Safrole as Starting Material for the Synthesis of 7-Metoxy-3',4'-Methylenedioxy Isoflavanone

Marcelo C. Saraiva, Débora F. Santos, Paulo R.R. Costa* and Jaime A. Rabi*

Núcleo de Pesquisas de Produtos Naturais, Universidade Federal do Rio de Janeiro, CCS, Bloco H, Cidade Universitária, 21941, Rio de Janeiro, RJ, Brasil

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Hidroboração do éter **8**, obtido por interação entre o brometo **7** e 3-metoxifenol, seguido de oxidação levou ao ácido **10**. Reação de **10** com anidrido trifluoracético, forneceu a isoflavanona **11**.

The reaction of the bromide **7** with 3-methoxyphenol gave the ether **8** which upon hydroboration followed by Jones oxidaton gave the acid **10**. Treatment of **10** with trifluoroacetic anhydride gave the isoflavanone **11**.

Key words: *7-methoxy-3',4'-methylenedioxy isoflavanone, safrole, synthesis.*

Introduction

The number of known biologically active isoflavonoids is ever increasing. They can be subdivided into classes, such as isoflavones, isoflavanones, pterocarpans, coumestans and rotenoids[1].

Biochanin A (**1**), an isoflavone, is a weak oestrogen, while the pterocarpanoid pisatin (**2**) is inhibitory to a wide range of phytopathogenic fungi[1]. The pterocarpans cabenegrin A-I (**3a**) and A-II (**3b**) are active, *in vivo*, against the venoms of some snakes[2]. On the other hand wedelolactone (**4**), a coumestan, has been shown to neutralize the lethal and myotoxic activities of South American Rattlesnake venom[3].

Desoxibenzoins[4], chromens[5], chalcones[6] and 3-arylcoumarins[7] are the most commonly used starting materials for the synthesis of the isoflavonoid skeleton.

In this note we wish to report a new procedure for obtaining isoflavonoids as exemplified with the synthesis of the isoflavanone **11**. Our strategy considers the isoflavanone skeleton as derived from a monosubstituted resorcinol and a C_6-C_3 rearranged phenylpropane. The discovery in our laboratory[8] that reaction of safrole (**5**) with bromine may lead to the dibromide **6** provided an easy entry to the desired C_6-C_3 rearranged skeleton (Scheme 1).

Thus, **5** was allowed to react with bromine in 1,2-dichloroethane at r.t. to give a mixture (^{1}H NMR) of **6** (~66%) and the 1,2-dibromo isomer (~33%) in quantitative yield. After column chromatography, the isomeric dibromide **6** was obtained pure in 60% yield. Reaction of **6** with 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU)[9] in THF for 10 min at 0°C led to the allylic bromide **7** in 80% yield. Alkylation of 3-methoxyphenol with **7**, in acetone containing potassium carbonate[10], furnished **8** in 84% yield. The desired carboxylic acid **10** was obtained (50% overall yield) by hydroboration[11] of **8** followed by oxidation of the intermediate alcohol **9** with Jones reagent[12]. Finally, Friedel-Crafts cyclization of **10** using trifluoroacetic anhydride[13] led to the isoflavanone **11** in 53% yield[14,15].

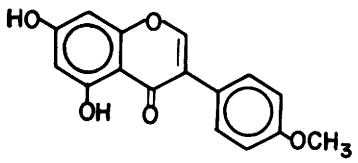
Work is now in progress in our laboratory to evaluate the possibility of further developing the described methodology towards a new synthetic procedure for pterocarpans.

Experimental

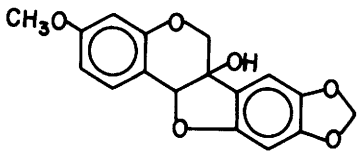
1. Reaction of safrole (**5**) with bromine. To a solution of safrole (1.62g, 10 mmoles) in 1,2-dichloroethane (50mℓ) at r.t., a solution of bromine (0.54 mℓ, 10.44 mmoles) in 1,2-dichloroethane (5mℓ) was added. After 5 min at r.t. the mixture was diluted with 1,2-dichloroethane (50mℓ) and washed with aqueous $NaHCO_3$ (10%, 50 mℓ) and water (2 × 50 mℓ). The organic layer was dried (Na_2SO_4) and the solvent eliminated *in vacuo*. Column chromatography using hexane-$CHCℓ_3$ (8:2, v/v) as eluent gave **6** (1.95 g, 60.5%) as colorless oil. ^{1}H NMR (100MHz, $CDCℓ_3$) δ 6.75 (3, m); 5.97 (2, s); 3.88-3.56 (4, m); 3.35 (l, m). M/z 320, 322, 324, (1, 2, 1; 31); 227, 229 (1:1, 25); 148 (100).

