# Synthesis of Coumarinolignans through Chemical and Enzymic Oxidation

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The first syntheses of coumarinolignans through chemical or enzymic oxidation of a dihydroxycoumarin and a phenylpropene are described.

Coumarinolignans are a relatively new class of natural product, five members having thus far been isolated; namely, propacin from *Protium opacum* (Burseraceae),[1] cleomiscosin A from *Cleome viscosa* (Capparidaceae),[2,3] *Simaba multiflora* (Simaroubaceae),[4] *Soulamea soulameoides* (Simaroubaceae),[4] and *Matayba arborescens* (Sapindaceae),[4] cleomiscosin B from *C. viscosa*,[3] aquillochin from *Aquilaria agallocha* (Thymelaeaceae),[5] and daphneticin from *Daphne tangutica* (Thymelaeaceae).[6]

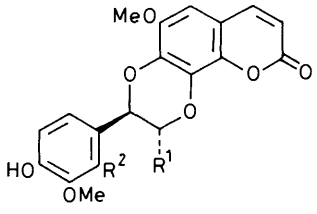
Because of our interest in the biological activity of these compounds,[4,6,7] particularly their cytotoxicity,[4,6] as well as the structure determination of certain isolates, we have initiated a program to synthesize these constituents and a number of new coumarinolignans which may be regarded as likely natural products. We report here the first synthesis of cleomiscosin A (**1**), cleomiscosin B (**2**), propacin (**3**), daphneticin (**4**), and aquillochin (**5**) and report preliminary results on the synthesis of several new coumarinolignans.

Prior work on the synthesis of flavonolignans[8] prompted us to attempt a similar strategy with the dihydroxycoumarin, fraxetin (**6**) and the phenylpropene, coniferyl alcohol (**7**) under oxidative ($Ag_2O$) conditions. After 20 h in benzene at room temperature (r.t.), two products, identified as cleomiscosin A (**1**) and cleomiscosin B (**2**), were obtained in 10.4 and 6.5% yield, respectively. However, when the same reactants were treated in buffered aqueous solution with horseradish peroxidase at room temperature for one week, (**1**) and (**2**) were isolated in 22.6 and 2.7% yield, respectively. In a similar manner, propacin (**3**) was synthesized from fraxetin (**6**) and isoeugenol (**8**) in 29% yield, aquillochin (**5**) from fraxetin (**6**) and sinapyl alcohol (**9**) in 17.5% yield, and daphneticin (**4**) from daphnetin (**10**) and sinapyl alcohol (**9**) in 5.8% yield. When hydrogen peroxide was added as an initiator in the reaction of (**6**) and (**8**), the regioselective yield of propacin (**3**) rose to 87.2%. Compounds were characterized by m.p., u.v., i.r., and n.m.r. spectra and by conversion into their corre-

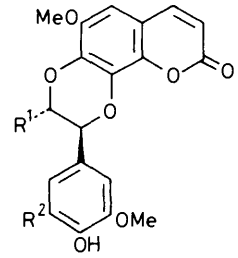
**Table 1.** Synthesis of coumarinolignans.

