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EUGENOL AND SAFROLE AS STARTING MATERIALS FOR THE SYNTHESIS OF 3-ALKYL MUCONIC ACID MONO AND DIMETHYL ESTERS AND 4,4-DIALKYL BUTENOLIDES

Paulo R.R. Costa*, Sergio Pinheiro and Cláudio C. Lopes

Núcleo de Pesquisas de Produtos Naturais, Universidade Federal do Rio de Janeiro,
Centro de Ciências da Saúde, Bloco H, 21941, Ilha do Fundão, Rio de Janeiro, R.J.,
Brazil.

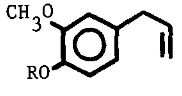
Summary: Compounds 1b-e and 2b-d prepared from eugenol (1a) and safrole (2a) respectively were submitted to ozonation in methanol at 0°C. The 3-alkyl muconic acid dimethyl esters 4b-e were produced from 1b-e (∿ 45%), while starting from 2b-d the 3-alkyl muconic acid monomethyl esters 6b-d were obtained regiospecifically (∿ 75%). These latter compounds were transformed (∿ 85%) into the 4,4-dialkyl butenolides 7b-d.

As part of a program[1] of study of abundant natural products available in Brazil we turned our attention to the transformation of eugenol (1a), safrole (2a) and vanillin (3) into aliphatic derivatives. Compounds 1b-g and 2b-d were prepared by usual methods from 1a, 3 and 2a respectively and were submitted to ozonation in methanol (0.4% O_3 in O_2, 0°C).

Under these reaction conditions compounds 1b-e were transformed into the 3-alkyl muconic acid dimethyl esters 4b-e (∿ 60% by gas-liquid chromatography; ∿ 45% after silica gel chromatography). The products were obtained as oils[2] and the ^{1}H NMR spectra indicated for all cases the presence of a mixture of Δ^2Z, Δ^4Z and Δ^2E,Δ^4Z isomers[3] (Scheme 1). By hydrogenation in Pd/C-EtOAc those mixtures were converted quantitatively to the corresponding adipates 5b-e. The vanillin derivatives 1f-g did not yield muconic acid derivatives when submitted to our ozonation conditions. For 1f the main product was the methyl ester of veratric acid (20%) while for 1g a complex mixture of products was formed.

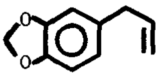
On the other hand, when safrole derivatives 2b-d were submitted to ozonation under the same conditions (Scheme 1), the 3-alkyl muconic acid monomethyl esters 6b-d were formed regiospecifically, contrasting with the oxidation of cathecols catalyzed by Cu^I

salts[4] were a mixture of muconic acid monomethyl ester is formed. The reaction products were purified by base extraction (∿ 75%) and the ^1H NMR spectra showed in all cases only the presence of Δ^2Z, Δ^4Z isomers[5]. The structures of 6b-d were confirmed by their cyclization (∿ 85%) catalized by silica gel[4] to the corresponding 4,4-dialkyl butenolides 7b-d[6,7].

