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Access to a key intermediate for the synthesis of 1-thia-analogue of quercetin

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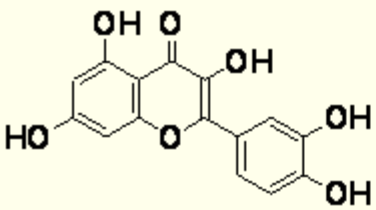
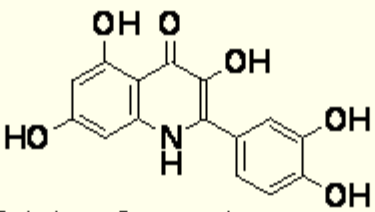
Abstract : We described here the access to 2-mercapto-4,6-dimethoxy-benzoic acid a key intermediate in the synthesis of the thia-analogue of quercetin. Two syntheses were attempted. The first one using a previously described strategy afforded only very modest yields of the requested compound. The second one which is original is based on the transposition by thermolysis of the appropriately functionalized phenol *O*-thiocarbamate precursor into the corresponding thiophenol *S*-thiocarbamate gave fair results which are currently under optimisation.

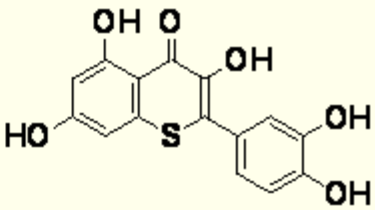
Quercetin **1** is the subject of many investigations due to its biologic and medicinal properties. Flavonoids, such as flavones and flavonols, are secondary plant metabolites [1, 2] particularly found in the upper parts of plants. As a consequence, they are present in a great variety of food and especially in fruit and vegetables. Quercetin is the main flavonoid occurring in food and is present at an average level of 10 mg per kg. Higher concentrations can even be found in some common vegetables like onions (300 mg/kg). Nowadays, according to dietary habits, the average daily intake [3] of flavonoid has been assessed from 6 mg in Finland to 70 mg in Japan, and more precisely, quercetin amount represents 60 to 75 % of this average intake. Moreover, quercetin is a very efficient antioxidant [4, 5] and appears to be active in many diseases related to ageing like cancer [6], cardiovascular [7] and neurodegenative [8] diseases, as widely described in the literature (see [9, 10] for recent reviews). Furthermore, the quercetin skeleton is the main part of the drug Flavopiridol, which is now under phase I clinical trials [11, 12].