| Coumarin | Phenylpropene | Oxidizing agent | Conditions | Yield of isomeric coumarinolignans[a] (%) |
|---|---|---|---|---|
| (**6**) | (**7**) | $Ag_2O$ | 20 h, r.t. | 10.4 : 6.5 [(**1**) : (**2**)] |
| (**6**) | (**7**) | HRP[b] | 1 week, 37 °C | 22.6 : 2.7 [(**1**) : (**2**)] |
| (**6**) | (**8**) | $Ag_2O$ | 20 h, r.t. | 4.1 : 2.6 [(**3**) : (**11**)] |
| (**6**) | (**8**) | DDQ | 28 h, r.t. | — : 10.8 [(**3**) : (**11**)] |
| (**6**) | (**8**) | HRP | 1 week, 37 °C | 29.0 : — [(**3**) : (**11**)] |
| (**6**) | (**8**) | HRP–$H_2O_2$ | 2 weeks, 37 °C | 87.2 : — [(**3**) : (**11**)] |
| (**6**) | (**9**) | $Ag_2O$ | 18 h, r.t. | 6.8 : 6.2 [(**5**) : (**12**)] |
| (**6**) | (**9**) | HRP | 2 weeks, 37 °C | 17.5 : 0.5 [(**5**) : (**12**)] |
| (**13**) | (**8**) | $Ag_2O$ | 6 h, r.t. | 8.4 : 1.1 |
| (**13**) | (**8**) | DDQ | 24 h, r.t. | 2.4 : — |
| (**13**) | (**8**) | HRP | 2 weeks, 37 °C | 8.3 : — |
| (**13**) | (**8**) | CP[c] | 3 weeks, 37 °C | 4.6 : — |
| (**13**) | (**7**) | $Ag_2O$ | 20 h, r.t. | 1.9 : 0.8 |
| (**13**) | (**7**) | HRP | 2 weeks, 37 °C | 7.9 : — |
| (**10**) | (**8**) | $Ag_2O$ | 24 h, r.t. | 5.0 : 1.3 |
| (**10**) | (**8**) | HRP | 2 weeks, 37 °C | 19 : — |
| (**10**) | (**9**) | $Ag_2O$ | 24 h, r.t. | 1.0 : — [(**4**)] |
| (**10**) | (**9**) | HRP | 19 days, 37 °C | 5.8 : — [(**4**)] |

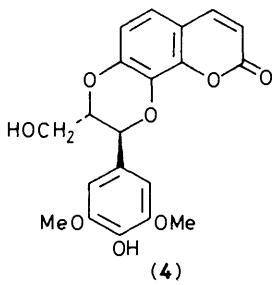
[a] The spectral data (u.v., i.r., and n.m.r.) of the products clearly indicated that they were *trans*-substituted coumarinolignans. However, distinction between the two regioisomers was not always possible. [b] HRP = Horseradish peroxidase (Sigma Chemical Co., St. Louis, Missouri). [c] CP = Chloroperoxidase (Sigma Chemical Co.).



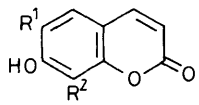
(**1**) $R^1 = CH_2OH$, $R^2 = H$
(**5**) $R^1 = CH_2OH$, $R^2 = OMe$
(**11**) $R^1 = Me$, $R^2 = H$



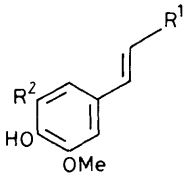
(**2**) $R^1 = CH_2OH$, $R^2 = H$
(**3**) $R^1 = Me$, $R^2 = H$
(**12**) $R^1 = CH_2OH$, $R^2 = OMe$



(**4**)



(**6**) $R^1 = OMe$, $R^2 = OH$
(**10**) $R^1 = H$, $R^2 = OH$
(**13**) $R^1 = OH$, $R^2 = H$



(**7**) $R^1 = CH_2OH$, $R^2 = H$
(**8**) $R^1 = Me$, $R^2 = H$
(**9**) $R^1 = CH_2OH$, $R^2 = OMe$

sponding acetate derivatives for direct comparison with authentic samples.

Table 1 summarizes our preliminary results to date in this area and indicates that with the exception of (**6**) and (**7**), and (**6**) and (**9**), the enzymic oxidation is regioselective, whereas the chemical oxidation is not. CP and 2,3,5,6-dichlorodicyanobenzoquinone (DDQ) are also capable of effecting this oxidative coupling, although the yields are not yet competitive with those using horseradish peroxidase. We are in the process of distinguishing the isomers produced in these reactions through the use of our selective n.m.r. technique,[4] and potentiating yields through the addition of hydrogen peroxide and using other enzyme systems.

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