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ENANTIOSELECTIVE SYNTHESIS OF (R)-(+)-β-PIPERONYL-γ-BUTYROLACTONE

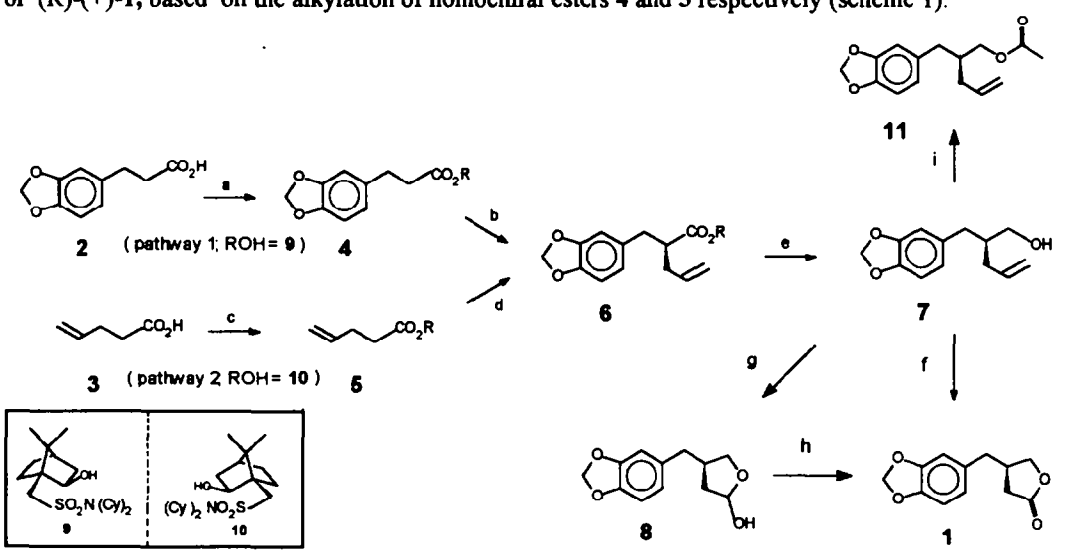
Hiram C. A. Filho[a], Ubiracir F. L. Filho[b], Sergio Pinheiro[c], Mario L. A. A.Vasconcellos[b] and Paulo R. R. Costa[b*].

[a] Escola Tecnica Federal de Quimica - Rio de Janeiro, RJ, Brazil.
[b] Nucleo de Pesquisas de Produtos Naturais - Universidade Federal do Rio de Janeiro - Centro de Ciencias da Saude , Bloco H , Ilha da Cidade Universitaria - . 21941 - Rio de Janeiro, RJ, Brazil.
[c] Departamento de Quimica Organica , Instituto de Quimica , Universidade Federal Fluminense , Niteroi, RJ, Brazil.

Abstract: Lactone (R)-(+)-**1**, was prepared from (2S)-(−)-2-allyl-[3',4'-(methylenedioxy)phenyl] propan-1-ol (**7**). This intermediate was synthesized by two complementary pathways, using as the key steps the diastereoselective alkylation of esters **4** and **5**, respectively.

The (R)-(+)-β-piperonyl-γ-butyrolactone (**1**) and related lactones have been used as key intermediates for the synthesis of naturally occurring lignans.[1] These intermediates have been obtained optically pure or with high enantiomeric excess by resolution of synthetic precursors[2], by manipulation of homochiral starting materials[3] and by asymmetric synthesis.[4]

In this report we describe two complementary synthetic pathways for the enantioselective synthesis of (R)-(+)-**1**, based on the alkylation of homochiral esters **4** and **5** respectively (scheme 1).



scheme 1: a) oxalyl chloride, benzene; AgCN, then compound **9**, 80°C, 4 h, 65%, b) LDA, THF, − 78°C, then allyl bromide, 60%; c) oxalyl chloride, benzene; AgCN, then compound **10**, 80°C, 4h, 96%; d) LDA, THF, − 78°C, then piperonyl iodide, 62%; e) $LiAlH_4$, THF, 0°C, 82%; f) $NaIO_4$, $KMnO_4$ cat., *t*-BuOH, H_2O, pH 8, 17 h, 64%; g) O_3, CH_2Cl_2, − 78°C, Me_2S, 52%; h) CrO_3, pyridine, CH_2Cl_2, 72%; i)Ac_2O, pyridine, 94%.

The easily accessible carboxylic acids **2**[5] and **3**[6] were used as starting materials in pathways 1 and 2, respectively. These compounds were transformed into the corresponding acyl chlorides and these intermediates were esterified with homochiral enantiomeric alcohols **9** and **10**.[7] The resulting esters **4** and **5** were kinetically deprotonated (LDA, THF, −78°C) leading probably to the corresponding E-enolates. The enolate derived from **4** was alkylated with allyl bromide (pathway 1, step b) and that derived from **5** was alkylated with piperonyl iodide (pathway 2, step d). The alkylated ester **6** was obtained, in both cases, in similar chemical yields but a better diastereoselection was observed in step d (94% d.e. *versus* 78% d.e.). This difference could be attributed to the greater bulky of piperonyl iodide.

The ester **6** obtained in pathway 2 (94% d.e.), was reduced to the homoallylic alcohol **7**. The ^{1}H-NMR of its acetate derivative **11** was recorded in the presence of Eu(hfc)$_3$.[8] The e.e. obtained (86%) was similar to that one observed for the corresponding ester **6**.

Compound **7** was transformed into the desired lactone **1** either by ozonolysis followed by oxidation of the hemiketal intermediate (steps g, h)[9] or by a one pot oxidation in the presence of catalytic potassium permanganate and sodium periodate (step f).[10]

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10. Leumieux, R.U.; von Rudloff, E., *Can. J. Chem.*, 1955, **33**, 1701, $[\alpha]_D$, ^{1}H-NMR and ^{13}C-NMR of (R)-(+)-**1** are in agreement with those described in the literature (see ref. 2).

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