1 Quercetin

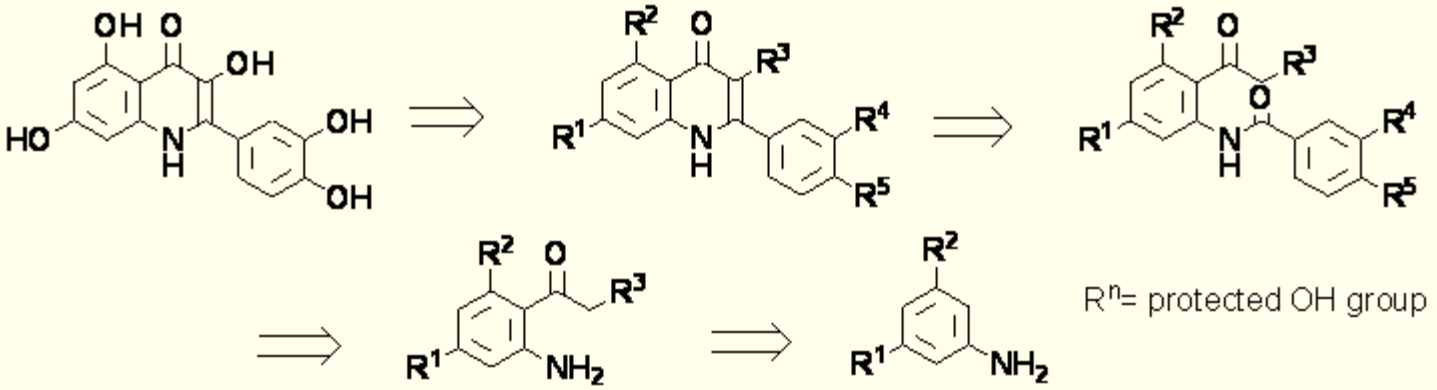


2 1-Aza-Quercetin

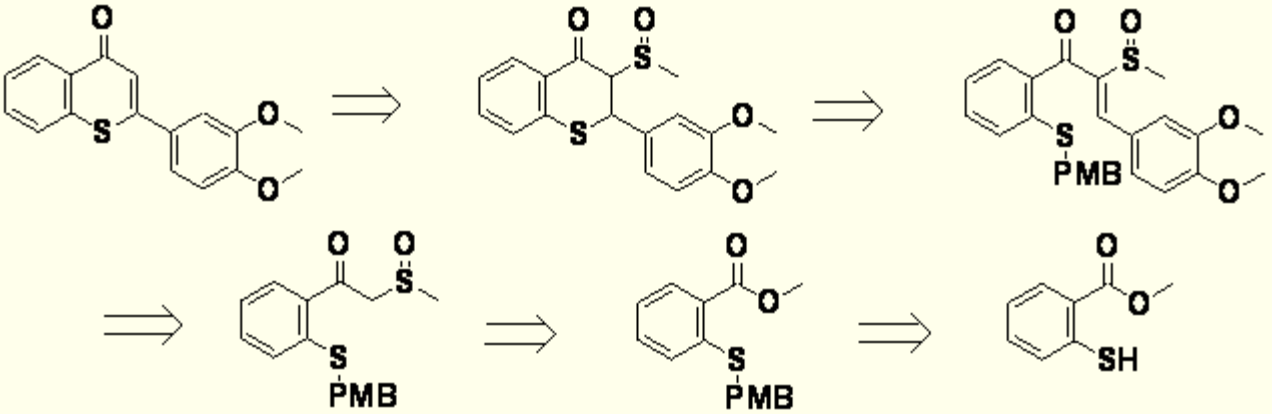


3 1-Thia-Quercetin

More recently the aza-analogue **2** of quercetin has received some attention and different derivatives of **2** have been prepared and evaluated as topoisomerase inhibitors. The synthesis [13, 14] of these compounds have been performed from the suitable amide of *o*-acylaniline which is cyclised in quinolone.

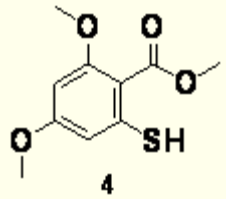


We described previously the selective synthesis of all the mono *O*-methylated analogues of quercetin which are the major metabolites [15] apart the conjugated form of quercetin with glucuronic acid [16]. The very different activity of these compounds pushed us to synthesize new analogues of quercetin. The 1-thia-analogue of quercetin **3** in which the sufur atom replaces the oxygen of the chromone ring is to the best of our knowledge unknown. The synthesis of the unfunctionalized skeleton of 1-thia-quercetin **3** has been developed by Taylor *et al* [17] and by Kataoka *et al* [18]. The key steps use sequentially the multiple facet of the reactivity of b-ketosulphoxides: (i) alkylation of the active methylene; (ii) ring closure by Michael addition of the deprotected thiol and finally (iii) thermal elimination of the sulfinyl group which creates the conjugated double bond.