2. Reaction of **6** with DBU. To a solution of compound **6** (0.4g, 1.24 mmoles) in THF (1,5 mℓ) at 0°C, DBU was added (0.33 mℓ, 2.19 mmoles). After 10 min the reaction mixture was partitioned between ethyl acetate (15 mℓ) and 10% aqueous $HCℓ$ (15 mℓ). The organic layer was washed with brine (2 × 15mℓ), dried (Na_2SO_4) and evaporated. The crude oil (0.240g, 80%) was purified by flash chromatography giving **7** as a colorless oil. ^{1}H NMR (60MHz, $CCℓ_4$)δ 6.90 (3, m); 6.00 (2, s); 5.42 (2, bs); 4.28 (2, s).

3. Reaction of **7** with 3-methoxyphenol. To a solution of 3-methoxyphenol (0.21g, 1.69 mmoles) in acetone (16 mℓ) K_2CO_3 (1.19g, 8.162 mmoles) was added and the mixture boiled for 10 min. Compound **7** (0.408g, 1.69 mmoles), dissolved in acetone (4 mℓ), was added and the reflux continued for 3 h. The reaction mixture was cooled to r.t. and the solid filtered off. The filtrate was concentrated and the resulting



1



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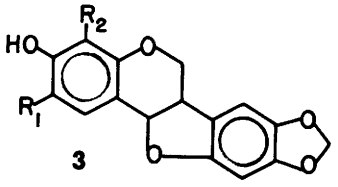
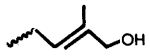
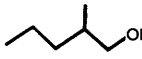


