# A New Synthesis of *o*-Prenyl Phenols

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Phenylthiyl radicals add regiospecifically to isoprenoid chrom-3-enes to yield 3-phenylthiochromans which open to *o*-prenylphenols on electron transfer from metal naphthalenides or a mercury cathode; the two–step process is tolerant of free phenol and carbonyl functions, and trisubstituted double bonds.

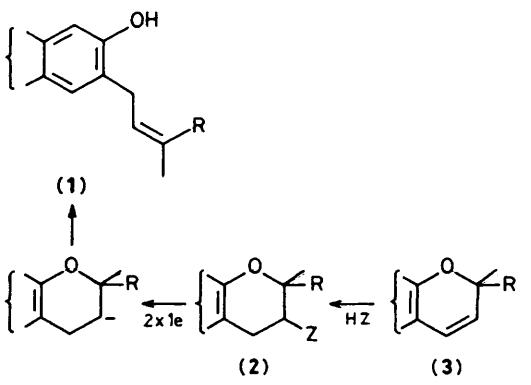


The *ortho*-prenylphenol substructure (**1**; R = –[$CH_2CH$=$^{E}C$Me-$CH_2$]$_n$–H) is of biogenetic importance in the meroterpenoid group, as the first product from prenylpyrophosphate–phenol condensation.[1] Many modifications of this structure are observed in nature, *e.g.* the corresponding benzoquinone unit is found in the biologically important K vitamins, ubiquinone, and plastoquinone.

Although several synthetic routes to system (**1**), from a suitable phenol, are available (mostly through direct acid-[2] or base-[2a,3] catalysed alkylation, or by Claisen rearrangement[4]) the majority of such reactions reported are relatively low yielding; *O*- and di-alkylation and lack of regioselectivity are common problems.

In many cases the related chrom-3-enes (**3**) can be obtained in good yield from regioselective reactions.[5] We therefore sought a route for conversion of chrom-3-enes (**3**) into *o*-prenylphenols (**1**), which might be of use both in total synthesis and in natural product interconversion. Direct reduction, (**3**) → (**1**), using sodium–liquid ammonia, has been reported in a few cases,[6] but the method appears unsuitable for compounds with sensitive functional groups. Anti-Markownikow addition to a chrom-3-ene, (**3**) → (**2**), followed by electron-transfer-induced ring opening, (**2**) → (**1**), (formally *via* $E2_{cb}$) seemed possible, and we report here that this is indeed a viable process.

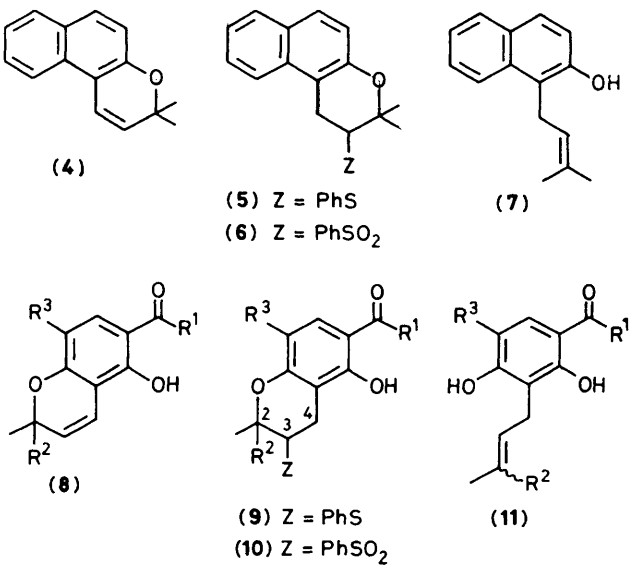
Since ionic additions to chrom-3-enes can be unsatisfactory we investigated the radical addition of benzenethiol. The naphthochromene (**4**), on heating with benzenethiol and azoisobutyronitrile, provided the 3-phenylthiochroman (**5**) (63%);† the isomeric 4-phenylthiochroman was not detected. Similarly, the chromene (**8a**), with free *o*-hydroxyketone functions, yielded the chroman (**9a**) (83%). The same method when applied to the chromene (**8c**) gave (**9c**) (28%), but irradiation of (**8c**) with benzenethiol and diphenyl disulphide raised the yield of (**9c**) to 90%. The addition reaction is thus regioselective for the aryl-conjugated double bond. Chromans (**9b**) and (**9d**) were obtained [*hν*, $(PhS)_2$, PhSH] in 56 and 63% yield, respectively, from (**8b**) and (**8d**); the aldehyde function is unaffected.




† All yields refer to purified products.

The reductive ring opening of the 3-phenylthiochroman (**5**) was effected by three methods; (i) lithium naphthalenide in tetrahydrofuran, (ii) potassium naphthalenide in tetrahydrofuran, and (iii) electrolysis, using acetonitrile–tetraethylammonium bromide, and a mercury cathode. 1-Isopent-2-enyl-2-naphthol (**7**) was obtained in 63, 60, and 53% yields respectively. The same product (**7**) was also prepared (70%) from the phenyl sulphone (**6**) using potassium naphthalenide. Similar reactions with the sulphides (**9a**—**c**) were investigated, and ring opening by reductive elimination proceeded satisfactorily in each case, without concomitant reduction of carbonyl functions or interference by free phenolic hydroxy groups. In this way were obtained (**11a**)[7] [59% using method (ii), 49% with method (iii)] and (**11b**) (49% using potassium naphthalenide). The latter product was obtained as a 1:1 mixture of (*E*)- and (*Z*)-isomers, as shown by $^{13}C$ n.m.r. The geranyltrihydric phenol (**11c**) was also obtained but was too unstable for it to be purified satisfactorily. Finally, the sulphone (**10**) also provided (**11a**) (method ii, 25%).

All new compounds had satisfactory analytical and spectroscopic data. The 3-phenylthiochromans were characterised by $^1H$ n.m.r.; the protons of the heterocyclic ring, in these examples, were resolved at 250 MHz showing *e.g.* for (**9d**), δ 2.74 (*J* 10.0, 17.5 Hz, 4-$H_{ax}$), 3.13 (*J* 5.6, 17.5 Hz, 4-$H_{eq}$), and 3.37 (*J* 5.6, 10.0 Hz, 3-H). Product (**11a**) had $^1H$ n.m.r. data very close to literature values[7], and $^{13}C$ n.m.r. data were in support, *e.g.* δ 17.9 (q), 25.8 or 26.1(q), 22.1(t), 123.1(d), and 131.5 p.p.m. (s) for the prenyl unit.




**a**; $R^1 = R^2 = Me$, $R^3 = H$

**b**; $R^1 = Me$, $R^3 = H$, $R^2$ =

**c**; $R^1 = Me$, $R^3 = OH$, $R^2$ =

**d**; $R^1 = R^3 = H$, $R^2 = Me$

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