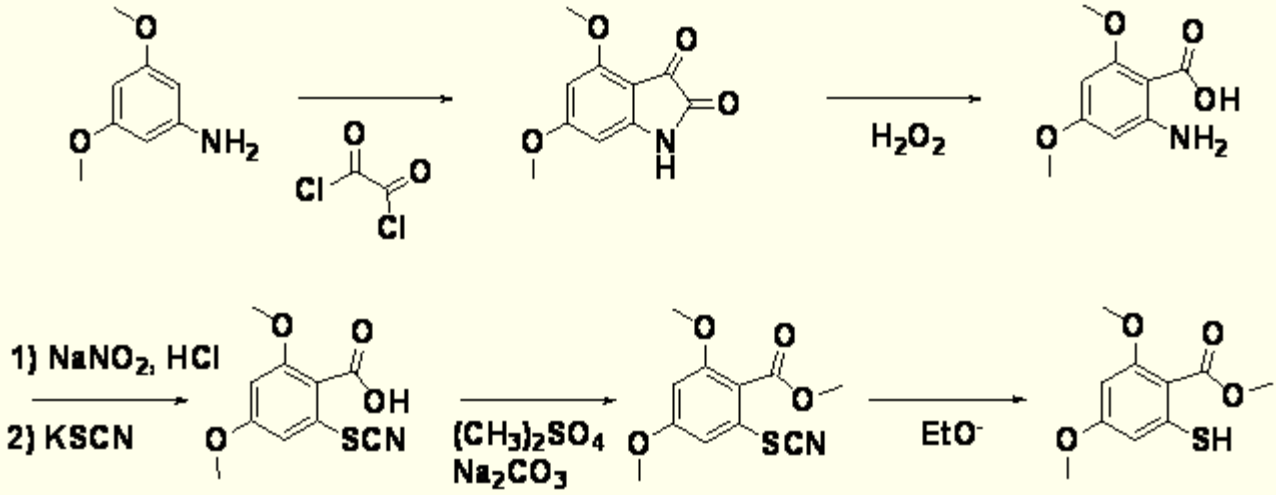
PMB = para-methoxybenzyl

We first attempted to synthesize the dimethoxy analogue **4** of the requested *ortho*-mercaptobenzoate in order to get the 1-thia-quercetin **3** by using the strategy described by Newman and Angier [19].

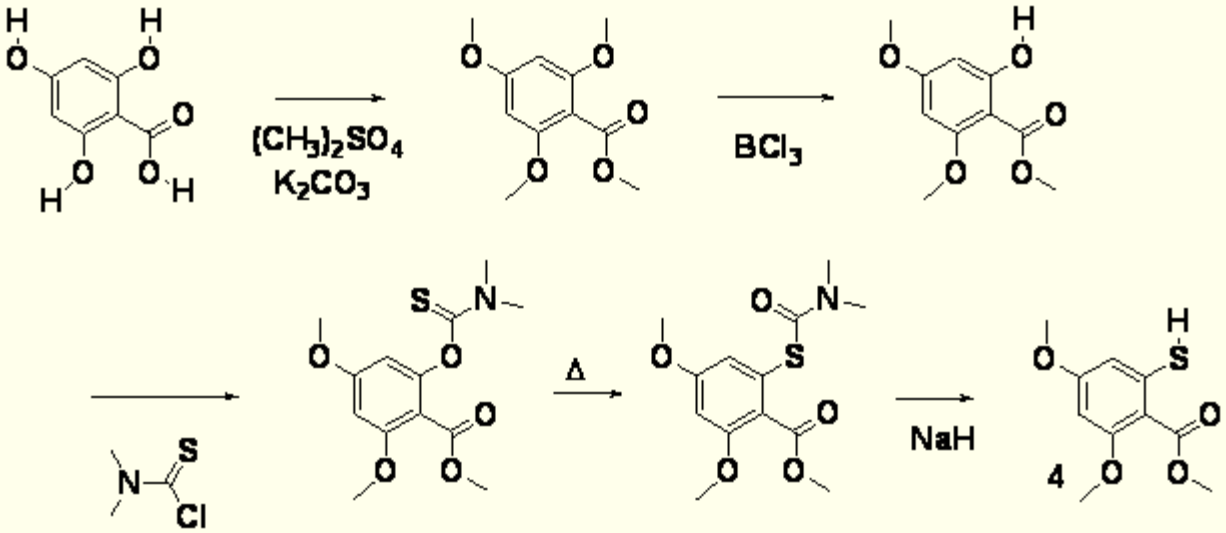


4

Reaction of 3,5-dimethoxyaniline with oxalyl chloride afforded isatin which was oxidised to 4,6-dimethoxyanthranilic acid. After diazotation by sodium nitrite, the corresponding diazonium salt was treated by potassium thiocyanate and the carboxylic acid esterified with dimethyl sulphate. Finally treatment with a solution of potassium hydroxide in ethanol gave compound **4**. Unfortunately, in our hands, the yields of the diazotization (36%) and of the thiol deprotection (15%) are low, so we decided to find another route to compound **4**.



