S. Churchill, D. G. *Chem. Sci.* **2015**, *6*, 5435–5439.

21 *Mp and NMR data of selected compounds (400 MHz, in $CDCl_3$):* **4-(Phenylselenyl)-2*H*-chromen-2-one (1aa).-** mp: 145-146ºC; ^{1}H NMR δ: 5.91 (s, 1H), 7.29-7.34 (m, 2H), 7.44-7.49 (m, 2H), 7.5-7.53 (m, 1H), 7.56 (ddd, *J* = 8.5, 7.3, 1.5, 1H), 7.66-7.71 (m, 3H). ^{13}C NMR δ: 112.9, 117.1, 119.2, 123.5, 124.2, 125.0, 130.4 (2C), 132.2, 137.2, 151.8, 156.1, 159.0. **4-((4-Chlorophenyl)selenyl)-2*H*-chromen-2-one (1ab).-** mp: 148-149ºC; ^{1}H NMR δ: 5.89 (s, 1H), 7.29-7.35 (m, 2H), 7.44 (d, *J* = 8.6, 2H), 7.56 (ddd, *J* = 8.5, 7.4, 1.5, 1H), 7.60 (d, *J* = 8.6, 2H), 7.67 (dd, *J* = 7.9, 1.4, 1H). ^{13}C NMR δ: 113.3, 117.2, 119.1, 121.7, 124.3, 124.9, 130.8, 132.4, 137.3, 138.4, 151.9, 155.4, 158.9. **4-(Benzylselenyl)-2*H*-chromen-2-one (1ad).-** mp: 150-153ºC; ^{1}H NMR δ: 4.29 (s, 2H), 6.46 (s, 1H), 7.22-7.27 (m, 1H), 7.29-7.36 (m, 4H), 7.39-7.42 (m, 2H), 7.52 (ddd, *J* = 8.6, 7.3, 1.5, 1H), 7.59 (dd, *J* = 7.9, 1.4, 1H). ^{13}C NMR δ: 30.6, 112.8, 117.2, 119.5, 124.2, 125.3, 127.9, 128.9, 129.1, 132.1, 134.8, 151.9, 154.5, 158.7. **6-Chloro-4-((4-chlorophenyl)selenyl)-2*H*-chromen-2-one (1af).-** mp: 164-166ºC; ^{1}H NMR δ: 5.9 (s, 1H), 7.28 (d, *J* = 8.8, 1H), 7.46 (d, *J* = 8.5, 2H), 7.51 (dd, *J* = 8.8, 2.4, 1H), 7.6 (d, *J* = 8.5, 2H), 7.64 (d, *J* = 2.4, 1H). ^{13}C NMR δ: 114.2, 118.6, 120.2, 121.4, 124.6, 129.8, 130.9, 132.3, 137.5, 138.4, 150.4, 154.2, 158.2. **8-Methyl-4-(phenylselenyl)-2*H*-chromen-2-one (1ai).-** mp: 143-144ºC; ^{1}H NMR δ: 2.45 (s, 3H), 5.9 (s, 1H), 7.2 (t, *J* = 7.7, 1H), 7.4-7.42 (m, 1H), 7.44-7.48 (m, 2H), 7.49-7.52 (m, 1H), 7.53-7.56 (m, 1H), 7.66-7.69 (m, 2H). ^{13}C NMR δ: 15.7, 112.6, 118.9, 122.6, 123.7, 123.8, 126.6, 130.3, 130.4, 133.5, 137.2, 150.2, 156.6, 159.2. **4-((4-Chlorophenyl)selenyl)-8-methyl-2*H*-chromen-2-one (1aj).