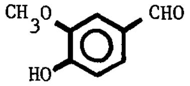


1a, R= H

1a', R= CH_3



2a



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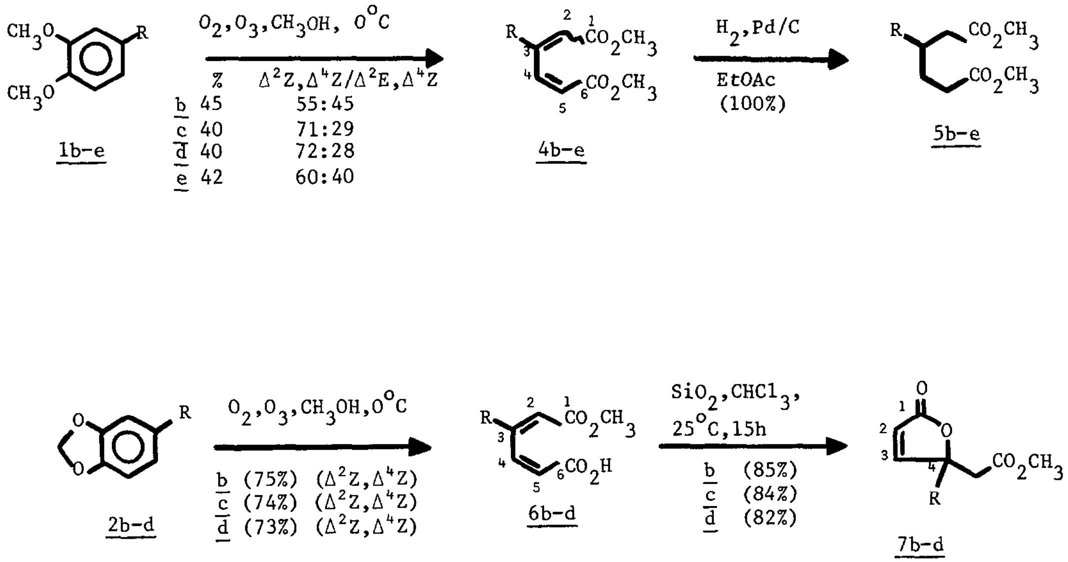
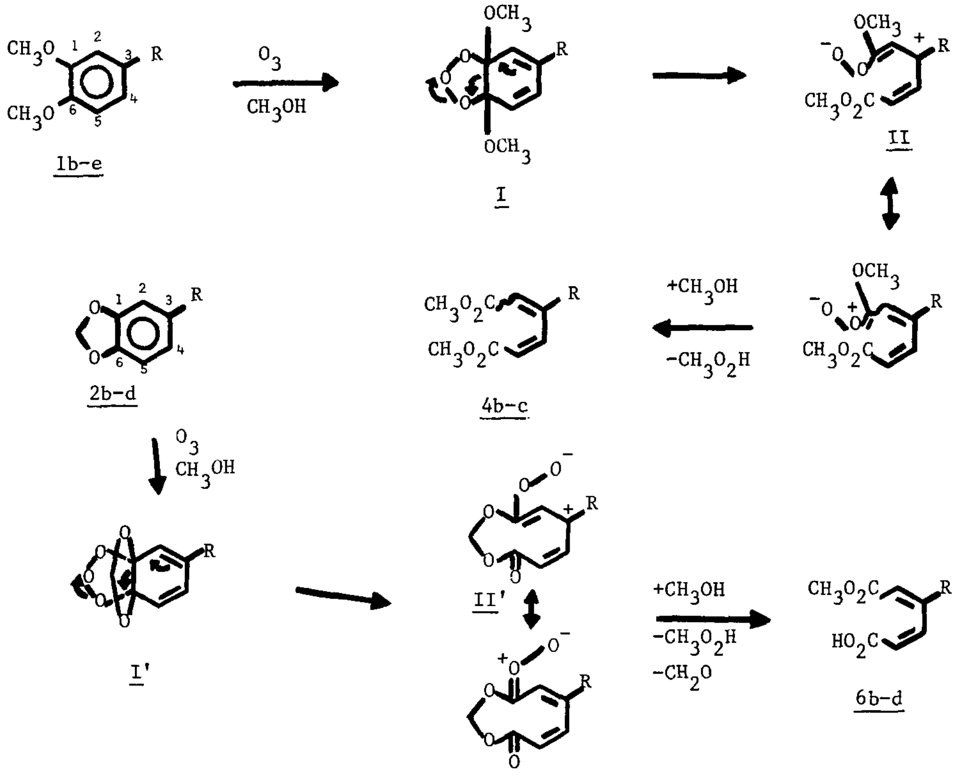
SCHEME 1