We choose 2,4,6-trihydroxybenzoic acid as starting material. In a first step we etherified all the phenol groups and esterified the carboxylic acid. The 2-methoxy group was then selectively cleaved by boron trichloride [20]. Then the phenoxy group was treated by *N*,*N*-dimethylthiocarbamoyl chloride. Thermolysis of the O-thiocarbamate afforded the S-thiocarbamate key compound which after treatment with sodium hydride [21] led to 2-mercapto-4,6-dimethoxy-benzoic acid methyl ester **4** in a fair yield. Optimizations of the thermolysis and of the final step are in progress.



The transformation of the key compound **4** in 1-thia-quercetin **3** is currently under investigation in our laboratory. Finally we wish point out that the same strategy may be applied to the synthesis of the thia analogue of catechin and epicatechin which are very active flavanols [22] as we have demonstrated for the methylated metabolites [23].

References

[1] Bohm, Bruce A. *Introduction to Flavonoids*, 1998.
[2] Packer, Lester; Editor. *Flavonoids and Other Polyphenols. [In: Methods Enzymol., 2001; 335]*, 2001.
[3] Hollman, Peter C. H.; Arts, Ilja C. W. Flavonols, flavones and flavanols - nature, occurrence and dietary burden. *Journal of the Science of Food and Agriculture* **2000**, *80*, 1081-1093.
[4] Cren-Olive, Cecile; Hapiot, Philippe; Pinson, Jean; Rolando, Christian. Free Radical Chemistry of Flavan-3-ols: Determination of Thermodynamic Parameters and of Kinetic Reactivity from Short (ns) to Long (ms) Time Scale. *Journal of the American Chemical Society* **2002**, *124*, 14027-14038.
[5] Pietta, Pier-Giorgio. Flavonoids as Antioxidants. *Journal of Natural Products* **2000**, *63*, 1035-1042.
[6] Choi, Jung- A.; Kim, Ja-Young; Lee, Jeong-Yim; Kang, Chang-Mo; Kwon, Ho-Jeong; Yoo, Young-Do; Kim, Tae-Whan; Lee, Yun-Sil; Lee, Su-Jae. Induction of cell cycle arrest and apoptosis in human breast cancer cells by quercetin. *International Journal of Oncology* **2001**, *19*, 837-844.

