Biomimetic Synthesis of Natural Silybin

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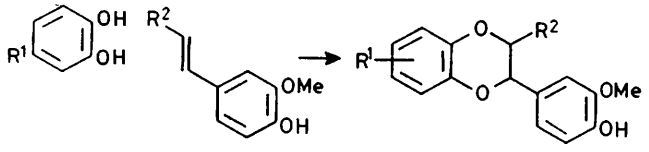
Summary A one-step biomimetic synthesis of the natural flavolignan silybin is reported.

ENCOURAGING results obtained by two of us[1] in the synthesis of the natural benzodioxan eusiderin by oxidative coupling of propenylcatechols have stimulated further investigation of the scope of this reaction. Oxidation of equimolar amounts of the catechol (**1**) with isoeugenol (**2a**) or coniferyl alcohol (**2b**) with Ag_2O in benzene containing methanol or acetone afforded, in good yield, the 6-(or 7-)-substituted 2,3-*trans*-benzodioxans (**3**),[2] most probably *via* a free radical coupling pathway[1] (Scheme).



(1) (2) (3)

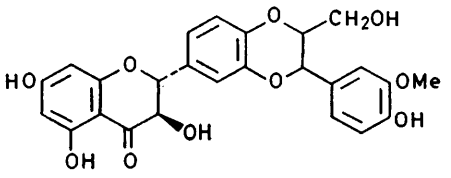
a, R^2 = Me
b, R^2 = CH_2OH

SCHEME

The reaction, which results in only 2,3-*trans* products, shows remarkable regioselectivity when R is an alkyl group, but much less when it is an electron-withdrawing substituent.

Herein we report the successful application of this reaction to a one-step biomimetic synthesis of the natural flavolignan silybin (**4**),[3] an extract of *Silybum marianum* Gaertn., which shows interesting antihepatotoxic activity.[4] The structure of silybin was established in 1975 by degradative evidence[5] and synthesis of dehydrosilybin pentamethyl ether.[6]

Oxidation of equimolar amounts (3 mmol) of (2*R*,3*R*)-dihydroquercetin and coniferyl alcohol (**2b**) in dry benzene–acetone (90:25, 1200 ml) for 45 h at 55 °C gave, after filtration through silica gel (chloroform–methanol 95:5), a mixture (78% yield) of two compounds (57:43, h.p.l.c. MeCN–water). The major compound, easily purified by simple crystallization of the mixture from methanol–water (9:1) and then from EtOAc, is silybin, as shown by mixed m.p., t.l.c., h.p.l.c., u.v., i.r., mass, and ^1H and ^{13}C n.m.r. spectral comparison with the natural compound. The c.d. spectrum of the synthetic sample, corrected for the optical purity of the starting dihydroquercetin (68%), is superimposable with that of natural silybin.‡ The second compound produced in the synthesis was identified with the product of the regioisomeric coupling, *i.e.* isosilybin.[7]



(4)

In this case the regioselectivity of the reaction is poor. The large distance between the chiral centres of dihydroquercetin and the reaction site should lead to small, or no stereoselectivity. This was indeed the case as synthetic silybin and isosilybin, like the natural compounds, appear in the n.m.r. spectrum in benzene and pyridine as 1:1 mixtures of diastereoisomers[7] at C-2′ and C-3′. This is again in agreement with a free radical coupling mechanism[8] both *in vitro* and *in vivo*.[7,9]

This simple one-step condensation is not only the first synthesis of natural silybin, but lends itself to the preparation of analogues. The long synthesis of racemic silybin by Mishima *et al.*,[10] performed before the correction of the structure of silybin, is in fact that of the regioisomer isosilybin.

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‡ This confirms the 2*R*,3*R* configuration for natural silybin.

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