b, R= $CH_2CH_2CH_3$; c, R= CH_2CH_2OAc; d, R= $CH_2CH_2CH_2OAc$; e, R= $CH_2CH_2CO_2CH_3$;
f, R= CHO; g, R= CH_2OAc

While ozonation of veratrolic systems is already known[8] this paper is, to our knowledge, the first report about ozonation of aromatic compounds substituted by the dioxolane group. The total control of the stereochemistry of the double bonds, contrasting with the ozonation of eugenol derivatives, and the observed regiospecificity with respect to the position of the ester and acid functions can be explained by the mecanistic interpretation showed in Scheme 2. From the primary ozonides I and I', formed by attack of ozone to 1b-e and 2b-d respectively, a regiospecific breakdown of the C_1-C_6 σ bond is proposed. This cleavage, most probably controlled by the R group at position 3, would give the carbonyl oxide intermediates II and II'. The stereochemistry of the resulting olefins may be explained considering the structures of intermediates. While II would allow C_2-C_3 bond rotation thus leading to a mixture of Δ^2 isomers the nine-membered ring II', in wich trans double bond is disfavored, would lead to the Δ^2Z, Δ^4Z isomers only.

SCHEME 2



The synthesis of 7b-d as reported here may represent a novel approach to the obtention of more complex natural products possessing a butenolide moiety.

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2. All the compounds gave satisfactory elemental and spectral data.
3. In different experiments with 4b, purified products containing different proportions of geometrical isomers Δ^2Z, Δ^4Z and Δ^2E, Δ^4Z were obtained. This fact permits easy interpretation of the ^{1}H NMR spectra of the mixtures. The hydrogens atoms attacked at C_4 and C_5 shows identical chemical shifts and multiplicities in both geometrical isomers, while for hydrogen atom at C_2 and the methoxyl groups the chemical shifts differ. The same was observed for 4c-e. 4b (Δ^2Z,Δ^4Z) (100MHz, $CDCl_3$) δ 7.06 (1H, dd, J= 12.0 and 2.0Hz, C_4-H), 5.88 (1H, d, J= 12.0Hz, C_5-H), 5.74 (1H, sl, C_2-H), 3.70 (3H, s, CO_2CH_3), 3.68 (3H, s, CO_2CH_3), 2.42 (2H, t, J= 7.0Hz), 1.60 (2H, m), 0.88 (3H, t, J= 7.0Hz); 4b (Δ^2E, Δ^4Z) (100MHz, $CDCl_3$) δ 7.06 (1H, dd, J= 12.0 and 2.0Hz, C_4-H), 6.68 (1H, m, C_2-H), 5.88 (1H, d, J= 12.0 Hz, C_5-H), 3.86 (3H, s, CO_2CH_3), 3.84 (3H, s, CO_2CH_3), 2.55 (2H, t, J= 7.0 Hz), 1.60 (2H, m), 0.88 (3H, t, J= 7.0Hz).
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5. 6b(Δ^2Z, Δ^4Z) (100MHz, $CDCl_3$) δ 8.2-7.4 (1H, sl), 7.12 (1H, dd, J=12.0 and 2.0Hz, C_4-H), 5.87 (1H, d, J= 12.0Hz, C_5-H), 5.72 (1H, sl, C_2-H), 3.68 (3H, s, CO_2CH_3), 2.38 (2H, t, J= 7.0Hz), 1.50 (2H, m), 0.92 (3H, t, J= 7.0Hz).
6. 7b (100MHz, $CDCl_3$) δ 7.60 (1H, d, J= 6.0Hz, C_3-H), 6.07 (1H, d, J= 6.0Hz, C_2-H), 3.70 (3H, s, CO_2CH_3), 2.98 (1H, d, J= 15.0Hz, $CH_2CO_2CH_3$), 2.66 (1H, d, J= 15.0Hz, $CH_2CO_2CH_3$), 1.83 (2H, m), 1.27 (2H, m), 0.92 (3H, t, J= 6.0Hz).
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