[7] Yoshizumi, Masanori; Tsuchiya, Koichiro; Kirima, Kazuyoshi; Kyaw, Moe; Suzaki, Yuki; Tamaki, Toshiaki. Quercetin inhibits Shc- and phosphatidylinositol 3-kinase-mediated c-Jun N-terminal kinase activation by angiotensin II in cultured rat aortic smooth muscle cells. *Molecular Pharmacology* **2001**, *60*, 656-665.
[8] Schroeter, Hagen; Spencer, Jeremy P. E.; Rice-Evans, Catherine; Williams, Robert J. Flavonoids protect neurons from oxidized low-density-lipoprotein-induced apoptosis involving c-Jun N-terminal kinase (JNK), c-Jun and caspase-3. *Biochemical Journal* **2001**, *358*, 547-557.
[9] Lamson, D. W.; Brignall, M. S. Antioxidants and cancer, part 3: quercetin. *Alternative medicine review: a journal of clinical therapeutic* **2000**, *5*, 196-208.
[10] Wang, Hui-Kang. The therapeutic potential of flavonoids. *Expert Opinion on Investigational Drugs* **2000**, *9*, 2103-2119.
[11] Gross, A.; Borcherding, D. R.; Friedrich, D.; Sabol, J. S. A stereocontrolled approach to substituted piperidones and piperidines: flavopiridol D-ring analogs. *Tetrahedron Letters* **2001**, *42*, 1631-1633.
[12] Murthi, Krishna K.; Dubay, Marja; McClure, Christopher; Brizuela, Leonardo; Boisclair, Michael D.; Worland, Peter J.; Mansuri, Muzammil M.; Pal, Kollol. Structure-activity relationship studies of flavopiridol analogues. *Bioorganic & Medicinal Chemistry Letters* **2000**, *10*, 1037-1041.
[13] Pain, Christophe; Celanire, Sylvain; Guillaumet, Gerald; Joseph, Benoit. Synthesis of 5-substituted 2-(4- or 3-methoxyphenyl)-4(1H)-quinolones. *Tetrahedron* **2003**, *59*, 9627-9633.
[14] Sui, Zhihua; Nguyen, Van N.; Altom, Jason; Fernandez, Jeffrey; Hilliard, Jamese J.; Bernstein, Jeffrey I.; Barrett, John F.; Ohemeng, Kwasi A. Synthesis and topoisomerase inhibitory activities of novel aza-analogues of flavones. *European Journal of Medicinal Chemistry* **1999**, *34*, 381-387.
[15] Bouktaib, Mohamed; Lebrun, Stephane; Atmani, Aziz; Rolando, Christian. Hemisynthesis of all the O-monomethylated analogues of quercetin including the major metabolites, through selective protection of phenolic functions. *Tetrahedron* **2002**, *58*, 10001-10009.
[16] Bouktaib, Mohamed; Atmani, Aziz; Rolando, Christian. Regio- and stereoselective synthesis of the major metabolite of quercetin, quercetin-3-O-b-D-glucuronide. *Tetrahedron Letters* **2002**, *43*, 6263-6266.
[17] Taylor, A. W.; Dean, D. K. A new synthesis of thioflavones. *Tetrahedron Letters* **1988**, *29*, 1845-1848.
[18] Kataoka, Tadashi; Watanabe, Shin-ichi; Mori, Eiji; Kadomoto, Ryoji; Tanimura, Susumu; Kohno, Michiaki. Synthesis and structure-activity relationships of thioflavone derivatives as specific inhibitors of the ERK-MAP kinase signaling pathway. *Bioorganic & medicinal chemistry* **2004**, *12*, 2397-2407.
[19] Newman, Howard; Angier, Robert B. Synthesis of the ring-b sulfur, analog of epigriseofulvin. *Journal of Organic Chemistry* **1969**, *34*, 3484-3491.
[20] Rossi, Renzo; Carpita, Adriano; Bellina, Fabio; Stabile, Paolo; Mannina, Luisa. Synthesis of 3-arylisocoumarins, including thunberginols A and B, unsymmetrical 3,4-disubstituted isocoumarins, and 3-ylidenephthalides via iodolactonization of methyl 2-ynylbenzoates or the corresponding carboxylic acids. *Tetrahedron* **2003**, *59*, 2067-2081.
[21] Berryman, K. A.; Edmunds, J. J.; Bunker, A. M.; Haleen, S.; Bryant, J.; Welch, K. M.; Doherty, A. M. Endothelin receptor antagonists: synthesis and structure-activity relationships of substituted benzothiazine-1,1-dioxides. *Bioorganic & medicinal chemistry* **1998**, *6*, 1447-1456.
[22] Cren-Olive, Cecile; Teissier, Elisabeth; Duriez, Patrick; Rolando, Christian. Effect of catechin O-methylated metabolites and analogs on human LDL oxidation. *Free radical biology & medicine* **2003**, *34*, 850-855.
[23] Cren-Olive, Cecile; Lebrun, Stephane; Rolando, Christian. An efficient synthesis of the four mono methylated isomers of (+)-catechin including the major metabolites and of some dimethylated and trimethylated analogues through selective protection of the catechol ring. *Journal of the Chemical Society, Perkin Transactions 1* **2002**, 821-830.