-** mp: 153-155ºC; ^{1}H NMR δ: 2.45 (s, 3H), 5.89 (s, 1H), 7.19 (t, *J* = 7.7, 1H), 7.4-7.45 (m, 3H), 7.52 (dd, *J* = 7.9, 0.7, 1H), 7.59 (d, *J* = 8.5, 2H). ^{13}C NMR δ: 15.7, 112.8, 118.8, 121.9, 122.6, 123.8, 126.7, 130.7, 133.7, 137.2, 138.5, 150.2, 155.9, 159.8. **3-Bromo-4-(*p*-tolylselenyl)-2*H*-chromen-2-one (1bc).-** mp: 104-106ºC. ^{1}H NMR δ: 2.30 (s, 3H), 7.05-7.09 (m, 2H), 7.16 (ddd, *J* = 8.1, 7.3, 1.2, 1H), 7.3 (ddd, *J* = 8.3, 1.2, 0.4, 1H), 7.33-7.36 (m, 2H), 7.49 (ddd, *J* = 8.3, 7.3, 1.5, 1H), 7.94 (ddd, *J* = 7.7, 1.5, 0.4, 1H). ^{13}C NMR δ: 21.1, 116.9, 120.4, 120.8, 124.8, 125.8, 130.0, 130.6, 132.0, 132.7, 138.6, 150.6, 151.6, 155.6. **3-Bromo-4-((4-chlorophenyl)selenyl)-8-methyl-2*H*-chromen-2-one (1bj).-** mp: 159-161ºC; ^{1}H NMR δ: 2.46 (s, 3H), 7.1 (t, *J* = 8.1, 1H), 7.22 (d, *J* = 8.7, 2H), 7.36 (d, *J* = 8.7, 2H), 7.37-7.39 (m, 1H), 7.77 (ddd, *J* = 8.1, 1.5, 0.6, 1H). ^{13}C NMR δ: 15.6, 120.4, 121.1, 124.5, 126.6, 127.8, 129.9, 133.5, 133.7, 134.5, 149.9 (2C), 155.6. **3-Bromo-8-methyl-4-(*p*-tolylselenyl)-2*H*-chromen-2-one (1bk).-** mp: 115-118ºC; ^{1}H NMR δ: 2.29 (s, 3H), 2.45 (s, 3H), 7.03-7.07 (m, 3H), 7.32-7.35 (m, 3H), 7.81 (d, *J* = 8.1, 1H). ^{13}C NMR δ: 15.5, 21.1, 120.3, 120.7, 124.3, 126.0, 126.4, 127.9, 130.6, 132.7, 133.4, 138.4, 149.9, 150.8, 155.7. **4-(Phenylselenyl)-3-(phenylthio)-2*H*-chromen-2-one (1ca).-** mp: 113-116ºC; ^{1}H NMR δ: 7.09 (ddd, *J* = 8.2, 7.3, 1.2, 1H), 7.18-7.29 (m, 7H), 7.32-7.34 (m, 2H), 7.4-7.46 (m, 3H), 7.84 (ddd, *J* = 8.1, 1.5, 0.4, 1H). ^{13}C NMR δ: 116.9, 120.6, 124.3, 127.2, 128.0, 129.1, 129.6, 129.8 (2C), 130.2, 130.8, 132.0, 132.3, 134.5, 152.4, 155.1, 157.0. **4-((4-Chlorophenyl)selenyl)-3-(phenylthio)-2*H*-chromen-2-one (1cb).-** mp: 132-134ºC; ^{1}H NMR δ: 7.17 (ddd, *J* = 8.1, 7.3, 1.2, 1H), 7.21-7.25 (m, 2H), 7.25-7.28 (m, 1H), 7.28-7.3 (m, 1H), 7.31-7.32 (m, 1H), 7.32-7.35 (m, 3H), 7.37 (d, *J* = 8.7, 2H), 7.45 (ddd, *J* = 8.3, 7.3, 1.5, 1H), 7.85 (ddd, *J* = 8.2, 1.5, 0.4, 1H). ^{13}C NMR δ: 117.0, 120.5, 124.5, 127.3, 128.8, 129.2, 129.6, 129.9, 130.0, 132.2, 133.7, 134.3, 134.4, 152.4, 154.2, 156.8.