3

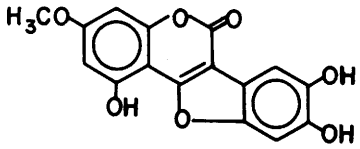
a) R_1 = H, R_2 =



b) R_1 =

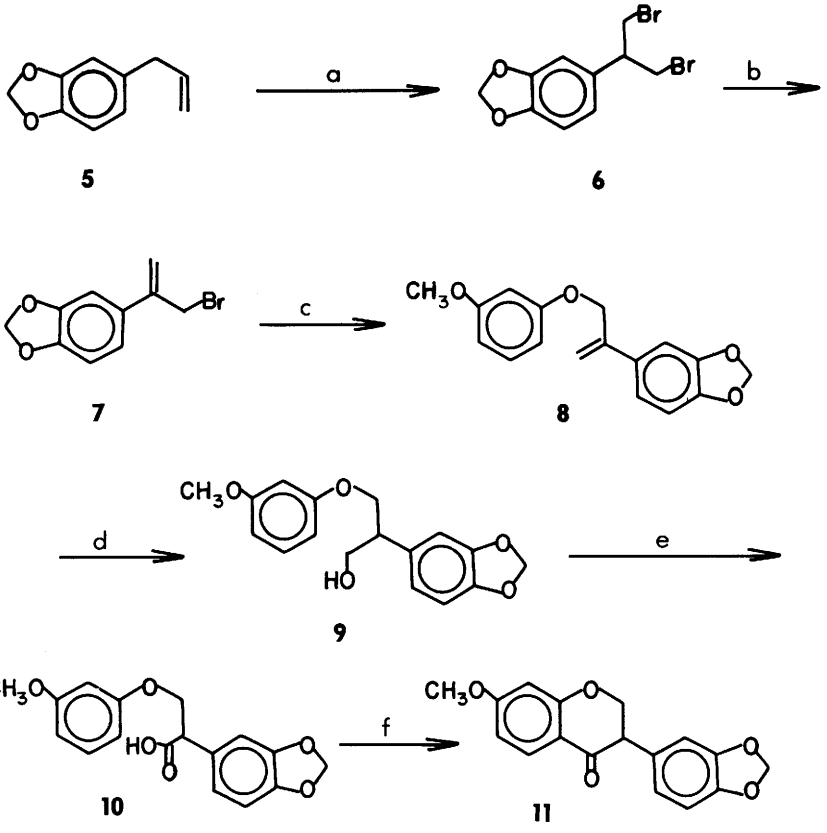


R_2 = H



4

WEDELOLACTONE



5 6 7 8 9 10 11

a) Br_2, $C_2H_4Cl_2$, r.t; SiO_2 separation, 50%
b) DBU, THF, 0 °C, 80%
c) 3-methoxyphenol, K_2CO_3, acetone, Δ
d) 1) B_2H_6, THF
2) NaOH 6N, H_2O_2 30%
e) Jones reagent, acetone, 0 °C
f) trifluoroacetic anhydride, 0 °C

Scheme 1

oil (0.405g, 84%) purified by flash chromatography to give **8** (0.306g, 64%). ^{1}H NMR (100MHz, $CDCl_3$)δ 7.3 – 6.4 (7, m); 5.94 (2, s); 5.49 and 5.36 (l each, bs); 4.80 (2, bs); 3.78 (3. s).

4. Hydroboration of **8**. Compound **8** (0.109g, 0.384 mmoles) was dissolved in THF (1.0 mℓ) and 1 mℓ of a solution of B_2H_6 in THF (0.5M) was added. After 1 h at r.t. the mixture was cooled to 0°C, followed by addition of H_2O (5 mℓ), H_2O_2 (30%, 0.05 mℓ) and 6N NaOH to pH 8. The mixture was allowed to stand for 8 h at r.t. and H_2O (5mℓ) was added. The resulting mixture was extracted with ether (3 × 10 mℓ), and the organic layer was washed with brine, dried (Na_2SO_4) and evaporated to give an oil. Purification by flash chromatography gave **9** as a clear oil (0.095g, 82%). ^{1}H NMR (100MHz, $CDCl_3$)δ 7.30-6.40 (7, m), 5.92 (2, s); 4.17 (2, d, 7Hz); 3.96 (2, m); 3.78 (3m,s); 3,23 (1, m); 1.58 (l, b signal).

5. Reaction of compound **9** with Jones reagent. To a solution of **9** (0.160g, 0.529 mmoles) in ethyl acetate (4 mℓ) a solution of Jones reagent (0.26 mℓ) was added. After 1 h at 0°C, isopropanol was added and the mixture partitioned between ethyl acetate (20 mℓ) and water (20 mℓ). The organic layer was washed with brine, dried and evaporated to give **10** as a brown oil (0.108g, 65%).

6. Reaction of compound **10** with trifluoroacetic anhydride. Crude **10** as obtained above (0.712g) was dissolved in trifluoroacetic anhydre (2 mℓ) at 0°C. After 1 h, water (20 mℓ) was added and the mixture extracted with ethyl acetate (30 mℓ); the organic layer was washed with aqueous $NaHCO_3$ followed by brine, dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by preparative thin layer chromatography to give **11** as a white solid (0.265g, 40%), mp 113-115°C (lit.[15], 118-119°C); ^{1}H NMR[16] (100MHz, $CDCl_3$)δ 7.84 (l, d, 9Hz); 6.75 (3, bs); 6.57 (l, dd, 3 and 9Hz); 6.41 (l, d, 9Hz); 5.91 (2, s); 4.60 (2, d, 7Hz); 3.84 (3, s); 3.82 (l, t, 7Hz); ^{13}C NMR (25.2MHz, $CDCl_3$)δ 190.54 (s); 165, 83 (s); 163.24 (s); 147,75 (s); 146.91 (s); 129.83 (d); 128.83 (s); 121.73 (d); 114.63 (s); 110.05 (d); 108.76 (d); 108.43 (d); 100.95 (d); 100.52 (t); 71.78 (t); 55.51 (q); 51.44 (d); U.V.$_{max}$ ($CHCl_3$) 312, 276, 240 nm; IR(film): 1680; MS m/z (rel. in.): $|M|^+$ 298 (10%), 148 (100%).

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