22 Kobayashi, N.; Furuyama, T.; Satoh, K. *J. Am. Chem. Soc*. **2011**, *133*, 19642–19645; b) Furuyama, T.; Satoh, K.; Kushiya, T.; Kobayashi, N. *J. Am. Chem. Soc*. **2014**, *136*, 765−776.

23 Satyapati Devi, A.; Helissey, P.; Nongkhlaw, R. L.; Vishwakarma, J. N. *Synth. Commun*. **2013**, *43*, 1653–1660.

24 Rappoport, Z. *Acc. Chem. Res.* **1981**, *14*, 7–15; b) Rappoport, Z.; Gazit, A. *J. Org. Chem.* **1985**, *50*, 3184–3194; c) Avramovitch, B.; Weyerstahl, P.; Rappoport, Z. *J. Am. Chem. Soc.* **1987**, *109*, 6687–6699.

25 a) Lubineau, A.; Bienayme, H.; Le Gallic, J. *J. Chem. Soc., Chem. Commun*. **1989**, 1918–1919; b) Silveira, C. C.; Guerra, R. B.; Comasseto, J. V. *Tetrahedron Lett.* **2007**, *48*, 5121–5124.

26 a) Jitsuzaki, D.; Onizuka, K.; Nishimoto, A.; Oshiro, I.; Taniguchi, Y.; Sasaki, S. *Nucl. Acid. Res.* **2014**, *42*, 8808–8815; b) Onizuka, K.; Taniguchi, Y.; Sasaki, S. *Bioconj. Chem.* **2009**, *20*, 799–803; c) Hirokane, T.; Hirata, Y.; Ishimoto, T.; Nishii, K.; Yamada, H. *Nat. Commun*. **2014**, *5*, 3478.

27 a) Person, M. D.; Mason, D. E.; Liebler, D. C.; Monks, T. J.; Lau, S. S. *Chem. Res. Toxicol.* **2005**, *18*, 41–50; b) Monks, T. J.; Lau, S. S. *Toxicol. Pathol.* **2013**, *41*, 315–321; c) Elfarra, A. A.; Krause, R. J. *Michael Addition–Elimination Reactions: Roles in Toxicity and Potential New Therapeutic Applications*. In: *Biotechnology: Pharmaceutical Aspects, Volume IX. Advances in Bioactivation Research*. Ed.: Elfarra, A. A.; Springer, New York, USA, 2008. Chapter 3, pp. 57–68.

28 a) Uher, R.; Mors, O.; Rietschel, M.; Rajewska-Rager, A; Petrovi, C. A.; Zobel, A.; Heingsberg, N.; Mendkewicz, J.; Aintchison, K. J.; Farner, A.; Vaváková, M.; Uracková, Z.; Trebatichá, J. *J. Oxid. Med. Call. Longev*. **2005**, 1–12; b) Loetchutinat, C.; Kothan, S.; Dechsupa, S.; Meesungnoen, J.; Jay-Gerin, J. P., Makhetkorn, S. *Radiat. Phys. Chem*. **2005**, *72*, 323–331.

29 The tissue was incubated with DCHF-DA (1 mM) and NaN_3 in Tris-HCl buffer (10 mM pH 7.4). The fluorescence was measured at 520 nm, exciting at 488 nm. Results are in fluorescence units.

30 Halliwell, B.; Gutteridge, J. M. C. *Free Radical Biol.Med.* **1995**, *18*, 125–126.

31 Wang, X.; Michaelis, E. K. *Front. Aging Neurosci.* **2010**, *2*, 9–12.

32 Okawa, N.; Ohiahi, K. Yagi, *Anal. Biochem.* **1979**, *95*, 351–358.

Highlights:

1. Efficient Michael addition/β-elimination approach toward 4-organoselanyl coumarins
2. Diselenides as suitable selenium sources for a Michael addition/β-elimination process
3. Readily accessible selenium-substituted heterocycles with antioxidant properties
4. Antioxidant profile of 4-organoselanyl coumarins in mice cortex and hippocampus